

Perceptuo-motor control of walking and navigation in post-stroke unilateral spatial neglect: en route towards the development of a novel assessment and advancement of current clinical practices

Tatiana Ogourtsova

School of Physical and Occupational Therapy

Faculty of Medicine

McGill University, Montreal

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STATEMENT OF AUTHORSHIP

I, Tatiana Ogourtsova, certify that I am the primary author of this thesis. I claim full responsibility for the content and study of the text included herein.

STATEMENT OF ORIGINALITY

This thesis contains material that has been published elsewhere, except where specific references are made. The studies in Chapters 2, 3, 4, 5, and 6 are original material and represent contributions to knowledge in the field of post-stroke unilateral spatial neglect (USN), its effects on goal-directed locomotion and navigation and on visual-perceptual abilities; virtual reality (VR) assessment for post-stroke USN and knowledge translation initiatives. This work blends quantitative and qualitative research methodologies. I have used novel, virtual reality setups to estimate the extent to which post-stroke USN affects goal-directed locomotion, navigation and detection abilities in different cognitive/perceptual conditions. Further, computerized psychophysical tests were used to estimate the effects of post-stroke USN on visual-perceptual abilities and how those contribute to goal-directed locomotion impairments. Moreover, a novel VR-based assessment for post-stroke USN, named EVENS, was designed and examined in this population. Lastly, knowledge translation initiatives were undertaken, where through qualitative research methods and analysis, I determined the barriers and facilitators to the use of VR for post-stroke USN management among clinicians, as well as additional optimal features for a VR-based USN assessment as per collaborative inputs from clinicians and experts in the field. The results of this PhD thesis offer new knowledge on the perceptuo-motor control in post-stroke USN during locomotion and navigation; as well as grounds for the design, refinement, and eventual clinical implementation of a novel VR-based USN assessment tool.

All data presented in this thesis were collected at the Feil & Oberfeld Research Center of the Jewish Rehabilitation Hospital; Centre Intégré de Santé et de Services Sociaux de Laval (CISSS de Laval); and research site of the Center for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR), affiliated to McGill University. All studies have been approved by the Ethics Board of CRIR (refer to Appendix 1 for English and French consent forms used in the projects related to this dissertation).

DEDICATIONS

I dedicate this thesis to my family. To my mother, Elena Tesler (Ogourtsova), and my departed father, Oleg Ogourtsov, for offering me the best upbringing in their capacities, the happiest childhood that one can ask for and for fostering my curiosity, passion for learning, and compassion for those in need. I am forever thankful for their continuous support, patience and love.

To my beloved, one and only husband, Deian Ivanov, for being my best friend, my soul partner, to whom I can always run in times of need and despair and put my head on a strong shoulder to take a breath as we go through this chaotic life style. I love you so much, I do not say it enough. Thank you for always being so supportive, loving, caring, understanding and fun. I am the luckiest girl in so many ways that our paths have crossed that cold winter. I would not accomplish this chapter in my life without you. I am looking forward to celebrating this success and turning point in my life with you and to our future together as we watch our kids grow.

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In this PhD, I had the outmost opportunity to learn from two extraordinary supervisors who each contributed to several aspects of my development in their own ways. I would like to thank my supervisor, Dr. Anouk Lamontagne, and my co-supervisor, Dr. Philippe S. Archambault. I could not ask for a better supervisory team. You provided me with continuous support, guidance, encouragements, critical feedback and fostered a great learning environment. You showed me the importance of careful research planning, ethically-sound practices, team work, concision and attention in writing, and critical thinking in results analysis. I sincerely appreciate all your time and efforts that you have dedicated towards my work, addressing all arising issues in a timely manner and viewing my mistakes as learning opportunities. You are real experts in what you do and I am fortunate to have had the chance to learn from you. Thank you for being always present, easily reachable, and understanding towards me and my family. I felt that I was always supported, that I can talk to you and you will understand. Thank you for going along with my interests and endeavors that I wanted to undertake during this thesis. You have set an example for me of what a great graduate supervisor should be, and for that I am very thankful. You played a big part in making this PhD journey as wonderful as it was.

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aspects of my professional advancement and learning; and offered me a very strong fundament for the PhD. Until this day, she continues to provide me with invaluable advice, constant encouragement and support; for which I am forever grateful and consider myself extremely fortunate to have her by my side.

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CONTRIBUTION OF AUTHORS

This thesis is presented in a manuscript format and includes five manuscripts: all of which are sent for publication to peer-reviewed journals (3/5 are published and 2/5 are in press). In addition, excerpts from two manuscripts (2/2 are published) are included in the background section. I, Tatiana Ogourtsova, am the main contributor and lead author of all the manuscripts (and manuscripts excerpts) included in this thesis content. My contribution includes the research design, data collection and analyses, interpretation of findings, preparation of figures/tables/appendices, submission for publication, revisions following peer review and resubmission, and writing of the dissertation.

Manuscripts presented in Chapters 2 to 6: Study design, data collection, data analyses, statistical analysis and manuscript preparation and modifications following journals' peer review were done by Tatiana Ogourtsova. Co-authors, Dr. Anouk Lamontagne, Dr. Philippe S. Archambault and Dr. Samir Sangani (manuscript presented in Chapter 5 only) critically reviewed and improved manuscripts. All authors have read and approved the final manuscripts. This dissertation was also read and approved by Dr. Anouk Lamontagne (supervisor) and Dr. Philippe S. Archambault (co-supervisor).

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LIST OF ABBREVIATIONS

10MWT	10 Meter Walking Test
2-D	2-dimensional
3-D	3-dimensional
ANOVA	Analyses of variance
AP	Anterior-posterior
APT	Apples Test
BIT	Behavioral Inattention Test
CAREN	Computer Assisted Rehabilitation Environment
CBS	Catherine Bergego Scale
CIHR	Canadian Institutes of Health Research
CISSS de Laval	Centre Intégré de Santé et de Services Sociaux de Laval
CMSA	Chedoke McMaster Stroke Assessment
CRIR	Center for Interdisciplinary Research in Rehabilitation of Greater Montreal
CT	Computer tomography
EVENS	Ecological virtual reality-based evaluation of neglect symptoms
F	Female
FRSQ	Fonds de Recherche Santé – Québec
HC	Healthy controls
HE	Heading error
HMD	Helmet mounted display
VPAs	Visual-perceptual abilities
JRH	Jewish Rehabilitation Hospital
KT	Knowledge Translation
KTA	Knowledge to Action Model
L	Left
LBT	Line Bisection Test
M	Male or Middle (as per context)
MLD	Mediolateral displacement
MOCA	Montreal Cognitive Assessment
n	number of
OF	Optic flow
R	Right
RMI	Rivermead Mobility Index
S	Subject
SAS	Statistical Analysis Software
SCT	Star Cancellation Test
USN	Unilateral spatial neglect
USN-	Individuals with stroke but no USN

USN+	Individuals with post-stroke USN
UTAUT Model	Unified Theory of Acceptance and Use of Technology Model
VE	Virtual environment
VR	Virtual reality
VR-ATT	VR-based USN Assessment and Treatment Toolkit

ABSTRACT

Unilateral spatial neglect (USN) is a debilitating deficit that commonly occurs following a cerebrovascular accident or a stroke. Post-stroke USN is characterized by a difficulty in orienting to or responding to events that generally occur in the space opposite to that of the brain lesion. In other words, if a person has had a stroke in their right brain hemisphere, he/she is likely to have neglect predominantly within the left visual hemisphere. USN is a very complex deficit. In spite of several decades of research in this field, it remains that this deficit is very challenging for clinicians to properly detect and to treat with efficiency. Specifically, clinicians are currently limited in the use of traditional paper-and-pencil tools to evaluate USN. These tools are known to lack sensitivity and responsiveness, where they fail to pick up mild but clinically significant deficits. This leads to the risk of discharging patients home and into the community to resume pre-stroke roles and activities, despite possible underlying visual neglect, and putting them and others at risk of injury and deterioration. With the emerging field of virtual reality (VR), it is possible to improve these current practices and create tools that are functional, representative of real daily activities, and that are sensitive in detecting clinically important deficits.

Another emerging and crucial issue in the field of post-stroke USN is community mobility. Mobility, that includes walking or navigation in space (e.g. using a wheelchair), is essential for adequate performance in numerous self-care and instrumental activities of daily life, participation in leisure and/or productivity. Most individuals with post-stroke neglect never regain independent community mobility and research in that area is limited with inconclusive findings. Moreover, humans heavily rely on visual perception to walk or to navigate in space towards their goal. For instance, when one wishes to get to an object that is beyond the arm reach, walking or navigation is required. This process is guided by visual perceptual abilities such as perception of motion as one moves through space, texture, shape and location of the object to be reached, whether this object remains static or can become dynamic and whether one needs to readjust its trajectory to get to it, etc. Deficits in these visual perceptual abilities could be involved in influencing mobility in individuals with post-stroke USN. Nevertheless, the extent to which they are affected by post-stroke USN and how they contribute to mobility was not previously determined and warranted investigation.

The present dissertation consists of five manuscripts (Chapters 2 to 6), together addressing aforementioned research and practice gaps. In Manuscript №1, the effects of USN on goal-directed locomotion in different conditions: visually-guided, memory-guided and those involving representational updating component (i.e. adaptation to unexpected changes in the surrounding environmental features), were examined. In this study, participants with (USN+, n=15) and without (USN-, n=15) USN and healthy age-matched control individuals (HC, n=15) performed goal-directed locomotion trials to the following target conditions: *actual* (stationary and visible target), *remembered* (i.e. stationary and visible target that disappears and participant is asked to walk to its remembered location; involving a memory component) and *shifting* (i.e. visible and centrally located target that suddenly shifts location and participant is asked to reorient their walking trajectory to reach the new location, involving representational updating component). Targets were located 7 m away at 0° and ±15° to right/left and walking trials were performed while immersed in a 3-D VR environment. Greater end-point mediolateral displacement and heading errors (end-point accuracy measures) were found for the *remembered* vs. *actual* and for the *remembered* vs. *shifting* conditions for the left target among USN+ participants ($p<0.05$). They also showed altered locomotion abilities (end-point accuracy measures) vs. the other two groups in *actual* and *remembered* conditions to the left and right targets (±15°); and a delayed onset of reorientation in the *shifting* condition vs. USN- and HC groups ($p<0.05$). Overall, this study determined that post-stroke USN affects goal-directed locomotion end-point measures to left and right targets in visually-guided and memory-guided tasks, as well as the onset of reorientation measure in the condition involving representational updating.

In this manuscript, however, USN+ participants were also found to be slower walkers vs. stroke participants without USN. Whether the observed goal-directed alterations were influenced purely by perceptual-attentional deficits or resulted from associated sensorimotor post-stroke dysfunctions, such as decrease in walking speed, remained to be determined. Therefore, analogous to the previously used goal-directed locomotor paradigm, in Manuscript №2, a seated, joystick-driven navigation experiment, minimizing locomotor demands, was employed to investigate that important nuance. The objective was to examine goal-directed navigation and perceptual abilities in individuals with (USN+, n=15) and without (USN-, n=15) USN and healthy age-matched control individuals (HC, n=15). The same participants as in Manuscript №1 performed a navigation and a detection time tasks to targets 7 m away at 0°, ±15°/30° in *actual*,

remembered, and *shifting* conditions while immersed in 3-D VR environment. Greater end-point mediolateral errors to left-sided targets (*remembered* and *shifting* conditions) and overall lengthier onsets in reorientation strategy (*shifting* condition) were found for the USN+ group vs. other two study groups ($p<0.05$). USN+ participants mostly overshoot left targets ($-15^{\circ}/-30^{\circ}$). Greater delays in detection time for target locations across the visual spectrum (left, middle and right) were found in USN+ vs. USN- and HC groups ($p<0.05$). Manuscript №2 showed both, lateralized and non-lateralized deficits in object detection. We determined that navigation behavior alterations are present in a memory-guided task and in a condition involving representational component, even during an experimental condition that minimized locomotor demands. Thus, USN related attentional-perceptual deficits alter navigation abilities, independently of post-stroke locomotor deficits.

In Manuscript №3, we considered visual-perceptual abilities that are essential for mobility. The objective was to estimate the extent to which these abilities in left and right visual hemispaces are affected in post-stroke USN and contribute to goal-directed locomotion determined in Manuscript №1. The same participants as in Manuscript №1 ($n=45$, 15 individuals per group) completed a psychophysical evaluation of contrast sensitivity, optic flow direction and coherence and shape discrimination. Higher discrimination thresholds were found for all subtests in USN+ group vs. the other two study groups ($p<0.05$). Psychophysical tests showed high sensitivity in detecting deficits in individuals with history of USN or with no USN on traditional assessments; and were found to be significantly correlated with goal-directed locomotor impairments. Overall, Manuscript №3 evidenced that deficits in visual-perceptual abilities may account for the functional difficulties related to post-stroke USN.

In Manuscript №4, the lack of sensitive and ecological assessment for post-stroke USN was addressed. In this manuscript, we aimed to examine the feasibility of a newly designed assessment, the **E**cological **V**R-based **E**valuation of **N**eglect **S**ymptoms (EVENS). EVENS is immersive and consists of simple and complex (e.g. cluttered) 3-D scenes depicting grocery shopping shelves, where joystick-based object detection and navigation tasks are performed while seated. Effects of virtual scene complexity on navigational and detection abilities in patients with (USN+, $n=12$) and without (USN-, $n=15$) USN following a right hemisphere stroke and in age-matched healthy controls (HC, $n=9$) were determined. Longer detection times, larger

mediolateral deviations from ideal paths and longer navigation times were found in USN+ vs. other two groups, particularly in the complex scene ($p < 0.05$). EVENS detected lateralized and non-lateralized USN related deficits, performance alterations that were dependent and independent of USN severity, and performance alterations in three USN- subjects vs. HC. EVENS' ecological environment of changing complexity, along with the functional tasks of far space detection and navigation could potentially evidence USN-related deficits and may unveil difficulties otherwise not detected using traditional tools.

Nonetheless, EVENS is yet to be implemented in clinical practice beyond a research context. As a first step towards this objective, in Manuscript №5, we aimed to explore the barriers and facilitators perceived by clinicians in the use of VR for USN evaluation; and to identify additional optimal features for EVENS. A qualitative descriptive process, in the form of focus groups, self-administered questionnaire and individual interviews was used. Two focus groups (n=11 clinicians) were conducted and national and international experts in the field (n=3) were individually interviewed. Several barriers and facilitators, including personal, institutional, client suitability and equipment factors, were identified. Clinicians and experts in the field reported numerous features for the virtual tool optimization. Factors identified through this study lay the foundation for the development of a knowledge translation initiative towards EVENS clinical implementation and use-adherence in clinical settings.

Collectively, this PhD dissertation addressed important knowledge gaps with the aim to investigate the perceptuo-motor control in post-stroke USN during locomotion and navigation, as well as to improve and facilitate future changes in the field of post-stroke USN management. Presented studies evidenced: 1) that post-stroke USN negatively affects a) goal-directed locomotion and navigation in visually and memory-guided conditions, tasks with representational updating and increased perceptual demands; and b) bilateral visual-perceptual skills; 2) that goal-directed locomotion and navigation in VR, testing of visual-perceptual abilities, and EVENS, are potentially sensitive in unveiling “dormant” USN related deficits; 3) barriers and facilitators to the clinical implementation of VR for post-stroke USN management; and 4) supplementary features to be incorporated into the existing VR-based assessments. This work answered several key questions and laid solid grounds for clinical practice change towards improved management of this common and highly debilitating deficit.

ABRÉGÉ

La négligence spatiale unilatérale (NSU) est un déficit débilitant qui survient suite à un accident vasculaire cérébral (AVC). La NSU est caractérisée par une incapacité à s'orienter vers, ou à répondre à des stimuli survenant dans l'hémi-espace visuel contralésionnel. En d'autres termes, si un individu est victime d'un AVC de l'hémisphère droit, ce dernier est susceptible de négliger davantage l'hémi-espace visuel gauche. La NSU est un trouble déficitaire très complexe. Malgré plusieurs décennies de recherche dans le domaine, il demeure difficile d'une part, de la détecter et d'autre part, de la traiter efficacement. Pour détecter et évaluer ce problème, les cliniciens se limitent encore aujourd'hui à la méthode traditionnelle papier-crayon. Cette méthode d'évaluation est cependant reconnue pour être déficiente dans sa capacité à identifier des troubles plus légers de la NSU, troubles qui ont pourtant un impact cliniquement important. Cela augmente les risques potentiels de donner congé à un patient, de le laisser retourner à la maison et dans la communauté et reprendre ses activités, malgré l'existence possible d'une NSU sous-jacente. Ainsi, ces patients mal-diagnostiqués se retrouvent rapidement de retour dans la société avec un potentiel de détérioration de leur état de santé. L'émergence du domaine de recherche en réalité virtuelle (RV) ouvre la porte à de nouvelles possibilités au niveau des méthodes d'évaluation et d'intervention, laissant donc présager d'éventuelles améliorations des pratiques courantes. En effet, grâce à la RV, il est possible de développer des outils d'évaluation plus sensibles à l'impact d'une NSU sur la réalisation d'activités de la vie quotidienne et aussi plus sensibles pour détecter les troubles légers de la NSU.

Un autre enjeu émergent et crucial lié à la NSU post-AVC est l'impact sur la mobilité d'une personne dans la communauté. La mobilité inclut la marche ou la navigation dans un espace (par exemple, l'utilisation d'une chaise roulante pour se déplacer). La mobilité est essentielle et primordiale pour effectuer adéquatement diverses activités de la vie quotidienne. La plupart des patients victimes de la NSU post-AVC ne regagnent jamais l'indépendance totale de la mobilité dans la communauté, et les études se limitent à des résultats peu concluants. De plus, l'homme s'appuie fortement sur la perception visuelle pour marcher ou naviguer dans un espace et arriver à son but. Par exemple, lorsqu'une personne souhaite atteindre un objet qui n'est pas à distance de leur bras, marcher ou naviguer vers ce dernier requiert d'être guidé par des habiletés de perception visuelle. Ceci inclut la perception du mouvement (au fur et à mesure que l'individu

avance dans l'espace), la perception de la texture, la perception de la forme et de la localisation de l'objet à atteindre. Aussi, ceci comprend la perception de l'objet en mouvement où ce dernier peut devenir dynamique, et l'individu a besoin de réajuster sa trajectoire pour s'y rendre. Ces habiletés de perception visuelle peuvent influencer la mobilité des individus avec la NSU post-AVC. Néanmoins, l'ampleur de cet impact et comment cela affecte la mobilité de ces patients n'a jusqu'à présent pas été investigué ni déterminé.

La présente thèse est constituée de cinq manuscrits (Chapitre 2 à 6). Ensemble, ils adressent les lacunes en recherche et en pratique mentionnées ci-haut. Le Manuscrit N°1 examine les effets de la NSU sur la locomotion orientée vers une cible dans diverses conditions cognitives : guidée par la vision, guidée par la mémoire, et une condition qui inclut une mise à jour représentationnelle (dont entre autres l'adaptation aux changements impromptus des caractéristiques de l'environnement). Dans cette étude, des participants avec (NSU+, n=15) et sans (NSU-, n=15) NSU post-AVC, ainsi que des individus en santé et d'âge équivalent (groupe contrôle (CTL), n=15) ont exécuté une tâche de locomotion orientée vers une cible dans des conditions spécifiques : *actuelle* (cibles immobiles et visibles, donnant lieu à une locomotion visuellement guidée); *de mémoire* (cibles immobiles et visibles disparaissant et dont le participant doit se souvenir afin de se diriger vers leur localisation respective, sollicitant ainsi la mémoire spatiale); *changeante* (cibles immobiles et visibles qui soudainement changent de localisation et où le participant doit réorienter sa trajectoire pour atteindre la nouvelle localisation, sollicitant ainsi une mise à jour représentationnelle). Les cibles étaient localisées à 7m des participants, à 0° et à ±15° à droite/gauche et des essais préalables étaient effectués par les participants en immersion 3-D dans l'environnement de RV. Dans le groupe NSU+, un important effet de déplacement médiolateral et d'erreurs directionnelles ont été notés dans la condition *de mémoire* comparativement à la condition *actuelle* et comparativement à la condition *changeante* ($p < 0.05$). Les résultats ont également démontré l'altération des habiletés de locomotion chez les participants NSU+ comparativement aux deux autres groupes, dans les conditions *actuelles* et *de mémoire*, pour les cibles gauches et droites (±15°) ($p < 0.05$). Aussi, un délai dans l'initiation de la réorientation (condition *changeante*) a été constaté chez les participants NSU+ par rapport aux deux autres groupes ($p < 0.05$). Globalement, cette étude démontre que la NSU post-AVC a un impact sur la locomotion orientée vers des cibles situées à gauche et à droite dans les mesures de précision du point final, autant dans les conditions où les participants ont une cible visuelle

réelle, que dans celles où ils doivent faire appel à leur mémoire spatiale. De plus, l'effet de la NSU post-AVC a été constaté lors de l'initiation de stratégies de réorientation de la trajectoire dans la condition *changeante*, où les participants doivent effectuer une mise à jour représentationnelle.

Toutefois, cette étude montre aussi que les participants NSU+ sont des marcheurs plus lents que ceux victimes de l'AVC mais n'ayant pas de NSU (NSU-). Il reste néanmoins à déterminer si l'altération directionnelle durant la tâche de locomotion orientée vers une cible fut purement influencée par un déficit d'attention perceptuelle, ou bien si cela fut le résultat de déficits sensorimoteurs post-AVC. À cet effet, et pour investiguer cette nuance importante, un paradigme analogue à celui de la locomotion orientée vers une cible fut mis en place pour le Manuscrit N°2. Par contre, dans ce nouveau contexte, les participants étaient en position assise et devaient utiliser une manette de jeu (*joystick*) afin de naviguer dans l'environnement virtuel sans avoir à se déplacer physiquement. L'objectif était d'examiner la navigation orientée vers une cible et les habiletés perceptuelles chez les individus avec (NSU+, n=15) et sans (NSU-, n=15) NSU et chez des individus en santé et d'âge équivalent (CTL, n=15). Les mêmes participants que ceux du Manuscrit N°1 ont exécuté des expérimentations en position assise, navigant grâce à la manette de jeu et détectant des cibles situées à 7m du participant et à des angles de 0° et ±15°/30° dans des conditions où ces dernières étaient visibles et immobiles (*actuelle*), disparaissant (*de mémoire*) ou changeant de localisation (*changeante*) tout en étant en immersion dans un environnement 3-D de RV. Le groupe NSU+, comparativement aux deux autres groupes ($p<0.05$), a démontré une erreur positionnelle médiolatérale importante en fin de trajectoire pour les cibles de gauche dans les conditions *de mémoire* et *changeante*, de même qu'un délai prolongé dans l'initiation de stratégies de réorientation de la trajectoire dans les conditions de *changement* de localisation de la cible. Les individus NSU+ ont majoritairement dépassé les cibles localisées à gauche (-15°/- 30°). Un plus grand retard dans la détection des localisations des cibles sur l'ensemble du spectre visuel (gauche, centre et droite) a été noté chez le groupe NSU+ par rapport aux deux autres groupes ($p<0.05$). Le Manuscrit N°2 démontre la présence de déficits latéralisés et non-latéralisés dans la détection d'objet. Ce manuscrit a aussi permis de déterminer que les altérations dans le comportement de navigation sont présentes à la fois lors des circonstances de mémorisation spatiale et lors des conditions de mise à jour représentationnelle, et cela, même en l'absence de mouvements locomoteurs. Ainsi, le déficit

d'attention et de perception lié à la NSU altère les habiletés de navigation indépendamment d'un déficit de locomotion post-AVC.

Dans le Manuscrit №3, nous avons pris en compte des habiletés visuelles et perceptuelles de haut niveau qui sont essentielles pour la mobilité. L'objectif était d'estimer à quel point ces habiletés d'hémi-espace visuel droit et gauche sont affectées par la présence de la NSU et déterminent la locomotion orientée vers une cible du Manuscrit №1. Les mêmes participants du Manuscrit №1 (n=45, 15 individus par groupe) ont complété une évaluation psychophysique de la sensibilité aux contrastes, de la direction et cohérence du flux optique et de la discrimination des formes. De plus grands seuils de discrimination ont été trouvés pour toutes ces habiletés de perception visuelle de haut niveau chez les individus ayant de la NSU post-AVC comparativement aux deux autres groupes étudiés ($p < 0.05$). Les tests psychophysiques ont aussi démontré une grande sensibilité de détection de déficits chez les individus avec un passé de NSU et chez ceux n'ayant aucune hémiparésie visuelle identifiée par les évaluations cliniques traditionnelles. De plus, des corrélations significatives ont été identifiées entre les évaluations psychophysiques (surtout ceux liées au flux optique) et les altérations de la locomotion orientée vers une cible détectées dans l'étude du Manuscrit №1. De manière globale, le Manuscrit №3 témoigne du fait que les habiletés visuelles et perceptuelles de haut niveau pourraient expliquer les difficultés fonctionnelles expérimentées par les individus ayant subi de la NSU post-AVC.

Dans le Manuscrit №4, nous avons adressé le manque d'outils d'évaluation sensibles et écologiques pour l'évaluation de la NSU post-AVC. Dans ce quatrième manuscrit, nous avons donc eu comme but d'examiner la faisabilité d'un tout nouveau mode d'évaluation, soit - l'évaluation écologique basée sur la RV des symptômes de négligence visuelle (EVENS). EVENS est constitué de scènes immersives, simples et complexes, en 3-D où l'on retrouve des étagères de supermarché. L'individu assis peut, grâce à une manette de jeu, y détecter des objets et effectuer des exercices de navigation dans l'espace. Nous avons examiné les effets de la complexité scénographique virtuelle sur la navigation et sur les habiletés de détection des objets chez les patients avec (NSU+, n=12) et sans (NSU-, n=15) NSU qui ont subi un AVC droit ainsi que chez les individus en santé du groupe contrôle (CTL, n=9). Des délais de détection, de plus grandes déviations médiolatérales du chemin optimal, et de plus longues durées de navigation ont été enregistrées chez les sujets NSU+ comparativement aux deux autres groupes, et cela

particulièrement lors de la scène complexe ($p < 0.05$). Aussi, EVENS a détecté des déficits latéralisés et non-latéralisés liés directement à la NSU, des altérations de performance qui étaient dépendantes et indépendantes de la sévérité de la NSU ainsi que des altérations de performance chez trois sujets NSU-. L'environnement écologique à complexité changeante d'EVENS ainsi que les tâches de navigation et de détection d'objets lointains dans l'espace peuvent possiblement attester des difficultés chez les individus souffrant de la NSU post-AVC et dévoiler des lacunes autrement non-détectées par les outils traditionnels d'évaluation clinique.

Nonobstant ce qui vient d'être dit et au-delà du contexte de recherche, certaines étapes sont nécessaires à la mise en place d'EVENS dans la pratique clinique. Un premier pas dans cette direction est présenté dans le Manuscrit N°5. D'une part, nous avons exploré les barrières et les facilitateurs perçus par des cliniciens dans l'utilisation de la RV pour évaluer la présence de la NSU et, d'autre part, nous avons tenté d'identifier des fonctionnalités optimales pour l'utilisation d'EVENS. Nous avons mis en place une procédure d'évaluation qualitative impliquant des groupes de discussion, des questionnaires auto-administrés et des entrevues individuelles. Ainsi, nous avons mené deux groupes de discussion ($n=11$ cliniciens) et avons interviewé des experts nationaux et internationaux dans le domaine ($n=3$). Plusieurs barrières et facilitateurs, incluant des facteurs personnels, institutionnels, liés à la pertinence vis-à-vis du patient et en lien avec la fonctionnalité des équipements, ont été identifiés. Les cliniciens ainsi que les experts dans le domaine ont identifié de nombreux éléments pour optimiser un outil virtuel. Les divers facteurs mis à jour dans cette étude posent les jalons pour le développement d'une initiative de transfert des connaissances liée à l'implantation d'EVENS dans un contexte clinique. En adressant les barrières et les facilitateurs associés à son utilisation et en incorporant les fonctionnalités optimales lors de la conception d'EVENS, nous pourrions fort bien assister à une éventuelle adoption et utilisation de cet outil dans un cadre clinique.

En résumé, cette thèse doctorale s'est intéressée à mettre en évidence les importantes lacunes au niveau des connaissances concernant le contrôle perceptivo-moteur dans la locomotion et la navigation chez les individus avec une NSU post-AVC. Il est espéré que les résultats des études présentées dans cette thèse permettront d'améliorer et de faciliter de futurs changements dans la gestion de la NSU post-AVC. Les résultats ont démontré que : 1) la NSU post-ACV a un impact négatif sur la locomotion orientée vers une cible ainsi que sur la navigation à travers divers

contextes cognitifs et perceptuels; 2) la NSU post-AVC a également un impact négatif sur les habiletés visuelles et perceptuelles de haut niveau dans les deux hémisphères visuels; 3) la navigation et la locomotion orientée vers une cible dans un environnement de RV, les résultats des tests psychophysiques déterminant les habiletés visuelles et perceptuelles de haut niveau ainsi qu'EVENS sont toutes des méthodes potentiellement efficaces pour détecter des déficiences liées à la NSU post-AVC; certaines de ces déficiences étant autrement indétectables par les outils d'évaluation conventionnels du type papier-crayon; 4) il existe actuellement des lacunes en terme de gestion des barrières et des facilitateurs pour assurer l'implantation de la RV dans l'évaluation de la NSU; et 5) il est nécessaire, d'après les cliniciens et experts interviewés, d'incorporer des fonctionnalités supplémentaires et complémentaires à l'évaluation existante basée sur la RV. En conclusion, cette thèse a répondu à plusieurs questions importantes et pose des bases solides pour guider la pratique clinique vers une meilleure gestion du problème très commun et hautement débilitant qu'est la NSU post-AVC.

CHAPTER 1: BACKGROUND AND RESEARCH OBJECTIVES

1.1 PREAMBLE

My interest in rehabilitation practices related to unilateral spatial neglect (USN), a prevalent and disabling post-stroke deficit characterized by difficulty in orienting to, responding or reporting to contralesionally located stimuli [9], was sparked early on during my clinical career as an Occupational Therapist at the Montreal Neurological Hospital of the McGill University Health Center. I came to quickly realize the devastating impacts of post-stroke USN. Particularly, I was consulted to assess a newly admitted patient, Mr. C., who suffered a right hemisphere stroke in his early forties. He was fully independent, a successful real estate broker and led an active and exciting life style prior to his stroke. Mr. C. had a severe post-stroke left USN, and after a few weeks of early rehabilitation by our stroke team, he was sent to a rehabilitation center. Five weeks later he came back with the status of “failed rehabilitation”, the reason being persistent left USN. Sadly, three months later, he was discharged to a long-term care facility. Within those three months of desperately trying to help him, I came to understand that post-stroke USN is a very complex disorder, that its underlying neuro-mechanisms are still poorly understood, that the current traditional assessments available to clinicians are not sensitive nor responsive to change [10], and that the very few existing treatment strategies are not effective in improving functional outcomes [11-13]. This caught so much of my interest that I devoted my MSc project (Dr. Nicol Korner-Bitensky and Dr. Alain Ptito) and subsequent PhD projects (Dr. Anouk Lamontagne and Dr. Philippe S. Archambault) to advance the knowledge in this specific field and to lay grounds for clinical practice advancements and change.

It is through my MSc studies that we have explored an underlying mechanism of hemineglect and contributed to the related theoretical knowledge [14, 15]. In this research, we determined that contrast sensitivity (i.e. the ability to distinguish a grating from its background) is affected by the presence of post-stroke USN. Alike to these research findings, others (e.g. [14, 16-24]) have proposed that the examination of visual processing skills could serve as a more in-depth investigation into neglect and provide insights into the related functional impairments. Visual perception is imperative for activities of daily living, and besides contrast sensitivity, it also involves the perception of motion (i.e. optic flow) and that of the depth and texture of the object

(reviewed in [25]), all of which are yet to be studied in post-stroke USN. ***This represented one of the aspects I wished to further explore during the PhD.***

As I continued my clinical work on the stroke team at the Montreal Neurological Hospital, I frequently faced similar issues to that of Mr. C. in relation to USN persistence and devastating impacts on stroke recovery and functional independence. Furthermore, now equipped with better understanding of its presentation and heterogeneity, I started observing subtle USN signs and symptoms in several patients. For instance, in individuals with normal results on traditional paper-and-pencil and functional USN clinical tests, I noticed instances of bumping into left sided obstacles and/or door frames when walking through an unfamiliar hospital corridor. Despite having a strong hunch about USN presence, these observations were insufficient nor based on standardized evaluation methods that would normally prompt a treatment plan of rehabilitation services. Instead, with an out-patient referral in their hands, these individuals were discharged home and into the community to resume their pre-stroke life roles and activities (e.g. parenting, cooking, household chores, driving, working, etc.), regardless of possibly having to deal with the aftereffects of underlying visual perceptual deficits. I would, however, make sure to follow-up with them in the out-patient clinic. Interestingly, at their follow-up visits, several of these individuals would report avoiding busy environments such as grocery stores, shopping malls and public transportation, as they recurrently kept bumping into environmental structures, other pedestrians and “getting too overwhelmed” with the diversity and extent of surrounding features (i.e. increased perceptual and/or more demanding cognitive conditions).

In relation to this, a recent prospective observational study found acute USN as one of the most significant predictors of community mobility and that its severity in the acute stage forecasts the extent of community mobility efficiency in chronic phase of stroke recovery [26]. The rehabilitation of skills needed for community mobility, an instrumental activity of daily living that contributes to one’s quality of life, independence, participation in life roles, leisure and other meaningful activities, is an essential part of post-stroke therapy and one of the most sought goals of stroke survivors [27]. While less than 40% of individuals with post-stroke USN regain independent walking ability within the community [28], ***the role of USN on post-stroke mobility has been underappreciated and necessitated further investigation. Moreover, the concurrent investigation of visual-perceptual abilities, along with variable levels of cognitive and***

perceptual demands, and their impact on mobility in post-stroke USN warranted examination and constituted additional study components of my PhD.

Similarly to my clinical observations, previous studies have reported participants with recovered USN based on conventional paper and pencil tests showing residual altered walking trajectory [29], goal-directed reaching impairments [30] or USN symptoms in a 3-D virtual reality (VR) task involving challenging and dynamic activities [31-33]. Overall, it emerges that the commonly employed USN tests are not sufficiently sensitive to detect subtle but clinically important deficits [34], to predict functional performance in daily life and are constrained to assessing USN within the near-extraperpersonal space only, using static, 2-D methods. This is of great concern given that these individuals are at risk of being discharged into the community to resume their pre-stroke life roles and activities without proper diagnosis of the impact of USN or symptoms of USN on functional performance. *Therefore, with current advancements in the use of technologies in rehabilitation, it is highly relevant and timely to further the development of USN assessment and rehabilitation techniques, by incorporating state of the art technologies like VR, leading to final components I wished to address in my PhD.*

With the ultimate aim to improve health care services and recovery outcomes for numerous affected individuals by addressing the aforementioned critical and inter-related gaps in practice and research, my wonderful and enriching PhD journey had begun...

1.2 BACKGROUND

Chapter 1 of this PhD dissertation reviews the current research literature with the goals of: 1) stressing the complexity of post-stroke USN and its debilitating effects on functional performance, including mobility; 2) identifying existing knowledge and practice gaps, particularly with respect to post-stroke USN assessment and its effects on mobility and navigation under different cognitive and perceptual conditions, and underlying visual-perceptual abilities; and 3) building a strong rationale for my overall PhD research agenda. This chapter includes excerpts from two first-author published manuscripts, entitled “*The Impact of Post-Stroke Unilateral Spatial Neglect on Goal-Directed Arm Movements: Systematic Literature Review*” [35]; and “*Virtual Reality Treatment and Assessments for Post-Stroke Unilateral Spatial Neglect: a Systematic Literature Review*” [36].

1.2.1 Stroke: definition, overview of epidemiology, consequences

A stroke, or a cerebrovascular accident, is defined by the World Health Organization as “a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin” [37]. In Canada, stroke has become the leading cause of adult disability and the third leading cause of mortality. Each year, nearly 50,000 Canadians suffer a stroke, which is equivalent to one stroke every ten minutes. Stroke costs the Canadian economy more than \$3.6 billion a year in physician services, hospital costs, lost wages, and decreased productivity [38]. Every year, Canadians with stroke spend more than 639,000 and 4.5 million days in acute care hospitals and in residential care facilities, respectively [39].

Moreover, stroke has dramatic impacts on the survivors’ physical and mental health, quality of life and imposes great social and economic burden on the individual, caregivers, communities and countries [40, 41]. A devastating number of approximately 426,000 Canadians or 80% of all individuals who had a stroke, are living with long-term post-stroke disabilities [38]. It is further estimated that this already alarming number will almost double in the next twenty years [42]. One of the most prevalent and disabling post-stroke deficits is unilateral spatial neglect (USN).

1.2.3 USN: definition and scope of the problem

USN is characterized by a difficulty to orient, respond, or report to the stimuli appearing on the contralesional side [43]. Terms such as USN, neglect, hemineglect, visuospatial neglect and spatial neglect are used interchangeably. USN is experienced by nearly 50% of individuals with a right hemisphere lesion [10]. Less common and not as persistent as following a right hemisphere injury, right USN can also occur following a left hemisphere stroke [44]. While neglect can resolve spontaneously within the acute post-stroke period, its symptoms and their dramatic impact on functional performance may persist in up to 75% of initially diagnosed cases [10]. Unfortunately, those numbers are expected to surge with the rise in the aging population, given that USN is found to be associated with an increase in age [45]. In addition, the disability associated with neglect is often “neglected”, and affected individuals are reported to be less likely to receive acute medical attention than those with left hemisphere stroke [45-48]. Moreover, longer rehabilitation stays [49], heightened need to assistance and long-term placement [50], and increased family/caregiver burden [10] all have been associated with neglect and further hamper its already high estimated direct and indirect costs.

1.2.4 USN: conceptualization and heterogeneity in clinical presentation

USN can be conceptualized as per *modality* (input/output), *spatial representation* (egocentric and/or allocentric), and/or *range of space* (personal, near and/or far-extrapersonal) [51]. Vallar [52] proposed the *modality* categorization, distinguishing between perceptual/attentional (i.e. sensory input) and premotor/intentional (i.e. output) USN. Sensory neglect is characterized by decrease awareness to different type of stimuli (e.g. visual, tactile, auditory, etc.) located in the contralesional hemispace. Premotor neglect is characterized by difficulty in initiating and/or executing movements to the contralesional hemispace stimuli, despite normal awareness of that hemispace. Moreover, dissociations also exist with respect to what exactly the individual is neglecting, or USN *spatial representation*. Egocentric USN refers to a deficit in directing attention to the space on the left side of one’s body. On the other hand, allocentric USN refers to neglecting one side of an object, irrespective of whether the object is present in the right or left visual hemispaces. It is suggested that these two types of USN can occur independently or co-occur in the same individual [reviewed in 53]. For the *range of space*, USN can be present in the personal (i.e. neglecting hemibody), near-extrapersonal (i.e. neglecting space within the reaching

distance) and/or far-extraperpersonal space (i.e. neglecting space beyond the reaching distance) [54]. In addition, studies in the early nineties found presence of neglect for line bisection but not cancellation tasks [55], and for bisection of long but not short lines [56], for faces but not for other complex visual stimuli [57], and for imagery but not real life objects [58].

Furthermore, in terms of functional motor tasks performance, the latter distinction of near vs. far-space USN is of particular importance. To explain, for successful interaction within the physical environment, visual perception is used to understand the location of the goal with respect to self. Subsequently, different types of action are available to an individual depending on the distance away from the goal, where a person has a possibility of reaching to a target that is within his/her reaching distance (i.e. near-space), versus walking to it if the object's location is beyond reaching distance (i.e. far-space) [59, 60]. To perform these actions successfully, the brain must estimate the distance of the object from the individual's body [61]. Neuropsychological research identified distinct neural processes for the perception of near and far-space [62]. Therefore, one can speculate that functional performance within near vs. far-space would be differently affected depending on the USN range of space. While this is an interesting and pertinent hypothesis, it is important to understand what is the actual impact of post-stroke USN presence on overall functional performance, along with near and far-space functional activities such as reaching and walking, as well on other potentially related and underlying abilities (e.g. visual perceptual abilities and non-spatial factors).

1.2.5 USN: clinical impact on overall functional performance, upper extremity motor function and mobility

USN can become long-standing and introduce major disability, activity restrictions [63], and reduced quality of life [64]. Individuals with post-stroke USN, in comparison to those without USN, have longer rehabilitation stays, are at lower levels of independence post discharge, have greater difficulty performing activities of daily living, are at higher risk of functional deterioration at one-year [63], and are more prone to frequent falls [43].

We conducted a systematic review and analysis, where twenty studies (n=20) investigating the impact of USN on *goal-directed ipsilesional/non-paretic upper extremity movements* [35, 65]. Findings indicate that impairments specific to individuals with USN as compared to those

without USN emerged predominantly in behaviors that are perceptual/memory-guided/delayed (e.g. delayed pointing task to remembered target location, bisection/perceptual judgment task) or *offline* actions; and less in behaviors that required an immediate response to visual targets (e.g. immediate pointing task to actual targets, pointing in unpredictable conditions, motor response in pressing task) or *online* actions.

Results of this review are complementary and consistent with the view and hypothesis that there are two different types of action control (*online* vs. *offline*) [66] processed via distinct visual streams, ventral and dorsal; and that the presence of USN can affect those actions in different ways (Figure 1.1A&B). In fact, recent voxel-based lesion-symptom mapping studies on individuals with right hemisphere stroke suggest that the actual observed deficits in *online* conditions are associated with brain lesions in specific areas that include: basal ganglia, frontal regions, and parieto-occipital regions (i.e. dorsal stream) [67]. Those regions are often spared in most individuals with post-stroke USN, where the parieto-temporal junction [68], angular gyrus, right inferior parietal lobe, parahippocampal region [69], and the right superior temporal cortex [70] are found to be predominantly affected. In line with this concept, our review did find that the majority of outcome measures in online conditions were not significantly different between individuals with vs. without post-stroke USN. However, impairments in *offline* tasks were previously correlated to lesions in occipito-temporal and parahippocampal cortex (i.e. ventral stream) [1, 67], also considered as the core regions responsible for USN presentation. Overall, the results are in concordance with the suggestion of Milner and Goodale (2006) [6] that USN is associated with the damage to the high-level representation ventral stream of processing.

Similar to reaching, locomotion is an important part of one's activities of daily life. It is therefore highly pertinent to study how the presence of post-stroke USN can affect one's navigation through space while walking. Nevertheless, the research on the effects of post-stroke USN on mobility remains scarce. Presently, seven studies were found examining locomotion/navigation in individuals with post-stroke USN [61, 71-76]. Two of those studies assessed walking through a doorway-like aperture [72, 73], one analysed hallway navigation using a wheelchair and/or during walking [77], one examined obstacle avoidance strategies [74, 75] and effect of dual-tasking on obstacle avoidance strategies [76], and only one study investigated goal-directed locomotion to a defined target [71]. While these studies overall found larger deviations in the

walking and/or navigation trajectories in individuals with post-stroke USN as compared to other study groups (stroke without USN and/or healthy controls), the results are inconsistent in terms of the direction of lateral deviation. In fact, some report rightward deviations [61, 72], but also deviations to both the left and the right sides [71, 73]. It has been suggested that the direction of the deviation can possibly depend on the severity of neglect [73] as well as other factors such as standing balance and walking speed [71]. In addition to the scarce number of studies investigating locomotion in USN, the past studies present with low sample sizes (ranging from 2 to 13 patients per group), heterogeneous samples, and inconsistent assessment of USN severity in far space, which further affects the validity and the interpretation of results. Moreover, although evidenced in the upper extremity movement studies, how visually-guided vs. memory-guided task conditions affect individuals with post-stroke USN while walking remained to be determined.

1.2.6 USN: relation to visual-perception

The visual-perceptual hierarchy introduced in the early 1990's by Warren [7, 78] suggests that visual perception can be conceptualized as a hierarchy of skill levels; where skills at the bottom form the foundation for each successive level (Figure 1.2). This notion leads to further speculation that, in presence of USN, the underlying and potentially related visual-perceptual abilities might also be affected and play a role in the ensuing functional impairments.

In the last two decades, an ample body of research focused on investigating the ability of patients with post-stroke USN to perform cognitive visual processing tasks of the stimuli located in the contralateral visual hemispace, presumably the neglected hemispace. This literature suggests that even in the absence or lack of attention to the neglected visual hemifield, there is still a certain degree of information processing from the unattended stimuli that can influence behavior [24, 79-82]. Nevertheless, there is only a limited number of studies that have directly examined the effect of post-stroke USN on visual processing abilities of the neglected hemifield, mostly focusing on disturbed contralesional ocular visual search patterns (e.g. [16-20]) and loss of contralesional contrast sensitivity (e.g. [14, 21-24]). Collectively, these studies suggest that the examination of visual processing skills could serve as a more in-depth investigation into neglect and provide insight into functional impairments. Visual perception as needed for activities of

daily living, however, also involve the perception of motion or optic flow and the depth and texture of the object (reviewed in [25]), which were yet to be studied in post-stroke USN.

Optic flow is an essential source of visual information that is used to control one's heading direction [83-85] and speed [86] during locomotion. Two earlier studies have shown that stroke individuals with a history of USN (n=2 out of 9 stroke participants [87]; and 2 out of 10 stroke participants [88]) present with the largest deficits in the control of their walking trajectory or heading when exposed to optic flows of changing direction. However, the extent to which optic flow perception is affected in post-stroke USN and whether it influences the locomotor behavior remained unclear. Given its role in the control of locomotor heading, it is possible that visual-perceptual abilities such as optic flow perception, contribute to further explain goal-directed walking deficits in post-stroke USN.

In addition, Marotta and colleagues [89] found a decrease in shape discrimination ability and subsequent loss of grasp stability of these shapes in individuals with post-stroke USN compared to those post-stroke but without USN. This study, however, did not rigorously differentiate between shape discrimination abilities within the contralesional vs. ipsilesional visual hemispace, and an association with goal-directed walking deficits was yet to be examined.

Furthermore, since that the most apparent issue in USN is the failure or dramatic slowing of response to occurrences in the contralesional hemispace [90-95], much of the above-mentioned research has focused on USN-related lateralized spatial deficits (reviewed in [96, 97]). Although less obvious, deficits that are non-lateralized are also fundamental to persistent neglect [98-102]. In fact, the severity of non-lateralized deficits would be a stronger predictor of USN chronicity than the spatially lateralized deficits themselves [100, 101, 103-105]. As a result, non-lateralized deficits, when combined with lateralized ones, can limit recovery potential and therefore constitute important targets for treatment [106]. However, whether visual-perceptual abilities are laterally vs. non-laterally affected in post-stroke USN remained unclear and called for further investigation.

1.2.7 USN: theories and models

A number of theoretical explanations that could account for the observed behavioral manifestations in individuals with USN have been proposed. Current views tend to favor the implications of the attentional mechanisms, although others propose representational, transformational, and intentional factors. Namely, theories of USN include the (1) attentional (i.e. spatial or directional attention deficits), (2) representational (space perception/representation deficit), (3) transformational (egocentric frame of reference shift); (4) pre-motor (spatial or directional motor deficit), and (5) non-spatial factors (e.g. spatial working memory, alertness, etc.) [97] (Figure 1.3). Though earlier viewed as distinct USN accounts, these theories are now suggested to possibly share common neural pathways and concurrently contribute to produce the observable USN symptoms. The following paragraphs provide an overview of these theories.

Attentional Theory

The attention theory of USN is comprised of two models: (1) the hemispheric imbalance, and (2) the attentional shift/disengagement model.

Hemispheric imbalance model

The hemispheric imbalance model postulates three different hypotheses: (a) the opponent processor/orienting vector; (b) hemispheric specialization; and (c) the global/local processing.

(a) The opponent processor/orienting vector hypothesis

The opponent processor/orienting vector hypothesis proposes that there are two opponent processors, situated in the left and the right brain hemispheres, that control attention towards the contralateral portion of the visual hemisphere [107]. Those processors are suggested to inhibit one another via callosal connections. The direction of attention is therefore viewed as a vectorial/gradient outcome of the interaction between the right and left attention processors. According to the opponent processor model, USN is a result of the hemispherical imbalance subsequent to the brain lesion created by the stroke event. To explain, it proposes that when an individual has a right hemisphere stroke, the damaged right hemisphere can no longer inhibit the left hemisphere, resulting in a hyperactivity of the left hemisphere. Consequently, an exaggerated

attentional bias towards the ipsilesional (right) side (i.e. left neglect) is observed. More specifically, Kinsbourne (1993) clarifies that the observable left neglect is characterised by two attention gradients, where: (1) the attention gradient in the left/contralesional visual hemispace decreases from center to periphery; whereas (2) the attention gradient in the right/ipsilesional visual hemispace increases from center to periphery [107]. Kinsbourne also argues that individuals with post-stroke USN do not simply neglect left sided objects, but rather are attracted by or favoring the right-sided ones. This assumption was confirmed in studies of simple visual reaction tests where patients with left USN following a right hemisphere stroke demonstrated a slowing down of their reaction from the rightmost to the leftmost shares of visual space [108-110]. More recently, investigations using functional brain imaging and transcranial magnetic stimulation (TMS) verified the assumptions of the opponent processor model [111-113], where higher excitability of the left posterior parietal cortex circuits was found in individuals with post-stroke USN when compared to those without post-stroke USN; and where repetitive TMS over left posterior parietal cortex normalized the initially observed over-activity, and also improved USN on one experimental measure [113, 114].

(b) Hemispheric specialization hypothesis

Heilman et al., (1980, 1985) argue that the right and the left hemisphere of the brain is provided with an attentional system [9, 115]. It is further proposed that the right hemisphere system mediates attention to both right and left visual hemispaces, whereas the left hemisphere system directs attention only to the right visual hemispace. Thus, following a left hemisphere stroke, a right USN is rarely observable given that the intact right hemisphere compensates by directing attention to both right and left visual hemispaces. On the other hand, when a right hemisphere stroke occurs, left USN is highly probable given that no compensation from the intact left brain hemisphere is available. In contrast to the opponent-processor model, this account implies that the mid-sagittal plane represents a margin for the deficit, such that attention within the ipsilesional hemispace is normal. The fact that USN is more severe and more frequently observed following a right rather than a left hemisphere stroke and that the attention function of the right hemisphere is extended to both the right and the left visual space was supported in numerous studies (reviewed in Mesulam, 1981 [116]). Later, with the rise in the use of imaging techniques in the nineties, Heilman's hemispacial attentional theory was confirmed with

neuroimaging studies indicating that the extent of activations in the right hemisphere are larger than in the left hemisphere in tasks involving shifts of visuospatial attention [117-119].

(c) The global/local processing hypothesis

The global/local processing hypothesis offers a different explanation for the fact that USN is more prevalent following a right hemisphere rather than a left hemisphere stroke [120-123]. This hypothesis assumes that the right brain hemisphere hosts the *global* attention processing system and is mainly responsible for leftward attentional shifts; whereas the left hemisphere is responsible for *local* attention processing and rightward attentional shifts. In a normal brain with adequate interhemispherical balance, the global attention processing system is actually viewed to be a *guidance system*, where it further directs *local* attention processors of the left hemisphere to viewed targets for additional analysis. Therefore, it is assumed that when a right hemisphere stroke occurs, USN is likely to occur given that (1) the damaged right hemisphere global attentional mechanisms fail to further direct local attention processors of the left hemisphere towards the left visual hemispace; and (2) the left-hemisphere presents with an amplified local attentional processing of the ipsilesional hemispace. In support of this hypothesis, several case-reports have been published in the nineties indicating that there is an impairment of coordinating attention between global and local levels of viewed targets in patients with left USN following a right hemisphere stroke, where they can recognize the global form of the left sided stimuli, but fail to perceive its local details [120-123]. The roles of the right and the left hemisphere in attentional processing of global versus local type of stimuli was evidenced in normal healthy controls using functional neuroimaging studies of event-related potentials [124-126], positron emission tomography [127-129], and functional magnetic resonance imaging [130-132]. Moreover, Lux et al., (2006) investigated the global/local processing hypothesis in individuals with left USN following a right brain hemisphere stroke (n=12) and healthy normal control subjects (n=12) using hierarchically organized global and local types of figures (e.g. a large D letter composed of small E letters) in a directed (i.e. answer whether a viewed letter is local or global) and divided attention (i.e. answer whether the stimuli encompassed the targeted letter regardless if it is global or local) tasks. During the directed attention task, individuals with USN presented with slower reaction times than healthy control subjects, specifically when responding to *global* type of stimuli. During the divided attention task, individuals with USN showed

significantly more error rates than the healthy control subjects, and an increase in errors in comparison to the directed attention task for *global* targets [133]. Those results support the view that the right brain hemisphere is responsible for global information system processing and that impairment in this system is observable in individuals with left USN following a right hemisphere stroke. In addition, it is suggested that the finding of larger errors rates in the divided vs. the directed attention task may be related to the disengagement deficit discussed below, where individuals have difficulty to disengage the attention from one target (e.g. local figure) to another (e.g. global figure).

Attentional Shift/Disengagement Model

The attentional shift model is viewed as the following sequence of three internal mental operations: (1) disengagement of attention from current stimulus; (2) moving attention towards a new stimulus and; (3) engagement of attention on the new stimulus. Individuals with right hemisphere parietal lesions and USN were found to have a deficit in disengagement of attention from ipsilesional target [134] [135] [136]. In 2001, Losier and Klein conducted a meta-analysis examining the disengagement deficit and included studies (n=14) investigating reaction times to left and right stimuli following precues in individuals with left and right hemisphere stroke with and without USN [137]. They concluded that the disengagement deficit is in fact larger in individuals with a right hemisphere lesion (especially with parietal lobe damage) and USN than in those with a left hemisphere stroke and no USN [137].

Representational Theory

In the last decade, USN was also suggested to be considered as a disorder of different types of space perception and/ or representations (e.g. deficit in mental representations, perceptual anisometry of horizontal extension and size distortion). This model of topological space representation proposed that every sensory event has a mental representation that can be activated via different sensory afferents or memory. In individuals with USN, the left side of the representational space is suggested to be enlarged; whereas the right side is suggested to be compressed compared to healthy control individuals [138-140]. For example, Bisiach & Luzzatti (1978) described a case-report of two individuals with left post-stroke USN who were asked to imagine viewing the central square (Piazza del Duomo) in Milan, from the cathedral in the centre

of the square. It was found that those individuals omitted to mention places and/or street on the left side of the square from that particular central viewing point. Following that, they were asked to imagine that they are looking directly at the cathedral (180° viewpoint shift); and subsequently demonstrated failure in mentioning places on the side of the square that they reported in the first viewing conditions (i.e. which now was on their left/contralesional side); and ability to recall places that were now viewed on the right side [138]. This experiment was then replicated 1981 by Bisiach and colleagues and confirmed the earlier findings using a larger sample size of 50 individuals with left USN and/or hemianopia and 41 healthy control subjects, suggesting a deficit in mental representation of the contralesional hemisphere [139].

Transformational Theory

The transformational theory proposes that the behavioral manifestations of USN are a result of an altered neural representation of body-centered space; where the egocentric space representation deviates towards the unaffected/ipsilesional side, following a rotation around the earth-vertical body axis. Subsequently, this ipsilesional deviation precludes individuals with USN to explore and respond to stimuli located on the contralesional hemisphere. The transformation theory is based on a notion that spatially-directed behavior is coded “in a system of coordinates (a motor “map” of space) referred to the body axis, different from the visual map on which the retinal position of objective is specified” [141] . Normally, this system is superimposed to the sagittal middle; however, a unilateral hemisphere brain lesion would result in a deviation of the egocentric frame of reference given an imbalance between the bilateral neural processes that constitute this representation [141, 142]. The transformational theory also assumes that: (1) there is a positive and significant correlation between the magnitude of the egocentric frame of reference deviation and the presence and/or severity of USN symptoms and that: (2) the restoration of the objective/true position of the egocentric frame of reference can improve USN symptoms [142, 143]. To determine the internal representation of egocentric space in individuals with USN, recordings of spontaneous/exploratory eye movements while performing a searching task in complete darkness, measures of subjective straight-ahead pointing were used [143-147], proprioceptive [148-150] and auditory methods [151, 152].

Pre-Motor Theory

According to the pre-motor theory, USN is viewed as a disorder of neural space representation and results from cerebral damage to perceptuo-motor, cortical and subcortical pragmatic maps that underline oculomotor abilities, head movements, arm movements and mobility [153]. It further suggests that the pragmatic maps serve to code their respective space representation and also program movements towards the coded space. Therefore, USN is revealed by lack of visual-perceptual information processing coming from the neglected hemifield and ensuing difficulty to direct movement towards that area. For example, studies evidenced deficits in eye movement or visual space exploration in patients with neglect, characterized by frequent ipsilateral re-fixations/asymmetry of fixation distribution favoring the contralateral hemifield [16, 17]. Others reported a strong tendency towards ipsilateral head and neck rotation [143], greater ipsilateral vs. contralateral weight bearing [154] and longer latency in leftward upper extremity movements such as pointing [2, 30, 95, 155].

Non-Lateralized Factors

In addition to USN spatially lateralized left-sided impairments, non-lateralized deficits in individuals with post-stroke USN have been reported. These non-lateralized factors are reported to be strong predictors of persistent neglect in comparison to spatially lateralized deficits, and are found to exacerbate USN severity and ensuing functional disability (reviewed in [99]). These factors include 1) the level of arousal and alertness; 2) sustained attention; 3) selective attention; 4) attentional capacity; 5) spatial memory; and 6) representational updating. Heilman et al., (1978) proposed that there is a general decrease in physiological arousal in patients with post-stroke USN [156]. This was later confirmed by other research teams examining those with left USN following a right hemisphere lesion [104, 106, 157]. Studies also demonstrated a causal relationship between USN and level of alertness, where an increase in the level of alertness led to the alleviation of USN symptoms [158, 159] and vice versa [160]. Moreover, sustained attention is reported to be affected in patients with post-stroke USN. Indeed, individuals have difficulty in attending to spatial locations over a period of time and show a decrease in performance over time [161]. Similarly, multiple studies show USN-related deficits in speeded or time-related selective attention [100, 162-165]. In relation to that, a reduction in overall attentional capacity in post-stroke USN is evidenced via examination of dual-tasking paradigms (e.g. [166] [105]). In

addition, USN has also been related to spatial memory deficits (reviewed in [167]), where individuals with post-stroke neglect tend to “revisit” previously attended stimuli (e.g. during a cancellation task [168]).

Furthermore, following an extensive review of the literature, Shaqiri et al., 2013 [169] proposed that representational updating, defined as the “ability to build mental models and adapt these models to changing experiences [...] that depends on processes of priming, working memory, and statistical learning”, is significantly affected in those with post-stroke neglect. To clarify, functional performance within different environments (e.g. grocery shopping) is suggested to be influenced by the regularities of that setting (e.g. shelves, products, carts, etc.) and the ability to notice and adapt to changes of these regularities (e.g. moved cart, needing to walk to another shopping aisle, etc.). Although Shaqiri et al., 2013 [169] provide substantial evidence for deficits in representation updating in USN and relevant implications for rehabilitation strategies, all the related studies focused predominantly on near-space USN and near space activities (e.g. scanning for functional objects within near space). Consequently, the effect of USN on the abilities to detect and adapt to changes in far space environmental features (e.g. recall a target location - a task condition involving spatial memory; or a shift of a target location - a task condition involving representational updating) and act upon those (e.g. goal-directed walking and/or navigation) remained unclear and warranted investigation.

1.2.8 USN: pathophysiology and neuroanatomy

Damage to the right parieto-temporal junction [68], angular gyrus, right inferior parietal lobe, parahippocampal region [69], and the right superior temporal cortex [70] were all previously identified as the critical brain areas responsible for USN.

Two conceptual frameworks of visuospatial attention have been proposed for USN and constitute the frontoparietal and the occipito-parietal/temporal networks, both based on the dorsal vs. ventral stream processing. In 2002, Corbetta & Shulman [170] suggested that visuospatial attention is mediated by the dorsal and ventral frontoparietal pathways. Bilateral dorsal pathways were proposed to connect the superior parietal lobes and the intraparietal sulci with the dorsal frontal lobes and assist in processing of goal-directed, top-down attention processing (i.e. voluntary attention allocation to features, objects, or spatial locations). On the other hand, the ventral pathway, connecting the temporal parietal junction and the inferior parietal lobe with the

ventral frontal lobe, is suggested to be involved in stimulus-driven, bottom-up attention processing (i.e. involuntarily directed by the saliency of the stimuli that attracts attention). Corbetta & Shulman (2002) suggest that the right bottom-up attention processing of the ventral pathway, overlapping with neural basis of USN, underlies neglect's signs and symptoms [170].

Moreover, the two-stream hypothesis for neural processing of vision initially proposed by Milner & Goodale in early nineties, [171] is currently widely accepted. It suggests that there are two different processing streams, ventral and dorsal, originating from a common source in the visual cortex. The ventral stream (also referred to as the "what pathway") is proposed to play a role in visual identification and recognition; whereas the dorsal stream (also referred to as the "where pathway") is argued to be involved in the processing the object's spatial location with respect to the viewer and in guiding ensuing actions towards the object. The ventral stream commences at the primary visual cortex (V1) in the occipital lobe and projects into the parietal lobe; whereas the dorsal stream stretches from parvocellular layer of the lateral geniculate nucleus to V1 sublayers, following by projections to areas V2 and V4 of the inferotemporal lobe (posterior, central and anterior sections).

It emerges however, that USN cannot be viewed and explained by a single underlying concept, theory, or neuro-mechanistic disruption, but is rather recognized as a heterogeneous and multi-component disorder.

1.2.9 USN: assessment and treatment

Clinically, a severe USN is easily observable, whereas mild or moderate USN (mild - positive result on 1-3, moderate/severe - positive result on 4 or more tests [172]) often goes undetected [173]. Regardless of an extensive body of research on USN assessment tools, there is currently no gold standard method. The commonly employed paper and pencil evaluations can result in misdiagnosis of subjects with mild USN [10]. In fact, despite the convenience of conventionally used paper-and-pencil tests, their easy application and scoring, most of them are designed to assess USN of near-extraperosnal space only, and do not address essential everyday activities within the far-extraperosnal space. Among nearly thirty available standardized USN assessment tools [174] only the Behavioral Inattention Test (BIT) [175] and the Catherine Bergego Scale (CBS) [176] contain some form of daily activities evaluation (e.g. BIT: picture scanning, phone dialing, menu reading, article reading, telling and setting time, coin sorting, address and sentence

copying, map navigation and card sorting; CBS: grooming, adjusting left sleeve/slipper, eating, cleaning mouth after meal, looking left, forget left hemibody, paying attention to people/objects in left side of the room, collision with left objects, finding their way in hospital on the left, finding personal belongings on the left). Those tests are easily applied in clinical practice, are cost effective and time efficient, requiring minimal equipment. Nevertheless, the activities are still performed predominantly within the *personal* and *near extrapersonal* spaces, which is not entirely representative of common daily activities (e.g. cooking, driving, mobility, etc.) that involve far-extrapersonal space. Therefore, if an individual has far-extrapersonal space USN, he/she is at higher risk of not being properly diagnosed and treated. In addition, given that the scoring of BIT or the Catherine Bergego Scale is based solely on clinicians' observation (i.e. subjective measure), mild deficits and their actual effects on more complex activities can go undetected. This particular limitation can easily be counteracted by the use of VR (described more in detail below), where data collection is standardized, specific, performance-based, and is objectively quantified using valuable outcomes of interest (e.g. detection times, navigation traces, endpoint accuracy measures, side and direction of navigation/walking trajectories, etc.).

In relation to that, studies have reported participants with recovered USN based on conventional paper and pencil tests showing residual altered walking trajectory [29] and goal-directed reaching impairments [30]. Also, recent studies identified patients having mild USN, or no USN on paper-and-pencil tests but showing difficulty and USN on a VR task involving more challenging and dynamic type of tasks within an ecological or a 3-D environment [31-33]. These findings further evidence the lack of conventional evaluation tools' sensitivity. Indeed, the large range of USN incidence that is commonly reported in the literature (i.e. 13% to 81% [177]) is suggested to be a result of different evaluation methods used and lack of their sensitivity [178].

In addition to its challenging proper detection, previous studies evidence that clinicians fail to use standardized USN assessment tools. For instance, an Ontario survey indicate that only 13% of clinicians across acute care facilities used a standardized USN assessment or screening, and that only the near-extrapersonal USN was assessed [173]. A Canada-wide survey in subacute care, showed that 27% of clinicians used a standardized USN assessment tool [179]. Inefficient USN detection, or lack thereof, is a significant issue, given that USN is associated with greater risk for falls, functional deterioration, difficulty performing activities of daily living and

instrumental activities of daily living [10, 43, 63, 64]; therefore, posing an important hazard when discharging these patients home and to community living.

Correspondingly, while several rehabilitation strategies for USN are available (e.g. visual scanning, prism adaptation, caloric stimulation, eye patching, etc.), the efficacy and effectiveness of those are still questionable. As suggested by recently completed meta-analyses, there is a limited number of high quality studies suggesting that USN interventions are effective in improving functional outcomes and reducing disability [11-13].

1.2.10 USN: the potential of virtual reality

Recently, with the emergence of knowledge translation (KT) in the field of rehabilitation sciences, efforts have been made to enhance the use of evidence-based practice in USN management in form of multi-modal KT intervention (e.g. [180]). Despite these formal KT activities in the right direction to promote evidence-based practice in post-stroke USN management, the recommended evidence-based screening (Line Bisection Test [181]) and assessment tools (BIT [175] and CBS [176]) to be used as per the Canadian Stroke Guidelines 2013 [182] are not grasping all the facets of USN's multimodal and heterogeneous presentation previously presented. In conjunction with proper KT intervention, the rapidly growing field and industry of virtual reality (VR) could serve to enhance and augment USN diagnostic techniques beyond the conventional methods. For example, VR affords us the possibility to employ 3-D images or stereovision, far space and dynamic targets, functional everyday tasks (e.g. mobility, navigation), and modifiable spatial and non-spatial factors (e.g. variable cognitive and perceptual conditions). Therefore, VR could tackle multiple gaps in practice and research that were previously discussed in earlier sections.

KT is a process that attempts to bridge the gap between evidence-based practice and current clinical practices. The Canadian Institutes of Health Research defines KT as “a dynamic and interactive process that includes synthesis, dissemination, exchange, and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system” [183]. The Knowledge to Action Model (KTA) [8], is a KT approach aiming to highlight practice gaps and designing KT intervention addressing these gaps in practice (Figure 1.4). It contains a knowledge creation funnel (i.e. inquiry, synthesis, development of tools and products) and a seven step action cycle:

((1) identifying and selecting gaps in knowledge; (2) adapting knowledge for users; (3) assessing barriers to knowledge use; (4) selecting, tailoring, and implementing a KT intervention for knowledge application, (5) monitoring knowledge use, (6) evaluating outcomes related to knowledge use; (7) identifying strategies for sustained knowledge use) as concepts to promote knowledge application into practice.

Given that VR for post-stroke USN management is an emerging and an exploratory field, and is still majorly in its pilot testing phase, the evidence behind its application is limited. Nevertheless, a collaboration between knowledge or end users (i.e. clinicians) and research users (i.e. experts in the field, academics, researchers) is possible and highly relevant to advance the current knowledge and yield findings and potential products that are more suitable to and representative of the needs of end users. Therefore, in this PhD dissertation, the knowledge creation funnel and step (3) of the action cycle (i.e. assessing barriers to knowledge use) were applied to guide the related project activities.

To establish best-practice recommendations of the use of VR in post-stroke management and guide development of a novel VR-based assessment tool, it was necessary to appraise the existing evidence. As a results, through a systematic review and analysis, we aimed to identify and appraise existing VR-based USN assessments; and, to determine whether VR is more effective than conventional therapy [36]. All found assessment tools were critically evaluated using standard criteria. Treatment trials' methodological quality was rated by two independent raters. The level of evidence according to stage of recovery was determined. Findings were compiled into a *VR-based USN Assessment and Treatment Toolkit (VR-ATT)*. In this review, we identified twenty-three studies. Some of the existing VR-based assessment tools were found to be more sensitive in detecting the presence of deficits in cases where conventional USN assessment was negative [31-33, 184-189]. However, these studies have several limitations including the use of non-functional tasks (e.g. [184, 190]) that do not easily translate into real functional performance in daily life; small sample sizes (e.g. [191]); comparing performances of patients with USN to that of healthy control individuals, rather than to those with stroke but no USN (e.g. [184]); or using 2-D displays (e.g. [31, 34, 189, 191]) that lack immersiveness and interactivity [192]. We believe that the latter limitation is of particular importance, given that USN is largely viewed as an attention-based deficit and the use of full immersion in its

assessment can help limit possible attentional shifts to the physical world that could influence performance.

In addition, previous VR-based studies have not evaluated the impact of increased perceptual-attentional demands (e.g. a more crowded, ecological scene with multiple objects) within an immersive VR scene on the functional performance of object-detection and space navigation patients with post-stroke USN. Previously, detection time and the time to complete a task have both been found to be affected in USN+ patients, compared to either USN- patients or healthy controls [75, 185, 193], suggesting that such measures can be sensitive to the presence of USN. In addition, there is some indication that USN influences navigation abilities (e.g. wheelchair navigation [77]), as such tasks involve both the near and far space perception and adjustment, and can be performed towards changing directions and within different environments. Thus, examining target detection and goal-directed navigation in the far extrapersonal space, while covering both the contra- and ipsilesional space and manipulating perceptual-attentional demands, is relevant and has the potential to complement previous findings and deepen our understanding of the poor functional recovery that so often accompanies USN. It is possible that a more complex virtual environment, as opposed to a simple environment, will result in more noticeable deficits in patients with post-stroke neglect and thus, and potentially be more predictive of and generalizable to the real-life performance. A VR assessment that is performance-based thus has the potential to further inform clinicians managing stroke survivors with USN on their functional performance, while providing additional benefits in terms standardization, space, safety, objectivity and possibly sensitivity and responsiveness.

1.2.11 Rationale: overview of gaps in research and clinical practice

From the above presented background information, USN unfolds to be a highly prevalent and disabling deficit in individuals with stroke. Being a major barrier to stroke recovery, USN has been shown to affect motor performance in different functional activities, including mobility, an activity that is crucial to one's reintegration into home and community living. Nevertheless, our understanding of the visuo-perceptual control of goal-directed locomotion and navigation in post-stroke USN is poor, where existing literature lacks consensus on the expression of the deficits, and questions remain as to the potential influences of underlying visual perceptual abilities and variable cognitive/perceptual demands. Furthermore, there is currently no gold

standard USN measure that encompasses its high heterogeneity and complexity, that is sensitive in identifying subtle but clinically meaningful USN's signs and symptoms, that is responsive to change, and that is representative of functional self-care and instrumental activities of daily life. This results in poor detection and qualification of USN in practice and research and inappropriate post-evaluation management, putting patients and others at risk. The emerging field of VR presents suitable opportunities to address these significant gaps.

1.3 RESEARCH OBJECTIVES AND HYPOTHESES

The general goal of this PhD thesis was to investigate perceptuo-motor control in locomotion and navigation in post-stroke USN and thereby, to work towards improving current clinical practices in post-stroke USN management, mainly in the development and implementation of a novel VR-based USN assessment tool.

To that end, effects of USN, its severity, underlying visual perceptual skills, and variable cognitive and perceptual conditions on goal-directed locomotion, navigation and object-detection were examined. A novel, Ecological, VR-based Evaluation of Neglect Symptoms (EVENS) tool has been designed, developed and tested. This was followed by the identification of barriers and facilitators to the clinical use of VR for post-stroke USN management, and identification of essential features of an optimal VR-based USN assessment tool as per clinicians and experts in the field.

Below are the specific objectives and hypotheses that were addressed and hereby separated by respective **Manuscripts №1-№5** with a brief overview of respective rationales and in-between Manuscripts links.

Manuscript № 1: *“Post-stroke visual neglect affects goal-directed locomotion in different perceptuo-cognitive conditions and on a wide visual spectrum”*

The **general objective (1)** of this study was to further our understanding of goal-directed locomotion control in post-stroke USN.

The following target conditions were designed and used in a goal-directed locomotion experiment performed in VR: (1) *actual* condition - where the target is static and remains visible

throughout the walking trial (i.e. visually-guided movement); (2) *remembered* condition - where the target that is first viewed, then disappears and one is instructed to walk to its remembered location (i.e. memory-guided movement); and (3) *shifting* condition - where the target shifts its location and one is instructed to re-orient the walking trajectory towards the new location (i.e. visually-guided movement incorporating a component of representational updating).

The following **specific objectives** were addressed in **Manuscript № 1**:

- 1.1. To determine the extent to which goal-directed locomotion performance towards actual vs. remembered vs. shifting targets is affected in participants with post-stroke USN as compared to those with stroke but without USN and age-matched healthy control individuals.
- 1.2. To determine the association between goal-directed locomotion performances with USN severity in near and far space.
- 1.3. To determine the preliminary sensitivity of the goal-directed virtual reality locomotion task in detecting deficits otherwise left undetected using conventional evaluation methods.

It was hypothesized that post-stroke USN alters goal-directed locomotion abilities to left-located target to a larger extent than a stroke without USN, with more pronounced alterations to be observed possibly for all conditions. We expected to find greater association between USN severity in far vs. near space and alterations in goal-directed walking performance to the left target. Further, we anticipated that goal-directed locomotion performance to the left target in the remembered condition would be sensitive in detecting related deficits in individuals with history of USN (but no USN on testing during the study) vs. stroke participants without USN; and possibly in stroke participants without USN or without history of USN vs. healthy control individuals.

Manuscript № 2: *“Post-stroke unilateral spatial neglect: virtual reality-based navigation and detection tasks reveal lateralized and non-lateralized deficits in tasks of varying perceptual and cognitive demands”*

The **general objective (2)** of this study was to further our understanding of the role of post-stroke USN in the control of mobility/navigation.

Hereby, we proposed to examine USN effects in a joystick-driven goal-directed navigation task which is analogous to the goal-directed locomotion paradigm used in **Manuscript № 1**. The main premise behind this paradigm is that the use of a joystick for navigation with the non-paretic hand, performed while seated, minimizes the biomechanical demands of locomotion and its concurrent sensorimotor aspects. Thus, it permits to essentially examine the role of attentional-perceptual abilities involved, by eliminating potential confounding factors related to gait capacity, balance and posture. In addition, the proposed joystick-driven seated task represents a more feasible mean to assess certain aspects of mobility in post-stroke individuals in comparison to a goal-directed locomotion task, which requires more resources in terms of equipment, space and time. Therefore, the VR joystick-driven task could potentially be more suitable to be implemented in the clinical setting.

The following **specific objectives** were addressed in **Manuscript № 2**:

- 2.1 To estimate the extent to which goal-directed navigation abilities in actual, remembered and shifting target conditions are affected in individuals with post-stroke USN vs. individuals without post-stroke USN vs. health control individuals.
- 2.2 To estimate the extent to which post-stroke USN affects target detection abilities as well as the relationship of navigation abilities with measures of detection abilities and clinical measures of USN.

We hypothesized that post-stroke USN would affect navigation and detection abilities, such that greater end-point accuracy errors, longer re-orientation of navigation trajectories and greater detection times would be observed for the group with vs. those without USN and healthy controls, possibly in all conditions (but predominantly in remembered and shifting conditions). We also hypothesized that clinical USN measures would be minimally associated with navigation outcomes.

Manuscript № 3: *“Visual-perceptual deficits and their contribution to walking dysfunction in individuals with post-stroke visual neglect”*

The **general objective (3)** of this study was to further our understanding of the impact of post-stroke USN on visual-perceptual abilities and their influence on the control of mobility.

Visual-perceptual abilities are essential in activities involving mobility. However, whether and to which extent post-stroke USN affects those and how they contribute to mobility impairments found in **Manuscript № 1** remained unclear.

The following **specific objectives** were addressed in **Manuscript № 3**:

- 3.1. To estimate the extent to which visual-perceptual abilities, including: contrast sensitivity, optic flow direction and coherence, and shape discrimination in bilateral (left/right) visual hemispaces, are affected in individuals with post-stroke USN vs. those with stroke but no USN vs. healthy control individuals.
- 3.2. To estimate the relationship between USN clinical tests and psychophysical tests of visual perceptual abilities.
- 3.3. To estimate the preliminary sensitivity of psychophysical tests in detecting deficits that were otherwise left undetected using conventional USN clinical tests.
- 3.4. To determine the extent to which visual-perceptual abilities contribute to goal-directed locomotion impairments in individuals with post-stroke USN.

It was hypothesized that individuals with vs. those without USN and healthy controls would present with higher thresholds in all psychophysical tests, indicating worse behavior, possibly in both visual hemispaces. Moreover, we hypothesized to find significant but low-magnitude correlations between USN clinical tests and psychophysical measures. Further, we speculated that psychophysical measures would be highly sensitive in detecting deficits in those with history of USN and potentially in those without post-stroke USN as assessed by traditional paper-and-pencil tests. Finally, we hypothesized that visual-perceptual abilities, specifically those related to optic flow processing, would significantly contribute in explaining impairments found in goal-directed locomotor behavior.

Manuscript № 4: *“Ecological Virtual Reality Evaluation of Neglect Symptoms (EVENS): Effects of virtual scene complexity in the assessment of post-stroke unilateral spatial neglect”*

The **general objective (4)** of this study was to assist the development and examine the feasibility of a newly created VR-based USN assessment tool.

Considering the limitations of conventional measures and existing VR-based assessments for USN, we have developed a novel tool, the Ecological VR-based Evaluation of Neglect Symptoms (EVENS). EVENS consists of two ecological scenes with variable perceptual-attentional demands (simple vs. complex) where functional tasks of object detection and goal-directed navigation are performed.

The following **specific objectives** were addressed in **Manuscript № 4:**

- 4.1 To estimate the effects of scene complexity on functional VR tasks performance in individuals with post-stroke USN vs. those with stroke but without USN and healthy control individuals.
- 4.2 To estimate preliminary sensitivity of EVENS in detecting deficits that were otherwise left undetected using conventional USN clinical tests.

We hypothesized that the presence of post-stroke USN will alter object detection and navigation performances, specifically in the complex vs. simple scenes. We also hypothesized that EVENS would identify deficits in individuals with history of USN, but no USN on testing using conventional methods, and also in individuals with no USN on testing prior and during the present study.

Manuscript № 5: *“Exploring barriers and facilitators to the clinical use of virtual reality for post-stroke unilateral spatial neglect assessment”*

The **general objective (5)** of this study was to employ KT strategies in promoting the development and future clinical implementation of a VR-based USN assessment tool.

Despite numerous and important advantages that VR can offer to current clinical practice in the field of post-stroke USN management, its application in clinical settings remains limited. There is a need to refine our understanding of the barriers and facilitators to the use of VR for USN management. Further, to promote its application and usage adherence in clinical practice, we seek to tailor VR-based USN assessment to clinicians' needs, while also considering the opinions of experts as to the tool's optimal features.

The following **specific objectives** were addressed in **Manuscript № 5**:

- 5.1 To identify the facilitators and barriers that affect the use of VR for post-stroke USN assessment by clinicians;
- 5.2 To identify the features of an optimal VR-based USN assessment that could be implemented and used by clinicians in the management of post-stroke USN.

We expected clinicians to identify various barriers and facilitators to VR use in post-stroke USN assessment. We hypothesized that study participants (clinicians and experts in the field) will identify several features of an optimal VR USN assessment tool.

Figure 1.1A: Ventral vs. dorsal stream processing

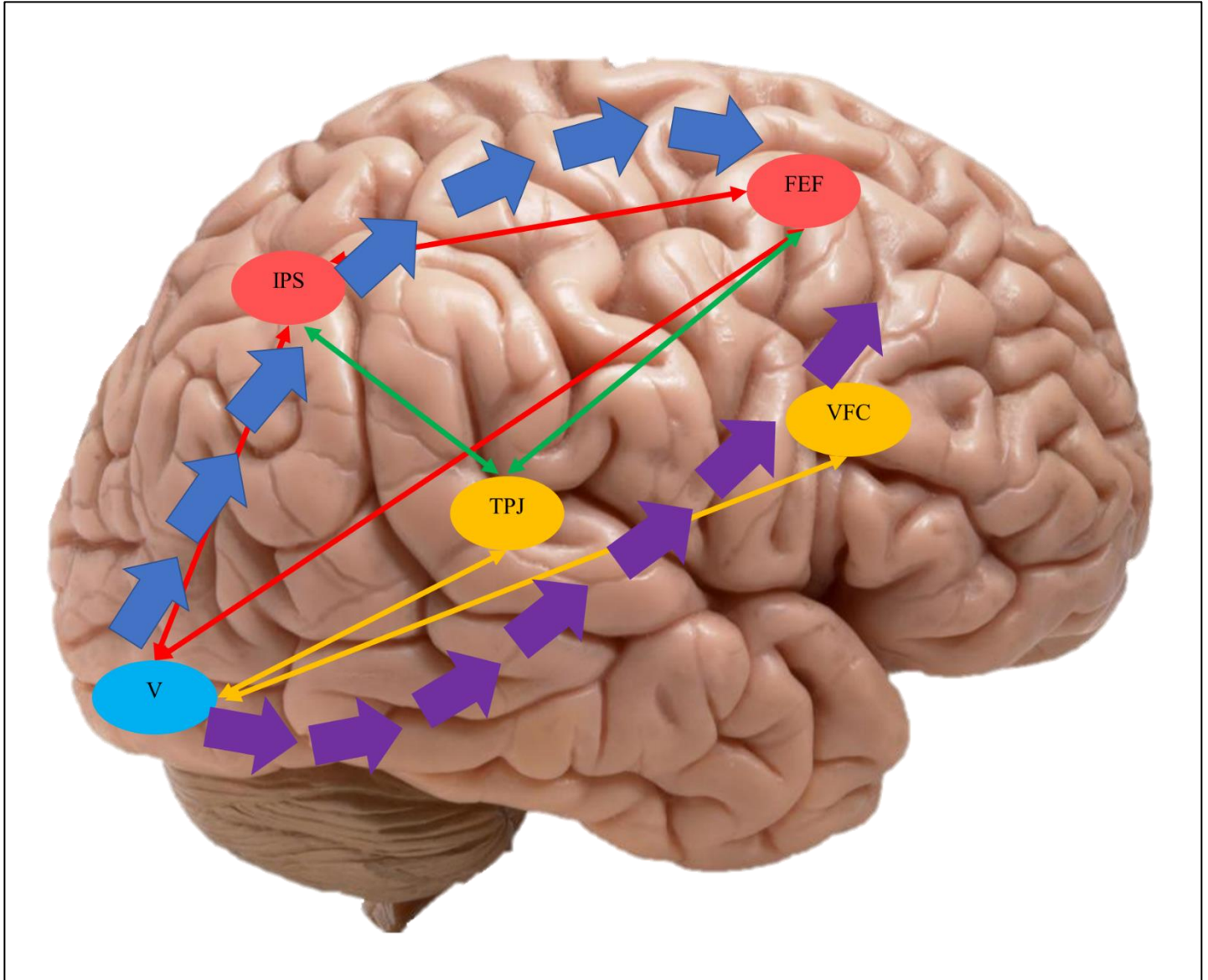


Figure 1.1A Ventral (indicated in purple) vs. dorsal (indicated in blue) streams processing hypothesis in USN. Legend: visual cortex (V); temporal-parietal junction (TPJ); ventral frontal cortex (VFC); frontal eye fields (FEF); intraparietal sulcus (IPS).

Figure 1.1B: Ventral vs. dorsal stream processing, upper limb movements and USN

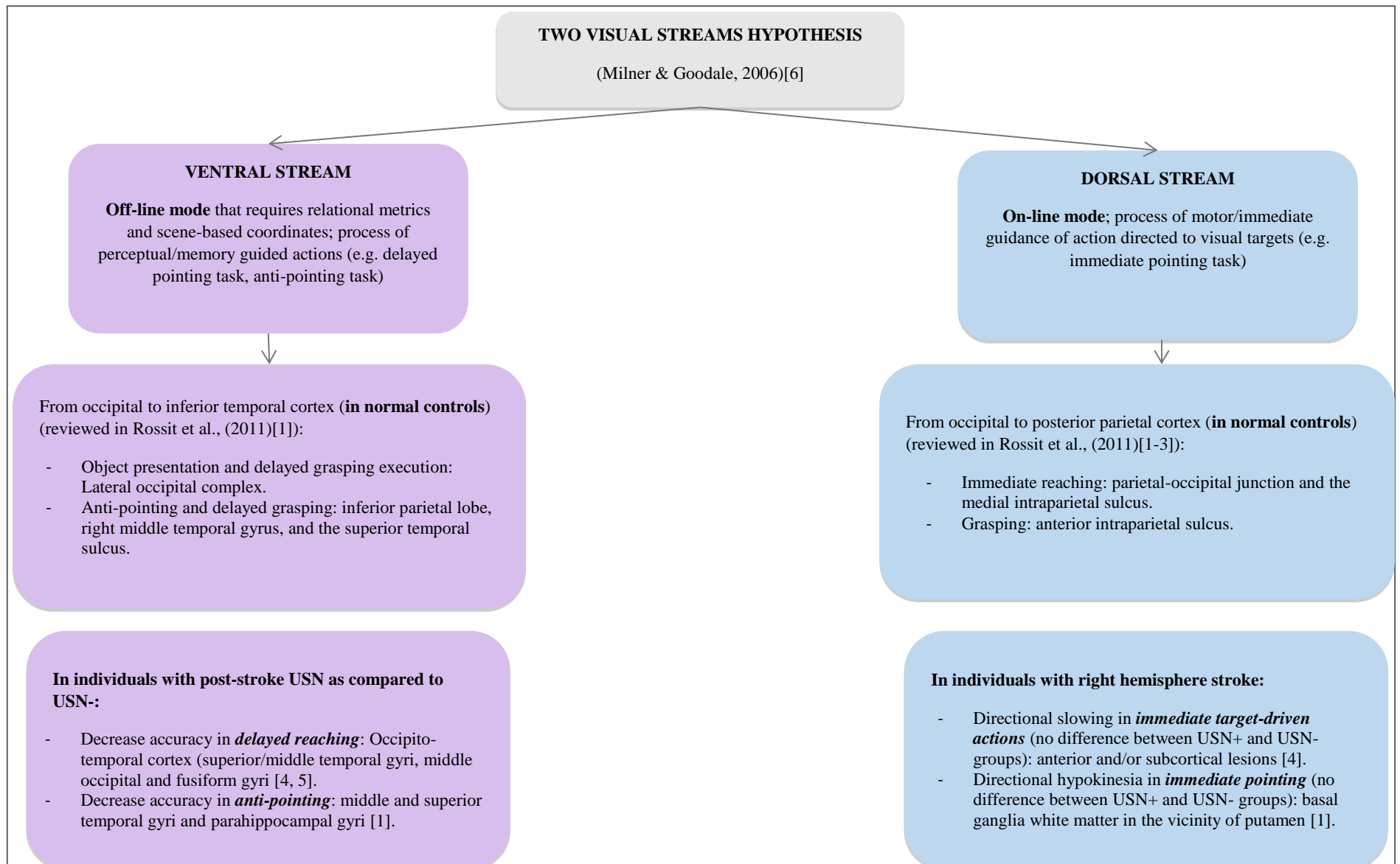


Figure 1.1B Ventral vs. dorsal stream processing, upper limb movements and USN.

Figure 1.2: Visual perception hierarchy

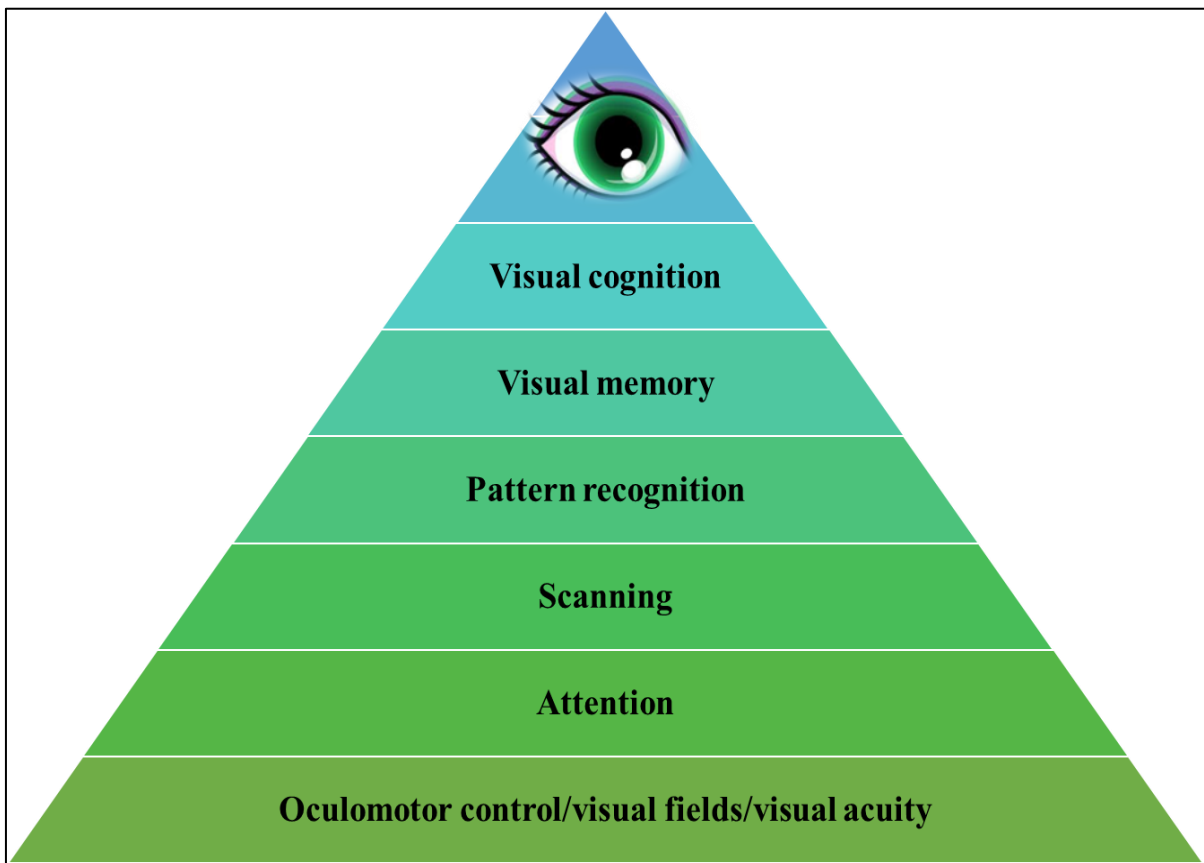


Figure 1.2 The visual-perceptual hierarchy introduced by Warren, 1993 [7].

Figure 1.3: USN theoretical models

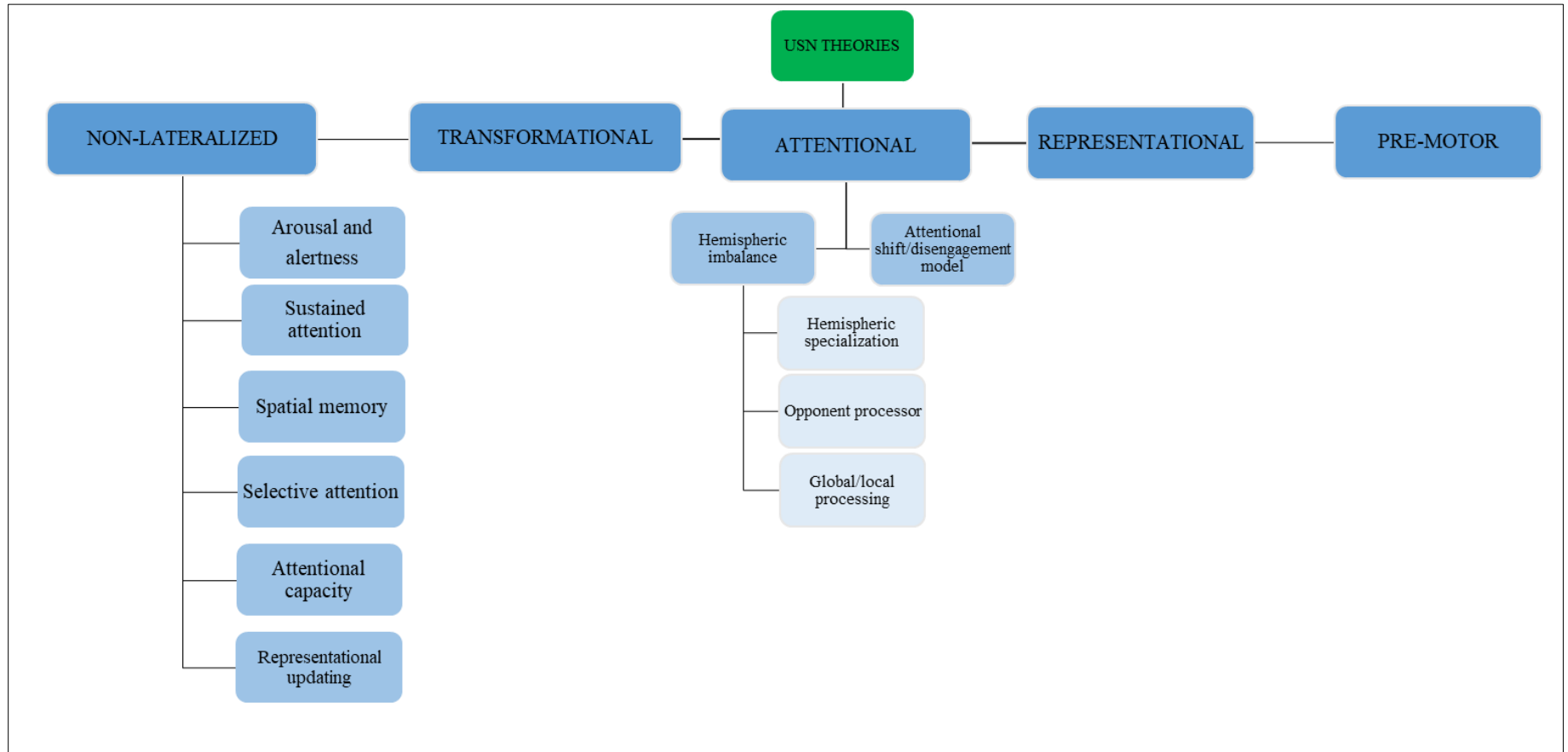


Figure 1.3 USN theoretical models

Figure 1.4: Knowledge to Action model

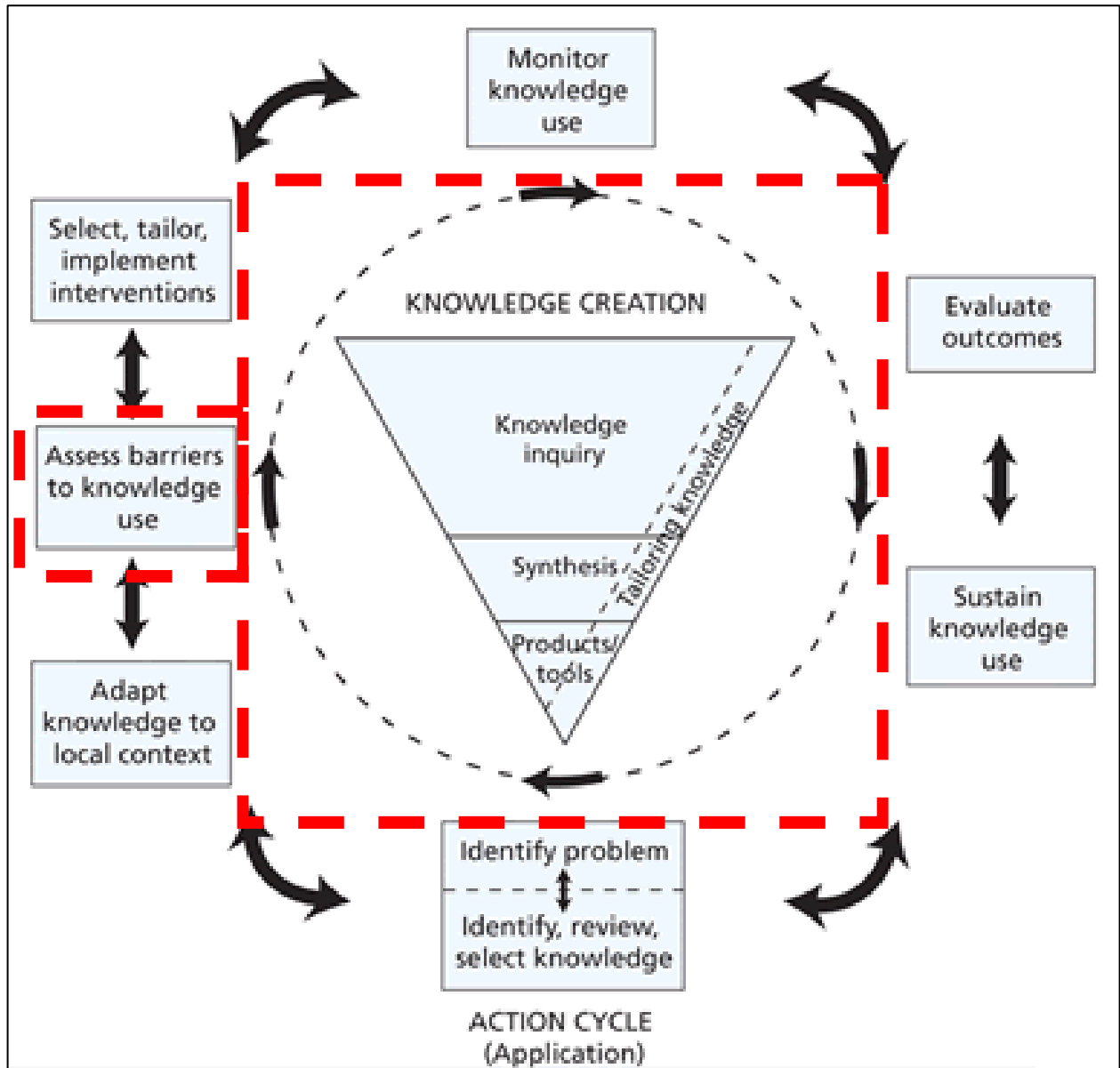


Figure 1.4 The Knowledge to Action (KTA) model introduced by Graham et al., 2006 [8]. Areas delineated in red represent those addressed in this PhD dissertation.

CHAPTER 2

2.1 PREFACE

The rehabilitation of skills needed for community mobility, an instrumental activity of daily living that contributes to one's quality of life, independence, participation in life roles, leisure and other meaningful activities, is an essential part of post-stroke therapy and one of the most sought goals of stroke survivors [27]. While less than 40% of individuals with post-stroke USN regain independent walking ability within the community [28], the role of post-stroke USN on post-stroke mobility has been underappreciated, where only one study investigated goal-directed locomotion to a defined target [71] and collectively, related studies provide inconsistent results.

Formerly, we conducted a systematic review examining the effects of post-stroke USN on goal-directed upper extremity movements performed within the near-space [35]. Impairments among individuals with post-stroke USN were found mostly in perceptual, memory-guided or delayed tasks; but not in immediate, visually-guided tasks. Whether the type of task condition (e.g. visually-guided vs. memory-guided) also affects functional performance in far space, involving goal-directed locomotion to a far space target, remained to be determined.

Moreover, functional performance is suggested to be influenced by the regularities of the environment and the ability to notice and adapt to changes of these regularities (i.e. representational updating). Although Shaqiri et al., 2013 [169] provide substantial evidence for deficits in representation updating in those with post-stroke USN, all the reviewed studies focused predominantly on near space USN, and near space activities. Subsequently, the extent to which post-stroke USN influences the ability to detect and adapt to changes in far space environmental features (e.g. recall target location, shift of target location) and act upon those (e.g. goal-directed walking) was yet to be ascertained.

Chapter 2 of this PhD dissertation addresses the **general objective 1** and **specific objectives 1.1 – 1.3** of my PhD research agenda. This chapter includes **Manuscript №1** of this dissertation, entitled "*Post-stroke visual neglect affects goal-directed locomotion in different perceptuo-cognitive conditions and on a wide visual spectrum*".

MANUSCRIPT № 1

POST-STROKE VISUAL NEGLECT AFFECTS GOAL-DIRECTED LOCOMOTION IN DIFFERENT PERCEPTUO-COGNITIVE CONDITIONS AND ON A WIDE VISUAL SPECTRUM

Tatiana OGOURTSOVA^{1,2*}, Philippe S. ARCHAMBAULT^{1,2}, Anouk LAMONTAGNE^{1,2}

¹School of Physical and Occupational Therapy,
McGill University,
3654 Promenade Sir-William-Osler
Montreal, Quebec, Canada
H3G 1Y5

²Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital,
Site of Centre for interdisciplinary Research
in Rehabilitation of Greater Montreal
3205 Place Alton-Goldbloom
Laval, Quebec, Canada
H7V 1R2

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DECLARATION OF INTEREST

The authors report no declarations of interest. T.O. was supported by the Richard & Edith Strauss Fellowship in Rehabilitation Sciences and The Fonds de Recherche du Québec – Santé (FRQS). This project was supported by the Canadian Institutes of Health Research (MOP – 77548) and A.L. and P.S.A. are the recipients of a Research Scientist FRQS Salary Award.

2.2 ABSTRACT

Background: Unilateral spatial neglect (USN), a highly prevalent and disabling post-stroke deficit, has been shown to affect the recovery of locomotion. However, our current understanding of USN role in goal-directed locomotion control, and this, in different cognitive/perceptual conditions tapping into daily life demands, is limited. **Objectives:** To examine goal-directed locomotion abilities in individuals with and without post-stroke USN vs. healthy controls. **Methods:** Participants (n=45, n=15 per group) performed goal-directed locomotion trials to actual, remembered and shifting targets located 7 m away at 0° and 15° right/left while immersed in a 3-D virtual environment. **Results:** Greater end-point mediolateral displacement and heading errors (end-point accuracy measures) were found for the actual and the remembered left and right target among those with post-stroke USN compared to the two other groups ($p < 0.05$). A delayed onset of reorientation in the shifting condition to left and right targets was also observed in USN+ participants vs. the other two groups ($p < 0.05$). Results on clinical near space USN assessment and walking speed explained only a third of the variance in goal-directed walking performance. **Conclusion:** Post-stroke USN was found to affect goal-directed locomotion in different perceptuo-cognitive conditions, both to contralesional and ipsilesional targets, demonstrating the presence of lateralized and non-lateralized deficits. Beyond factors such as neglect severity and walking capacity, other factors related to executive functioning and visual perceptual abilities (e.g. optic flow perception) may account for the goal-directed walking deficits observed in post-stroke USN. Goal-directed locomotion can be explored in the design of future VR-based evaluation and training tools for USN to improve the currently used conventional methods.

Keywords: cerebrovascular accident, hemineglect, gait, locomotion, trajectory deviation.

2.3 BACKGROUND

Nearly fifteen million individuals worldwide suffer a stroke every year, and five million of them are left with permanent post-stroke deficits [194] in motor, sensory, perceptual and/or cognitive areas [195]. One of the most serious and disabling post-stroke perceptual deficit is unilateral spatial neglect (USN), experienced by nearly 50% of individuals with a right hemisphere lesion [10]. USN is characterized by difficulty to orient, respond, or report to the stimuli appearing typically on the contralesional side [196]. USN can be present in the personal (i.e. neglecting hemibody), near extrapersonal (i.e. neglecting space within reaching distance) and/or far extrapersonal space (i.e. neglecting space beyond reaching distance) [54]. While it can resolve spontaneously within the acute post-stroke period, symptoms of USN and their dramatic impact on functional performance may persist in up to 75% of initially diagnosed cases [10]. Unfortunately, those numbers are expected to surge with the rise in the aging population, given that USN is found to be associated with increase in age [45].

USN is a strong predictor of poor functional recovery and is shown to have significant limitations on rehabilitation process and outcomes [197]. For example, a recent prospective observational study found acute USN as one of the most significant predictor of community mobility and that its severity in the acute stage predicts the extent of community mobility in the chronic phase of stroke recovery [198]. The rehabilitation of skills needed for community mobility, an instrumental activity of daily living that contributes to one's quality of life, independence, participation in life roles, leisure and other meaningful activities, is an essential part of post-stroke therapy and one of the most sought goals of stroke survivors [199]. While less than 40% of individuals with post-stroke USN regain independent walking ability within the community [200], the role of USN on post-stroke mobility has been underappreciated. To that effect, only a handful of studies have addressed locomotion in individuals with post-stroke USN [61, 72, 201-203]. Of these, only one investigated goal-directed locomotion to a defined target [201]. While these studies found larger deviation in the walking trajectories in individuals with post-stroke USN as compared to other study groups, the results are not consistent in terms of the direction of the mediolateral deviation, where some report rightward deviations [61, 72, 204], but also deviations to both the left and the right sides [201, 202]. This inconsistency could possibly

result from small and heterogeneous samples, walking trials to middle/centered target only, and lack of far-space USN assessment.

Moreover, we live in busy, cluttered, and constantly dynamic environments, where we profoundly rely on all our senses, including visual perception and cognition, to function safely and to successfully perform everyday life activities. However, to the best of our knowledge, none of the existing studies evaluated the impact of different cognitive/perceptual conditions on the locomotor performance in individuals with post-stroke USN. Indeed, mobility heavily depends on cognitive processes when one needs to anticipate and adapt to the dynamic environment while maintaining postural control and motor coordination [205, 206]. Specifically, gait, imposes the interaction of cognitive processes of attention, executive function, and visuospatial memory processing (reviewed in [207]). As a result, potential post-stroke deficits in one or more of these perceptuo-cognitive functions may negatively affect one's mobility.

In fact, previous research evidence that immediate and delayed spatial memory is affected in stroke patients with USN in activities performed in near space [208] [209]. For instance, individuals with neglect tend to “revisit” stimuli to which they have previously attended (e.g. during a cancellation task [168]). Moreover, a formerly conducted systematic review and analysis by our team on the impact of post-stroke USN on upper extremity movements performed in near space (e.g. reaching, pointing, grasping) determined that memory-guided/perceptual/delayed movements (e.g. reaching to a remembered target location) and not actual/visually-guided/immediate movements (e.g. pointing to a visual and stationary target) are found to be affected by post-stroke USN [65]. In addition, functional performance is suggested to be influenced by the regularities of the environment and the ability to notice and adapt to changes of these regularities (also referred to as representational updating). In relation to that, Shaqiri et al., 2013 [210] provide substantial evidence for deficits in representation updating in individuals with post-stroke USN, in near-space activities.

The extent to which post-stroke USN affects mobility in *far* space (goal-directed locomotion to a far space target) in activities of different cognitive demands that tap into everyday functional performance (i.e. that are memory-guided and that involve a representational updating component) remains to be ascertained. A better understanding of such interactions could ultimately provide insights (1) into the underlying mechanisms of post-stroke USN, and (2)

towards the development of more sensitive diagnostic methods and/or effective treatment strategies. To that effect, the following targets conditions were designed and used in a goal-directed locomotion experiment performed in virtual reality (VR): (1) *actual* condition - where the target is static and remains visible throughout the walking trial (i.e. visually-guided condition); (2) *remembered* condition - where the target that is first viewed, then disappears and one is instructed to walk to its remembered location (memory-guided condition); and (3) *shifting* condition - where the target shifts its location and one is instructed to re-orient the walking trajectory towards the new location (condition with a representational updating component).

The following specific objectives were addressed: (1) To determine the extent to which goal-directed locomotion performance towards *actual* vs. *remembered* vs. *shifting* targets is affected in participants with post-stroke USN as compared to those without USN and age-matched healthy control individuals; (2) To determine the association between goal-directed locomotion performances with USN severity in far and near space, and; (3) To determine the preliminary sensitivity of a goal-directed VR locomotion task in detecting deficits that were otherwise left undetected by conventional USN evaluations.

We hypothesized that post-stroke USN alters goal-directed locomotion abilities to left/ “neglected” target to a larger extent than for a stroke participant without USN, with more pronounced alterations to be observed for remembered and possibly shifting target conditions (as these are more cognitively and perceptually demanding) than for the actual target condition. However, we do not exclude the possibility of finding deficits in the actual condition as well. Locomotion involves perception and processing of optic flow as one moves through space [211], which was previously reported to be potentially affected in stroke individuals with USN [87]. Moreover, this speculation is partly based on an earlier body of research on the USN representational theory, first proposed by Bisiach & Luzzatti [138]. It stipulates that individuals with post-stroke USN have deficits in the ability to form mental images of neglected objects, including those in far space and that USN is possibly a deficit in the mental representation of the contralesional hemispace [138-140]. In addition, this latter hypothesis relies on previous findings of USN related deficits in representational updating in near space [210]. Further, we expected to find greater association between USN severity in the far vs. near space and alterations in goal-directed walking performance to the left target. Lastly, we anticipated that goal-directed

locomotion performance to the left target would be sensitive in detecting performance deficits that were otherwise left undetected using conventional tests, as these methods are reported to be not sensitive in detecting USN-related deficits that are mild but clinically significant (e.g. [10]).

2.4 METHODS

2.4.1 Participants

Individuals with stroke were included based on the following inclusion criteria: (1) presence of a first time right hemisphere stroke (as per CT report, neurological examination, and medical chart), (2) with or without left USN (as per one or more of the following tests: Line Bisection Test (LBT) [181], Star Cancellation Test (SCT) [212], and/or Apples Test (APT) [53] on testing, or history of USN as per medical chart); (3) age ≥ 40 to 85 years old; (4) right handedness (as per interview and/or medical chart containing Edinburgh Handedness Inventory scores [213]) and; (5) independent walker with or without a walking aid over 5-7 meters (as per medical chart, interview and the Rivermead Mobility Index [214]). Individuals were excluded based on the following exclusion criteria: (1) presence of primary visual impairment that impedes normal or corrected-to-normal binocular visual acuity (score $\leq 20/20$ on the Early Treatment Diabetic Retinopathy Study Chart [215]); (2) presence of moderate cognitive impairment (score $\leq 22/30$ the Montreal Cognitive Assessment [216]); (3) presence of a documented visual field deficit in stroke patients without USN (Goldmann's perimetry or computerized equivalent, as per medical chart); and (4) any premorbid neurological and/or orthopedic condition that can impede locomotion. Age-matched (± 5 years) healthy controls were also recruited following the same inclusion/exclusion criteria where applicable.

Participants with and without post-stroke USN were recruited from the inpatient discharge lists of three clinical sites of Centre de Recherche Interdisciplinaire en Réadaptation du Montreal Métropolitain (CRIR), including the Jewish Rehabilitation Hospital (JRH), Centre de Réadaptation Lucie Bruneau and the Institut de Réadaptation Gingras-Lindsay de Montréal. These sites provide inpatient and outpatient post-stroke rehabilitation for patients living in the Greater Montreal area, Quebec, Canada. Healthy controls were recruited from the research database of the JRH and word-of-mouth using snowball sampling technique. Pre-authorized advertisement in form of wall mounted notice was also used to recruit healthy controls and participants with stroke. The study was approved for ethics by the CRIR Institutional Review

Board. All study participants reviewed and signed the informed consent before enrolling in the study.

2.4.2 Data Collection

The process of data collection consisted of a clinical USN evaluation and a VR-based goal-directed locomotion task. All evaluations were carried out in one testing session of approximately 3 hours or two separate sessions of 1.5 hours within the same week, depending on participants' endurance and preference. Prior to experimental data collection, each participant also completed a set of clinical measures of walking speed (10 Meters Walking Test (10MWT) [217-219]), mobility (Rivermead Mobility Index (RMI) [220]), and post-stroke recovery of lower extremities motor function (Chedoke McMaster Stroke Assessment (CMSA) - Leg and Foot [221]).

Clinical USN evaluation

Apparatus and stimuli: Presence, severity and type of USN were determined using the LBT, SCT, and the APT which all show excellent psychometric properties [53, 222, 223]. These tests were selected aiming to cover a variety of USN sign and symptoms presentations. First, they are commonly employed in clinical practice by clinicians (near-space version). Second, they contain bisection and cancellation type of activities (i.e. where presence of USN could affect one behavior and not the other, and vice-versa) within the near and far space. Lastly, the APT can distinguish between ego and allocentric type of USN. The LBT and SCT were repeated in the near and far extrapersonal space, using a procedure previously employed [61, 224]. Participants were positioned 40 cm and 320 cm away from the screen for near and far USN testing, respectively. The LBT and SCT were displayed on a projector screen using MS Paint® with the appropriate sizes (near space: 21 x 28 cm; far space: 168 x 224 cm) to keep the visual angle of each array and the retinal size image constant during both testing conditions (Appendix 2). Each displayed test contained a middle point, with respect to which the participants' sternum was aligned with a laser. A chin rest was used to minimize head movements and to ensure a constant viewing angle. Responses were provided by the participants using a hand-held laser pointer and were marked directly on the computerized test form by the investigator using a wireless mouse and the pencil in MS Paint®. The order of tasks (bisection vs. cancellation) and distance conditions (near vs. far) was randomized across participants. The APT was presented on a sheet

of paper on a steady table, aligned with the participant's midline (i.e. sternum) and fixed on the table with tape to prevent possible shifts.

Procedure: In the LBT, participants were asked to find the midline of each presented line (n=18), starting from the top line. In the SCT, participants were instructed to find all the small stars (n=52) among the distractors. In the APT, participants were instructed to find all the complete-shaped apples (n=50). For the scoring of the LBT, the deviation from the center in each line was measured and averaged across all lines. An absolute mean deviation of more than 6.0 mm to the right is indicative of *left near space USN* on the near LBT test, and 4.8 cm to the right is indicative of *left far space USN* on the far LBT test. An average percentage of deviation from midline was also computed for near and far-space LBT to estimate the difference in severity between near and far space USN. For the scoring of the SCT, the number of small cancelled stars was divided by the total number of small stars to compute the laterality index score. Scores between 0 and 0.46 are indicative of *left near space USN* [181]. For the scoring of the APT, the total number of crossed out complete and incomplete shape apples was computed, and an asymmetry scores for egocentric (i.e. difference between the numbers of complete shape targets crossed out on the right versus left side of the page) and allocentric (i.e. difference between the numbers of incomplete shape targets crossed out with a right and with a left opening) USN were calculated [53]. The overall cutoff of <42/50 is indicative of *near space USN*. Asymmetry cutoff score across the page of <-2 or >2 (difference between right side and left sided targets cancelled) is indicative of *egocentric near space USN*. Asymmetry cutoff score across the cancelled distractors on the page with left vs right sided openings of <-1 or >1 is indicative of *allocentric near space USN*. All cancellation tests were timed.

Severity of USN was characterized by a positive result on 1 to 3 (mild), 4 (moderate), and 5 or more (severe) clinical test scores out of 7. This classification was modified from Lindell et al. (2007) for mild (positive result on 1-3 tests) vs. moderate/severe USN (positive result on 4 or more tests) [172] to separate moderate vs. severe cases.

Outcomes: Outcomes retained for analysis included: *overall USN severity* (history, mild, moderate or severe), (2) *USN range of space severity* (near and/or far space), and (3) *USN spatial representation type* (allocentric vs egocentric). Participants were included in the group of individuals with USN (USN+) if they had USN on one or several of the aforementioned tests, or

if they had a history of USN as per their medical chart typically assessed by clinicians using a cancellation test (e.g. SCT, Bells Test), LBT, Clock Drawing, and/or the Behavioral Inattention Test.

VR-based goal-directed locomotion task

Apparatus and Stimuli: The VR-based experiment was performed while immersed in a 3D virtual environment (VE) representing a symmetrical richly-textured room (9 m x 15 m) including a visual display of walls and ceiling (i.e. giving an impression of closed space and providing superior depth cues than an open type of environment [225]). All the presented targets were of the same dimension. The targets (i.e. red ball) appeared at the same height in the visual field to avoid differences in distance perception [226, 227], 7 m away from the starting position (i.e. far-space) and at the following 3 possible locations: $\pm 15^\circ$, 0° (Figure 2.1).

The VE scene was created in Softimage XSI®. During the experiments, the real-time CAREN-3™ (Computer Assisted Rehabilitation Environment; Motek BV, Amsterdam) software was employed to control the VE scene. The viewing media was a helmet mounted display (HMD) (NVisor™ - field of view of 60° diagonal, resolution of 1084 x 1280), blocking all peripheral vision with only the VE visible to the participant.

Participants' displacements (3D body coordinates) were recorded using a 12-camera Vicon™ 512 motion capture system (Denver, CO). Passive reflective markers were attached to specific body landmarks according to the Plug-In-Gait model from Vicon™, with the exception of the head was represented by a 3-marker model with markers located on the front, left and right sides of the HMD. The 3D head coordinates were tracked in real time by the Tarsus real-time engine from Vicon™ and fed to the CAREN-3™ VR software. This feedback system synchronized the virtual scene in real time with head motions through the physical space (delay ≤ 10 ms) [228]. All data were recorded at 120 Hz in CAREN-3™ and Vicon™ and stored for offline analyses in Matlab®2016a.

Procedure: Practice trials were performed prior the experiment until the participant felt comfortable in executing the tasks. For each testing condition (actual, remembered and shifting), five trials per target location ($\pm 15^\circ$, 0°) were performed, for a total of 45 walking trials or 15 trials per condition. Target location within each condition was randomized. The order of

condition presentation was also randomized, but presented in blocks (e.g. all actual, followed by all shifting, followed by all remembered condition trials). Prior to each trial, a “GET READY” sign appeared. At the end of each walking trial, a “STOP” sign appeared; following which, the participant was accompanied back to the starting position by an assistant. While the target was at 7 m away from the starting position, the participants were stopped at 5 m of forward displacement (delineated by a white line on the floor) so not to have an impression of collision with the target (Fig. 1B).

In the *actual* target condition, a single target appeared and after 2000 ms and a beep sound, the participant was instructed to walk towards the seen target. In the *remembered* target condition, a single target appeared and after 2000 ms and a beep sound, it disappeared, and the participant was instructed to walk towards the remembered target location. In the *shifting* target condition, a single target appeared at 0° (center). After 2000 ms and a beep sound, the participant was instructed to walk towards the target. Following 1.5 m of forward displacement, the target either shifted its location to the right or left (-15° or +15°) or remained in the center. In the shifting condition, the trials where the target remained in the middle were included as “null” trials to minimize response bias.

Outcomes: Outcomes related to the goal-directed locomotion task included the following: (1) *Endpoint heading error (HE)*, defined as the difference in degrees between the ideal and the actual individual’s position in space with respect to the target at 5 m of forward displacement; (2) *Endpoint mediolateral displacement (MLD) error*, defined as the difference in meters between the mediolateral position of the target and that of the individual at 5 m of forward displacement; (3) *Head orientation*, defined as the position of the head in degrees at the end of the trial; (4) *Endpoint direction*, defined over or undershooting the target at the end of the trial ; (5) *Onset of reorientation strategy* (for shifting condition only) was determined using a variation of the extrapolation method [229]. First, movement trajectory segments before (i.e. control movement) and after (i.e. adjusted movement) the shift event were outlined and fitted using linear regression. Following this, a line between 15% and 85% of the fitted trajectory was delineated and extrapolated. The onset of reorientation strategy (temporal value) is thus defined by the time at which the target was shifted (i.e. at 1.5 meters of forward displacement) minus the time at which the extrapolated lines for pre- and post-shift crossed each other (Appendix 3).

2.4.3 Sample size consideration

Sample size was estimated using G*Power® 3.1.2 calculator [230] while considering an analysis of variance (ANOVA) for repeated measures (within and between interactions) with target condition (actual, remembered and shifted) and target location (left, right and middle) as within-subject effects and group (post-stroke USN+, post-stroke USN- and healthy controls) as the between-subject effect. An effect size (i.e. standardized mean difference) of $d=1.02$ was computed from the only previous study on goal-directed walking abilities in USN that found significant changes in maximum mediolateral displacement between USN+ ($0.197 \pm 0.136\text{m}$, $n=6$) and USN- stroke participants ($0.097 \pm 0.028\text{m}$, $n=14$) [201]. Given the potential heterogeneity of USN presentation and severity, however, it was therefore deemed suitable and cautious to assume a small-to-medium effect size of 0.35. Accordingly, a sample size of 13 individuals per group was obtained at a power of 80%, type I error of 0.05, assuming a moderate correlation between variables (0.50), and a non-sphericity correction e of 0.125 ($1 / [\text{repetitions} - 1]$) between target positions and conditions. To account for possible missing data and heterogeneity, we aimed to recruit 15 individuals per group for a total of 45 participants.

2.4.4 Data and statistical analyses

Response of participants on USN tests and goal-directed locomotion tasks were averaged across conditions and target locations, such that mean values could later be compared across groups and between conditions.

All subsequent statistical analyses were performed using SAS® 9.4. Significance was accepted at $p \leq 0.05$. Demographics were compared between groups using one-way ANOVAs (normally distributed data) and Kruskal-Wallis test (not normally distributed data). If significant differences were detected, contrasts analyses were performed using independent sample t-test (normally distributed data) and Wilcoxon-Mann-Whitney test (not normally distributed data). The difference in USN severity (near vs. far) within the USN+ group was evaluated using the Wilcoxon Signed Rank Sum test.

The effects of target condition and target location on goal-directed locomotion performances were examined using mixed-model, repeated-measures analysis approach, with ‘Group’ [USN+ vs. USN- vs. HC] as between subject factor as well as ‘Condition’ [actual vs. remembered vs.

shifting) and ‘Target Location’ [-15°, 0°, +15°] as within subject factors. In the event of significant 3-way interaction, pairwise comparisons that were determined a priori were examined.

Further, to estimate the effect of post-stroke USN on the delay in reorientation to the left (-15° target shift) and to the right (+15° target shift), a mixed-model, repeated-measures analysis with ‘Group’ as the between-subject factor was used separately for the left and right shift conditions.

Kendall rank correlation coefficients were used to quantify the relationship of goal-directed locomotion performances to the left (-15°) target in the remembered condition with clinical assessments of neglect within near and far spaces (LBT, SCT, APT) given that the data was not normally distributed in the USN+ group. The size of the correlation coefficient was interpreted as per guidelines: very high (0.90-1.00), high (0.70-0.90), moderate (0.50-0.70), low (0.30-0.50) or negligible (0.00-0.30) [231]. Moreover, a backward stepwise multiple regression analysis was used to verify the extent to which the severity of neglect in near space and far space, along with walking speed, predicted goal-directed locomotion behavior deficits to the left/ “neglected” (-15°) target in the remembered condition.

To gain a better understanding of the preliminary sensitivity of the locomotor task in detecting deficits otherwise not detected using traditional tests, single case analyses were used to compare the performance of each USN+ participant with respect to the average performance of the USN- group; as well as to compare the performance of each USN- participant with respect to the average performance of the HC group. Precisely, the Crawford and Garthwaite (2002) approach (Singlims.exe, University of Aberdeen, Aberdeen, UK) [232], which implements classical methods for comparison of a single case’s score to scores obtained in a control sample, was used. The interval estimate of the effect size for the difference between each case and controls (as normative data) was obtained. For significant results, effect sizes were calculated and reported on using Cohen’s criteria r effects as small $\geq .10$, medium $\geq .30$, and large $\geq .50$ [233].

2.5 RESULTS

Fifteen individuals with post-stroke USN (n=15, USN+), fifteen individuals post-stroke without USN (n=15, USN-), and fifteen age-matched healthy control individuals (n=15, HC) were recruited in the period between December 2014 and March 2016. Each participant successfully completed all study experimental trials. Table 2.1 outlines the demographic and clinical variables

for the three groups. Both the USN+ and USN- groups predominantly consisted of male participants and were statistically similar in terms of stroke chronicity. No significant between-group differences were found on all baseline characteristics across the 3 study groups with the exception of walking speed, where USN+ participants were significantly slower compared to both HCs and USN- participants ($p < 0.05$).

2.5.1 USN characteristics

Table 2.2 presents the clinical USN evaluation results for the participants with stroke. The USN+ group included five ($n=5$) individuals with history of USN, and ten ($n=10$) individuals with actual USN on testing. Overall, the USN+ group demonstrated significantly greater deficits than the USN- group on all USN related measures both in the near and far space ($p \leq 0.05$), and none of the USN- individuals scored positive in any of the USN assessments. The deviation percentages on the LBT and laterality indices on the SCT in the USN+ group were also found to be similar between the near and far space ($p = 0.50$ to 1.00). Those with history of USN also took longer to complete the APT and SCT in the near space ($p \leq 0.05$) vs. USN- group. No other significantly greater deficits were found in those with history of USN vs. USN- group.

When considering individuals' scores on USN related measures in the 10 participants with actual neglect, however, some variability in the expression of USN was observed; Four ($n=4$) participants had more severe far than near space USN, two ($n=2$) had more severe near than far space USN, and four ($n=4$) had only near space USN. Allocentric (object-centered) USN was more common and found in seven out of 10 participants. Egocentric (viewer-centered) USN was found in 2 out of 10 individuals, and 2 participants presented with both allocentric and egocentric USN. Mild, moderate and severe USN was present in six ($n=6/10$), two ($n=2/10$), and two ($n=2/10$) participants, respectively.

2.5.2 Goal-directed locomotion

Figure 2.2 depicts typical traces of mediolateral displacement (MLD), head orientation and heading error (HE) during the goal-directed locomotion task performance of a USN+ and a USN-stroke participant in the remembered target condition. It can be observed that the USN-participant's MLD and heading orientation is tightly modulated as a function of the remembered target location, leading to small heading errors approximating 0° . Head orientation is also

aligned with the target. A similar behaviour was observed in healthy controls (not illustrated). By contrast, the USN+ participant shows a large variability in performance, with larger deviations in walking trajectory, head orientation, and heading to all targets (shown by larger MLD and larger HEs, especially for the left (-15°) target). Interestingly, the USN+ participant undershoots the left/ “neglected” target to arrive on the right of the target at the end of the trial. Similarly, this participant also undershoots the right/ “non-neglected” target and arrives to the left of the target at the end of the trial.

Figure 2.3 outlines the results for the HE and head orientation for the 3 study groups during the goal-directed locomotion task. A significant three-way interaction of Group x Condition x Target Location was observed ($F(8, N = 45) = 2.16, p = 0.03$). USN+ individuals displayed significantly larger HEs compared to USN- and HCs for the **left** target location (-15°) in the *actual* ($p = 0.0012$, large effect size, $r = 0.64$ (vs. USN-); $p = 0.0039$, large effect size, $r = 0.57$ (vs. HC)) and in the *remembered* target conditions ($p < 0.0001$, large effect size, $r = 0.61$ (vs. USN-); $p = 0.0012$, large effect size, $r = 0.58$ (vs. HC)), but not the *shifting* condition. USN+ individuals further displayed significantly larger HEs compared to USN- and HCs for the **right** target location (+15°) in the *actual* ($p = 0.0115$, large effect size, $r = 0.78$ (vs. USN-); $p = 0.03$, medium effect size, $r = 0.30$ (vs. HC)) and in the *remembered* target conditions ($p = 0.0452$, large effect size, $r = 0.69$ (vs. USN-); $p = 0.01$, large effect size, $r = 0.36$ (vs. HC)), but not the *shifting* condition.

Within USN+ group only, larger HEs were found for *remembered* vs. *actual*; and for *remembered* vs. *shifting* conditions for the **left** (-15°) target ($p = 0.02$; 0.01 , medium effect size, $r = 0.54$; 0.36 respectively). No significant differences in HE for any target locations were found between USN- and HCs. Identical findings compared to HEs were observed for MLD.

For head orientation, the three-way interaction of Group x Condition x Target Location was found to be not significant ($F(6, N = 45) = 1.59, p = 0.13$). Nonetheless, a significant Group effect was observed ($F(2, N = 45) = 3.64, p = 0.0397$), where USN+ participants showed greater variability on head orientation compared to HC individuals ($t = 2.67, p = 0.0127$), but not with respect to USN- individuals. Likewise, on Figure 2.3 Panel B, we can note the larger variability in the USN+ group. Possibly, for those individuals, more head orientation readjustment is needed to compensate for the lack of walking trajectory adjustments at the endpoint when aligning with the target.

As further illustrated in Figure 2.3, most USN+ individuals undershot the left target located on the neglected side (13 to 14 out of 15 individuals, depending on the condition). A large variability, however, was observed across USN+ participants when walking to the right located targets: approximately 50% of participants consistently overshot the target by ending on its right side, whereas the others undershot the target by ending on its left side. Further analyses showed that those who overshot the right/non-neglected target mostly had more severe egocentric USN (2.4 ± 1.3 vs. 1.4 ± 2.4 , $p < 0.05$), whereas those who undershot that same target presented mostly with allocentric USN (7.8 ± 2.4 vs. 2.4 ± 1.3 $p < 0.05$). The two groups were found to be statistically comparable in terms of the age, chronicity, lower extremities motor function recovery, walking speed, MLD error and HE to all target locations and in all task conditions ($p > 0.05$).

Results for the onset of reorientation strategy during the shifting condition for the left (-15°) and right ($+15^\circ$) target are shown in Figure 2.4. A group effect was found to be significant for the left and right shifting targets ($F(2, N = 45) = 12.72/5.53$, $p < 0.05$), where the USN+ group demonstrated greater latencies in their reorientation strategy compared to USN- and HC ($p < 0.05$) groups when walking to the left and to the right shifting target. No significant differences in onset of reorientation strategy was found between USN- and HC participants.

2.5.3 Relationships and sensitivity analysis

Correlation analyses were performed between USN clinical tests and goal-directed locomotion performance when heading towards to left target in the remembered condition (HE), which was the condition that showed the largest alteration in the USN+ individuals. Significant but negligible to low magnitude ($p < 0.05$) correlations were found between the HE outcome and LBT/SCT in near space ($r = 0.42/r = -0.34$), SCT in far space ($r = -0.30$), and SCT near/far time performances ($r = 0.28/r = 0.26$), indicating that a poor performance on USN tests was only *somewhat* associated with a poor performance on the goal-directed locomotion task in the remembered condition.

Given that the results of the LBT in the near space presented with the highest correlation coefficient, they were used in a forward stepwise regression analysis, along with walking speed as independent variables to estimate their effects on the depending variable: endpoint HE to the left target (-15°) in remembered condition (Table 2.3). Walking speed was added to the model as

it was found to be significantly different in USN+ vs. USN- and HCs as well as based on previous reports suggesting its effects on goal-directed locomotion in USN (e.g. [71, 77]). Results indicated that LBT in the near space together with walking speed explained only 34.3% of the variance of endpoint HE to the left target (-15°) in remembered condition ($R^2=0.34$, $F(2, 27) = 7.05$, $p=0.003$). Further, the LBT in near space, and not walking speed, significantly predicted endpoint HE to left (-15°) target in the remembered condition ($\beta = 1.15$, $p=0.001$).

Single case analyses for single USN+ participants vs. USN- group, as well as for single USN- participant vs. HC group were also performed (Table 2.4) for two outcomes that were found to be significantly affected in USN+ vs. other two study groups: HE in the actual and remembered conditions. An interesting finding was that the locomotor task in the actual and in the remembered condition allowed the detection of worse performances in 3 out of 5 individuals with history of USN (S3, S4, S5) compared to USN- group ($p<0.05$) and in 1 (S18) out of 15 USN- participants vs. the HC group ($p<0.05$).

2.6 DISCUSSION

This hypothesis-driven study aimed to describe the effect of USN on goal-directed locomotion abilities in different perceptual-cognitive conditions that tap into functional activities demands. The main findings indicated that, firstly, post-stroke USN affected goal-directed locomotion, but task condition influenced presentation of the deficit. Second, post-stroke USN altered behavior in a larger visual spectrum than initially anticipated: mainly, its severity in near space was associated with observed deficits. These deficits could not be solely described by USN and a decrease in walking speed; indeed, they likely involved deficits in underlying visual-perceptual abilities. Finally, goal-directed locomotion could potentially unveil USN related deficits otherwise left undetected by traditional methods.

Post-stroke USN affects goal-directed locomotion, but task condition influences presentation of deficits

Present findings revealed that goal-directed locomotion in visually and memory-guided task conditions was affected by post-stroke USN, as shown by USN+ participants displaying greater end-point accuracy errors for left and right sided targets in both the *actual* and *remembered* conditions vs. the other two groups. The larger end-point accuracy errors for the memory-guided

condition are in accordance with previous findings reporting that USN impacts on near space memory-guided/delayed type of movements (reviewed in [65]) and with a body of work evidencing spatial memory deficits in individuals with post-stroke USN [168, 208, 209]. Visually-guided movement performed with the upper extremity in the near space, however, were reported to be unaffected in post-stroke USN (reviewed in [65]). Nonetheless, the altered goal-directed walking performance in the visually-guided condition (*actual*) in the present study does align with our initial stated hypothesis and existing literature on goal-directed walking (e.g. [201]). This apparent discrepancy between goal-directed walking vs. reaching/pointing performance could be explained by the fact that the former but not the latter involves self-motion and thus relies on the perception of optic flow which may be affected in post-stroke USN [87, 88]).

For the shifting condition, our results showed delayed onset of reorientation strategy but preserved endpoint accuracy in goal-directed walking performance among USN+ individuals. The delayed onset during the shifting condition is in line with Rossit and colleagues' work on reaching who observed that their participants with post-stroke USN, as compared to USN- individuals, were slower in the adjustment of arm movement to a left target jump in a task where the target could suddenly change its location from the middle to a right or left location [234]. This latency in the correction of movement could partly be explained by impairments in motor initiation that can co-occur with post-stroke USN (e.g. [95]). The perceptual bias accompanying post-stroke USN could also account for the delay in the processing of the visual information and its ensuing use by the motor regions to act accordingly. Moreover, the results for the shifting condition in the present study are in line with previous research on representational updating (i.e. building mental models of the environmental settings and update these when environmental features are modified) that were conducted in near-space exploration [210], supporting our initially stated hypothesis and showing for the first time that representational updating may also be affected in far-space exploration.

As for the absence of group effects for end-point accuracy measures in the *shifting*, as opposed to *actual* condition, we propose that the event of target shift during the *shifting* condition offered an additional visuospatial cue to the participant (i.e. target lateral jump) and a possible position priming effect (i.e. where the participant used an implicit memory effect, in which the exposure

to the middle target influenced the subsequent response to the shifting target). However, in the *actual* condition, as the target remained stationary and no visuospatial cues were presented, individuals with post-stroke USN demonstrated alteration in behavior related to end-point accuracy measures, as they needed to remain focused on the same target position over a longer period of time. Thus, this possibly required greater sustained attention resources.

Post-stroke USN alters a larger visual spectrum than initially anticipated: evidence of lateralized and non-lateralized deficits

We further found that USN impacted goal-directed locomotion on a wider visual space spectrum than initially hypothesized. Our study evidenced, for the first time, that individuals with post-stroke USN demonstrated performance alterations in goal-directed locomotion towards the left/ “neglected” as well as right/ “non-neglected” target in end-point accuracy (actual and remembered condition) and temporal outcomes (shifting condition). Non-spatial deficits such as decrease level of arousal and alertness, sustained attention, and selective and attentional capacity in individuals with post-stroke USN could have contributed to these findings. These non-spatial deficits were reported to be strong predictors of persistent neglect in comparison to spatially lateralized deficits, and were found to exacerbate USN severity and ensuing functional disability (reviewed in [235]). For instance, sustained attention was reported to be affected in patients with post-stroke USN, causing difficulty in attending to spatial locations over a sustained period of time [161]. Similarly, multiple studies showed USN-related deficits in speeded or time-related selective attention [100, 162, 163, 236, 237]. In relation to that, a reduction in overall attentional capacity in post-stroke USN was evidenced using dual-tasking paradigms (e.g. [166] [105]). Together, these non-spatial deficits could account for the observed alterations in goal-directed walking performance in both visual hemispaces.

Associations with near vs. far space and direction of deviation

The displacement pattern noted among USN+ participants is analogous to those found by Berti et al. (2002) [61], where the walking trajectories to a far space target were not corrected as the patient was approaching a far-space target. The patients thus followed a path that was related to the first computation of space carried out at the starting point and failed to remap and readjust the heading direction. Similarly, and as opposed to our initially stated hypothesis with respect to far space USN implication, we found that solely the LBT in the *near* space significantly

predicted endpoint accuracy to left located target in the remembered condition, and to a greater extent than other clinical tests. However, we determined that the LBT in *near* space and walking speed could only explain nearly a third of the variance of goal-directed walking abilities. This finding could indicate that other factors (e.g. executive function [238] and higher order visual perceptual abilities, such as optic flow perception [239, 240]) could be at cause.

Moreover, our results add to the growing body of literature showing walking trajectories divergences as a distinct feature of individuals with post-stroke USN, while potentially explaining discrepant results as to the actual side of deviation [61, 72, 201, 204]. Specifically, while most individuals with USN undershot the left target located in the neglected hemifield, some of them overshot and others undershot the right target located in the non-neglect hemifield. Participants who overshot the right target were found to have more egocentric type of USN compared to those who were undershot that same target. We can speculate that given their “egocentric” type of USN, the perception of the midline with respect to self is “shifted” rightwards; thus, those individuals tend to overshoot and go further right the middle and right targets to compensate for that shift. Understanding the impact of USN on underlying visual processing skills (e.g. optic flow) could provide further insight into the causes of the behavior and the observed differences across individuals.

Goal-directed locomotion may reveal “dormant” USN deficits left undetected by traditional methods

The performance to the left target (-15°) in the actual and the remembered conditions allowed detecting deficits in 3 out of 5 participants with “recovered” USN as per the conventional paper-and-pencil tests (i.e. having a history of USN) and one individual of the USN- group, supporting the observation that conventional USN assessment tools may fail to predict performance in visually-guided functional tasks [33, 203, 239, 241]. This finding suggests that although individuals with “recovered” (or undiagnosed) USN may perform within the norms in a static, 2-D environments, perhaps their compensatory strategies fall short and deficits emerge when these individuals are exposed to a moving 3-D environment and performing a more complex, functional task. It can be speculated that a real environment, more complex than the one used in this experiment, would add even greater demands on the perceptual and cognitive resources, leading to the difficulties in performing self-care and instrumental activities so often encountered

by individuals with post-stroke USN in the chronic phase [242]. Our results warrant for development of novel, more sensitive evaluation methods that could potentially incorporate the use of VR and tasks requiring mobility.

Limitations and conclusion

In the present study, we did not measure eye movements which could have offered valuable information on gaze shifts, spatial fixations and re-fixations impairments underlying USN. Also, only participants with left USN were included, limiting findings' generalizability. Furthermore, some of the observed alterations could be a result of sensorimotor post-stroke deficits in gait, balance and/or postural control. This limitation was addressed to the most possible extent by including a USN- comparison group. Nevertheless, to assess the specific effects of USN on mobility in the absence of its indirect and deleterious sensorimotor effects, a complementary assessment using a joystick-driven experiment performed while seated that minimizes gait, balance and postural control demands can be used (e.g. [243]).

In conclusion, we demonstrated that goal-directed locomotion in VR is affected by post-stroke USN in different perceptual-cognitive task conditions that are visually and memory-guided (end-point accuracy measures) and that involve representational updating (temporal measure) in both visual hemispaces. Factors such as neglect severity and walking capacity explain only a fraction of the variance in goal-directed walking performance, suggesting the involvement of other factors (e.g. deficits in executive functioning and/or higher order visual perceptual abilities). We further suggest that goal-directed walking performance is potentially a sensitive method to detect “dormant” USN related deficits that are otherwise left undetected using conventional clinical assessments.

Table 2.1 Descriptive variables of study groups

Participant	Sex (M/F)	Age (years)	Stroke Chronicity (years)	Type of Stroke	Stroke Location	10 MWT Fast/Comfortable (m/s)	CMSA Leg/Foot	RMI	
USN+ (n=15)									
1	M	53.5	4.1	Ischemic	P-T	1.5/1.0	6/6	14	
2	M	72.3	2.7	Ischemic	Sylvian	1.2/0.9	6/6	13	
3	M	45.7	1.6	Hemorrhagic	P	2.1/1.5	7/7	15	
4	M	57.2	3.5	Hemorrhagic	P-T	1.7/1.4	7/7	14	
5	M	69.2	1.3	Ischemic	P-O	1.7/1.1	7/6	14	
6	M	51.5	1.6	Hemorrhagic	P-T	1.8/1.3	7/7	15	
7	M	54.3	0.8	Ischemic	Periventricular and cerebral peduncle	1.3/0.5	6/6	14	
8	F	69.0	0.9	Hemorrhagic	Subarachnoid hemorrhage grade 3, common right artery	1.6/1.2	7/7	15	
9	M	67.7	1.3	Ischemic	Pontocerebellar fibers	2.1/1.4	7/7	15	
10	F	50.8	2.5	Ischemic	P-T	0.7/0.6	5/5	12	
11	M	61.6	0.9	Ischemic	P-O	1.5/1.2	6/6	15	
12	M	73.1	0.3	Ischemic	P-O + midline shift	1.5/1.2	6/6	14	
13	M	67.6	1.5	Ischemic	F-P	0.9/0.7	6/6	13	
14	M	53.7	0.9	Ischemic	F-T-Ins	0.3/0.3	5/1	10	
15	F	56.5	1.3	Ischemic	Sylvian	0.3/0.3	6/5†	12	
Mean ± SD									
Range (-)		12:3	60.2±8.8	1.6±1.0	11:4	NA	1.3±0.5 / 0.9±0.4	5-7 / 1-7	10-15
Ratio (:)									
USN- (n=15)									
16	M	50.6	0.5	Ischemic	P-O	1.6/1.3	7/7	15	
17	F	81.1	1.7	Ischemic	F-P	1.3/1.0	7/7	14	
18	F	43.0	1.7	Ischemic	Globus pallidus, putamen, anterior limb of internal capsule, caudate nucleus, cortical F-P-T	1.2/1.0	7/7	15	
19	M	58.0	1.4	Ischemic	Lateral medulla	2.0/1.6	6/6	15	
20	M	57.0	0.6	Ischemic	Sylvian: corona radiata, internal capsule, subcortical center	1.9/1.2	7/7	15	
21	M	40.8	4.0	Hemorrhagic	Basal ganglia and external capsule	1.6/1.2	6/6	14	
22	M	68.2	8.8	Ischemic	MCA territory	1.4/1.1	6/6	15	
23	M	51.5	1.3	Ischemic	Cerebellar, right lateral medullary	1.9/1.5	7/7	15	
24	M	54.0	1.2	Ischemic	Internal capsule, globus pallidus, lacunar corona radiata, F	1.9/1.5	7/7	15	
25	M	75.5	0.8	Ischemic	F + MCA territory	1.5/1.1	7/7	15	
26	M	46.7	1.1	Ischemic	Sylvian	1.1/0.9	7/7	15	

27	M	52.1	2.3	Ischemic	Posterior limb of right internal capsule	2.3/1.3	7/7	15
28	M	73.8	0.7	Ischemic	Internal capsule	1.5/1.1	7/7	14
29	M	77.3	2.9	Ischemic	MCA territory	1.3/1.0	7/6	15
30	M	48.3	1.3	Hemorrhagic	Brainstem, periaqueductal	1.9/1.8	7/7	15
Mean ± SD								
Range (-)	13:2	58.5±13.2	2.0±2.1	13:2	NA	1.6±0.3 / 1.2±0.2	6-7 / 6-7	14-15
Ratio (:)								
HC (n=15)								
Mean ± SD								
Range (-)	7:8	61.0±11.3	NA	NA	NA	2.1±1.0 / 1.4±0.3	NA	NA
Ratio (:)								

Table 2.1 Descriptive variables of study groups. Unilateral spatial neglect (USN); Chedoke McMaster Stroke Assessment (CMSA); Standard Deviation (SD); Frontal (F); Parietal (P); Middle cerebral artery (MCA); Temporal (T); Occipital (O); Insular (Ins); 10 Meter Walk Test (10 MWT); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Healthy Controls (HC); Not applicable (N/A); Rivermead Mobility Index (RMI); † use of walker during goal-directed locomotor experiments.

Table 2.2 USN descriptive variables

Participant	LBT near deviation (cm)	LBT near deviation (%)	LBT far deviation (cm)	LBT far deviation (%)	SCT near	SCT near time (min)	SCT far	SCT far time (min)	AP total	AP time (min)	AP allocentric	AP egocentric	USN type	USN severity
USN+ (n=15)														
1	0.5	3.5	3.1	3.1	1.0	2.1	1.0	1.4	0.92	2.5	0	1	Hx	Hx
2	0.3	2.2	2.0	2.0	1.0	1.5	1.0	1.3	0.92	2.3	0	2	Hx	Hx
3	0.2	1.6	2.0	1.9	1.0	2.1	1.0	2.1	0.98	3.4	0	1	Hx	Hx
4	0.4	2.7	1.6	1.6	1.0	1.2	1.0	1.0	0.98	2.2	0	1	Hx	Hx
5	0.5	3.8	2.2	2.2	1.0	1.5	1.0	2.1	1	3.3	0	0	Hx	Hx
Mean ± SD	0.4±0.1	2.8±0.9	2.2±0.6	2.2±0.6	1.0±0.0	1.7±0.4 *	1.0±0.0	1.6±0.5	0.9±0.0	2.6±0.6*	0.0±0.0	1.0±0.7	NA	NA
Range (-)	(0.2-0.5)	(1.6-3.8)	(1.6-3.1)	(1.6-3.1)	(1.0-1.0)	(1.2-2.1)	(1.0-1.0)	(1.0-2.1)	(0.2-0.98)	(2.2-3.4)	(0-0)	(1-2)		
6	1.3	9.3	12.2	12.1	0.9	1.6	1.0	1.2	0.90	4.3	6	0	Far > near, allocentric	Mild
7	0.2	1.7	2.0	2.0	1.0	1.2	1.0	1.1	0.92	1.3	0	4	Near, egocentric	Mild
8	1.2	8.4	3.6	3.5	1.0	1.1	1.0	1.3	0.88	1.3	0	4	Near, egocentric	Mild
9	2.6	18.2	21.0	20.8	1.0	2.0	1.0	2.1	1	3.3	1	0	Far > near	Mild
10	0.8	5.9	3.7	3.6	1.0	1.2	1.0	1.1	1	3.2	3	0	Near, allocentric	Mild
11	1.1	7.8	4.4	4.3	1.0	2.5	0.9	4.5	0.88	8.1	10	2	Near, allocentric	Mild
12	2.2	15.3	17.9	17.7	0.9	3.2	0.9	2.5	0.94	14.6	7	3	Far > near, allocentric, egocentric	Moderate
13	1.2	8.6	13.1	13.0	1.0	1.5	1.0	2.2	0.78	4.4	3	2	Near > far, allocentric	Moderate
14	0.4	2.8	5.3	5.3	0.6	1.5	0.7	1.4	0.76	3.0	7	1	Far > near, allocentric	Severe
15	1.1	7.8	6.6	6.6	0.7	2.0	0.9	2.3	0.82	3.5	35	7	Near > far, allocentric, egocentric	Severe
Mean ± SD	0.9 ± 0.7	6.6 ± 4.9	6.7 ± 6.2	6.6 ± 6.2	0.9±0.11	1.7 ± 0.5	0.9 ± 0.09	1.8 ± 0.9	0.9 ± 0.08	4.0 ± 3.3	4.8 ± 8.9	1.8 ± 1.9		
Range (-)	0.2-2.6	1.7-18.2	1.6-21.0	1.6-20.8	0.7-1.0	1.1-3.2	0.7-1.0	1.0-4.5	0.7-1.0	1.2-14.6	0-35	0-7	NA	NA
SI-SI5	***	***	**	**	**	**	*	**	**	**	**	**		
USN- (n=15)														
Mean ± SD	0.2 ± 0.1	1.4 ± 0.8	2.0 ± 0.6	2.0 ± 0.8	0.9±0.0	1.1 ± 0.4	0.9±0.0	1.1 ± 0.6	0.9±0.0	1.9 ± 0.6	0.06±0.2	0.6±0.7	NA	NA
Range (-)	0.03-0.4	0.2-3.2	0.9-3.5	1.2-4.3	0.9-1.0	0.4-2.3	0.9-1.0	0.3-3.1	0.9-1.0	1.1-3.5	0-1	0-2		

Table 2.2. USN descriptive variables. Unilateral spatial neglect (USN); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Not applicable (NA); Line bisection test (LBT); Star Cancellation Test (SCT); Apples Test (AP); minutes (min); History of USN: Hx; Standard deviation (SD); Numbers in bold correspond to values above or below (where applicable) cut-off values. *, **, *** p-value <0.05, 0.01, 0.001, respectively; USN severity is delineated by shades ranging from light (those with history of USN) to dark grey (those with severe USN).

Table 2.3 Regression analysis results

Dependent variable: endpoint HE to left target (-15°) in remembered condition				
$R^2=0.34, F(2, 27) = 7.05, p = 0.003$				
<i>Variable</i>	β	<i>Pr > t </i>	<i>95% CI</i>	
Intercept	1.49	**	0.73	2.25
LBT in near space (cm)	1.15	**	0.50	1.80
10MWT (comfortable speed, m/s)	-0.15	NS	-0.74	0.44
				Adj $R^2 = 0.29$

Table 2.3 Regression analysis with endpoint heading error to left target (-15°) in remembered condition as the dependent variable; parameter estimates (β); confidence interval (*CI*); heading error (HE); not significant (NS); Line Bisection Test (LBT); *, **, *** *p*-value <0.05, 0.01, 0.001, respectively.

Table 2.4 Single Case Analysis

Outcome	HE to LEFT target (-15°)			HE to LEFT target (-15°)		
	ACTUAL Condition			REMEMBERED Condition		
Subject	<i>t</i> -value	Z score (effect size)	95% CI	<i>t</i> -value	Z score (effect size)	95% CI
USN+ group vs. USN- group						
S1 (Hx)	1.00	1.03	0.38-1.65	0.71	0.73	0.15-1.29
S2 (Hx)	-1.23	-1.27	-1.95- -0.5	0.78	0.81	0.21-1.38
S3 (Hx)	1.46	1.51	0.74-2.24	3.14**	3.25	1.94-4.53
S4 (Hx)	3.24**	3.35	2.01-4.67	1.90*	1.97	1.07-2.84
S5 (Hx)	5.05***	5.22	3.23-7.19	4.58** *	4.73	2.92-6.5
S6	0.40	0.41	-0.12-0.93	0.11	0.11	-0.39-0.62
S7	2.63**	2.71	1.59-3.82	1.84*	1.90	1.03-2.75
S8	1.95*	2.02	1.11-2.90	1.53*	1.58	0.80-2.34
S9	3.25**	3.35	2.02-4.68	8.78**	9.07	5.70-12.42
S10	2.50**	2.58	1.49-3.64	2.60**	2.68	1.57-3.78
S11	3.25**	3.35	2.02-4.68	0.71	0.73	0.15-1.29
S12	4.50***	4.65	2.86-6.42	5.88** *	6.08	3.79-8.35
S13	2.10**	2.17	1.22-3.11	1.16	1.19	0.51-1.85
S14	1.28	1.32	0.61-2.01	0.71	0.73	0.15-1.29
S15	2.83**	2.92	1.73-4.09	2.48**	2.56	1.49-3.62
USN- group vs. HC group						
S16	0.15	0.16	-0.35-0.66	-0.72	-0.75	-1.31- -0.16
S17	0.65	0.67	0.10-1.22	-0.58	-0.60	-1.15- -0.04
S18	3.25**	3.35	2.01-4.67	1.60**	1.66	0.85- 2.44
S19	0.25	0.25	-0.26- 0.76	-0.04	-0.04	-0.55-0.46
S20	0.86	0.89	0.28-1.48	1.20	1.24	0.54-1.91
S21	-0.43	-0.44	-0.96-0.09	-0.84	-0.87	-1.46- -0.26
S22	0.33	0.34	-0.18-0.86	0.07	0.08	-0.42-0.58
S23	0.41	0.42	-0.11-0.94	0.28	0.29	-0.22-0.80
S24	-0.73	-0.76	-1.32- -0.1	1.20	1.24	0.54-1.91
S25	-1.39	-1.43	-2.1- -0.69	0.41	0.43	-0.10-0.95
S26	-1.12	-1.15	-1.8- -0.48	-1.13	-1.16	-1.82- -0.49
S27	0.73	0.74	0.16-1.31	0.47	0.48	-0.05-1.01
S28	-1.31	-1.35	-2.0- -0.63	0.10	0.11	-0.39-0.61
S29	-0.36	-0.37	-0.89-0.15	0.12	0.12	-0.38-0.63
S30	-1.00	-1.04	-1.6- -0.39	-0.12	-0.13	-0.63-0.38

Table 2.4 Single-case analysis of single USN+ participants vs. USN- group (as control data); and single USN- participants vs. HC group (as control data) on the performance of locomotor task in the actual and remembered conditions to the left target at -15°. History (Hx); Subject (S); Subjects with post-stroke USN (USN+); Subjects post-stroke without USN (USN-); Healthy controls (HC); Unilateral spatial neglect (USN); Light grey selections represent individual cases whose performance is considerably worse than the comparison group ($p < 0.05$); Star symbols indicate p -value < 0.05 (*), < 0.01 (**), and < 0.001 (***)

Figure 2.1 The VR scene used in the experiment

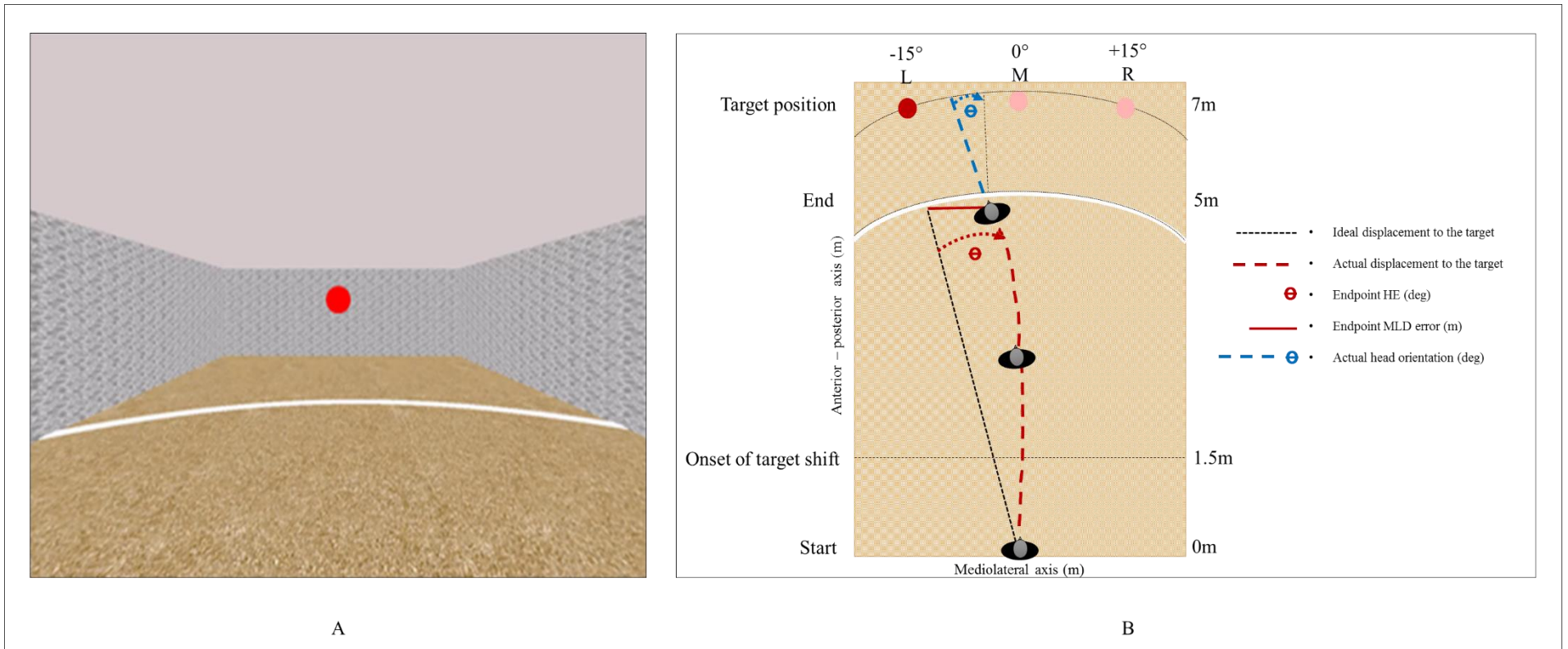


Figure 2.1 A. The VR scene used in the experiment. The target (i.e. red ball) appeared 7 m away from the starting position and at the following 3 possible locations: $\pm 15^\circ$, 0° ; scene viewed through a helmet mounted display (centered target location illustrated). Walking trials were performed while immersed in the VR scene under actual, remembered and shifting target conditions B. Bird-eye view of the VR scene illustrating the start position (0m), the 3 possible target locations (7m radius from start position), onset distance for target shift in the shifting target condition (1.5m) and endpoint position (5 m radius from start position). Outcomes measures of heading error (HE) and endpoint mediolateral displacement (MLD) error and head orientation are described for a walking trial to the left target (-15°).

Figure 2.2 Displacement traces

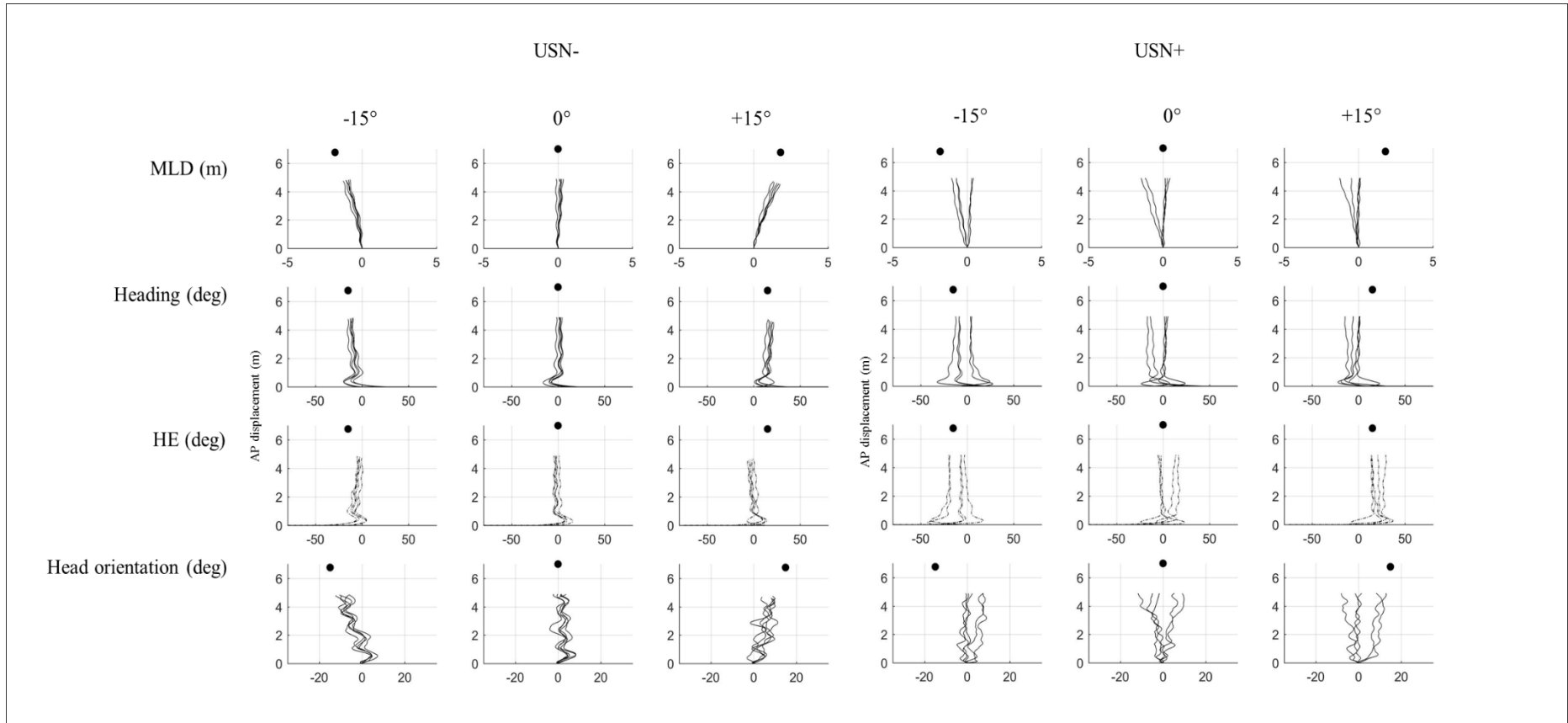


Figure 2.2 Birds eye view of mediolateral displacement (MLD – 1st row), heading (2nd row), heading error (HE – 3rd row), and head orientation (4th row) traces, as performed by one individual without post-stroke neglect (USN-) and one individual with post-stroke neglect (USN+) for the 3 target positions at -15°, 0°, and +15° (left, middle, right) in the remembered condition. The anterior-posterior (AP) displacement is on the y-axis. Target position is shown with the black dot.

Figure 2.3 Heading error and head orientation results

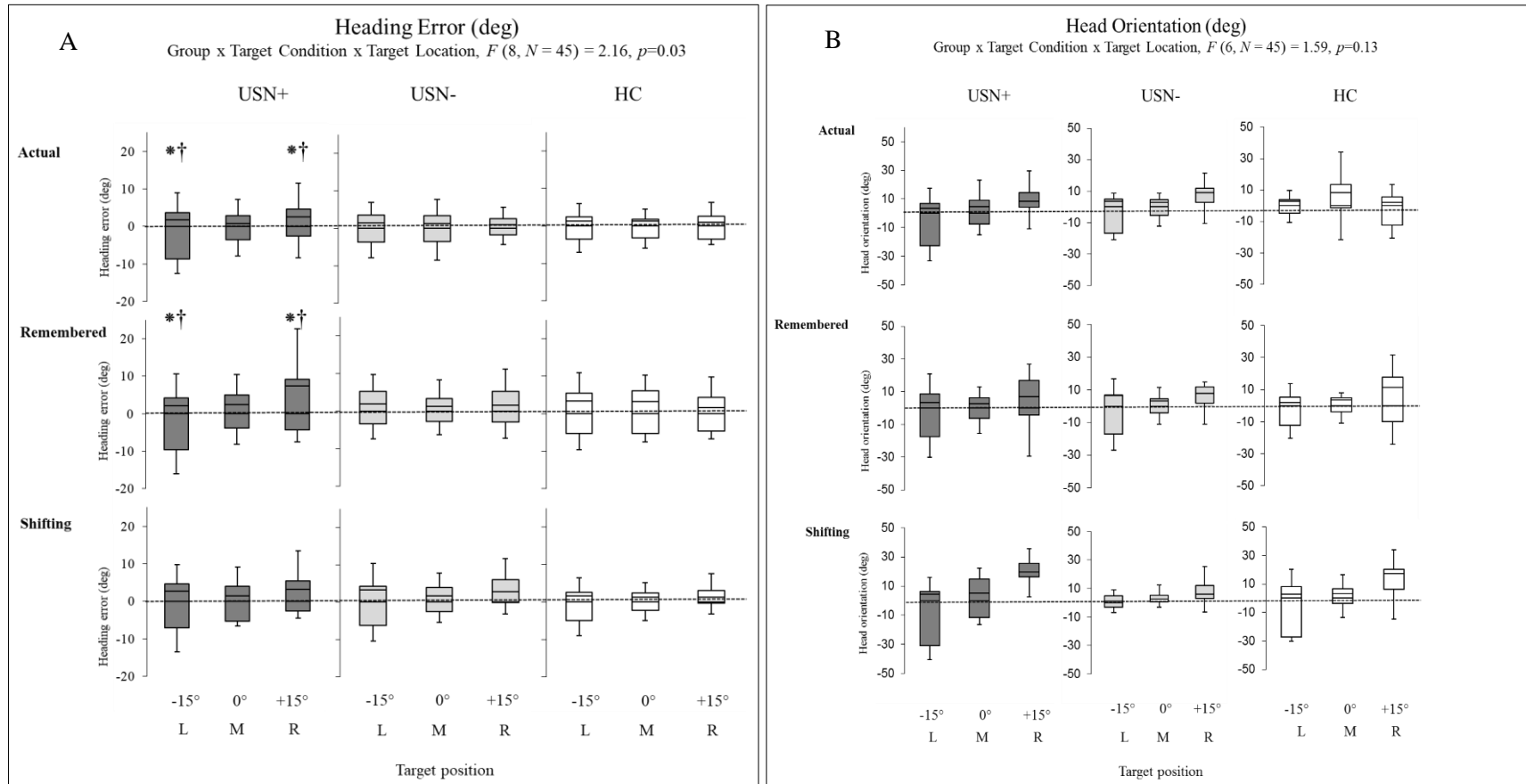


Figure 2.3. Heading error (HE – Panel A) and head orientation results (Panel B) for the 3 study groups in the actual, remembered and shifting target conditions to the three target locations (Left (L) -15° ; Middle (M) 0° ; Right (R) $+15^\circ$). Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). * indicate statistically significant differences between USN+ vs. USN- groups ($p < 0.05$); † indicate statistically significant differences between USN+ vs. HC groups ($p < 0.05$). For HE results, negative values symbolize that the endpoint position is to the *right* of the respective target; whereas positive values symbolize that the endpoint position is to the *left* of the target. For head orientation, negative values symbolize head orientation to the *left* visual field; whereas positive values symbolize head orientation to the *right* visual field.

Figure 2.4 Onset of reorientation result

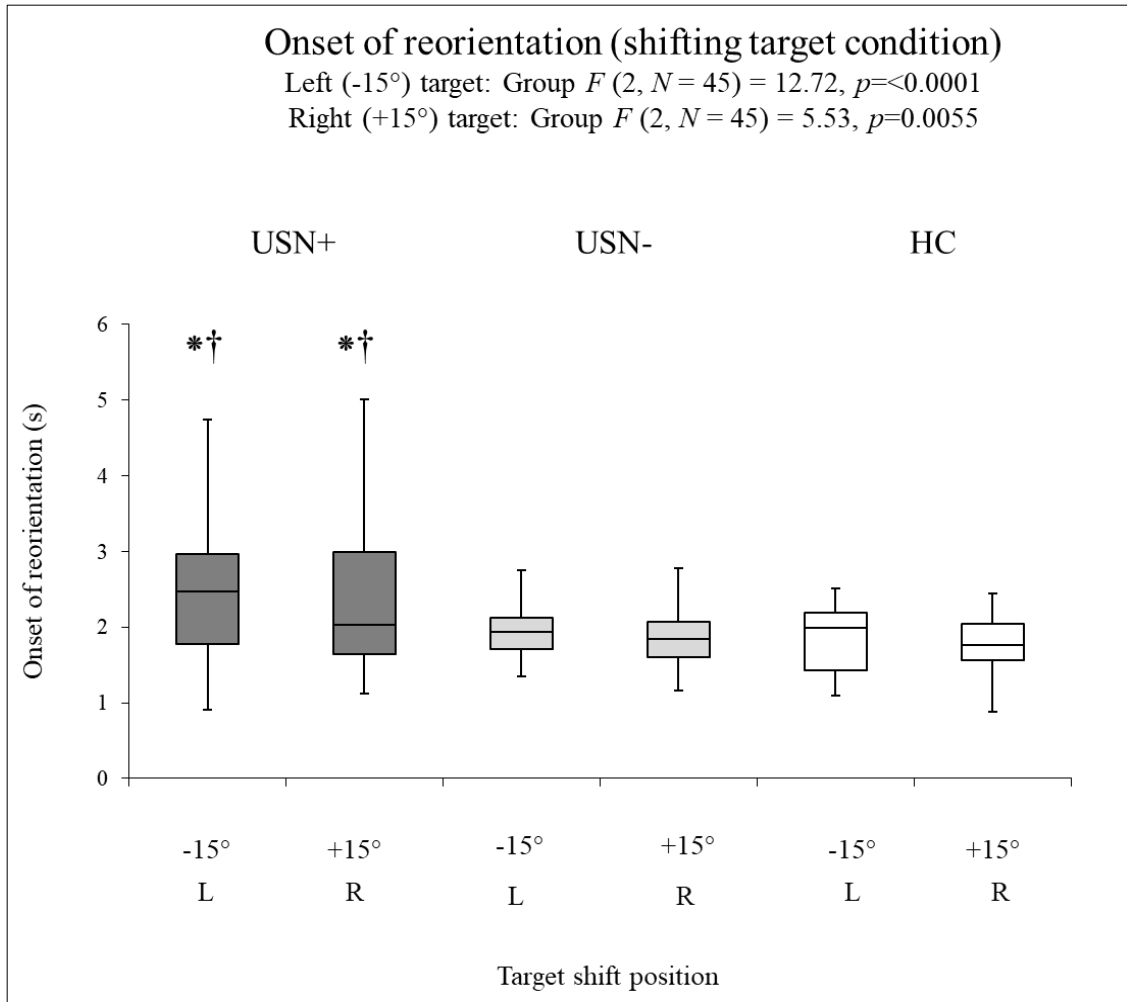


Figure 2.4 Onset of reorientation (s) for the 3 study groups for left (L; -15°) and right (R; +15°) target shifts. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). * indicate statistically significant differences between USN+ vs. USN- groups ($p < 0.05$); † indicate statistically significant differences between USN+ vs. HC groups ($p < 0.05$).

CHAPTER 3

3.1 PREFACE

In **Manuscript №1** we demonstrated that individuals with post-stroke USN show altered goal-directed walking abilities when heading towards left and right located targets in visually-guided, memory-guided conditions (end point accuracy measures) and in a task requiring representational updating capacities (temporal measures) compared to stroke individuals without USN and healthy controls. Given the well-recognized negative impact of USN on walking capacity, however, participants with USN walked considerably slower compared to those without USN, making walking speed a potential confounding factor when comparing the performance of the two groups. Therefore, whether goal-directed walking deficits result from perceptual-attentional deficits caused by USN or are also mediated by post-stroke sensorimotor dysfunctions which affects gait, balance and posture warranted investigation.

To further our understanding of the role of post-stroke USN in the control of goal-directed walking, in the following **Manuscript №2** we proposed to examine USN effects in a joystick-driven goal-directed navigation task which is analogous to the goal-directed walking tested in the previous project. The main premise behind this paradigm is that the use of a joystick for navigation with the non-paretic hand, performed in sitting, minimizes the biomechanical demands of locomotion and its concurrent sensorimotor aspects. Thus, it permits to essentially examine the role of attentional-perceptual abilities involved by eliminating potential confounding factors related to gait capacity, such as walking speed. In addition, the proposed joystick-driven seated task represents a more feasible mean to assess certain aspects of mobility in post-stroke individuals in comparison to a goal-directed locomotion task, that requires more resources in terms of equipment, space/setup and time.

Chapter 3 of this PhD dissertation addresses **general objective 2** and **specific objectives 2.2** and **2.3** of my PhD research agenda. This chapter includes **Manuscript №2** of this dissertation, entitled “*Virtual reality-based navigation and detection tasks reveal deficits in ventral and dorsal stream processing along with lateralized and non-lateralized performance alterations in post-stroke unilateral spatial neglect*”.

MANUSCRIPT № 2

VIRTUAL REALITY-BASED NAVIGATION AND DETECTION TASKS REVEAL DEFICITS IN VENTRAL AND DORSAL STREAM PROCESSING ALONG WITH LATERALIZED AND NON-LATERALIZED PERFORMANCE ALTERATIONS IN POST-STROKE UNILATERAL SPATIAL NEGLECT

Tatiana OGOURTSOVA^{1,2*}, Philippe S. ARCHAMBAULT^{1,2}, Anouk LAMONTAGNE^{1,2}

¹School of Physical and Occupational Therapy,
McGill University,
3654 Promenade Sir-William-Osler
Montreal, Quebec, Canada
H3G 1Y5

²Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital,
Site of Centre for interdisciplinary Research
in Rehabilitation of Greater Montreal
3205 Place Alton-Goldbloom
Laval, Quebec, Canada
H7V 1R2

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DECLARATION OF INTEREST

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3.1 ABSTRACT

Background: Unilateral spatial neglect (USN), a highly prevalent and disabling post-stroke impairment, has been shown to affect the recovery of locomotor and navigation skills needed for community mobility. We recently evidenced that USN alters goal-directed locomotion in conditions of different cognitive/perceptual demands. However, participants with USN were also found to be slower walkers than stroke participants without USN. Whether these alterations are influenced purely by perceptual-attentional USN deficits or result from associated sensorimotor dysfunctions, such as decrease in walking speed, remains to be determined. **Objectives:** Analogous to the previously used goal-directed locomotor paradigm, a seated, joystick-driven navigation experiment, minimizing locomotor demands, was employed to investigate that important nuance in individuals with and without post-stroke USN (USN+ and USN-, respectively) and healthy controls (HC). **Methods:** Participants (n=15 per group) performed a seated, joystick-driven navigation and detection time task to targets 7 m away at 0°, ±15°/30° in actual (visually-guided), remembered (memory-guided) and shifting (visually-guided with representational updating components) conditions while immersed in 3D virtual reality environment. **Results:** Greater end-point mediolateral errors to left-sided targets (remembered and shifting conditions) and overall lengthier onsets in reorientation strategy (shifting condition) were found for USN+ vs. USN- and vs. HC ($p<0.05$). USN+ individuals mostly overshoot left targets (-15°/-30°). Greater delays in detection time for target locations across the visual spectrum (left, middle and right) were found in USN+ vs. USN- and HC groups ($p<0.05$). **Conclusion:** Present study shows lateralized and non-lateralized deficits in object detection. Navigation behavior alterations are present in memory-guided condition and in condition requiring representational updating, even during a task that minimized locomotor demands. Thus, USN-related attentional-perceptual deficits alter navigation abilities, independently of post-stroke locomotor deficits and task condition. Results provide important evidence into the mechanism of post-stroke neglect. The navigation and detection paradigm could be considered in the design and development of sensitive and functional assessment methods for neglect; thereby addressing the drawbacks of currently used traditional paper-and-pencil tools.

Keywords: stroke, hemineglect, navigation, detection time, virtual reality.

3.2 BACKGROUND

Unilateral spatial neglect (USN) is a highly disabling disorder, that is present in at least 30% of all stroke survivors [244] and in nearly 50% of individuals with right hemisphere lesions following a stroke [10]. USN is characterized by a decrease in orientation and/or response time to contralesionally located stimuli [245]. It is known to persist into the chronic stages of stroke recovery, poorly respond to available treatment methods, and significantly contribute to functional deterioration (reviewed in [246]) and reduced quality of life [247] of the affected individuals.

One of the most sought rehabilitation goals among stroke survivors is to regain independent mobility within the community environments [27], as safe and efficient locomotion and/or navigation in space is necessary for numerous self-care and instrumental activities of daily life. Alas, less than 40% of individuals with post-stroke USN regain independent walking abilities [28]. Consequently, it is paramount to investigate the role of spatial cognition on locomotion and navigation in individuals with post-stroke USN, with a general aim to improve rehabilitation practice in that field and ameliorate patient-related health outcomes. Yet, the literature addressing the effects of USN on walking and/or navigation abilities remains limited and necessitates further investigation before practice recommendations can be implemented (e.g. [61, 71-73, 248, 249]). Up to now, studies reported deviations of walking/navigation trajectories in patients with post-stroke USN [34, 61, 71-73, 77], as well as collisions with stationary [34, 73, 77] and moving obstacles [75, 248]. Our team has recently demonstrated that individuals with post-stroke USN vs. stroke individuals without USN show defective goal-directed walking abilities when heading towards left located (contralesional/ “neglected”) and right located (ipsilesional/ “non-neglected”) targets in conditions of variable cognitive/perceptual demands: where the visual target could remain stationary, disappear or shift position during walking. Nevertheless, participants with USN walked considerably slower compared to those without USN, making walking speed a potential confounding factor when comparing the performance of the two groups. Therefore, whether goal-directed walking deficits result from perceptual-attentional deficits caused by USN or are also mediated by post-stroke sensorimotor dysfunctions which affects gait, balance and posture, remains unresolved and warrants investigation. To further our understanding of the role of post-stroke USN in the control of goal-directed walking,

we propose to examine its effects in a joystick-driven goal-directed navigation task which is analogous to the goal-directed walking tested earlier [249]. The main premise behind this paradigm is that the use of a joystick for navigation with the non-paretic hand, performed in sitting, minimizes the biomechanical demands of locomotion and its concurrent sensorimotor aspects. Thus, it permits to essentially examine the role of attentional-perceptual abilities involved by eliminating potential confounding factors related to gait capacity, such as walking speed. In addition, the proposed joystick-driven seated task represents a more feasible approach (to assess certain aspects of mobility in post-stroke individuals in comparison to a goal-directed locomotion task, that requires more resources (in terms of equipment, space/setup and timing). Therefore, the joystick-driven task could potentially be more suitable to be implemented in the clinical setting.

The navigation scene and conditions employed in this study were analogous to a previously conducted goal-directed locomotor experiment [249] and included three conditions: navigation to an actual target (always present and visible to the participant, online condition); navigation to a remembered target (present at first then disappears during navigation, offline condition); and navigation to a shifting target (changes location following forward displacement of the participant, online condition). The primary objective of this study was to estimate the extent to which post-stroke USN affects goal-directed navigation abilities in online and offline conditions. Secondary objectives were to estimate the extent to which post-stroke USN affects target detection abilities, what is the relationship of navigation abilities with measures of detection abilities and clinical measures of USN, and whether the navigation task can detect USN-related deficits that were otherwise left undetected using conventional methods. We hypothesized that post-stroke USN would affect navigation and detection abilities, such that greater end-point accuracy errors, longer re-orientation of navigation trajectories and greater detection times would be observed for the group with USN vs. those without USN and healthy controls, possibly in all conditions. We also hypothesized that clinical USN measures would be minimally associated with navigation/detection outcomes. In addition, we speculated that the navigation task in more cognitively/perceptually demanding conditions (i.e. remembered and shifting) would be sensitive in detecting deficits that were otherwise left undetected using conventional paper and pencil USN assessment tools.

3.3 METHODS

3.3.1 *Participants*

Fifteen individuals (n=15) per group were recruited, tested and analyzed for the study.

Individuals with stroke were included based on the following criteria: (1) presence of a first-time right hemisphere stroke (as per computer tomography (CT) report, neurological examination, and medical chart), (2) with or without left USN (as per one or more of the following tests: Line Bisection Test (LBT) [181], Star Cancellation Test (SCT) [175], and/or Apples Test (APT) [53] on testing, or history of USN as per medical chart); (3) age between 40 and 85 years old; (4) right handedness (as per interview and/or medical chart containing Edinburgh Handedness Inventory scores [213]). Given that participants were also involved in a walking experiment, they were all walking independently with or without a walking aid over a minimal distance of 5 m. Individuals were excluded based on the following criteria: (1) presence of primary visual impairment that impedes normal or corrected-to-normal binocular visual acuity (score $\leq 20/20$ on the Early Treatment Diabetic Retinopathy Study Chart [250]); (2) presence of moderate cognitive impairment (score $\leq 22/30$ the Montreal Cognitive Assessment [251]); (3) presence of a documented visual field deficits (Goldmann's perimetry or computerized equivalent, as per medical chart); and (4) any premorbid neurological and/or orthopedic condition that can impede locomotion. Age-matched (± 5 years) healthy controls were also recruited, following the same inclusion/exclusion criteria (where applicable).

Participants with (USN+) and without (USN-) post-stroke USN were recruited from the inpatient discharge lists of three clinical sites of Centre de Recherche Interdisciplinaire en Réadaptation du Montreal Métropolitain (CRIR), including the Jewish Rehabilitation Hospital (JRH), Centre de Réadaptation Lucie Bruneau and the Institut de Réadaptation Gingras-Lindsay de Montréal. These sites provide inpatient and outpatient post-stroke rehabilitation for patients living in the Greater Montreal area, Quebec, Canada. Healthy controls (HC) were recruited from the research database of the JRH and word-of-mouth using snowball sampling technique. Pre-authorized advertisement in form of wall-mounted notice was also used to recruit participants. All study participants provided their informed consent before enrolling in the study, as approved by the CRIR Institutional Review Board (CRIR-935-0214).

3.3.2 Data Collection

The process of data collection consisted of (1) Clinical USN evaluation followed by the (2) virtual reality (VR) -based goal-directed navigation and detection time tasks. Experiments were carried out in a single session of approximately 30-45 minutes (including set-up time).

Clinical USN evaluation

Apparatus and stimuli: Presence, severity and type of USN were determined using the LBT, SCT, and the APT which all show excellent psychometric properties [53, 223, 252]. The LBT and SCT were repeated in the near and far extrapersonal space, using a procedure previously employed, where participants were positioned 40 cm and 320 cm away from the screen for near and far USN testing, respectively. [61, 224]. Both tests were projected on the screen with appropriate sizes (near space: 21 x 28 cm; far space: 168 x 224 cm) to keep the visual angle of each array and the retinal size image constant during the two testing conditions. Responses were provided with a laser. The APT was presented on a sheet of paper on a steady table, aligned with the participant's midline (i.e. sternum) and fixed on the table with tape to prevent possible shifts. Details pertaining to the full setup of the clinical USN evaluations are described in the previous manuscript on goal-directed locomotion (under review [249]).

Procedure: In the LBT, participants were asked to find the midline of each presented line (n=18), starting from the top line. In the SCT, participants were instructed to find all the small stars (n=52) among the distractors. In the APT, participants were instructed to find all the whole apples (n=50). An absolute mean deviation of more than 6.0 mm and 4.8 cm to the right is indicative of left near-space and far-space USN, respectively. An average percentage of deviation from midline was also computed for near and far-space LBT to estimate the difference in severity between near and far space USN. Scores between 0 and 0.46 are indicative of left near-space USN on the SCT, computed as the number of crossed out small start over the total number of small stars [181]. In the APT, the total number of crossed out complete and incomplete apples was computed, and asymmetry scores for egocentric (i.e. difference between the numbers of complete shape targets crossed out on the right versus left side of the page) and allocentric (i.e. difference between the numbers of incomplete shape targets crossed out with a right and with a left opening) USN were calculated [53]. The overall cutoff of <42/50 is

indicative of near-space USN. Asymmetry cutoff score across the page of <-2 or >2 (difference between right side and left-sided targets cancelled) is indicative of egocentric near-space USN. Asymmetry cutoff score across the cancelled distractors on the page with left vs right sided openings of <-1 or >1 is indicative of allocentric near-space USN. All cancellation tests were timed.

Severity of USN was characterized by a positive result on 1 to 3 (mild), 4 (moderate), and 5 or more (severe) clinical test scores out of 7. This classification was modified from Lindell et al. (2007) for mild (positive result on 1-3) vs. moderate/severe USN (positive result on 4 or more tests) [172] to distinguish moderate vs. severe cases.

Outcomes: Outcomes retained for analysis included: overall USN severity (history, mild, moderate or severe), (2) USN range of space severity (near and/or far-space), and (3) USN spatial representation type (allocentric vs. egocentric). Participants were included in the USN+ group if they had USN on one or several of the aforementioned tests, or if they had a history of USN as per their medical chart.

VR-based goal-directed navigation and detection time tasks

Apparatus and Stimuli: The VR-based navigation and detection tasks were performed while seated and immersed in a 3-D virtual environment (VE) representing a symmetrical and richly-textured room (9 m x 15 m) including a visual display of walls and ceiling (i.e. giving an impression of indoor space with appropriate depth cues [225]). The target, a red ball, was presented 7 m away from the starting position (i.e. far-space) and at the following 5 possible locations: $\pm 15^\circ/30^\circ$, 0° (Figure 3.1A). The target appeared at the same height and size in the visual field to avoid differences in distance perception [226, 227]. The VE scene was created in Softimage XSI®. During the experiments, the real-time CAREN-3™ (Computer Assisted Rehabilitation Environment; Motek BV, Amsterdam) software was employed to control the scene. The viewing media was a helmet mounted display (HMD - NVisor™, NVIS Inc, Reston, VA, USA) with a binocular field of view of 60° diagonal, 30° vertical by 40° horizontal, Extended Graphics Array resolution (1024 x 1280 pixels), refresh frequency of 60 Hz, 1 kilogram in weight, and blocking all peripheral vision with only the VE visible to the participant. Responses were provided with the dominant, non-paretic right hand using a joystick (Attack3™, Logitech, Newark, CA, USA), securely fixed on a table at a comfortable height, adjusted for

each participant. The joystick controlled a pointer (not visible to the participant) that represented the position of the individual in first-person view. The VE scene was viewer-centered and the HMD was not head-tracked, allowing the scene to remain stable despite head rotations. Navigation in the scene, when required, was possible using the joystick in the mediolateral (left/right) planes at constant and pre-set speed of 0.75 m/s, being the average speed of ambulatory stroke population [72].

Procedure:

Goal-directed navigation: Practice trials were performed (n=5-10) prior the actual experiment until the participant felt comfortable in executing the task. For each condition (actual, remembered and shifting), five trials per target location ($\pm 30^\circ \pm 15^\circ, 0^\circ$) were performed, for a total of 75 navigation trials or 25 trials per condition. Condition and target location were randomized. Prior to each trial, a “GET READY” sign appeared. At the end of each navigation trial, a “STOP” sign appeared; following which, the scene was recalibrated to the starting position for the beginning of a new trial. While the target was at 7 m away from the starting position, the navigation trial ended at 5 m of forward displacement, to avoid the cursor hitting the target (Figure 3.1B).

In all conditions, a single target first appeared on the screen for 2000 ms. This was followed by a beep sound, signalling participants to navigate towards the target using the joystick. In the *actual* condition, the target remained visible during movement while in the *remembered* condition, it disappeared after the beep. Finally, in the *shifting* condition, the target remained visible after the beep but following 1.5 m of forward displacement, it could either shift its location to the right or left ($+15^\circ/30^\circ$ or $-15^\circ/30^\circ$) or remain in the middle. If the shift occurred, participants were instructed to re-orient their navigation towards the new target location as soon as possible.

Detection task: The target appeared at the following 5 possible angles ($\pm 30^\circ, \pm 15^\circ, 0^\circ$) with randomized onset times. Participants were instructed to press the front joystick button with their index finger of the non-paretic, dominant, right hand as soon as they perceived the target. Catch trials (n=10 within each condition) lasting 2500 ms, with no target, were introduced to minimize response bias. Five trials per location were performed for total of 75 trials. Target location was randomized between trials.

Outcomes: Outcomes related to the goal-directed navigation and detection tasks included the following: (1) *Endpoint mediolateral displacement (MLD) error*, defined as the difference in meters between the mediolateral position of the target and that of the individual at 5 m of forward displacement; (2) *Direction of trajectory deviation*, defined as the side (left or right) from the target where the individual was located at the end of the trial; (3) *Onset of reorientation strategy* (for shifting condition only), was determined using a variation of the extrapolation method [253], based on the extrapolation of trajectory segments. First, movement trajectory segments before (i.e. control movement) and after (i.e. adjusted movement) the shift were outlined and fitted using linear regression. Following, a line between 15% and 85% of the fitted trajectory was outlined and extrapolated. The onset of reorientation strategy is thus defined by the time at which the target was shifted (i.e. at 1.5 meters of forward displacement) minus the time at which the extrapolated lines for pre- and post-shift crossed each other; and (4) *Detection time*, defined as the time difference between target appearance and its detection by the participant.

3.3.3 Data and Statistical Analyses

All data were recorded at 120 Hz in CAREN-3TM and stored for off-line analyses in Matlab 2016a (The Mathworks, USA). Participants' responses on goal-directed navigation and target detection tasks were averaged across conditions (navigation task) and target locations (navigation and detection tasks), such that mean values could later be compared across groups and between conditions. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc). Significance was accepted at $p \leq 0.05$.

The effects of post-stroke USN, target condition and target location on goal-directed navigation performances were examined using repeated measures mixed-model analysis, with 'Group' [USN+, USN-, HC] as between subject factor x 'Target Condition' [actual vs. remembered vs. shifting] x 'Target Location' [$\pm 15^\circ/30^\circ$, 0°] as within subject factors. In the event of significant 3-way interaction effect of Group x Target Condition x Target Location, post-hoc comparisons of simple effects were elaborated on using previously identified relevant pairwise comparisons and included 1) within USN+/USN-/HC groups comparisons with target condition and target location factors (e.g. responses to -30° target in actual vs. -30° target in remembered condition

within the USN+ group); and 2) between USN+/USN-/HC group comparisons for each angle and condition (e.g. responses to -30° target in actual condition for USN+ vs. USN- groups).

Further, to estimate the effect of post-stroke USN on the delay in re-orientation strategy to the left [-15°/-30° target shift] and to the right [+15°/+30° target shift] sides were examined separately for each side using the repeated-measures mixed-model analysis, with ‘Group’ [USN+ vs. USN- vs. HC] as the between-subject factor.

Following, the effects of USN and target location on detection times were examined using repeated-measures mixed-model analysis, with ‘Group’ [USN+ vs. USN- vs. HC] as a between subject factor x ‘Target Location’ [$\pm 15^\circ/30^\circ, 0^\circ$] as a within subject factor.

Kendall rank correlation coefficients were used to quantify the relationship of goal-directed navigation performances to the left (-30°) target with clinical assessments of neglect within near and far spaces (LBT, SCT, APT) and detection time outcome to the left-sided target (-30°) given that the data was not normally distributed in the USN+ group. The size of the correlation coefficient was interpreted as per established guidelines: very high (0.90-1.00), high (0.70-0.90), moderate (0.50-0.70), low (0.30-0.50) or negligible (0.00-0.30) [231].

To determine whether the navigation task can detect deficits otherwise not identified using traditional tests, single case analyses were used to compare the performance of each participant with history of USN as well as to compare the performance of each USN- participant with respect to the average performance of the HC group. Precisely, the Crawford and Garthwaite (2002) approach (Singlims.exe, University of Aberdeen, Aberdeen, UK) [232], implementing classical methods for comparison of a single case’s score to scores obtained in a control sample, was used. This approach tests whether an individual's score is significantly different from a control or normative sample. Results provide a point estimate of the effect size for the difference between the case and controls with an accompanying 95% confidence interval, and a point and interval estimate of the abnormality of the case's score, where it estimates the percentage of the population that would obtain a lower score.

3.4 RESULTS

Fifteen individuals with post-stroke USN (USN+, n=15, 60.2 ± 8.8 years old, 1.6 ± 1 year post-stroke, 11/15 ischemic stroke, 12 males), fifteen individuals post-stroke without USN (USN-

n=15, 58.5 ± 13.2 years old, 2.0 ± 2.1 years post-stroke, 13/15 ischemic stroke, 13 males), and fifteen age-matched healthy control individuals (HC, n=15, 61.0 ± 11.8 years old) were recruited in the period between December 2014 and March 2016 (Table 2.1). Each participant successfully completed all the experimental trials. Both the USN+ and USN- groups predominantly consisted of male participants and were statistically similar in terms of stroke chronicity. No significant between-group differences were found on all baseline characteristics across the 3 study groups.

3.4.1 USN characteristics

The USN+ group included five (n=5) individuals with history of USN, and ten (n=10) individuals with actual USN on testing (Table 2.2). All USN-related measures, both in the near and far space ($p \leq 0.05$), demonstrated deficits in patients with post-stroke USN. By contrast, none of the USN- individuals scored positive in any of the USN assessments. The deviation percentages on the LBT (near space: 6.6 ± 4.9 ; far space: 6.6 ± 6.2) and laterality indices on the SCT (near space: 0.9 ± 0.11 ; far space: 0.9 ± 0.09) in the USN+ group were also found to be similar between the near and far space ($p = 0.50$ to 1.00).

When considering individuals' scores on USN-related measures in the 10 participants with actual neglect, however, some variability in the expression of USN was observed. Four (n=4) participants had more severe far- than near-space USN, two (n=2) had more severe near- than far-space USN, and four (n=4) had only near-space USN. Allocentric (object-centered) USN was more common and found in 7 out of 10 participants. Egocentric (viewer-centered) USN was found in 2 out of 10 individuals, and 2 participants presented with both allocentric and egocentric USN. Mild, moderate and severe USN was present in six (n=6/10), two (n=2/10), and two (n=2/10) participants, respectively.

3.4.2 Goal-directed navigation and detection

Figure 3.2 depicts typical MLD traces during the goal-directed navigation task performance of a USN- and a USN+ participant with stroke in the *remembered* condition. It can be observed that the USN- participant's MLD was tightly modulated as a function of the remembered target location, leading to small errors approximating 0m. A similar behaviour was observed in healthy controls (not illustrated). By contrast, the USN+ participant demonstrated a large variability in performance, with larger deviations in the navigation trajectories to all targets which led to larger

MLD errors, especially for the left-sided target (-30° and -15°). It emerges that the USN+ participant overshoot most left-sided targets to arrive on their left side at the end of the trial.

Mean MLD errors and the direction of deviation for the 3 study groups during the joystick navigation task performance are shown in Figure 3.3. A significant 3-way interaction of Group x Condition x Target Location was found ($F(16, 326, N = 45) = 2.64, p < 0.0006$). Within the USN+ group, worse performance was noted for the left and right most eccentric targets ($\pm 30^\circ$) in the shifting vs. actual condition ($p < 0.05$); and for the left target (-15°) and right eccentric target (+30°) in the remembered vs. shifting condition ($p < 0.01$). Subsequent pairwise comparisons showed that USN+ demonstrated greater MLD errors only for the left most eccentric target (-30°) in the remembered and shifting conditions compared to the USN- and HC groups ($p < 0.05$). No significant between-group differences were found for USN- vs. HC groups. It can also be noted that most of the USN+ individuals overshoot the left-sided targets in the actual and remembered conditions, ending their navigation trial to the left of the target. For the middle and right sided targets, no such delineated performance was observed, where some participants overshoot, and others undershot the target at endpoint.

A comparison of onset times of reorientation strategy across the 3 groups for the shifting target condition (Figure 3.4) revealed a significant Group effect ($F(2, N = 45) = 3.68, p = 0.03$).

Pairwise comparisons further indicated that the USN+ group presented with longer onsets of reorientation strategies compared to the USN- and HC groups for all target locations ($p < 0.05$). No significant differences were found between USN- vs. HC groups.

As illustrated in Figure 3.5, a significant 2-way interaction of Group x Target Location was also found for the detection time on the target detection task ($F(8, N = 45) = 4.15, p = 0.0002$). The USN+ group showed longer detection times for the left target (-30°) compared to the right target (+30°), as well as longer detection times for left and right targets ($\pm 15^\circ/\pm 30^\circ$) compared to the middle target (0°) ($p < 0.05$). The USN+ group further demonstrated longer detection times for all target locations compared to USN- and HC groups ($p < 0.05$), with the latter two groups showed no significant differences.

3.4.3 Relationships and deficits' detection ability analyses

Relationship and deficits' detection ability analyses were performed between USN clinical tests and goal-directed navigation performances (MLD error and onset of reorientation outcomes) to the left eccentric target (-30°) in the remembered and shifting conditions, as these specific conditions showed the largest alteration in the USN+ individuals. No significant correlations were found between any USN clinical tests and detection time outcome with the MLD error in the remembered and shifting condition ($p>0.05$). Significant, but negligible to low magnitude, correlations were found between the onset time of reorientation strategy and scores on the LBT/SCT in near space ($r = 0.29/r=-0.33$) and LBT in far space ($r=0.34$) ($p < 0.05$), indicating that a poor performance on USN tests was somewhat associated with a poor performance on the goal-directed navigation task in the shifting condition. No significant correlations were found between the detection time outcome and the onset time of reorientation strategy outcome ($p>0.05$).

Further, single case analyses were performed (Table 3.1) for two outcomes that were found to be significantly affected in USN+ vs. other two study groups: MLD error in the remembered and shifting conditions. The navigation task in these conditions allowed the detection of significantly higher MLD errors vs. the normative sample (HC group) in 3 out of 5 individuals with history of USN (S2, S4, S5) ($p<0.05$) and in 4 (S16, S17, S22, S24) out of 15 USN- ($p<0.05$). In addition, significantly higher MLD errors vs. the normative sample (USN- group) were found in 3 out of 5 individuals with history of USN (S1, S2, S5) ($p<0.05$). Further, it is important to note that most participants with history of USN displayed statistically similar performances in comparison to those with actual USN on testing.

3.5 DISCUSSION

The present study investigated the effects of post-stroke USN on goal-directed navigation and detection abilities. We employed a joystick-driven navigation task, thereby eliminating the potential confounding effects of gait-related abilities which normally differ between individuals with vs. without USN [71, 77, 249]. Furthermore, such a task could be easier to implement in the clinical setting, as it necessitates a fairly easy setup within a compact area and requires a short administration time approximating 15 min. This is of particular importance for patients with

post-stroke USN, as they are known to have a decreased sustained attention and alertness over longer periods of time [156, 161].

Overall, USN-specific deficits in space navigation and object detection were identified and are in accordance with prior research, suggesting that a joystick-driven task may be reflective of actual perceptual motor abilities in neglect. Recently, Aravind et al., (2015) showed USN-specific deficits in a joystick navigation-based obstacle avoidance and obstacle detection task [75]. Congruently, the results of the present study demonstrate that individuals with post-stroke USN, as they performed the joystick task, showed greater endpoint mediolateral errors in the remembered condition. Moreover, the present study provides evidence for USN deficits in representation updating during navigation, where affected individuals showed altered behavior in their ability to detect and adapt to changes in far-space target locations (i.e. shifting condition). Collectively, these findings propose that post-stroke USN affects space navigation, even in the absence of greater sensorimotor demands otherwise present in locomotion. Another interesting finding is that during navigation, individuals predominantly overshoot left-sided targets, showing a left-side navigation deviation. This result is contrary to findings in previously conducted locomotor experiments, where individuals with post-stroke USN mainly presented with rightward walking trajectory deviations (i.e. to the “non-neglected” side) [71, 77]. We hypothesize that factors such as the differences in the mode of displacement in the walking vs. the joystick navigation tasks as well as the influence of walking dysfunctions could explain this discrepancy. To clarify, the joystick mode of control allowed the participant to make trajectory adjustments that were not limited in magnitude and not restricted by one’s walking capacity, as opposed to what was experienced during locomotion. For this reason, participants with USN, who also presented with a reduced walking ability, may have undershot the left (neglected) target in the walking task, while they overshoot that same target during joystick navigation. The joystick-driven task may thus reflect more accurately the perceptual-motor abilities of individuals with post-stroke USN but falls short in estimating the impact of USN on actual locomotion. For instance, Huitema et al., (2006) [71], in an experiment that involved walking to a centrally located target, reported that USN+ individuals who were also slow walkers (n=3) deviated to the ipsilesional/right side, whereas fast walkers (n=3) deviated to the contralesional/left side. The authors concluded that walking trajectory deviation in individuals with USN may have depended on their walking ability. Another difference between joystick

navigation and walking is that the former did not allow bodily horizontal rotation, such that the only way to align with a peripheral target is to terminate the trial while being in front of it. In contrast, locomotor steering is achieved through both body displacement and reorientation [254], such that while the endpoint trajectory ‘apparently undershoots’ the target in terms of MLD, participants may still be ‘on target’ when considering their body orientation with respect to that target [255].

Furthermore, our team previously conducted a systematic review examining the effects of post-stroke USN on goal-directed upper extremity movements performed within the near-space [65]. The findings were consistent with the hypothesis that there are two different types of action control, processed via distinct visual streams, ventral and dorsal [66]. More precisely, impairments in upper extremity movements among individuals with post-stroke USN were found mostly during perceptual, memory-guided or delayed tasks (e.g. delayed pointing to remembered target location – ventral stream processing/offline movements); but not in immediate tasks (e.g. pointing to an actual target – dorsal stream processing/online movements). We propose that the conditions used in the present experiment could tap into ventral vs. dorsal stream hypothesis such that: the actual condition is visually-guided/online as it requires a quick response with the joystick; the remembered condition is memory-guided/offline; and the shifting condition is visually-guided, but since it also necessitates representational updating, it could be partly an offline type. On one hand, what we found is that the proposed ventral vs. dorsal stream hypothesis does potentially hold for far-space exploration in navigation, given that significant between-group differences were shown in both conditions with offline components (i.e. remembered and shifting), but not in the actual/online condition. On the other hand, we speculate that this hypothesis does not entirely hold for far-space exploration in locomotion, given that significant between-group differences were shown in both, actual and remembered conditions. We argue that as opposed to joystick navigation in far space, far space exploration requiring goal-directed locomotion entails additional space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85] to transform perception into action. It is also a longer task to perform as opposed to joystick navigation, and is more physically demanding. As a result, the actual condition in the locomotor experiment is potentially no longer a clear-cut “online” condition, but rather incorporates both, online and offline components. These additional demands on the visual-perceptual, attention, and

sensorimotor systems during walking vs. navigation could account for these differences in findings between the two experiments. Overall, rather than fully supporting the ventral stream hypothesis in USN proposed by Milner and Goodale [6], our results of the locomotion vs. navigation experiment align with the model proposed by Rizzolatti & Matelli (2003) who suggested that a system encompassing both ventral and dorsal streams is underlying USN, such that action control in the dorsal system is affected by the disruption of visuospatial information from ventral regions (temporal-parietal) [257].

Lateralized and non-lateralized USN deficits found in far-space object detection

The detection task in the present experiment identified USN-related deficits in the detection time of left-sided (i.e. contralesional) targets. This is in accord with previous studies on contralesionally located object detection in post-stroke USN individuals [75, 110, 185, 193]. In fact, an ample body of research focused on lateralized spatial USN deficits occurring in the neglected/contralesional hemispace. To a large extent, the attentional theory of USN, namely its hemispheric imbalance model [107, 110], global/local processing model [120-123] and the disengagement deficit/attentional shift model [134-136]), could provide explanations into this type of impairment and support our findings. The attentional theory of USN overall proposes that the right brain hemisphere plays the key role in directing attention to the left visual hemispace. It further suggests that lateralized left USN deficits are observed following the right hemisphere lesion and: 1. ensuing lack of orientation to left hemispace due to hypoactive right hemisphere (i.e. hemispheric imbalance model [107, 110]); or 2. inability to direct global/local attention (global/local processing model [120-123]); or 3. inability to disengage attention from the right visual hemispace and shift attention to the left visual hemispace (disengagement deficit model [134-136]). Interestingly, through the detection task, we also identified deficits that were non-lateralized, where performances were not solely worse in the neglected hemifield, but also in the ipsilesional/“non-affected” hemispace. Previous studies have also reported presence of non-lateralized deficits in individuals with post-stroke USN [103, 162]. Functional imaging studies reported the intraparietal sulcus and the frontal cortex to play a role in non-lateralized visual processing [258, 259]. In relation to that, our sample of individuals with post-stroke USN was constituted of nearly 70% of those with parietal and/or frontal lesions [249] further indicating that the presence of non-lateralized deficits could be accounted for by the lesion areas involved.

Clinical USN measures are not reflective of navigation abilities, but the navigation task could detect dormant deficits

Traditionally, post-stroke USN is assessed using paper-and-pencil tests, such as those used in the present study (e.g. Line Bisection, Star Cancellation, Apples Tests). In our participants, the results on these tests did not show any significant associations with the outcomes of MLD error in the remembered and shifting conditions; and only negligible to low magnitude associations with the outcome of onset of reorientation in shifting condition. This lack of significant associations could be explained by the differences in the types of stimuli (e.g. static vs. dynamic) and the nature of the tasks (cancellation and bisection vs. navigation). Moreover, despite the convenience of paper-and-pencil tests, their easy application and scoring, most of them are designed to assess USN of near-extraperosnal space only, and do not address essential everyday activities within the far-extraperosnal space. In fact, studies have reported participants with recovered USN based on conventional paper and pencil tests showing residual altered walking trajectory [29] and goal-directed reaching impairments [30]. Also, recent studies identified patients having mild USN, or no USN on paper-and-pencil tests but showing difficulty and USN on a VR task involving more challenging and dynamic type of tasks within an ecological 3-D environment [31-33]. These findings further demonstrate the lack of conventional evaluation tools' sensitivity and help explain the negligible or low associations found in the present study. Compared to paper-and-pencil tests, our navigation task likely involved more complex processes of representational updating, spatial memory, and readjustments calculations/adaptability of self as one approaches the far-space target. Those skills and abilities are not accounted for in the paper-and-pencil tests, possibly leading to the lack of association. Therefore, our results confirm that conventional methods of USN assessment are not sufficient and sensitive enough to detect functional impairments in daily activities, such as goal-directed locomotion and/or navigation.

In addition, the performance to the left target (-30°) in the remembered and shifting conditions allowed detecting deficits in 3 out of 5 participants with "recovered" USN as per the conventional paper-and-pencil tests (i.e. having a history of USN) and in 4 individuals of the USN- group, supporting the observation that conventional USN assessment tools may fail to predict performance in visually-guided functional tasks [33, 203, 239, 241]. This finding suggests that although individuals with "recovered" (or undiagnosed) USN may perform within

the norms in static, 2-D environments, perhaps their compensatory strategies fall short and deficits emerge when these individuals are exposed to a moving 3-D environment and performing a more complex activity. Our results warrant for the development of novel, more sensitive evaluation methods that could potentially incorporate the use of VR and tasks requiring navigation.

Limitations

Only participants with left USN (i.e. right hemisphere stroke) were included, limiting the generalizability of results to the left hemisphere stroke population. In addition, a more detailed description of participants' lesional patterns would have been informative and valuable in explaining the observed findings. Further, the present study did not examine eye movements during the experiments that could offer valuable information on gaze shifts, spatial fixations and re-fixations, possible remapping and gaze shifting impairments underlying USN. Another limitation is that the task design did not allow rotations along the vertical axis to mimic head and body horizontal rotation strategies as used in goal-directed locomotion [254]; however, the task was designed this way, so as not to add extra complexities to the control interface. Moreover, the motor function and recovery of the non-paretic upper extremity used in the joystick experiment was not objectively evaluated in the present study using standardized measures and one could argue that a unilateral hemisphere stroke could possibly result in impairments of bilateral upper extremities, but to different degrees: "more vs. less affected". Nevertheless, we believe that the paradigm used in this study allowed, to the best possible, to minimize the contribution of post-stroke sensorimotor impairments. Further, no significant differences between USN- and HC participants were observed in any of the outcome measures, suggesting that sensorimotor deficits of the non-paretic upper extremity, if any, did not affect the joystick task performance. Lastly, given the challenge of disentangling visual neglect from visual field deficits in individuals with post-stroke USN, the Goldmann perimetry or computerized equivalent tests results were often absent from medical charts of these participants. This could have resulted in the inclusion of participants with concurrent visual field deficits and USN in the USN+ group.

Conclusions

The present study demonstrated complementary evidence to a previously conducted goal-directed locomotion experiment. We identified that even in the absence of biomechanical

demands of locomotion, goal-directed navigation is affected in a memory-guided condition and in a task requiring representational updating component in individuals with USN. In addition, lateralized and non-lateralized deficits were shown using the detection task in the individuals with USN. These deficits were not associated with observed performances with clinical USN measures; however, the navigation task was sensitive in detecting deficits otherwise left undetected by conventional assessments. While the joystick navigation show similarities with goal-directed walking in terms of the task itself and observed findings in individuals with USN, discrepancies were also identified in the side of the endpoint mediolateral deviations, and alterations found in the actual condition during locomotion, but not during navigation, which may be explained by factors such as the mode of displacement and the influence of walking ability (or lack of thereof). Taken together, these findings present preliminary steps towards the development of more sensitive evaluation tools and treatment approaches that incorporate VR-based navigation and object detection, and that account for lateralized and non-lateralized deficits, representational updating and spatial memory.

Table 3.1 Single case analyses

Outcome	MLD to LEFT target (-30°) REMEMBERED Condition			MLD to LEFT target (-30°) SHIFTING Condition		
	Subject	t-value	Z score (effect size) 95% CI	t-value	Z score (effect size) 95% CI	
Participants with history of USN vs. those with actual USN on testing (USN+)						
S1 (Hx)	-0.78	-0.82	-1.53- -0.08	-0.75	-0.79	-1.49- -0.05
S2 (Hx)	2.99*	3.14	1.57-4.67	0.59	0.63	-0.07- 1.29
S3 (Hx)	-1.79	-1.88	-2.92- -0.80	-0.68	-0.72	-1.40- -0.004
S4 (Hx)	-0.89	-0.94	-1.67- -0.17	-0.67	-0.70	-1.39- 0.005
S5 (Hx)	0.26	0.27	-0.36- 0.90	0.73	-0.77	-1.47- -0.04
Participants with history of USN vs. USN- group						
S1 (Hx)	-0.40	-0.42	-0.94-0.11	-2.08*	-2.15	-3.07 - -1.20
S2 (Hx)	3.02**	3.12	1.86- 4.36	9.44***	9.75	6.14-13.35
S3 (Hx)	-1.32	-1.36	-2.06- -0.64	-1.5	-1.55	-2.29- -0.77
S4 (Hx)	-0.51	-0.52	-1.06- 0.02	-1.40	-1.45	-2.17- -0.70
S5 (Hx)	0.54	0.56	0.006-1.09	-1.90*	-2.00	-2.87- -1.09
Participants with history of USN+ vs. HC						
S1 (Hx)	0.22	0.24	-0.28-0.74	-0.68	-0.70	-1.26- -0.12
S2 (Hx)	5.98***	6.17	3.85-8.48	3.09**	3.19	1.91-4.46
S3 (Hx)	-1.13	-1.35	-2.04- -0.63	-0.37	-0.38	-0.90-0.14
S4 (Hx)	0.05	0.06	-0.44-0.56	2.16*	2.23	1.23-3.18
S5 (Hx)	1.83*	1.88	1.01-2.72	4.5***	5.15	3.17-7.10
USN- participants vs. HC group						
S16	-0.11	-0.12	-0.62-0.39	15.2***	15.6	9.92-21.45
S17	4.39***	4.47	2.75-6.17	0.59	0.61	0.051-1.16
S18	-0.11	-0.12	-0.62-0.39	0.74	0.76	0.17-1.33
S19	-0.13	-0.14	-0.65-0.41	1.17	1.15	0.48-1.80
S20	0.45	0.47	-0.07-0.99	0.81	0.84	0.24-1.42
S21	-0.13	-0.14	-0.65-0.41	-1.17	-1.15	-1.80- -0.48
S22	2.09***	3.00	1.78-4.20	0.78***	9.07	5.71-12.43
S23	-0.65	-0.67	-1.23- -0.10	-1.11	-1.15	-1.80- -0.48
S24	3.67**	3.79	2.30-5.26	-0.74	-0.76	-1.33- -0.17
S25	0.25	0.26	-0.25-0.77	-1.22	-1.30	-1.99- -0.59
S26	1.08	1.11	0.45-1.75	1.41	1.46	0.71- 2.18
S27	2.05*	2.11	1.18-3.03	0.22	0.23	-0.28-0.74
S28	1.16	1.20	0.52-1.86	1.56	1.61	0.82-2.38
S29	-0.79	-0.79	-1.36- -0.20	-0.59	-0.61	-1.16- -0.05
S30	-0.78	-0.79	-1.35- -0.19	-1.86	-1.92	-2.7- -1.04

Table 3 Single-case analysis of participants with history of USN vs. those with actual USN on testing, vs. USN- group, and vs. HC group (as control data); and single USN- participants vs. HC group (as control data) on the performance of navigation task in the *Remembered* and *Shifting* conditions to the left target at -30°. History (Hx); Subject (S); Subjects with post-stroke USN (USN+); Subjects post-stroke without USN (USN-); Healthy controls (HC); Unilateral spatial neglect (USN); Light grey selections represent individual cases whose performance is considerably worse than the comparison group ($p < 0.05$); Star symbols indicate p -value < 0.05 (*), < 0.01 (**), and < 0.001 (***).

Figure 3.1 VR scene used in the present experiment

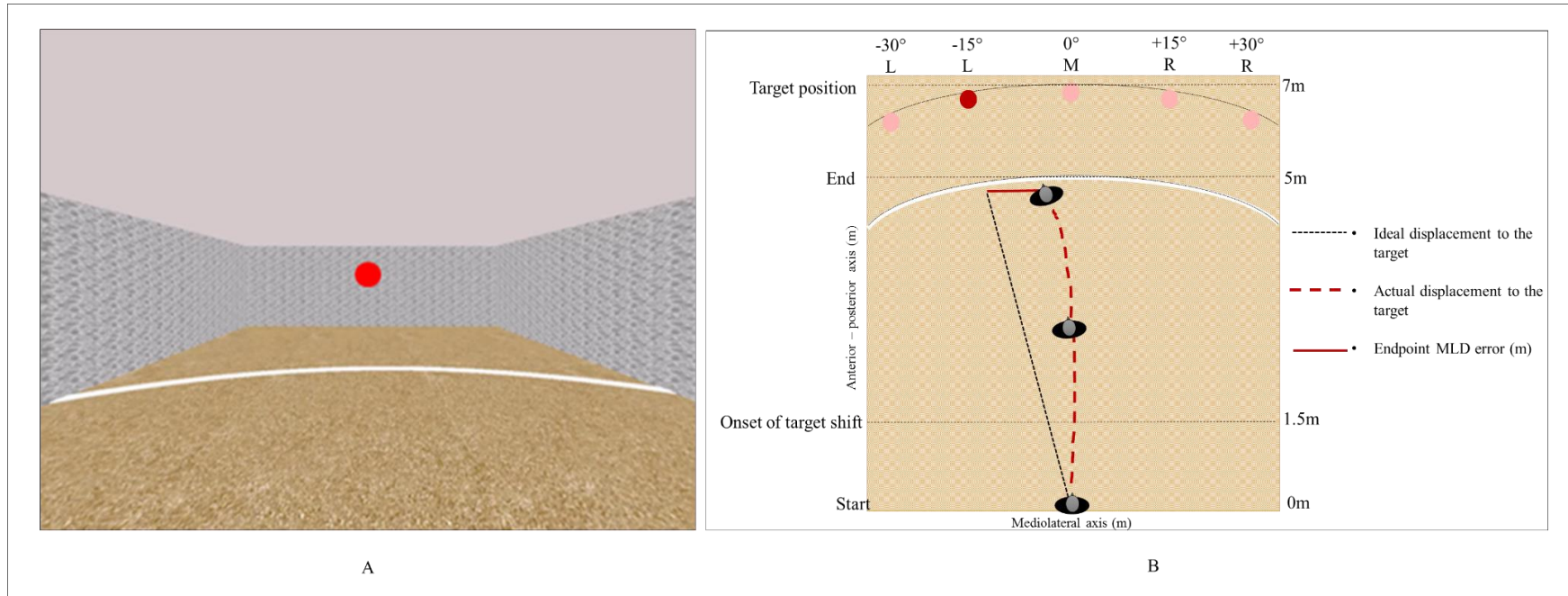


Figure 3.1 The VR scene used in the experiment. The target (i.e. red ball) appeared 7 m away from the starting position and at the following 5 possible locations: $\pm 15^\circ/30^\circ$, 0° (centered target location illustrated). Navigation trials were performed while immersed in the VR scene under actual, remembered and shifting target conditions B. Bird-eye view of the VR scene illustrating the start position (0m), the 5 possible target locations (7m radius from start position), onset distance for target shift in the shifting target condition (1.5m) and endpoint position (5 m radius from start position). Outcomes measures endpoint mediolateral displacement (MLD) error is shown for a navigation trial to the left target at -15°

Figure 3.2 Displacement traces

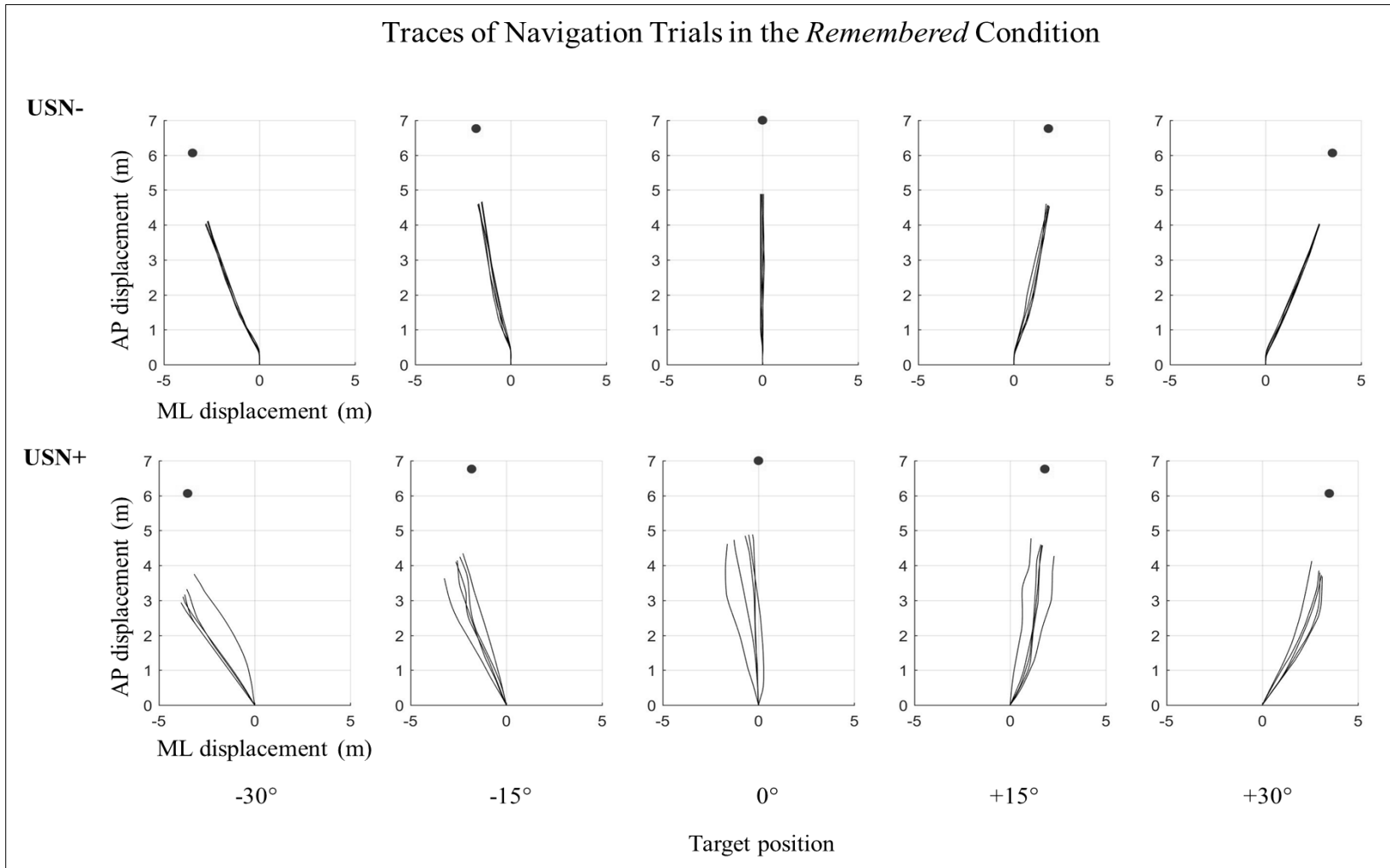


Figure 3.2 Birds eye view of mediolateral displacement (MLD), as performed by one individual without post-stroke neglect (USN-) and one individual with post-stroke neglect (USN+) for the 5 target positions during the remembered condition. The anterior-posterior (AP) displacement is on the y-axis. Target position is shown with the black dot.

Figure 3.3 Mediolateral displacement endpoint error results

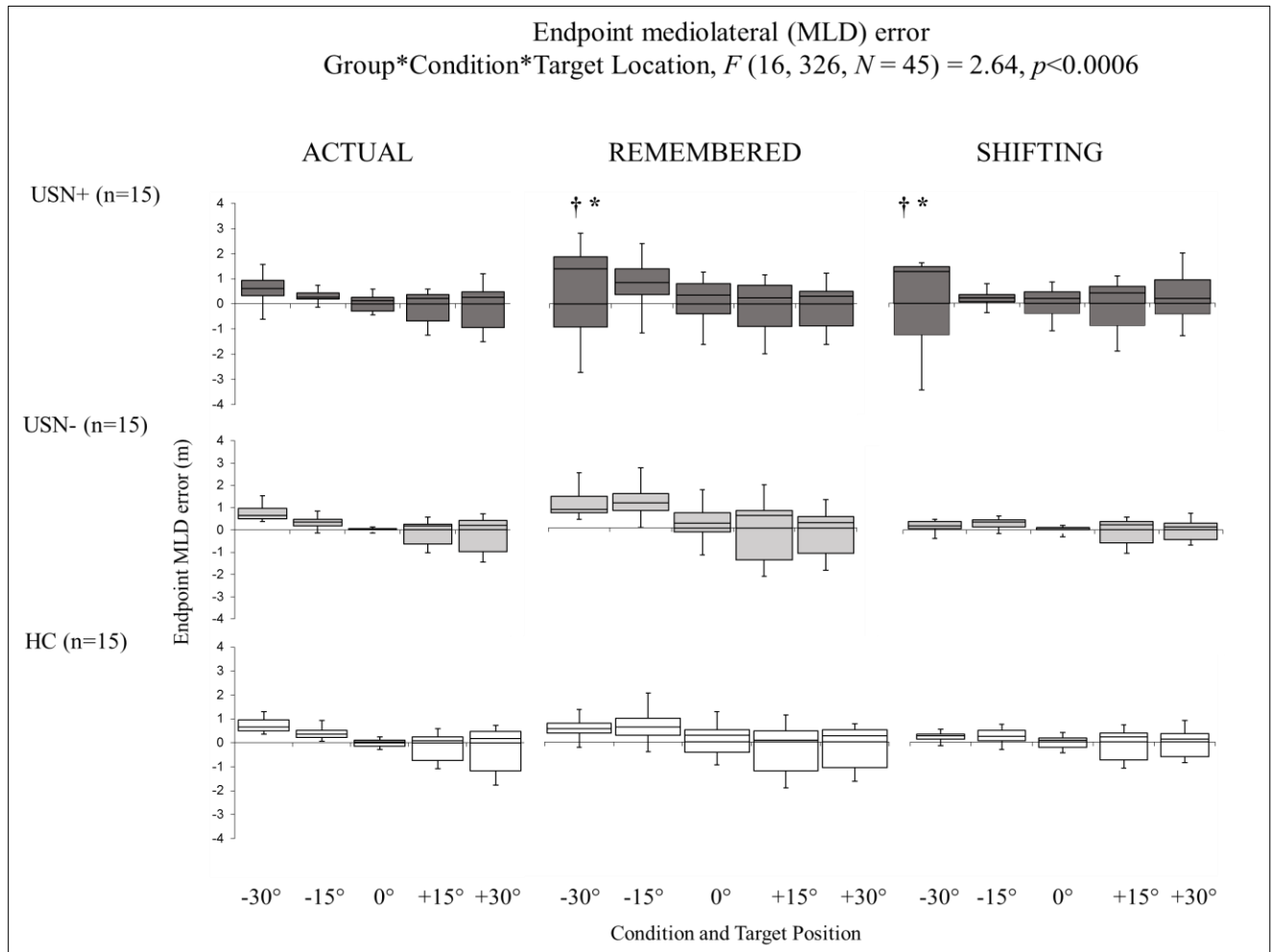


Figure 3.3 Mediolateral displacement (MLD) endpoint error results for the 3 study groups (USN+, USN-, HC ranging from dark grey to white, respectively) in actual, remembered and shifting conditions to the five target locations. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). Significant between-group differences at p-value < 0.05 are indicated for USN+ vs. USN- groups (†) and USN+ vs. HC groups (*), respectively. Negative and positive values symbolize, respectively, endpoint positions that undershoot (to the right of LEFT targets or left of RIGHT target) and overshoot the target (to the left of LEFT target or right of RIGHT target).

Figure 3.4 Onset of reorientation results

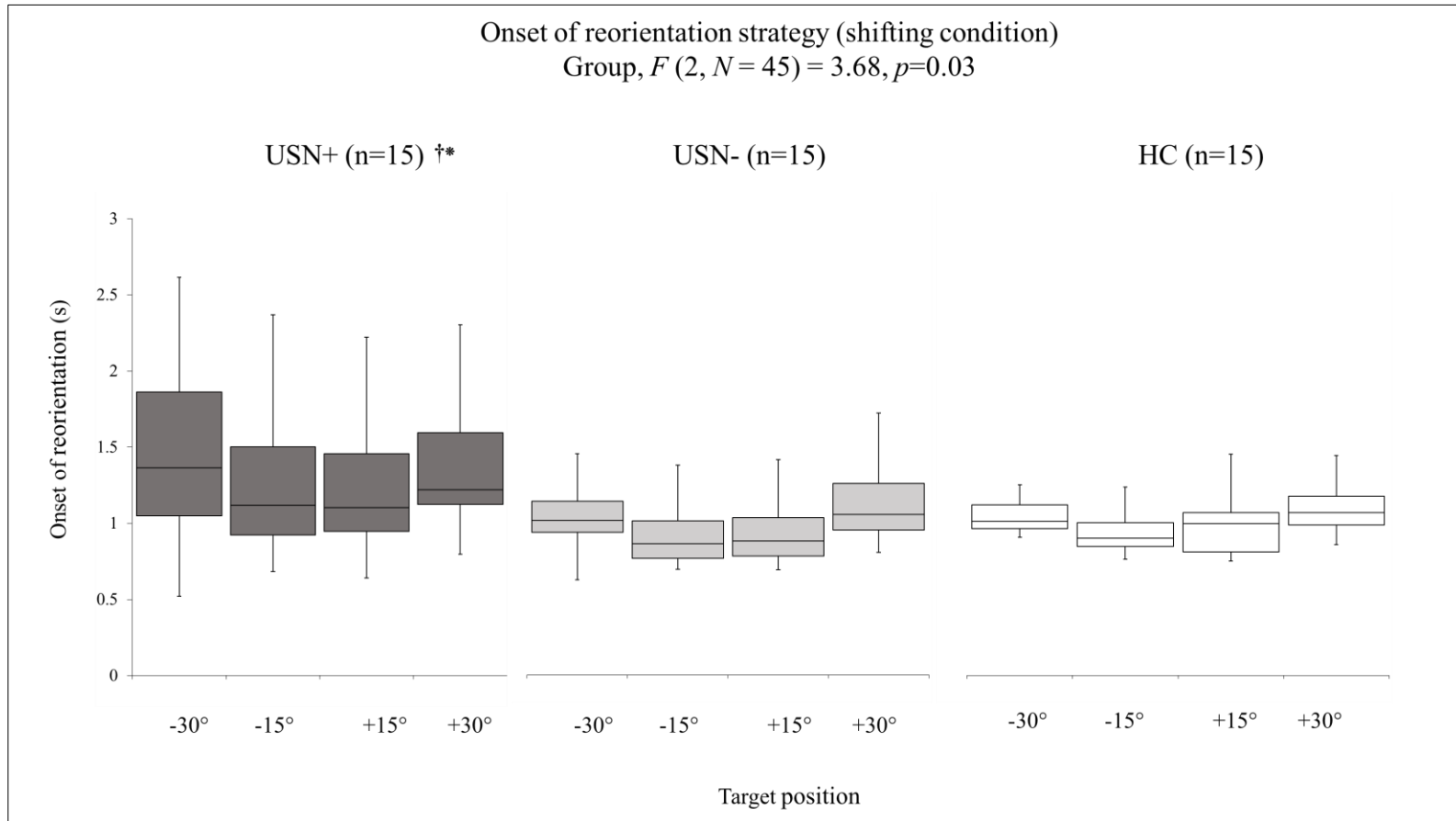


Figure 3.4 Onset of reorientation results for the 3 study groups (USN+, USN-, HC ranging from dark grey to white, respectively) to the 4 target locations. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). Significant between-group differences at p -value < 0.05 are indicated for USN+ vs. USN- groups (†) and USN+ vs. HC groups (*), respectively, next to USN+ group description (given that only a group effect was found to be significant).

Figure 3.5 Detection time result

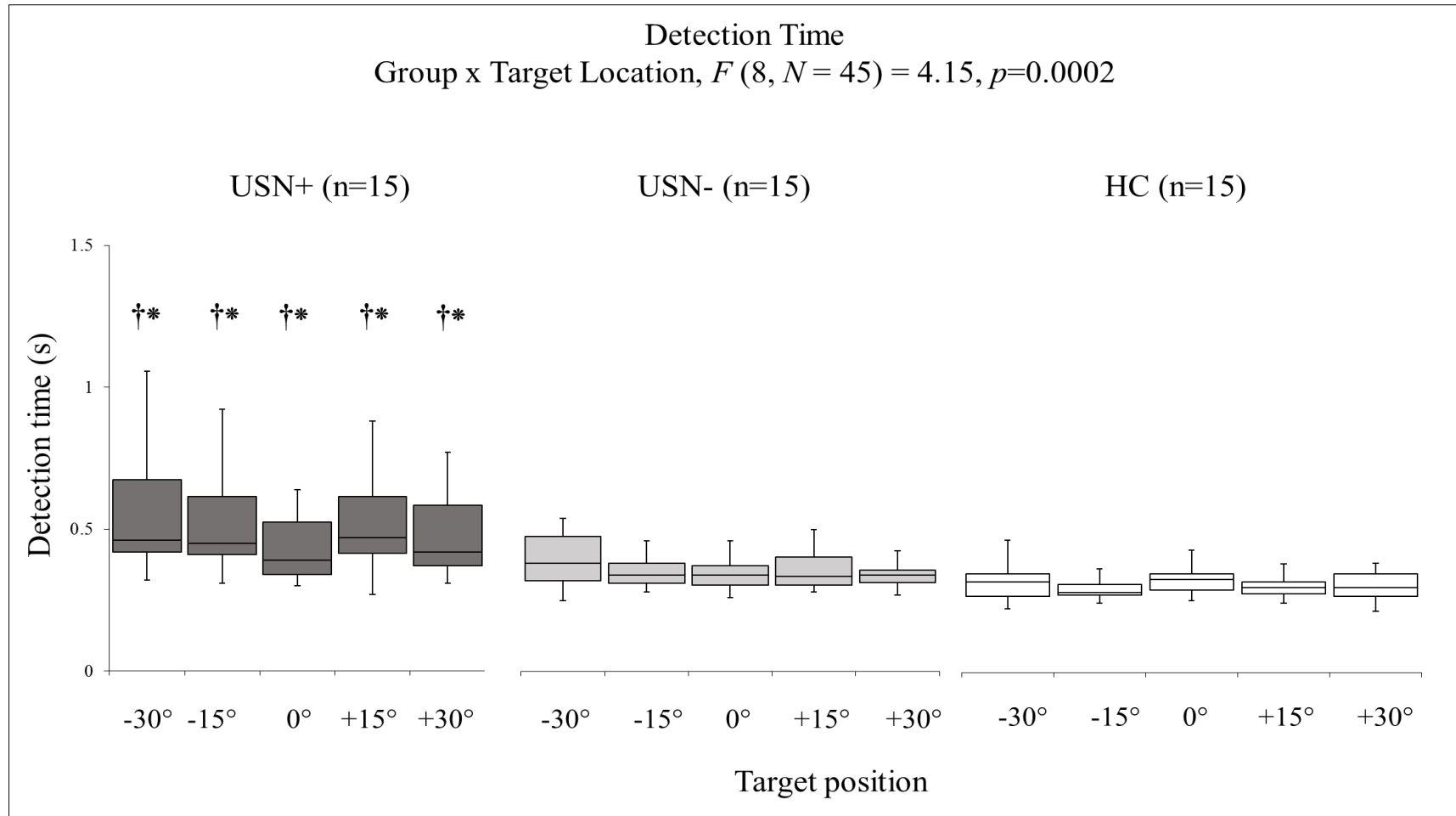


Figure 3.5 Detection time results for the 3 study groups (USN+, USN-, HC ranging from dark grey to white, respectively) to the five target locations. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). Significant between-group differences at p -value < 0.05 are indicated for USN+ vs. USN- groups (†) and USN+ vs. HC groups (*), respectively.

CHAPTER 4

4.1 PREFACE

Now that we have determined the extent to which post-stroke USN alters goal-directed locomotion and navigation, and how different cognitive task conditions, necessitating spatial memory and representational updating components, further impact these performances, in the following Chapter 4, we sought to estimate how post-stroke USN affects visual-perceptual abilities and their influences on the control of locomotion (as determined in Chapter 2).

Visual-perceptual abilities, such as optic flow, are essential in activities involving mobility. For instance, optic flow is an essential source of visual information that is used to control one's heading direction [83-85] and speed [86] during locomotion. Two earlier studies have showed that stroke individuals with a history of USN (n=2 out of 9 stroke participants [87]; and 2 out of 10 stroke participants [88]) presented with the largest deficits in the control of their walking trajectory or heading when exposed to optic flows of changing direction. However, the extent to which optic flow perception is affected in post-stroke USN and whether it influences the locomotor behavior remained unclear. In relation to this, as we evidenced (Chapter 2) that post-stroke USN significantly affects goal-directed locomotion abilities in online (actual, direct) and offline (perceptual, memory-guided) type of tasks [249]. Nonetheless, USN severity in near space, in conjunction with walking speed, could only explain nearly 30% of the variance in impairments observed during locomotion. Given its role in the control of locomotor heading, it is possible that concurrent deficits in high-order visual-perceptual abilities such as optic flow perception, further contribute to the observed walking deficits in post-stroke USN.

Chapter 4 of this PhD dissertation addresses **general objective 3** and **specific objectives 3.1 to 3.4** of my PhD research agenda. This chapter includes **Manuscript №3** of this dissertation, entitled “*Visual-perceptual deficits and their contribution to walking dysfunction in individuals with post-stroke visual neglect*”.

MANUSCRIPT № 3

VISUAL-PERCEPTUAL DEFICITS AND THEIR CONTRIBUTION TO WALKING DYSFUNCTION IN INDIVIDUALS WITH POST- STROKE VISUAL NEGLECT

Tatiana OGOURTSOVA^{1,2*}, Philippe S. ARCHAMBAULT^{1,2}, Anouk LAMONTAGNE^{1,2}

¹School of Physical and Occupational
Therapy,
McGill University,
3654 Promenade Sir-William-Osler
Montreal, Quebec, Canada
H3G 1Y5

²Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital,
Site of Centre for interdisciplinary Research
in Rehabilitation of Greater Montreal
3205 Place Alton-Goldbloom
Laval, Quebec, Canada
H7V 1R2

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DECLARATION OF INTEREST

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4.2 ABSTRACT

Background: Unilateral spatial neglect (USN), a highly prevalent and disabling post-stroke deficit, severely affects functional mobility. Visual-perceptual abilities (VPAs) are essential in activities involving mobility. However, whether and to which extent post-stroke USN affects VPAs and how they contribute to mobility impairments remains unclear. **Objectives:** To estimate the extent to which VPAs in left and right visual hemispaces are (1) affected in post-stroke USN and (2) contribute to goal-directed locomotion. **Methods:** Individuals with (USN+, n=15) and without (USN-, n=15) post-stroke USN and healthy controls (HC, n=15) completed 1) psychophysical evaluation of contrast sensitivity, optic flow direction and coherence and shape discrimination, and 2) goal-directed locomotion tasks. **Results:** Higher discrimination thresholds were found for all VPAs in the USN+ group compared to USN- and HC groups ($p < 0.05$). Psychophysical tests showed high sensitivity in detecting deficits in individuals with history of USN or with no USN on traditional assessments; and were found to be significantly correlated with goal-directed locomotor impairments. **Conclusion:** Deficits in VPAs may account for the functional difficulties experienced by individuals with post-stroke USN. Psychophysical tests used in the present study offer important advantages and can be implemented to enhance USN diagnostics and rehabilitation.

Keywords: Hemineglect, cerebrovascular accident, optic flow, contrast sensitivity, shape discrimination, visual perception.

4.3 BACKGROUND

One of the most prevalent and disabling post-stroke visual-perceptual deficits is unilateral spatial neglect (USN), experienced by 23 to 46 percent of individuals with stroke [63]. USN is typically characterized by a decrease in orientation and/or response to the stimuli appearing on the contralesional side [43]. Although 20% to 45% of USN resolves spontaneously within the acute post-stroke period, for the remainder, it becomes long-standing and can introduce major disability, activity restrictions [63], and reduced quality of life [64]. From a clinical perspective, USN has been recognized as a major barrier to stroke rehabilitation, functional recovery [10, 63], and a real endeavor for clinicians to properly detect and treat (reviewed in [260]).

The visual-perceptual hierarchy introduced in the early 1990's by Warren [7, 78] suggests that visual perception can be conceptualized as a hierarchy of skill levels; where skills at the bottom form the foundation for each successive level. This notion leads to further speculation that, in presence of USN, the underlying and potentially related visual-perceptual abilities might also be affected and play a role in the ensuing functional impairments.

In the last two decades, an ample body of research focused on investigating the ability of patients with post-stroke USN to perform cognitive visual processing tasks of the stimuli located in the contralateral visual hemispace, presumably the neglected hemispace. This literature suggests that even in the absence or lack of attention to the neglected visual hemifield, there is still a certain degree of information processing from the unattended stimuli that can influence behavior [24, 79-82]. Nevertheless, there is only a limited number of studies that have directly examined the effect of post-stroke USN on visual processing abilities of the neglected hemifield, mostly focusing on disturbed contralesional ocular visual search patterns (e.g. [16-20]) and loss of contralesional contrast sensitivity (e.g. [14, 21-24]). Collectively, these studies suggest that the examination of visual processing skills could serve as a more in-depth investigation into neglect and provide insight into the functional impairments. Visual perception as needed for activities of daily living, however, also involve the perception of motion or optic flow and the depth and texture of the object (reviewed in [25]), which are yet to be studied in post-stroke USN.

Optic flow is an essential source of visual information that is used to control one's heading direction [83-85] and speed [86] during locomotion. Two earlier studies have showed that stroke individuals with a history of USN (n=2 out of 9 stroke participants [87]; and 2 out of 10 stroke

participants [88]) presented with the largest deficits in the control of their walking trajectory or heading when exposed to optic flows of changing direction. However, the extent to which optic flow perception is affected in post-stroke USN and whether it influences the locomotor behavior remains unclear. In relation to this, we recently evidenced that post-stroke USN significantly affects goal-directed locomotion abilities in online (actual, direct) and offline (perceptual, memory-guided) type of tasks [249]. Nonetheless, clinical assessments of USN, in conjunction with walking speed, could only explain nearly 30% of the impairments observed during locomotion. Given its role in the control of locomotor heading, it is possible that high-order visual-perceptual abilities such as optic flow perception, contribute to further explain goal-directed walking deficits in post-stroke USN.

In addition, Marotta and colleagues [89] found a decrease in shape discrimination ability and subsequent loss of grasp stability of these shapes in individuals with post-stroke USN compared to those post-stroke but without USN. This study, however, did not rigorously differentiate between shape discrimination abilities within the contralesional vs. ipsilesional visual hemispace, and an association with goal-directed walking deficits is yet to be examined.

Furthermore, since that the most apparent issue in USN is the failure or dramatic slowing of response to occurrences in the contralesional hemispace [90-95], much of the above-mentioned research has focused on USN-related lateralized spatial deficits (reviewed in [96, 97]). Although less obvious, deficits that are non-lateralized are also fundamental to persistent neglect [98-102]. In fact, the severity of non-lateralized deficits is a stronger predictor of USN chronicity than the spatially lateralized deficits themselves [100, 101, 103-105]. As a result, non-lateralized deficits, when combined with lateralized deficits, can limit recovery potential and therefore constitute important targets for treatment [106]. However, whether visual-perceptual abilities are laterally vs. non-laterally affected in post-stroke USN remains unclear and calls for investigation.

Overall, it emerges that it is highly relevant to further build on aforementioned findings by thoroughly examining the impact of post-stroke USN on visual processing abilities in both visual hemispaces (i.e. left/"neglected" and right/"non-neglected"). The main objective of this study was thus to estimate the extent to which post-stroke USN affects visual-perceptual abilities, including: contrast sensitivity, optic flow direction and coherence, and shape discrimination in bilateral (left and right) visual hemispaces. Secondary objectives were to: i) estimate the

relationship between USN clinical tests and psychophysical tests; ii) estimate the preliminary sensitivity of psychophysical test in detecting deficits that were otherwise left undetected using conventional USN clinical tests (i.e. participants with USN history and those with no USN on conventional clinical tests) and; iii) determine the extent to which visual-perceptual abilities contribute to goal-directed locomotion impairments in individuals with post-stroke USN.

It was hypothesized that individuals with USN compared to those without USN and healthy controls would present with higher thresholds in all psychophysical tests, indicating worse behavior, possibly in both visual hemispaces. Moreover, we hypothesized to find significant but low-magnitude correlations between USN clinical tests and psychophysical measures. Further, we speculated that psychophysical measures would be highly sensitive in detecting deficits in those with history of USN and potentially in those without post-stroke USN as assessed by traditional paper-and-pencil tests. Finally, we hypothesized that visual-perceptual abilities, specifically those related to optic flow processing, would significantly contribute in explaining impairments found in goal-directed locomotor behavior.

4.4 METHODS

4.3.1 Participants

Individuals with stroke aged between 45 and 80 years were included based on the following criteria: presence of a first time right hemisphere stroke (as determined by CT scan, medical chart) in the subacute or chronic phase of stroke recovery (post ≥ 3 months), with or without left USN (as per one or more of the following tests: Line Bisection Test (LBT) [181], Star Cancellation Test (SCT) [175], and/or Apples Test (APT) [53] on testing, or history of USN as per medical chart); right handedness (as per interview and as per interview and/or medical chart containing Edinburgh Handedness Inventory scores [213]).

Individuals were excluded based on the following criteria: presence of primary visual impairment that impedes normal or corrected-to-normal visual acuity (score $\leq 20/25$ on the Early Treatment Diabetic Retinopathy Study Chart [250]); presence of moderate cognitive impairment (score $\leq 22/30$ on the Montreal Cognitive Assessment [251]); and presence of a documented visual field defect (as per medical chart, Goldmann's perimetry or computerized equivalent). In

addition, age-matched (+/- 5 years) healthy controls were recruited following the same inclusion/exclusion criteria where applicable.

Participants were recruited from three clinical sites of Centre de Recherche Interdisciplinaire en Réadaptation du Montreal Métropolitain (CRIR, Montreal, Quebec, Canada). The study was approved for ethics by the CRIR Institutional Review Board. All study participants reviewed and signed the informed consent before enrolling in the study.

4.3.2 Data Collection

The process of data collection for the present study consisted of two main experiments described in more detail below: 1. USN testing followed by 2. Psychophysical testing. They were carried out in one testing session of approximately 1 to 1.5 hours. Goal-directed locomotion testing, for which the procedure and results are also reported elsewhere in more details [249], was conducted either in the same or in a separate testing session (within the same week) from the USN and psychophysical testing. The latter assessment involved goal-directed locomotion trials to actual (i.e. online), remembered (i.e. offline) and shifting (i.e. online) targets located 7 m ahead at 0° and 15° right/left while immersed in a 3-dimensional virtual environment visualized in a helmet mounted display.

Experiment 1: USN Testing

Presence of near-extraperosnal USN and its type were determined using the LBT, SCT, and the APT which all show excellent psychometric properties [53, 223, 252].

Apparatus and Stimuli. Given that participants were part of a larger study examining near and far space USN [249], the LBT and SCT results which are reported in near space only in this manuscript were obtained by displaying the testing sheets on a projector screen (Microsoft Paint application), containing a middle point, with respect to which, the table and the participants' midline (i.e. sternum) was aligned using a laser measurer. Participants were positioned 40 cm away from the screen. A chin rest was used to minimize head movements and to ensure a constant viewing angle. Responses were provided by the participants using a hand-held laser pointer. Responses were marked directly on the test form by the investigator using a wireless mouse and the pencil in Paint Program. The order of tasks (bisection vs. cancellation) was randomized across participants to decrease potential learning effect. The APT was presented on a

sheet of paper on a steady table, aligned with the participant's midline (i.e. sternum) and fixed on the table with tape to prevent possible shifts.

Procedures. In the LBT, participants were asked to find the midline of each presented line (n=18), starting from the top line. In the SCT, participants were instructed to find all the small stars (n=52) among the distractors. In the Apples Test, participants were instructed to encircle all the complete-shaped apples (n=50) on the sheet.

Scoring. For the LBT, the deviation from the center in each line was measured and averaged across all the lines. An absolute mean deviation of more than 6.0 mm to the right is indicative of left near space USN on the near LBT test. For the SCT, the number of small cancelled stars was divided by the total number of small stars to compute the laterality index score. Scores between 0 and 0.46 are indicative of left USN. For the APT, the total number of crossed out complete and incomplete shape apples was computed, and asymmetry scores for egocentric (i.e. difference between the numbers of complete shape targets crossed out on the right versus left side of the page) and allocentric (i.e. difference between the numbers of incomplete shape targets crossed out with a right and with a left opening) USN were calculated. The overall cutoff is $<42/50$, indicative of near-space USN. Asymmetry cutoff score across the page of <-2 or >2 (difference between right side and left sided targets cancelled) is indicative of egocentric near space USN. Asymmetry cutoff score across the cancelled distractors on the page with left vs right sided openings of <-1 or >1 is indicative of allocentric near space USN. All cancellation tests were timed.

Outcome. Outcomes retained for analysis included: (1) *presence vs. absence of near space USN* and (2) *USN spatial representation type* (allocentric vs egocentric). Participants were included in the group of individuals with USN (USN+) if they had USN on one or several of the aforementioned tests, or if they had a history of USN as per their medical chart typically assessed by clinicians using a cancellation (e.g. SCT, Bells Test), LBT, Clock Drawing, and/or the Behavioral Inattention Test.

Experiment 2: Psychophysical Testing

Apparatus and stimuli. During the visual-perceptual testing, the participant was positioned in front of a computer screen within his/her reaching distance with the sternum aligned to the

middle of the screen. The height of the screen was adjusted so that the eye level is at the 2/3 of the screen. A chin rest was used to support the head and minimize head movements. The EyeTribe® eye tracker (Eye Tribe, Copenhagen, Denmark) was used during the experiment to ensure the position of gaze on the screen for each recorded response (60Hz sampling rate) (Figure 4.1). Trials that were included in the final threshold calculations when the subject maintained gaze fixation on a predefined circular area of the screen (radius of 5 degrees of visual angle). The stimuli were generated, and responses will be recorded with a Pentium 4 computer equipped with Matrix 10-bit Parhelia512 graphic card. Stimuli were presented on a ViewSonic E90FB .25 non-interlaced CRT monitor set to an 85 Hz refresh rate, 1024 x 768 resolution. Prior to testing, a gamma correction procedure was carried out to linearize the luminance output of the monitor.

Procedure. Experiments were conducted in a quiet and dark room. Prior to each set of subtests, a 16-points calibration procedure was performed with the eye tracker to ensure proper midline fixation. Following, participants were provided standardized instructions and a trial period, where the evaluator confirmed that the participant understood the instructions. During all psychophysical testing, participants were asked to keep fixating on the middle point of the screen. Breaks were permitted between subtests, but not between trials within each subtest. For all subtests, a 2-down 1-up staircase approach was used. The staircase began with a high intensity stimulus. The intensity was then reduced after 2 correct responses until the participant made an error, at which instance, the staircase reversed and the intensity increased until the participant gave the following 2 correct responses. This staircase approach is commonly employed and validated for psychophysical/vision research; thus, justifying its use in the present study [261].

Contrast sensitivity. The stimulus variable consisted of modulating the luminance depth of a sinusoid grating. The luminance modulation of the grating is described by the following equation: $L(x) = L_{mean}[1 + m \times \sin(f_s x + \varphi)]$, where L , m , f_s , x and φ respectively represent luminance, modulation depth, spatial frequency, horizontal position and start phase. The resulting threshold represents the value that is equivalent to the Michelson contrast of the grating, which is obtained by the equation: $m = \frac{L_{max} - L_{min}}{L_{max} + L_{min}}$. Stimulus was represented by a

circular Gabor patch (0.5SI of spatial frequency, 4° visual angle in diameter) that would appear in four possible locations: top/bottom and right/left of the middle fixation point with 5° of visual angle. A brief beep-sound accompanied each stimulus presentation. Stimulus duration and interstimulus interval were of 750ms and 500ms respectively. Participants were instructed to identify whether they perceived the stimulus appearing on top or on the bottom of the middle fixation point (Figure 4.2A).

Shape discrimination. The stimulus variable consisted of modulating the radius of a circle to achieve a deformation of its shape. Modulating the radius of the circle is described by the following equation: $r(\theta) = r_{mean}[1 + m \times \sin(\omega\theta + \varphi)]$, where r and θ represents polar coordinates (radius and angle, respectively); m , the amplitude of modulation; ω , the radial frequency of the stimulus; and φ , the start phase. The modulation amplitude is the difference between the peak and minimum values relative to the mean radius. The modulation amplitude of the standard stimulus was set to zero, representing a perfect-shaped circle. The stimulus appeared in two possible locations: right or left of the middle fixation point with 5° of visual angle. When presented with one perfect-shaped and one deformed-shaped circle, participants were asked to identify which one of the two presented stimuli is the perfect-shaped circle (Figure 4.2B). Stimulus duration and interstimulus interval were of 750ms and 500ms respectively.

Optic flow direction. The stimulus variable consisted of modulating the location of the focus of expansion (in degrees of visual angle from midline) of optic flow. In this experiment, two optic flow stimuli were displayed in random order subsequent to each other: one standard stimulus and one test stimulus. Standard stimulus' focus of expansion was always located at the center, concurrent with the fixation point. Test stimulus' focus of expansion was presented either to the right or to the left of the fixation point with a maximum of 10° of visual angle (increments of 0.5deg). When presented with two consecutive optic flow stimuli, standard and test, participants were asked to identify the test stimulus (Figure 4.2C). Stimulus and inter-stimuli duration was of 2000ms and 1000ms. The global perceived speed of optic flow was set to 1m/s.

Optic flow coherence. The stimulus variable modulated in this experiment was the proportion of dots moving coherently in expansion of in contraction. In each trial, a certain number of dots was

moving coherently (i.e. contraction) and a certain number of dots was moving incoherently (i.e. jittering randomly from frame to frame in a direction that is either consistent with expansion or contraction). The total number of moving dots remained constant throughout trials (n=150). However, the proportion of dots moving coherently changed from trial to trial based on response accuracy, where erroneous responses increased the number of dots moving coherently, and correct responses decreased that number. Participants were instructed to identify whether the optic flow pattern is expanding or contracting (Figure 4.2D). The focus of expansion of stimuli was presented either to the right or left of the fixation point at 5° of visual angle. Stimulus and interstimulus interval durations were of 2000ms and 1000ms. As for optic flow direction subtest, the global perceived speed of optic flow was set to 1m/s.

Scoring: All psychophysical subtests terminated at 16 reversals, and 10 reversals were used to calculate the thresholds for each subtest at 62% correct response rate; and separately for each visual hemispace, right and left. The 62% accuracy rate was selected as the 2-down 1-up staircase approach used in the study is known to converge at this point.

Outcomes: the following outcomes for left and right visual hemispaces were retained for analysis (1) *Contrast sensitivity:* ability to discriminate between the grating and the background with 62% accuracy; (2) *Shape discrimination:* ability to discriminate between a perfect and a deformed shape with 62% accuracy. (3) *Optic flow location/direction:* ability to discriminate between a centered and a lateral focus of expansion with 62% accuracy; (4) *Optic flow coherence:* ability to discriminate between optic flow expansion or contraction with 62% accuracy.

4.3.3 Data and Statistical Analyses

Response of participants on USN tests psychophysical experiments were averaged across conditions and hemispaces separately, such that mean values could later be compared across groups. All statistical analyses were performed using SAS® 9.4 (SAS Institute Inc). Significance was accepted at $p \leq 0.05$. Groups' demographics were compared between groups using one-way analyses of variance (ANOVAs; normally distributed data) and Kruskal-Wallis test (not normally distributed data). If significant differences were detected, contrasts analyses were performed using independent sample t-test (normally distributed data) and Wilcoxon-Mann-Whitney test (not normally distributed data). Due to not normally distributed data within the

USN+ group, the effects of post-stroke USN on each of the tested visual-perceptual ability were examined with non-parametric statistics using Kruskal-Wallis test and followed by the Wilcoxon-Mann-Whitney test for contrast analyses. In addition, effect sizes were calculated and reported on using Cohen's criteria r effects as small $\geq .10$, medium $\geq .30$, and large $\geq .50$ [233]. Within-group differences for left vs. right visual hemispaces were examined for the USN+ group using the Wilcoxon Signed Rank Sum Test.

Kendall rank correlation coefficients were used to quantify the relationship between clinical assessments of neglect and psychophysical tests results. The strength of the correlation coefficient was interpreted as per guidelines: very high (0.90-1.00), high (0.70-0.90), moderate (0.50-0.70), low (0.30-0.50) or negligible (0.00-0.30) [231].

To gain a better understanding of the preliminary sensitivity of the psychophysical measures in detecting deficits otherwise not detected using traditional tests, single case analyses were used to compare the performance of each USN+ participant with respect to the average performance of the USN- group; as well as to compare the performance of each USN- participant with respect to the average performance of the HC group. Precisely, the Crawford and Garthwaite (2002) approach (Singlims.exe, University of Aberdeen, Aberdeen, UK) [232], which implements classical methods for comparison of a single case's score to scores obtained in a control sample, was used. The 95% confidence interval estimate of the effect size for the difference between each case and controls (as normative data) was obtained.

Finally, a backward stepwise multiple regression analysis was used to verify the extent to which the severity of neglect in near space, along with visual perceptual abilities, predicted goal-directed locomotion behavior deficits to the left/"neglected" (-15°) target in the *actual/visually-guided* condition, as assessed and reported by our team in another manuscript [249]. This latter outcome was selected as this is where deficits were identified in the USN+ vs. USN- and vs. HC groups. In addition, the *actual/visually-guided condition* (but not the *remembered/memory-guided*) condition was chosen for the regression analysis as the target needs to be visible in the locomotor trials to understand the influence of target-ensuing optic flow, contrast sensitivity and shape discrimination visual control strategies used in goal-directed locomotion.

4.5 RESULTS

Fifteen individuals with post-stroke USN (n=15, USN+), fifteen individuals post-stroke without USN (n=15, USN-), and fifteen age-matched healthy control individuals (n=15, HC) were recruited in the period between December 2014 and March 2016. Each participant successfully completed all study experimental trials without missing data. Table 4.1 outlines the demographic and clinical variables for the three groups. Both the USN+ and USN- groups predominantly consisted of male participants and were statistically similar in terms of stroke chronicity. No significant between-group differences were found on all baseline characteristics.

In terms of the goal-directed locomotion performance, greater end-point mediolateral displacement and heading errors were found for the remembered vs. shifting conditions for the left target (-15°) in USN+ group ($p < 0.05$) [249]. USN+ group also showed altered locomotion abilities in actual and remembered conditions for the left and right targets ($\pm 15^\circ$), and a delayed onset of reorientation in the shifting condition vs. USN- and HCs ($p < 0.05$).

4.5.1 USN characteristics

Table 4.2 presents the clinical USN assessment results for the participants with stroke. The USN+ group included five (n=5) individuals with history of USN, and ten (n=10) individuals with actual USN on testing. Overall, the USN+ group demonstrated deficits on all USN related measures in near space. None of the USN- individuals scored positive on any of the USN assessments. When considering individuals' scores on USN related measures in the 10 participants with actual neglect, however, some variability in the expression of USN was observed. Allocentric (object-centered) USN was more common and found in seven out of 10 participants. Egocentric (viewer-centered) USN was found in 2 out of 10 individuals, and 2 participants presented with both allocentric and egocentric USN.

4.5.2 Visual-perceptual abilities

As illustrated in Figure 4.3A, USN+ group showed significantly higher contrast sensitivity thresholds compared to the USN- group ($Z=2.86$, $p=0.0021$, large effect size, $r=0.52$) and the HC group ($Z=2.84$, $p=0.0022$, large effect size, $r=0.51$) for the left/neglected visual hemispace. No significant between-group differences were observed for the right/non-neglected visual

hemisphere, or for USN- group vs. HC group in both visual hemispheres ($p>0.05$). Within-group analyses revealed that USN+ individuals needed significantly higher left vs. right contrast thresholds for accurate detection ($M=4.5$, $p=0.03$).

For shape discrimination, that is the ability to discriminate between a perfect vs. deformed circle, the USN+ group showed significantly higher radius amplitude compared to the USN- group ($Z=2.17$, $p=0.01$, medium effect size, $r=0.39$) and the HC group ($Z=2.82$, $p=0.0024$, large effect size, $r=0.50$) in the left/neglected visual hemisphere (Figure 4.3B). Similarly, the USN+ group showed significantly higher thresholds vs. USN- group ($Z=1.88$, $p=0.03$, medium effect size, $r=0.33$) and vs. HC group ($Z=2.15$, $p=0.02$, medium effect size, $r=0.38$) in the right visual hemisphere. No significant between-group differences were observed for USN- vs. HC groups in both visual hemispheres or within USN+ group for left vs. right visual hemisphere ($p>0.05$).

Optic flow direction resulting thresholds are illustrated in Figure 4.3C. USN+ group showed larger thresholds compared to the USN- group ($Z=2.70$, $p=0.0034$, medium effect size, $r=0.48$) and the HC group ($Z=3.37$, $p=0.0004$, large effect size, $r=0.60$) for the left/neglected visual hemisphere. Significantly higher thresholds for the right visual hemisphere of USN+ participants were also found compared to USN- group ($Z=2.99$, $p=0.0014$, large effect size, $r=0.53$) and vs. HC group ($Z=2.86$, $p=0.0021$, large effect size, $r=0.51$). No significant between-group differences were observed for USN- vs. HC groups in both visual hemispheres or within USN+ group for left vs. right visual hemisphere ($p>0.05$).

Optic flow coherence thresholds (Figure 4.3D) were found to be significantly higher in the right/non-neglected hemisphere of the USN+ group compared to the USN- group ($Z=2.38$, $p=0.0085$, medium effect size, $r=0.42$) and HC group ($Z=2.11$, $p=0.0024$, large effect size, $r=0.50$). No significant between group differences, however, were found in the left/neglected visual hemisphere in USN+ vs. USN- group ($Z=1.32$, $p=0.09$, small effect size, $r=0.23$) and in USN+ vs. HC group ($Z=1.47$, $p=0.07$, small effect size, $r=0.26$). Similarly, no significant between-group differences were observed for USN- vs. HC groups in both visual hemispheres or within the USN+ group for left vs. right visual hemisphere ($p>0.05$).

4.5.3 Relationships, sensitivity and regression analysis

In participants with USN, more affected performances on traditional paper-and-pencil assessment for USN (with exception of the APT – viewer centered) were associated ($p<0.05$) with higher discrimination thresholds on psychophysical testing for left contrast sensitivity, left/right shape discrimination and left/right optic flow direction thresholds. Correlation coefficients were of negligible to moderate magnitude ($r=0.25-0.53$) (Table 4.3).

Single case analyses for single USN+ participants vs. USN- group, as well as for single USN- participants vs. HC group were also performed (Table 4.4). An interesting finding was that the psychophysical tests allowed the detection of worse performances in 4 out of 5 individuals with history of USN compared to USN- group ($p<0.05$) and in 9 out of 15 USN- participants vs. HC group ($p<0.05$).

Results of optic flow direction (left), shape discrimination (left), contrast sensitivity (left), and optic flow coherence (right) were included in backward stepwise regression analysis, along with the LBT in the near space and walking speed (as per the 10 Meter Walk Test, measured in the goal-directed locomotion experiment) as independent variables to estimate their effects on goal directed walking performance (dependent variable: endpoint heading error to the left target (-15°) in actual condition, previously determined as being altered in USN+ participants by our team [249]) (Table 4.5). The independent variables were selected given that they were found to be affected in the USN+ participants and pertinent to be examined in the context of goal directed walking. Results show that the combination of the selected visual perceptual abilities along with the clinical measure of neglect (LBT in near space) and walking speed explains nearly 70% of the variance of endpoint heading error to the left/neglected target while walking ($R^2=0.67$, $F(6, 23) = 7.79$, $p = 0.0001$). LBT in near space, shape discrimination (left), optic flow location (left), optic flow coherence (right), and walking speed significantly predicted the outcome of interest ($\beta = 1.39, 3.16, -0.56, 0.24, -0.54$, $p<0.05$ respectively). Contrast sensitivity (left) emerged as a non-significant predictor ($\beta = 1.24$, $p=0.1198$). On the contrary, clinical USN tests along with walking speed are found to explain only 40% of the variance of endpoint heading error to the left/neglected target while walking ($R^2=0.40$, $F(4, 25) = 4.25$, $p = 0.0092$), where only the LBT in near space emerged as a significant predictor ($\beta = 1.26$, $p<0.05$).

4.6 DISCUSSION

The goal of this study was to estimate the extent to which post-stroke USN affects visual perceptual abilities of contrast sensitivity, shape discrimination, optic flow direction and coherence in left and right visual hemispaces. In addition, we sought to estimate the relationship between USN clinical tests and psychophysical tests, the preliminary sensitivity of psychophysical tests in detecting deficits that were otherwise left undetected using conventional methods, and the extent to which visual perceptual abilities contribute to goal-directed locomotion impairments in individuals with post-stroke USN. In support to our initially stated hypotheses, we identified that the presence of post-stroke USN significantly affects all visual perceptual abilities tested in the present study. Most of these psychophysical measures modestly correlated with USN clinical assessment outcomes. They also proved to be highly sensitive in detecting deficits in those with history of USN and several participants that were classified as USN- participants as per clinical USN assessment. Our findings also confirm the initially stated hypothesis in relation to the effects of these visual perceptual abilities on goal-directed walking alterations, where, in combination with USN clinical test result in near space and walking speed, they justify nearly 70% of the observed locomotor deficit.

Lateralized and non-lateralized deficits

For the first time, the present study identified both lateralized and non-lateralized visual perceptual deficits in individuals with post-stroke USN. For instance, contrast sensitivity was found to be more severely affected by USN in the left/”neglected” visual hemispace, suggesting a decreased ability to detect lower thresholds in the left/contralesional visual hemispace. This finding is consistent with previous research [14, 21-24], supporting a lateralized contrast sensitivity deficits. Contrast sensitivity is known to be dynamically modulated by saccades (e.g. [262]), predominantly in connection with the frontal eye fields (e.g. [263]) and the superior colliculi (e.g. [14, 15]), receiving retinal input predominantly from the contralateral hemifield [264]. As the sample of USN+ individuals in the present study constituted only those with right hemisphere lesions, the influence of the disrupted right hemisphere contrast sensitivity networks potentially accounts for the observed left/contralesional visual hemispace deficits.

In contrast, shape discrimination and optic flow direction discrimination abilities were found to be considerably worse in USN+ vs. the other two study groups in both the left/“neglected” and right/”non-neglected” hemispaces. It emerges that the parietal cortex hosts a common network that is involved in processing abilities of shape discrimination [265] and optic flow direction [266]. It is also established that the parietal lobe, known to be typically associated with neglect and spatial functions, is also involved in non-lateralized functions (e.g. sustained attention, spatial memory, alertness and arousal, etc.) [267, 268] that can co-exist and worsen spatial deficits in USN [99, 106]. We hypothesize that those possibly co-existing non-lateralized deficits could have led to the deficits in shape discrimination and optic flow direction abilities to emerge across the visual spectrum. This finding may also justify goal-directed locomotion deficits that were found in bilateral, left/ “neglected” and right/ “non-neglected” visual hemifields [36].

A question remains as to why the optic flow coherence ability was found to be affected by USN in the right/“non-neglected” visual hemisphere only. In this experiment, during a right motion coherence condition, moving dots in the left visual field are more spread (i.e. providing more motion coherence information), whereas those in the right visual field are more concentrated (i.e. providing less motion coherence information). Finding greater deficits in the right hemifield could be due to the fact that during that condition individuals actually had less motion coherence cues on the right (i.e. non-neglected hemifield) vs. left (i.e. neglected hemifield), leading to greater errors in detection. On the contrary, during a left motion coherence condition, participants benefited from more motion coherence cues on the right (“non-neglected” hemifield) where they were less dense, leading to fewer errors in detection. In relation to that, our team recently found that far-space navigation to left and right-sided targets in an ecologically designed virtual reality environment is affected in individuals with post-stroke neglect [269]. Thus, deficits in right hemifield’s optic flow coherence perception may actually play a role in ensuing mobility alterations to objects located in that hemifield.

Relationship and single case analyses: clinical implications

The current study evidenced that a low to moderate association between clinical assessments of USN and the majority of the tested higher-order perceptual abilities. Moreover, for the first time, we evidenced that measures of visual perceptual abilities are highly sensitive in detecting deficits related to USN that were otherwise left undetected using conventional USN paper-and-pencil

tests. All psychophysical tests were identified as being distinctly sensitive, where individuals with history of neglect in the acute phase of stroke recovery (i.e. no neglect on conventional tests during study) performed considerably worse in comparison to those without post-stroke neglect or without history of post-stroke neglect. More importantly, the testing paradigm used in this study unveiled worse performance in several individuals without post-stroke USN on the traditional evaluation tools (USN-) vs. healthy controls. This critical result points to potentially higher sensitivity of the psychophysical measures vs. traditional paper-and-pencil USN clinical tests in unveiling visual-perceptual deficits. In line with this, conventional paper-and-pencil tests have been criticized in the past for their lack of detecting subtle but clinically important deficits related to USN. For instance, studies reported that participants with ‘recovered’ USN based on conventional paper-and-pencil tests showed residual deficits when more complex, challenging and/or functional tasks were employed [32, 33, 74, 185]. This is particularly concerning given that these patients are at risk of being discharged into the community to resume their pre-stroke complex life roles and activities without proper diagnosis of the impact of USN or its symptoms on functional performance. Our results suggest that the visual-perceptual psychophysical testing could be an advantageous, affordable, simple, complementary and highly sensitive diagnostic method for this population.

USN is also known to be a strong prognosticator of poor functional recovery [63]. Acute USN was found to be one of the most significant predictors of community mobility and its severity in the acute stages relates to the extent of community mobility impairments in chronic phases of stroke recovery [26]. In fact, less than 40% of individuals with post-stroke USN regain independent walking abilities within the community [28]. Previous studies did address the issue of locomotor deficits in individuals with post-stroke USN [61, 71-73, 248, 249]. Deviations in walking trajectories [71] and collisions with environmental features such as moving [248] and static [73] obstacles may underlie the poor walking recovery and higher risk for falls observed in these individuals. In addition, a previous experiment in our laboratory determined that goal-directed locomotion in USN+ individuals is affected in both online (immediate/direct) and offline (perceptually/memory guided) type of conditions. This was reflected by larger mediolateral and heading endpoint errors when walking to left-sided targets [249]. Yet, in that same study, clinical assessment of USN in the near-space, along with walking speed, could only predict 30% of the observed locomotor deficits. We subsequently speculated that visual

perceptual abilities related to optic flow and visual attributes of the target to which the subject is moving towards can influence that relationship. The latter hypothesis is now supported by the results of the present study which demonstrates that USN in the near-space and walking speed, along with the abilities in visual perceptual functions, explain nearly 70% of the locomotor issues previously identified. This is in line with former studies evidencing that optic flow is an essential source of visual information that is used in functional activities such as the control of heading direction during locomotion [83-85]. Moreover, in accordance with two earlier studies providing preliminary evidence of USN affecting the use of optic flow information while walking [88, 270], the present study now offers leading evidence that i) USN+ individuals are severely affected in the processing of optic flow (direction and coherence) and ii) deficits in optic flow processing in USN+ individuals contribute to their locomotor impairments.

Additionally, our findings can be supported by functional neuroanatomy of the use of optic flow in heading estimation. For instance, Peuskens et al., 2001 [271] used positron emission tomography and functional magnetic resonance imaging to examine human cerebral activation pattern elicited when perceiving a ground plane optic flow pattern and arbitrating heading directions. The MT/V51 complex, including an inferior satellite, and dorsal intraparietal sulcus area, predominantly in the right hemisphere, and the dorsal premotor region bilaterally were found to be actively involved. Different brain areas such as the right parietotemporal junction [272], the angular gyrus, the right inferior parietal lobe, the parahippocampal region [69], and the right superior temporal cortex [70] have all been implicated in USN. It has been proposed that visual attention is mediated through a number of interconnected, yet functionally independent neuroanatomical networks, with the posterior parietal lobe being crucial for spatial attention and orienting [273, 274]. Therefore, the anatomical substrates of USN and those of optic flow processing in heading estimation are concurrent and underpins our findings.

This study has a few limitations. During the psychophysical assessments, an eye tracker was used to confirm that responses were provided when the participants were fixating on a given (central) area of the screen and not on surrounding areas, thus controlling for gaze angle at the time of response. In future studies, however, it would be valuable to study ocular movements such as fixations, re-fixations, and saccades during the entire experiments, as it could provide further insight into the observed behaviors. This study also excluded participants with USN

secondary to a left hemisphere stroke. The presence and expression of lateralized and non-lateralized deficits could differ in those with right vs. left hemisphere stroke, thus limiting the generalization of present findings to individuals with left neglect following a right hemisphere lesion.

Conclusion

In summary, the present study identified presence of lateralized and non-lateralized deficits in visual perceptual abilities in post-stroke USN and revealed that psychophysical measures of visual-perceptual abilities are sensitive in detecting USN-related deficits otherwise left undetected using USN conventional assessment tools. It further confirmed the initially stated hypothesis that alterations in visual-perceptual abilities constitute important contributors to goal-directed locomotion impairments observed in this population. This study provides substantial grounds for advancing the field of post-stroke USN rehabilitation, including the design and development of comprehensive and sensitive evaluation methods that will in return help guide treatment strategies. Our results highlight the importance of testing visual-perceptual ability to further understand the impact of USN on functional performance in daily life such as community mobility, the potential of integrating visual-perceptual testing in clinical practice to enhance its assessment and potentially guide intervention.

Table 4.1 Descriptive variables of study groups

USN+ (n=15)						
Participant	Sex (M:F)	Age (years)	Stroke Chronicity (years)	Type of Stroke	Stroke Location	
1	M	53.5	4.1	Ischemic	P-T	
2	M	72.3	2.7	Ischemic	Sylvian	
3	M	45.7	1.6	Hemorrhagic	P	
4	M	57.2	3.5	Hemorrhagic	P-T	
5	M	69.2	1.3	Ischemic	P-O	
6	M	51.5	1.6	Hemorrhagic	P-T	
7	M	54.3	0.8	Ischemic	Periventricular and cerebral peduncle	
8	F	69.0	0.9	Hemorrhagic	Subarachnoid hemorrhage grade 3, common right artery	
9	M	67.7	1.3	Ischemic	Pontocerebellar fibers	
10	F	50.8	2.5	Ischemic	P-T	
11	M	61.6	0.9	Ischemic	P-O	
12	M	73.1	0.3	Ischemic	P-O + midline shift	
13	M	53.7	0.9	Ischemic	F-T-Ins	
14	M	67.6	1.5	Ischemic	F-P	
15	F	56.5	1.3	Ischemic	Sylvian	
Mean ± SD Ratio (:)	12:3	60.2±8.8	1.6±1.0	11:4	NA	
USN- (n=15)						
16	M	50.6	0.5	Ischemic	P-O	
17	F	81.1	1.7	Ischemic	F-P	
18	F	43.0	1.7	Ischemic	Globus pallidus, putamen, anterior limb of internal capsule, caudate nucleus, cortical F-P-T	
19	M	58.0	1.4	Ischemic	Lateral medulla	
20	M	57.0	0.6	Ischemic	Sylvian: corona radiata, internal capsule, subcortical center	
21	M	40.8	4.0	Hemorrhagic	Basal ganglia and external capsule	
22	M	68.2	8.8	Ischemic	MCA territory	
23	M	51.5	1.3	Ischemic	Cerebellar, right lateral medullary	
24	M	54.0	1.2	Ischemic	Internal capsule, globus pallidus, lacunar corona radiata, F	
25	M	75.5	0.8	Ischemic	F + MCA territory	
26	M	46.7	1.1	Ischemic	Sylvian	
27	M	52.1	2.3	Ischemic	Posterior limb of right internal capsule	
28	M	73.8	0.7	Ischemic	Internal capsule	
29	M	77.3	2.9	Ischemic	MCA territory	
30	M	48.3	1.3	Hemorrhagic	Brainstem, periaqueductal	
Mean ± SD Ratio (:)	13:2	58.5±13.2	2.0±2.1	13:2	NA	
HC (n=15)						
Mean ± SD Ratio (:)	7:8	61.0±11.3	NA	NA	NA	

Table 4.1 Descriptive variables of study groups. Unilateral spatial neglect (USN); Standard Deviation (SD); Frontal (F); Parietal (P); Middle cerebral artery (MCA); Temporal (T); Occipital (O); Insular (Ins); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Healthy Controls (HC); Not applicable (N/A);

Table 4.2 USN descriptive variables

Participant	LBT near deviation (cm)	SCT near	SCT near time (min)	APT total	APT time (min)	APT allocentric	APT egocentric	USN type
USN+ (n=15)								
1	0.5	1.0	2.1	0.92	2.5	0	1	Hx
2	0.3	1.0	1.5	0.92	2.3	0	2	Hx
3	0.2	1.0	2.1	0.98	3.4	0	1	Hx
4	0.4	1.0	1.2	0.98	2.2	0	1	Hx
5	0.5	1.0	1.5	1	3.3	0	0	Hx
6	1.3	0.9	1.6	0.90	4.3	6	0	Allocentric
7	0.2	1.0	1.2	0.92	1.3	0	4	Egocentric
8	1.2	1.0	1.1	0.88	1.3	0	4	Egocentric
9	2.6	1.0	2.0	1	3.3	1	0	Near-space
10	0.8	1.0	1.2	1	3.2	3	0	Allocentric
11	1.1	1.0	2.5	0.88	8.1	10	2	Allocentric
12	2.2	0.9	3.2	0.94	14.6	7	3	Allocentric, Egocentric
13	0.4	0.6	1.5	0.76	3.0	7	1	Allocentric
14	1.2	1.0	1.5	0.78	4.4	3	2	Allocentric
15	1.1	0.7	2.0	0.82	3.5	35	7	Allocentric, Egocentric
<i>Mean ± SD</i>	0.9 ± 0.7	0.9±0.11	1.7 ± 0.5	0.9±0.08	4.0 ± 3.3	4.8±8.9	1.8±1.9	
<i>Range (-)</i>	0.2-2.6	0.7-1.0	1.1-3.2	0.7-1.0	1.2-14.6	0-35	0-7	NA
	***	**	**	**	**	**	**	
USN- (n=15)								
<i>Mean ± SD</i>	0.2 ± 0.1	0.9±0.0	1.1 ± 0.4	0.9±0.0	1.9 ± 0.6	0.06±0.2	0.6±0.7	
<i>Range (-)</i>	0.03-0.4	0.9-1.0	0.4-2.3	0.9-1.0	1.1-3.5	0-1	0-2	NA

Table 4.2 USN descriptive variables. Unilateral spatial neglect (USN); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Not applicable (NA); Line bisection test (LBT); Star Cancellation Test (SCT); Apples Test (APT); minutes (min); History of USN: Hx; Standard deviation (SD); Numbers in bold correspond to values above or below (where applicable) cut-off values. Star symbols indicate p-value <0.05*, 0.01** and 0.001***, respectively.

Table 4.3 Correlations between USN clinical tests and visual-perceptual thresholds

	Contrast Sensitivity L	Shape Discrimination L	Shape Discrimination R	OF Direction L	OF Direction R	OF Coherence R
LBT near (cm)	0.43 ***	0.23 NS	0.35 **	0.36 **	0.37 **	0.19 NS
SCT near	-0.32 *	-0.48 **	-0.36 **	-0.44 **	-0.49 ***	-0.14 NS
SCT near time (mins)	0.53 ***	0.35 **	0.26 *	0.38 **	0.4 **	0.25 *
APT	-0.4 **	-0.29 *	-0.08 NS	-0.31 *	-0.28 *	-0.1 NS
APT time (mins)	0.42 **	0.44 **	0.4 **	0.50 **	0.43 **	0.23 NS
APT – object centered	0.41 **	0.43 **	0.28 *	0.43 **	0.37 *	0.08 NS
APT – viewer centered	0.17 NS	0.11 NS	-0.02 NS	0.1 NS	0.06 NS	-0.09 NS

Tab. 4.3 Correlation coefficients for clinical USN tests and visual-perceptual (VP) abilities. Line bisection test (LBT); Star Cancellation Test (SCT); Apples Test (APT); minutes (mins); optic flow (OF); left (L); right (R); Tainted frames represent significant correlations: *, **, *** p-value <0.05, 0.01, 0.001, respectively. When significant, moderate (0.50-0.70), low (0.30-0.50) or negligible (0.00-0.30) are shown in black, dark grey, and light grey respectively.

Table 4.4 Single case analysis

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VP Test	Contrast Sensitivity LEFT			Contrast Sensitivity RIGHT			Shape Discrimination LEFT			Shape Discrimination RIGHT		
	USN+ vs. USN- Group											
Subject	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI
S1 (Hx)	4.01***	4.15	2.54-5.74	-0.75	-0.80	-1.37- -0.20	-0.15	-0.18	-0.69-0.33	-0.09	-0.09	-0.60-0.41
S2 (Hx)	3.09**	3.20	1.91-4.46	1.13	1.16	0.49-1.81	0.02	0.02	-0.47-0.53	1.12	1.16	0.48-1.80
S3 (Hx)	-0.14	-0.15	-0.65-0.36	-0.54	-0.56	-1.10- -0.01	-0.31	-0.32	-0.83-0.20	-0.38	-0.39	-0.91-0.13
S4 (Hx)	-1.64	-1.70	-2.4- -0.8	-0.75	-0.80	-1.37- -0.20	-0.32	-0.33	-0.84-0.19	-0.27	-0.28	-0.79-0.23
S5 (Hx)	1.45	1.50	0.74-2.23	-0.54	-0.56	-1.10- -0.01	19.75***	20.40	12.91-27.88	50.87***	52.54	33.30-71.77
S6	1.98*	2.05	1.13-2.94	-0.75	-0.80	-1.37- -0.20	-0.17	-0.18	-0.69-0.33	-0.01	-0.01	-0.51-0.49
S7	0.43	0.45	-0.09-0.97	-0.35	-0.36	-0.88-0.16	-0.22	-0.23	-0.73-0.28	-0.33	-0.34	-0.85-0.18
S8	1.54	1.60	0.81-2.36	-0.90	-0.93	-1.53- -0.31	-0.33	-0.34	-0.85-0.18	-0.21	-0.22	-0.730.29
S9	7.98***	8.25	5.18-11.30	9.55***	9.8	6.21- 13.50	-0.02	-0.03	-0.53-0.48	0.64	0.67	0.09-1.22
S10	-0.73	-0.75	-1.3- -0.16	-1.58	-1.63	-2.40- -0.83	-0.22	-0.23	-0.73-0.28	-0.24	-0.25	-0.76-0.26
S11	15.1***	15.60	9.86-21.32	3.93***	4.06	2.48-5.63	0.08	0.09	-0.42-0.59	-0.01	-0.01	-0.51-0.49
S12	480.92***	496.70	314.9-678.4	254.10***	262.43	166.40-358.45	2.17*	2.25	1.27-3.20	8.01***	8.27	5.20-11.34
S13	40.3***	41.70	26.4-56.9	2.84**	2.93	1.73-4.11	0.22	0.23	-0.28-0.73	-0.21	-0.22	-0.73-0.29
S14	2.03*	2.10	1.16-3.01	1.77*	1.83	0.98-2.66	5.80***	5.99	3.73-8.24	18.45***	19.0	12.06-26.05
S15	2.13*	2.20	1.23-3.14	0.42	0.43	-0.10-0.95	0.00	0.00	-0.50-0.50	-0.08	-0.09	-0.59-0.42
USN- vs. HC Group												
S16	-0.96	1.00	0.36-1.61	1.88*	1.95	1.06-2.81	-0.41	-0.42	-0.95-0.10	-1.45	-1.50	-2.23- -0.74
S17	0.80	0.82	0.22-1.40	0.73	0.75	0.16-1.31	1.66*	1.71	0.89-2.50	2.98**	3.08	1.83-4.31
S18	-0.20	-0.21	-0.71-0.30	-0.73	-0.75	-1.31- -0.16	0.06	0.07	-0.43-0.57	-1.45	-1.50	-2.23- -0.74
S19	0.00	0.00	-0.50-0.50	1.21	1.25	0.55-1.92	0.41	0.42	-0.10-0.95	-1.04	-1.08	-1.71- -0.42
S20	-0.26	-0.27	-0.78-0.24	-0.04	-0.05	-0.55-0.45	66.39***	68.57	43.47-93.66	28.80***	29.75	18.85-40.64
S21	0.60	0.62	0.05-1.16	0.14	0.15	-0.36-0.65	0.06	0.07	-0.43-0.57	-0.64	-0.66	-1.21- -0.09
S22	0.80	0.82	0.22-1.40	0.00	0.00	-0.50-0.50	0.89	0.92	0.30-1.52	2.09*	2.16	1.21-3.09
S23	-1.13	1.17	-1.8- -0.49	-2.66	-2.75	-3.86- -1.61	-1.24	-1.28	-1.96- -0.58	-1.69	-1.75	-2.55- -0.92
S24	0.53	0.55	-0.00-1.08	1.54	1.60	0.81-2.36	0.06	0.07	-0.43-0.57	-0.08	-0.08	-0.58-0.42
S25	1.53	1.58	0.80-2.34	2.76**	2.85	1.68- 4.00	0.89	0.92	0.30-1.52	-1.77	-1.83	-2.66- -0.98
S26	0.33	0.34	-0.18-0.86	-0.73	-0.75	-1.31- -0.16	2.07*	2.14	1.19-3.06	1.93*	2.00	1.09-2.87
S27	-0.06	-0.06	-0.57-0.43	-1.69	-1.70	-2.49- -0.88	-1.24	-1.28	-1.96- -0.58	0.16	0.17	-0.33-0.67
S28	0.46	0.48	-0.06-1.01	1.35	1.40	0.66-2.10	1.66*	1.71	0.89-2.50	0.40	0.42	-0.11-0.93
S29	-1.77	-1.82	-2.6- -0.97	1.79*	1.85	0.99-2.68	0.17	0.21	0.52-1.87	0.40	0.42	-0.11-0.93
S30	-1.30	-1.34	-2.0- -0.62	-0.38	-0.40	-0.92-0.13	-0.96	-1.00	-1.61- -0.36	-1.77	-1.83	-2.66- -0.98

B

VP Test	OF Direction LEFT			OF Direction RIGHT			OF Coherence LEFT			OF Coherence RIGHT		
	USN+ vs. USN- Group											
Subject	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI	t-value	Z score (effect size)	95% CI
S1 (Hx)	2.92**	3.09	1.79-4.22	6.93***	7.20	4.51-9.88	3.71**	3.83	2.33-5.32	4.75***	4.90	3.03-6.76
S2 (Hx)	3.60***	3.72	2.26-5.17	7.99***	8.26	5.19-11.32	0.13	0.143	-0.36-0.64	0.51	0.534	-0.01-1.06
S3 (Hx)	-0.65	-0.67	-1.2 - -0.1	0.16	0.17	0.34-0.68	-0.25	-0.25	-0.76-0.26	1.02	1.05	0.40-1.68
S4 (Hx)	-0.21	-0.22	-0.72-0.29	-0.52	-0.53	-1.0-0.01	1.90*	1.97	1.07-2.84	1.00	1.04	0.39- 1.66
S5 (Hx)	3.60***	3.72	2.26-5.17	7.99***	8.26	5.19-11.32	5.36***	5.53	3.44-7.62	5.01***	5.18	3.21-7.13
S6	0.34	0.35	0.17-0.87	2.10*	2.17	1.21-3.10	-0.23	-0.24	-0.74-0.27	0.75	0.77	0.18-1.34
S7	-0.74	-0.76	-1.3 - -0.1	-0.89	-0.85	-1.4- -0.2	0.05	0.05	0.44-0.56	1.28	1.33	0.61-2.02
S8	0.55	0.56	0.01-1.10	0.83	0.86	0.25-1.45	-0.78	-0.80	1.38- -0.21	-0.97	-1.00	-1.61- -0.36
S9	2.86**	2.95	1.75-4.14	6.66***	6.88	4.31-9.45	5.36***	5.53	3.44-7.62	5.01***	5.18	3.21-7.13
S10	-0.25	-0.26	-0.77-0.25	-0.48	-0.50	-1.0-0.04	0.04	0.04	-0.45-0.55	0.68	0.71	0.13-1.27
S11	3.60***	3.72	2.26-5.17	0.02	0.02	-0.47-0.53	0.03	0.03	-0.47-0.53	0.61	0.63	0.07-1.18
S12	3.60***	3.72	2.26-5.17	7.99***	8.26	5.19-11.32	-1.08	-1.11	-1.75- -0.45	-1.51	-1.56	-2.31- -0.78
S13	3.60***	3.72	2.26-5.17	7.99***	8.26	5.19-11.32	1.38	1.43	0.69- 2.14	3.88	4.00	2.44- 5.55
S14	2.61**	2.70	1.58-3.80	6.65***	6.86	4.29-9.42	-0.52	-0.53	-1.07-0.01	-0.91	-0.94	-1.54- -0.32
S15	3.60***	3.72	2.26-5.17	7.99***	8.26	5.19-11.32	1.35	1.40	0.66-2.11	2.20*	2.27	1.29-3.24
USN- vs. HC Group												
S16	-0.47	-0.48	-1.01-0.05	-0.91	-0.94	-1.54- -0.31	-0.98	-1.01	-1.62- -0.37	-0.75	-0.77	-1.34- -0.18
S17	1.71*	1.77	0.93-2.58	2.27*	2.34	1.33-3.33	-1.12	-1.16	-1.81- -0.49	-0.61	-0.63	-1.18- -0.06
S18	-0.66	-0.68	-1.2- -0.1	-0.80	-0.83	-1.40- -0.22	1.11	1.14	0.47-1.79	0.68	0.70	0.12-1.26
S19	-0.55	-0.57	-1.1- -0.01	-0.65	-0.67	-1.22- -0.10	-0.09	-0.09	-0.59-0.41	-0.23	-0.24	-0.75-0.27
S20	0.87	0.90	0.28-1.49	0.03	0.03	-0.46-0.54	-0.02	-0.02	-0.53-0.48	0.16	0.17	-0.34-0.68
S21	-0.56	-0.58	-1.1- -0.02	-0.96	-1.00	-1.61- -0.36	0.60	0.62	0.06-1.17	-0.10	-0.11	-0.61-0.40
S22	4.92**	5.08	3.15-7.01	-0.57	-0.59	-1.13- -0.03	0.02	0.02	-0.48-0.53	0.35	0.36	-0.16-0.88
S23	-1.23	-1.33	-2.0- -0.62	-1.07	-1.10	-1.74- -0.44	-0.19	-0.20	-0.71-0.31	-0.43	-0.44	-0.96-0.09
S24	-0.14	-0.15	-0.65-0.36	2.00*	2.06	1.14- 2.96	-0.10	-0.11	-0.61-0.40	0.70	0.72	0.14-1.28
S25	8.17***	8.43	5.30-11.56	1.37	1.42	0.68- 2.13	2.14*	2.21	1.25- 3.16	2.43**	2.51	1.45-3.55
S26	1.22	1.26	0.56-1.93	0.52	0.54	-0.005-1.08	-0.67	-0.69	-1.24- -0.11	-0.65	-0.67	-1.23- -0.10
S27	-0.32	-0.3	-0.85-0.18	-0.56	-0.58	-1.12- -0.02	-0.13	-0.14	-0.65-0.36	-0.73	-0.75	-1.32- -0.16
S28	0.82	0.85	0.24-1.43	0.0	0.0	-0.50-0.50	0.10	0.11	-0.40-0.61	-0.043	-0.04	-0.55-0.46
S29	2.33*	2.41	1.38-3.42	0.45	0.47	-0.07-0.99	-1.03	-1.04	-1.67- -0.39	-0.66	-0.68	-1.24- -0.11
S30	-0.73	-0.76	-1.3- -0.14	-0.86	-0.89	-1.48- -0.28	-0.90	-0.93	-1.53- -0.31	-0.82	-0.85	-1.43- -0.24

Table 4.4A&B Single-case analysis of single USN+ participants vs. USN- group (as control data); and single USN- participants vs. HC group (as control data) on the performance of all psychophysical tests. History (Hx); Subject (S); Optic Flow (OF); Subjects with post-stroke USN (USN+); Subjects post-stroke without USN (USN-); Healthy controls (HC); Unilateral spatial neglect (USN). Light grey selections represent individual cases whose performance is considerably worse than the comparison group ($p < 0.05$); *, **, *** p-value < 0.05 , 0.01 , 0.001 , respectively.

Table 4.5 Regression analysis results

Dependent variable: endpoint heading error to left target (-15°) in actual condition $R^2=0.67, F(6, 23) = 7.79, p = 0.0001$				
<i>Variable</i>	<i>B</i>	<i>Pr > t </i>	<i>95% Confidence Interval</i>	
Intercept	1.40	**	0.28	2.52
LBT near space	1.39	***	0.79	1.99
Contrast sensitivity L	1.24	NS	-0.34	2.83
Shape discrimination L	3.16	**	1.078	5.24
Optic flow location L	-0.56	***	-0.87	-0.25
Optic flow coherence R	0.24	**	0.001	0.48
Walking speed	-0.54	*	-1.02	-0.05
				Adj $R^2 = 0.58$

Dependent variable: endpoint heading error to left target (-15°) in actual condition $R^2=0.40, F(4, 25) = 4.25, p = 0.0092$				
<i>Variable</i>	<i>B</i>	<i>Pr > t </i>	<i>95% Confidence Interval</i>	
Intercept	-0.60	NS	-5.26	4.06
LBT near space	1.26	***	0.56	1.95
SCT near space	-0.81	NS	-6.57	4.95
Apples Test	4.10	NS	-3.38	11.60
Walking speed	-0.40	NS	-1.08	0.27
				Adj $R^2 = 0.30$

Tab. 4.5 Regression analysis with endpoint heading error to left target (-15°) in action condition as the dependent variable; parameter estimates (β); confidence interval (CI); not significant (NS); Line Bisection Test (LBT); Star Cancellation Test (SCT); left (L); right (R); *, **, *** p -value <0.05, 0.01, 0.001, respectively.

Figure 4.1 Psychophysical testing setup



Figure 4.1 Psychophysical testing setup includes a computer monitor, chin rest, and eye tracker.

Figure 4.2 Psychophysical testing paradigms

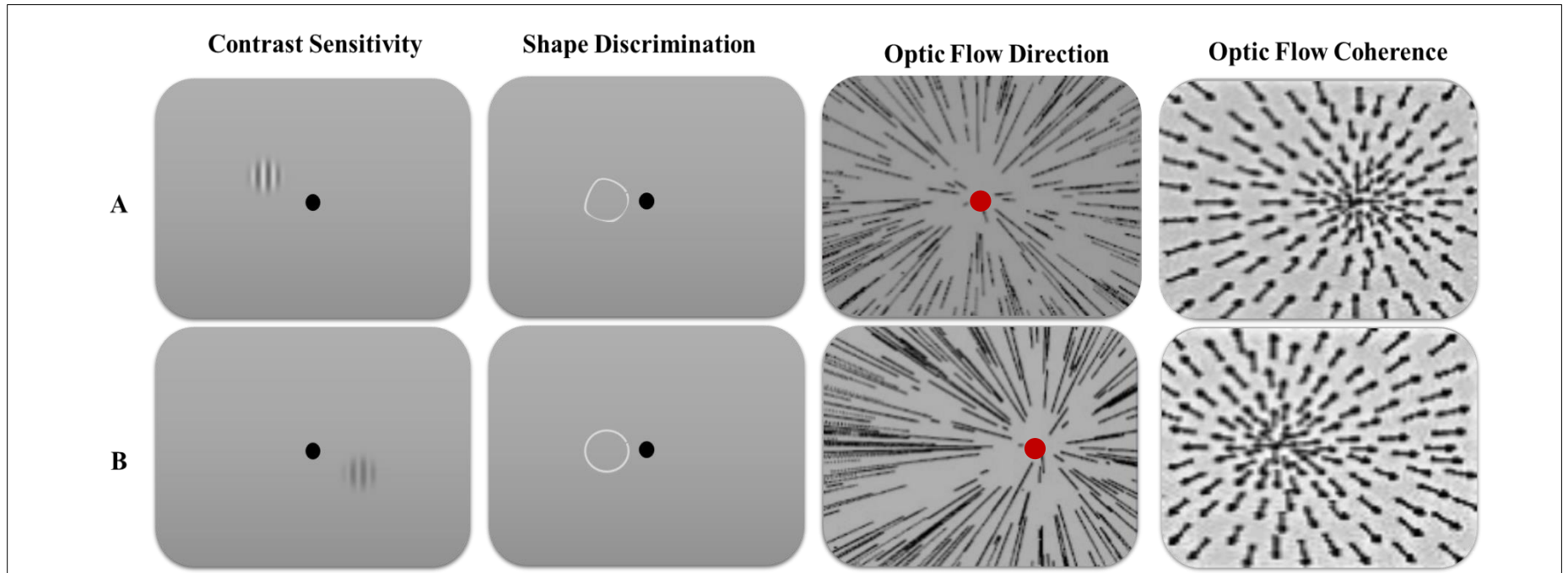


Figure 4.2 Example of the testing paradigms. In *contrast sensitivity* task, stimulus of a high contrast is presented in the top/left location (A) followed by a stimulus of a lower contrast presented in the bottom/right location (B). In *shape discrimination* task, test stimulus (i.e. deformed circle) is presented (A), followed by the standard stimulus (i.e. perfect-shaped circle) (B). In *optic flow direction* task, standard stimulus (i.e. optic flow with focus of expansion [red dot] in the middle) is presented (A), followed by the test stimulus (i.e. optic flow with a focus of expansion shifted to the right) (B). In the *optic flow coherence* task contraction in the right (A) vs. expansion (B) in the left hemispaces are presented.

Figure 4.3 Visual perceptual abilities results

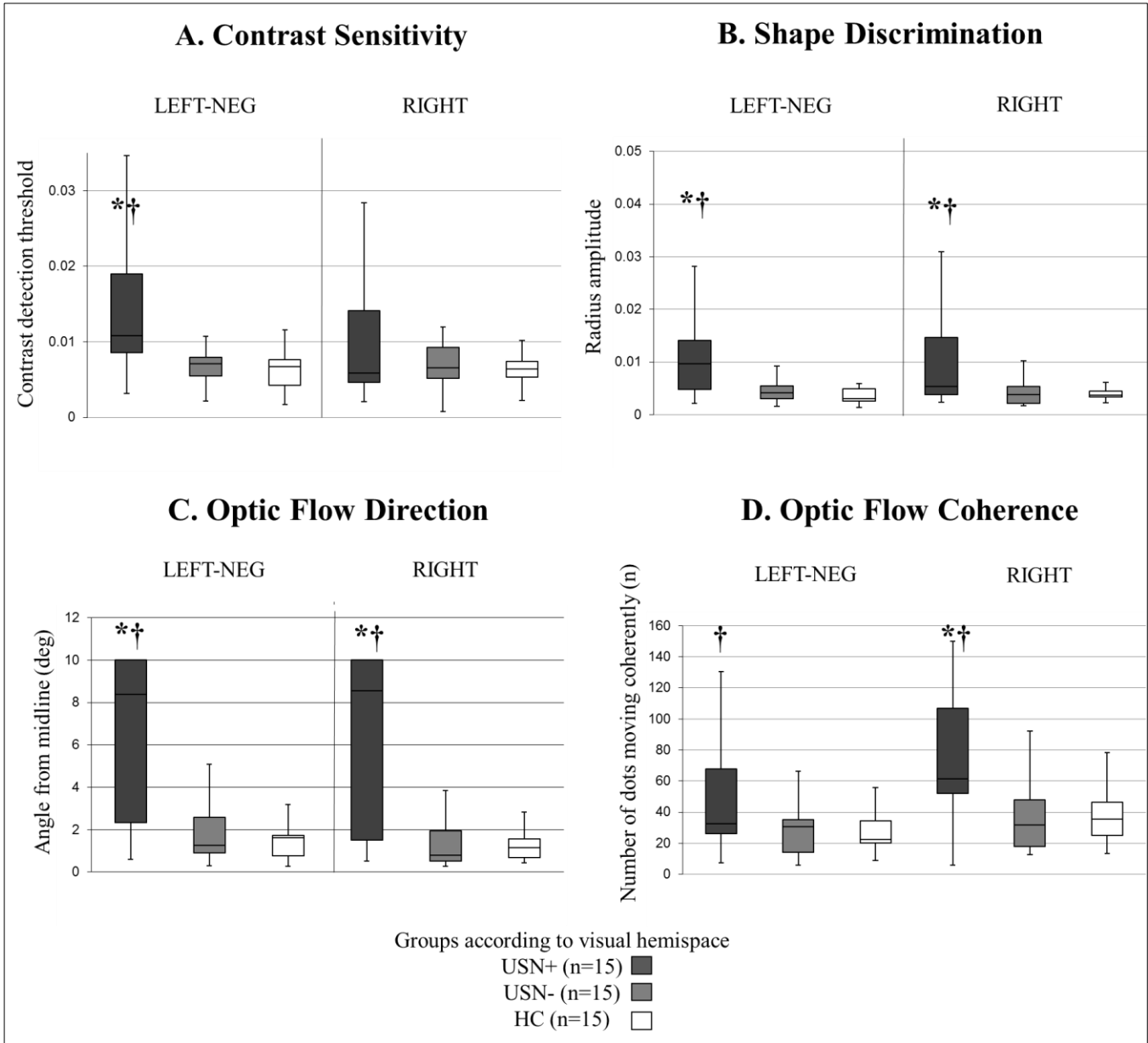


Figure 4.3 Results of the higher-order visual perceptual abilities of contrast sensitivity (A), shape discrimination (B), optic flow direction (C) and optic flow coherence (D) according to the three study groups (USN+ in dark grey; USN- in light grey, HC in white) for the left/neglected (neg) and right visual hemispaces. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). * and † symbols indicate statistically significant differences between USN+ vs. USN- group, and USN+ vs. HC groups, respectively.

CHAPTER 5

5.1 PREFACE

So far, we determined that: 1) post-stroke USN negatively impacts goal-directed locomotion (Chapter 2) and navigation in far space (Chapter 3) by using simple/single-target environments; 2) USN affects visual-perceptual abilities (Chapter 4) and; 3) that these tasks were sensitive in detecting USN signs and symptoms that were otherwise left undetected using conventional paper-and-pencil tests. We now sought to build and test a tool that is more representative of everyday environments and mobility-related activities (e.g. requiring space navigation), and that is potentially more ecologically valid than conventional methods.

Traditional USN measures are known to not grasp all the facets of USN's multimodal and heterogeneous presentation. Despite an extensive body of research on USN standardized assessment tools, there is currently no gold standard [174]. Similar to our results, others reported that participants with 'recovered' USN based on conventional paper-and-pencil tests showed residual deficits when more complex, challenging and/or functional tasks were employed [32, 33, 74, 185], indicating traditional tool's lack of sensitivity. With current advancements in the use of technologies in rehabilitation, it is highly relevant and timely to further the development of USN assessment and rehabilitation techniques, by incorporating state-of-the-art technologies like virtual reality (VR).

Accordingly, we have developed a novel tool, the Ecological VR-based Evaluation of Neglect Symptoms (EVENS) that is immersive and is in 3-D. It consists of two ecological scenes (simple vs. complex) with variable perceptual-attentional demands where functional tasks of object detection and goal-directed navigation are performed. To further assist its development and examine its feasibility, in **Manuscript №4**, we aimed to investigate the effects of post-stroke USN on functional VR tasks.

Chapter 4 of this PhD dissertation addresses **general objective 4** and **specific objectives 4.1** and **4.2** of my PhD research agenda. This chapter includes excerpts from **Manuscript №4** of this dissertation, entitled "*Ecological virtual reality evaluation of neglect symptoms (evens): effects of virtual scene complexity in the assessment of post-stroke unilateral spatial neglect*".

MANUSCRIPT № 4

ECOLOGICAL VIRTUAL REALITY EVALUATION OF NEGLECT SYMPTOMS (EVENS): EFFECTS OF VIRTUAL SCENE COMPLEXITY IN THE ASSESSMENT OF POST-STROKE UNILATERAL SPATIAL NEGLECT

Tatiana OGOURTSOVA^{1,2*}, Philippe S. ARCHAMBAULT^{1,2}, Samir SANGANI², Anouk LAMONTAGNE^{1,2}

¹School of Physical and Occupational Therapy,
McGill University,
3654 Promenade Sir-William-Osler
Montreal, Quebec, Canada
H3G 1Y5

²Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital,
Site of Centre for interdisciplinary Research
in Rehabilitation of Greater Montreal
3205 Place Alton-Goldbloom
Laval, Quebec, Canada
H7V 1R2

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DECLARATION OF INTEREST

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5.2 ABSTRACT

Background: Unilateral spatial neglect (USN) is a highly prevalent and disabling post-stroke impairment. USN is traditionally assessed with paper-and-pencil tests that lack ecological validity, generalization to real life situations and are easily compensated for in chronic stages. Virtual reality (VR) can, however, counteract these limitations. **Objective:** We aimed to examine the feasibility of a novel assessment of USN symptoms in a functional shopping activity, the Ecological VR-based Evaluation of Neglect Symptoms (EVENS). **Methods:** EVENS is immersive and consists of simple and complex 3-D scenes depicting grocery shopping shelves, where joystick-based object detection and navigation tasks are performed while seated. Effects of virtual scene complexity on navigational and detection abilities in patients with (USN+, n=12) and without (USN-, n=15) USN following a right hemisphere stroke and in age-matched healthy controls (HC, n=9) were determined. **Results:** Longer detection times, larger mediolateral deviations from ideal paths and longer navigation times were found in USN+ vs. USN- and HC groups, particularly in the complex scene. EVENS detected lateralized and non-lateralized USN-related deficits, performance alterations that were dependent or independent of USN severity, and performance alterations in three USN- subjects vs. HC. **Conclusion:** EVENS' environmental changing complexity, along with the functional tasks of far space detection and navigation can potentially be clinically relevant and warrant further empirical investigation. Findings are discussed in terms of attentional models, lateralized vs. non-lateralized deficits in USN, and tasks-specific mechanisms.

Keywords: CVA, hemispatial neglect, perceptual disorder, assessment, virtual reality immersion therapy, diagnostic techniques and procedures;

5.3 BACKGROUND

Unilateral spatial neglect (USN) is a common and highly debilitating consequence of stroke, characterized by a deficit in directing attention to stimuli located in the contralesional hemispace [43]. USN is experienced by nearly 50% of individuals with a right hemisphere lesion [10] and while it can resolve spontaneously within the acute post-stroke period, symptoms of USN and their dramatic impact on functional performance may persist in up to 75% of initially diagnosed cases [10]. Unfortunately, those numbers are expected to surge with the rise in the aging population, given that post-stroke USN is associated with increase in age [45].

USN is known to adversely affect patient-related outcomes such as functional independence, community reintegration and quality of life and the sensitive detection of USN symptoms and their effects on everyday functional tasks is crucial [63, 247]. Nevertheless, USN represents a real challenge for rehabilitation professionals to properly detect and to characterize its direct impact on functional performance given the lack of sensitivity and ecological validity of conventional assessment methods [10, 246]. This challenge could be accounted for by USN's high heterogeneity, which is evident in ongoing debates amongst researchers with respect to its anatomical, physiological, and conceptual models. The variety in behavioral manifestations of neglect includes different modality categories (sensory vs. premotor) [51], spatial representations (egocentric vs. allocentric) [53], and range of space (personal, near- and far-extraperosnal) [54, 275]. Other, "non-spatial" factors such as level of alertness [158, 276], sustained attention [101], increased cognitive load [277-280] and increased perceptual demands [281-283] are known to affect the severity of USN's spatial deficits.

It is therefore not surprising that conventional assessments do not grasp all the facets of USN's multimodal and heterogeneous presentation. Despite an extensive body of research on USN standardized assessment tools, there is currently no gold-standard [174]. Moreover, studies reported that participants with 'recovered' USN based on conventional paper-and-pencil tests showed residual deficits when more complex, challenging and/or functional tasks were employed [32, 33, 74, 185]. The commonly employed measures are not sufficiently sensitive to detect subtle but clinically important deficits [34], to predict functional performance in daily life and are constrained to assessing USN within the near-extraperosnal space only, using static, 2-D methods. This is of great concern given that these individuals are at risk of being discharged into

the community to resume their pre-stroke life roles and activities (e.g. community ambulation, instrumental activities of daily life, driving, parenting, etc.) without proper diagnosis of the impact of USN or symptoms of USN on functional performance. Therefore, with current advancements in the use of technologies in rehabilitation, it is highly relevant and timely to further the development of USN assessment and rehabilitation techniques, by incorporating state of the art technologies like virtual reality (VR), that could address the aforementioned restrictions.

VR affords us the possibility to employ 3-D images or stereovision, far space and dynamic targets, functional everyday tasks, and modifiable spatial and non-spatial factors. Different VR-based USN assessments have been proposed, and some were found to be more sensitive in detecting the presence of deficits in cases where conventional USN assessment was negative (reviewed in [36]). However, these studies have several limitations including the use of non-functional tasks (e.g. [184, 190]) that do not easily translate into real functional performance in daily life; small sample sizes (e.g. [191]); comparing performances of patients with USN to that of healthy control individuals, rather than to those with stroke but no USN (e.g. [184]); or using 2-D displays (e.g. [31, 34, 189, 191]) that lack immersiveness and interactivity [192]. We believe that the latter limitation is of particular importance, given that USN is largely viewed as an attention-based deficit and the use of full immersion in its assessment can help limit possible attentional shifts to the physical world that could influence performance.

In addition, previous VR-based studies have not evaluated the impact of increased perceptual-attentional demands (e.g. a more crowded, ecological scene with multiple objects) within an immersive VR scene on the functional performance of object-detection and space navigation patients with post-stroke USN. Previously, detection time and the time to complete a task have both been found to be affected in USN+ patients, compared to either USN- patients or healthy controls [75, 185, 193], suggesting that such measures can be sensitive to the presence of USN. In addition, there is some indication that USN influences navigation abilities (e.g. wheelchair navigation [77]), as such tasks involve both the near and far space perception and adjustment, and can be performed towards changing directions and within different environments. Thus, examining target detection and goal-directed navigation in the far-extrapersonal space, while covering both the contra- and ipsilesional space and manipulating perceptual-attentional

demands, is relevant and has the potential to complement previous findings and deepen our understanding of the poor functional recovery that so often accompanies USN. It is possible that a more complex/crowded virtual environment, as opposed to a simple/sparse environment, will result in more noticeable deficits in patients with post-stroke neglect and thus, be more predictive of and generalizable to the real-life functional performance. A VR assessment that is performance-based thus has the potential to further inform clinicians managing stroke survivors with USN on their functional performance, while providing additional benefits in terms standardization, space, safety, objectivity and possibly sensitivity and responsiveness compared to simulated task observation in a real environment.

Accordingly, we have developed a novel tool, the Ecological VR-based Evaluation of Neglect Symptoms (EVENS) that is immersive and is in 3-D. It consists of two ecological scenes with variable perceptual-attentional demands where functional tasks of object detection and goal-directed navigation are performed. To further assist its development and examine its feasibility, in this proof-of-concept study we aimed to investigate the effects of post-stroke USN on functional tasks of detection and navigation as performed in VR.

5.4 METHODS

5.4.1 Study design

A cross-sectional, observational study design was used.

5.4.2 Study participants

Adult individuals with stroke were included based on the following inclusion criteria: presence of a first time right hemisphere stroke, with or without left USN (as per one or more of the following tests: Line Bisection Test (LBT) [181], Star Cancellation Test (SCT) [175], and/or Apples Test (APT) [53] on testing, or history of USN as per medical chart); and right handedness. As a first step, it was deemed suitable to include individuals with left USN only (i.e. right hemisphere stroke), the latter being more prevalent [284-286] and known to have larger effects on functional outcomes such as detection time [193] than right USN following left hemisphere brain injury.

Individuals were excluded based on the following criteria: presence of primary visual impairment that impedes normal or corrected-to-normal visual acuity (score $\leq 20/25$ on the Early Treatment Diabetic Retinopathy Study Chart [250]); presence of moderate cognitive impairment (score ≤ 22 /on the Montreal Cognitive Assessment [251]); presence of apparent sensorimotor deficits of the right (ipsilesional/non-paretic) upper extremity that can interfere with the use of the joystick (as per observation); and presence of a visual field defect (as per medical chart, Goldman perimetry or computerized equivalent). In addition, age-matched (± 5 years) healthy controls were recruited following the same inclusion/exclusion criteria where applicable.

Participants were recruited from three clinical sites of Centre de Recherche Interdisciplinaire en Réadaptation du Montreal Métropolitain (CRIR). The study was approved for ethics by the CRIR Institutional Review Board. All study participants reviewed and signed the informed consent before enrolling in the study.

5.4.3 Experimental set-up and procedure

The process of data collection consisted of a clinical evaluation of USN, VR-based detection and navigation tasks.

Evaluation of USN

Presence, severity and type of USN were determined using the LBT, SCT, and the APT. All tests were chosen with care as to their psychometric properties [53, 223, 252].

Apparatus and stimuli: A previously employed set-up was used to assess near and far space USN [61, 224]. It was deemed relevant to assess far space USN, in addition to traditional near space evaluation, given that the VR-based task is performed in far space and one of the aims consisted of determining whether far and/or near space USN could explain the VR-based performance in far space. Participants were positioned 40 cm and 320 cm away from the screen for near and far USN testing, respectively. The LBT and SCT were displayed on a projector screen with the appropriate sizes (near space: 21 x 28 cm; far space: 168 x 224 cm) to keep the visual angle of each array and the retinal size image constant during both testing conditions. Each displayed test contained a middle point, with respect to which the participants' sternum was aligned with a laser. A chin rest was used to minimize head movements and to ensure a constant viewing angle.

Responses were provided by the participants using a hand-held laser pointer. Responses were marked directly on the computerized test form by the investigator using a wireless mouse and the pencil in Microsoft Paint®. The order of tasks and distance conditions was randomized across participants. The APT was presented on a sheet of paper on a steady table, aligned with the participant's midline (i.e. sternum) and fixed on the table with tape to prevent possible shifts.

Procedure: In the LBT, participants were asked to find the midline of each presented line, starting from the top line. In the SCT, participants were instructed to find all the small stars among the distractors. In the APT, participants were instructed to find all the complete-shaped apples. For the scoring of the LBT, the deviation from the center in each line was measured and averaged across all lines. An absolute mean deviation of more than 6.0 mm to the right is indicative of *left near space USN* on the near LBT test [181], and 4.8 cm to the right is indicative of *left far space USN* on the far LBT test. An average percentage of deviation from midline was also computed for near and far space LBT to estimate the difference in severity between near and far space USN. For the scoring of the SCT, the number of small cancelled stars was divided by the total number of small stars to compute the laterality index score. Scores between 0 and 0.46 are indicative of *left near space USN* [181]. For the scoring of the APT, the total number of crossed out complete and incomplete shape apples was computed, and an asymmetry scores for egocentric and allocentric USN were calculated [53]. The overall cutoff of <42/50 is indicative of *near space USN*. Asymmetry cutoff score across the page of <-2 or >2 (difference between right side and left sided targets cancelled) is indicative of *egocentric near space USN*. Asymmetry cutoff score across the cancelled distractors on the page with left vs right sided openings of <-1 or >1 is indicative of *allocentric near space USN*. All cancellation tests were timed.

In terms of neglect severity, it has been strongly suggested that a battery of tests is more sensitive to detect the presence of neglect than a single test [172]. However, no clear guidelines exist defining the overall USN severity rating when multiple tests are used. For instance, Lindell et al. (2007) defined mild vs. moderate/severe USN as positive results on 1-3 tests vs. 4 or more tests, respectively [172]. In the present study, this proposed classification was further modified to separate moderate vs. severe cases. Severity of USN was thus characterized by a positive result on 1 to 3, 4, and 5 or more clinical tests for mild, moderate and severe USN, respectively.

Outcomes: Outcomes retained for analysis included: *overall USN severity* (mild, moderate or severe), (2) *USN range of space severity* (near and/or far space), and (3) *USN spatial representation type* (allocentric vs egocentric) within one's reaching distance (near space) and/or beyond reaching distance (far space). Participants were included in the group of individuals with USN (USN+) if they had USN on one or several of the aforementioned tests, or if they had a history of USN as per their medical chart.

Detection and goal-directed navigation in simple vs. complex virtual scenes

Apparatus and Stimuli: A simulation consisting of two virtual scenes was created in the Unity® (Unity Technologies SF, California, USA) game engine: the complex and simple scenes (Figure 5.1). The viewing media was a helmet mounted display (HMD - NVisor™, NVIS Inc, Reston, VA, USA) with field of view of 60° diagonal, 30° vertical by 40° horizontal, Extended Graphics Array resolution 1024 x 1280, frequency of 60 Hz, 1 kilogram in weight, and blocking all peripheral vision with only the virtual environment (VE) visible to the participant. Responses were provided with the dominant, non-paretic right hand using a stationary and fixed joystick (Attack3™, Logitech, Newark, CA, USA).

The scenes contained a symmetrical and richly-textured room displaying a grocery shopping aisle with three shelves located in front and 3m away from the participants. For the simple scene, the target of interest (blue cereal box 'Pop Start') appeared stand-alone on the middle/eye level shelf at one of the following five locations, $\pm 40^\circ$, $\pm 20^\circ$, 0° , in a random order. For the complex scene, the target of interest appeared at the same locations but amongst additional grocery items on the same shelf (e.g. similar looking cereal boxes). Supplementary items on other shelves and grocery carts were also presented. A gradient in response to targets located centrally vs. laterally ($\pm 30^\circ$) was previously reported in USN+ individuals [75]. For the current experiment, we intended to capture neglect's gradient reported previously over a larger portion of the visual spectrum, while presenting maximal target eccentricities that can feasibly and comfortably be attained using eye in head horizontal shifts (i.e. $\pm 20^\circ$ and 40°). The scenes were viewer-centered, and the HMD was not head-tracked, allowing the scene to remain stable and centered despite head rotations and eliminating the need to stabilize the head during navigation and detection trials. This also allowed for standardization of VR tasks vs. traditional tests, where a chin rest was employed to prevent head rotations. Navigation in the scene, when required, was

possible using the joystick in the mediolateral (left/right) and anterior-posterior (front/back) planes using self-controlled speeds of displacement ranging from 0 m/s (i.e. complete stop) to 1.2 m/s (maximum speed). Both experiments were performed while seated.

The scene depicting grocery shelves and shopping items was selected given that grocery shopping in a store represents a common, universal, everyday activity that is neutral in terms of gender (male and female) / culture & class (performed by people all around the world, irrespective of social class or culture) /adult-age (young and older adults). In addition, since one of the aims was to determine the effects of the virtual-scene complexity (i.e. that is representative of the complexity of real life environment) on the performance of individuals with post-stroke USN, the scene of the grocery aisle was selected as it can be easily adjusted from its simple to complex presentation.

Procedure: Practice trials were provided prior to the actual experiment until the participant felt comfortable in executing the tasks. For the detection task, participants were instructed to press the joystick button with their index finger of the non-paretic (right) hand as soon as they detected the target. An auditory feedback (“beep” sound) was provided once the joystick button was pressed. Catch trials with no target appearing were also introduced to minimize response bias. Participants were instructed that in the absence of a target they should refrain from clicking the joystick button and wait for the next trial to appear. Five trials per condition (5 target locations + no target condition) were performed for a total of 30 responses each for the simple and complex scenes. In cases where the participant was not able to detect the target for more than 30 seconds, he/she was provided verbal encouragement from the examiner to continue visual scanning. In all trials except catch trials, the target remained on the screen until a response was provided by the participant.

For the navigation task, participants were instructed to navigate using the joystick in the mediolateral and anterior-posterior planes using self-controlled speed to reach the target in the most direct way possible. The navigation trials ended when the participant reached within 0.5m (anterior direction) of the target, so as not to collide with the shelf. Five trials per target location were performed for a total of 25 responses for the simple and complex scenes.

Outcomes: The outcomes for the detection task was *detection time (s)*, defined by the time at which the participant detected (i.e. pressed the joystick button) the target in the detection task.

Outcomes for the navigation task included: (1) *Maximal mediolateral deviation (mMDL)* from an ideal navigation trajectory that is represented by the most direct route possible from the start position to the respective target in the navigation task; and (2) *Navigation time to target (s)*, defined as the time required by the participant to navigate to the target.

5.4.4 Data and statistical analysis

The simulation data was recorded at 120 Hz and stored for off-line analyses in Matlab®. Participants' responses on the USN tests and detection/navigation tasks were averaged across conditions, such that mean values could later be compared across groups and between conditions. All statistical analyses were performed using SAS® 9.4 (SAS Institute Inc.). Significance was accepted at $p \leq 0.05$. Groups' demographics and USN characteristics were analysed using descriptive summary statistics and test of normality and equality of error variance were performed on all study variables. Depending on data distribution, one-way ANOVA or the Kruskal Wallis test were used to compare demographic characteristics between groups. Difference in USN severity (near vs. far) was evaluated using the Wilcoxon Signed Rank Sum test.

The effects of scene complexity and target location on detection time and goal-directed navigation performances were examined using a repeated measure mixed model approach, with 'Group [USN+ vs. USN- vs. HC]' as between-subject factor, as well as 'Scene Complexity' [simple vs. complex] and 'Target Location' [$\pm 40^\circ$, $\pm 20^\circ$, 0°] as within-subject factors. In the presence of significant effects, post-hoc comparisons of simple effects were elaborated on using previously identified relevant pairwise comparisons. The mixed model approach was selected given that it accounts for the large between-subject heterogeneity frequently present in individuals with post-stroke USN, and is also tolerant to small and unequal sample sizes as used in the present study. Recently, the mixed model approach was highly recommended as the favorable type of statistical analysis over repeated measures ANOVA for post-stroke USN-related research [287]. The *combined covariance structures* (unstructured as the reference structure and compound symmetry structure) and a *random coefficient structure* were used. The final model was chosen using the Akaike's Information Criterion, the Bayesian Information Criterion, and the restricted maximum likelihood ratio test. This chosen model was further

ascertained by evaluating the fit of the data and deviations from model assumptions using residuals' analysis.

To provide insight into EVENS' concurrent validity, Kendall's rank correlation coefficient was used to quantify the relationship of goal-directed navigation and detection abilities to the left eccentric (-40°) target in the complex scene with clinical assessments of neglect within near and far space. To gain a better understanding of how EVENS' detection and navigation tasks evidence functional deficits in USN of different severities; and how sensitive EVENS is in detecting deficits otherwise not detected using traditional tests, single case analyses were used to compare the performance of each USN+ participant with respect to the average performance of the USN- group as well as to compare the performance of each USN- participant with respect to the average performance of the HC group. Precisely, the Crawford and Garthwaite (2002) approach (Singlims.exe, University of Aberdeen, Aberdeen, UK) [232] which implements classical methods for comparison of a single case's score to scores obtained in a control sample was used. The interval estimate of the effect size for the difference between each case and controls (as normative data) was obtained.

5.5 RESULTS

Twelve individuals with post-stroke USN (n=12, USN+), fifteen individuals post-stroke without USN (n=15, USN-), and nine age-matched healthy control individuals (n=9, HC) were recruited in the period between September 2015 and March 2016. Each participant successfully completed all experimental trials, without any missing data. No adverse effects such as dizziness, nausea, or any other discomfort were reported by study participants during testing. Table 5.1A outlines the demographic and clinical variables for the three groups. USN+ and USN- groups predominantly consisted of male participants, both statistically similar in stroke chronicity and age.

5.5.1 USN characteristics

USN+ group demonstrated significantly greater deficits than the USN- group on all USN-related measures in the near and far space ($p \leq 0.05$) (Table 5.1B). The USN+ group took longer to complete the APT and SCT in the near and far space ($p \leq 0.05$) vs. USN- group. Similarly, those with history of USN also took longer to complete the APT and SCT in the near space ($p \leq 0.05$) vs. USN- group. No other significantly greater deficits were found in those with history of USN

vs. USN- group. None of the USN- individuals scored positive in any of the USN assessments. No statistically significant difference was found for USN severity (near vs. far space) within USN+ group ($p = 0.90$ for LBT; $p = 0.54$ for SCT).

5.5.2 Detection task

For detection time (Figure 5.2), a three-way interaction of Group x Scene Complexity x Target Location was found to be significant ($F(18, 231) = 1.78, p = 0.0287$). Within the USN+ group, significantly longer detection times were found all target locations in the complex (mean \pm standard deviation (SD) for targets at -40° to $+40^\circ$: $4.06 \pm 4.93s$, $4.05 \pm 4.06s$, $2.62 \pm 2.52s$, $2.04 \pm 1.48s$, $2.40 \pm 1.29s$) vs. simple scene (mean \pm SD for targets at -40° to $+40^\circ$: $1.41 \pm 1.78s$, $0.69 \pm 0.29s$, $0.59 \pm 0.26s$, $0.60 \pm 0.24s$, $0.75 \pm 0.43s$) ($p < 0.05$). Similarly, USN- and HC showed significantly longer detection times to all target locations in the complex vs. simple scene ($p < 0.05$). Between-group analyses revealed that USN+ individuals showed longer detection times for left and middle targets at -40° , -20° , 0° (mean \pm SD: $1.41 \pm 1.78s$, $0.69 \pm 0.29s$, $0.59 \pm 0.26s$) in comparison to both USN- (mean \pm SD: $1.67 \pm 0.78s$, $1.13 \pm 0.41s$, $1.14 \pm 0.57s$) and HC groups (mean \pm SD: $1.40 \pm 0.69s$, $0.95 \pm 0.20s$, $0.88 \pm 0.16s$) in the complex scene only ($p < 0.05$). No significant detection time differences were found between USN- and HCs.

5.5.3 Navigation task

Figure 5.3 depicts the displacement traces of both a USN+ and USN- stroke participant in the simple and complex scenes. While the USN- mostly selected a heading direction from the start, and maintained a nearly linear goal-directed route, the USN+ participant demonstrated a “searching” strategy, where he/she first searched for the target (shown by larger deviations of trajectories at the beginning or early in the trial) and only then advanced towards it, making final mediolateral corrections at the end of the trial.

A significant three-way interaction of Group x Scene Complexity x Target Location was observed for mMLD outcome ($F(18, 122) = 2.28, p = 0.0043$) (Figure 5.4). Within USN+ group, larger mMLDs were found for left and middle targets in the complex (mean \pm SD for targets at -40° , -20° , 0° : $1.10 \pm 0.70m$, $0.78 \pm 0.64m$, $0.34 \pm 0.33m$) vs. simple scene (mean \pm SD for targets at -40° , -20° , 0° : $0.89 \pm 0.42m$, $0.64 \pm 0.23m$, $0.31 \pm 0.25m$) ($p < 0.05$). No within-group differences depending on the complexity of the scene were found among USN- and HCs. USN+ individuals

displayed significantly larger mMLDs for the most eccentric targets ($\pm 40^\circ$) (mean \pm SD: $1.10 \pm 0.70\text{m}$, $0.84 \pm 0.42\text{m}$) compared to USN- (mean \pm SD: $0.82 \pm 0.44\text{m}$, $0.52 \pm 0.36\text{m}$) individuals under the complex VR scene condition only ($p < 0.05$). The mMLDs of USN+ individuals across the different target locations were generally larger compared those of HCs under both the simple and complex scene conditions ($p < 0.05$). No significant mMLD differences were found between USN- and HCs.

Time to target results (Figure 5.4) also showed a significant three-way interaction of Group \times Scene Complexity \times Target Location ($F(18, 122) = 3.57$, $p < .0001$). Within USN+ group, longer lasting navigations were observed for the most eccentric left target at -40° in the complex (mean \pm SD: $9.53 \pm 5.21\text{s}$) vs. simple scene (mean \pm SD: $6.61 \pm 1.84\text{s}$) ($p < 0.05$). No within-group differences depending on the complexity of the scene were found among USN- and HCs. USN+ individuals displayed significantly longer lasting navigations for the most eccentric left target at -40° and middle target at 0° under the complex scene (mean \pm SD: $9.53 \pm 5.21\text{s}$, $5.71 \pm 1.74\text{s}$) in comparison to the USN- group (mean \pm SD: $5.65 \pm 1.32\text{s}$, $4.25 \pm 1.38\text{s}$) ($p < 0.05$). The times to target of USN+ individuals across the different target locations were generally larger compared those of HCs under both the simple and complex scene conditions ($p < 0.05$). No significant time to target differences were found between USN- and HCs.

5.5.4 Severity of USN and EVENS' sensitivity

The outcomes of the detection (detection time) and navigation tasks (time to target, mMLD) to the left eccentric target (-40°) in the complex virtual scenes were used to examine how these outcomes vary as a function of USN severity. It was deemed suitable to select these outcomes as responses to that target location in the complex virtual scene were found to be consistently worse in USN+ vs. USN- and HC participants. Table 5.2 outlines the single case analyses of single USN+ participant vs. the USN- group, as well as single USN- participant vs. the HC group. The time to target outcome (navigation task) and to a lesser extent the detection time outcome (detection time task), but not the mMLD outcome (navigation task) appear to be responsive to USN severity, where performances worsen with increase in neglect severity (as per the effect size values). None of the participants, with the exception of S25, presented with deficits solely in the detection task. In other words, most USN+ participants who showed an altered object

detection performance also showed deficits in navigation, but participants could show an altered navigation performance with a preserved object detection ability.

Moreover, three individuals from the USN- group (S14 [both navigation task outcomes], S22 [time to target, navigation task], S25 [detection time outcome, detection time task]) were found to have significantly worse performance on EVENS in comparison to the HC group as the control normative sample ($p < 0.05$).

5.5.5 Correlation analyses

A supplementary table shows the correlation coefficients between USN clinical test and detection/goal-directed navigation to left eccentric target (-40°) performances in the complex scene. None of the USN tests showed correlation with the time taken to detect the targeted object. Significant ($p < 0.05$) but low-magnitude (0.38 - 0.49) correlations were found, however, between most USN clinical measures and the navigation time to target outcome, indicating that a poor performance on USN tests was somewhat associated with a poor performance on the navigation task.

5.6 DISCUSSION

This study investigated, for the first time, the effect of post-stroke USN on object-detection and goal-directed navigation in the far space while using a newly developed, immersive VR-based USN assessment, EVENS, which allows to systematically assess participants' performance in an environment of changing complexity. Key findings include the presence of altered performances on both, the detection and navigation tasks, in the USN+ individuals compared to individuals without USN; presence of deficits that varied as a function of environment complexity and which could present either unilaterally (lateralized) or bilaterally (non-lateralized); and unveiled deficits that were otherwise left undetected using traditional clinical measures. The following paragraphs discuss the implications of present findings, possible mechanisms for the observed findings, as well as benefits of further studying EVENS for the assessment of post-stroke USN.

Environment complexity influences USN related deficits

The present study found that while USN negatively affects perceptual and navigational abilities to targets located predominantly on the neglected side, deficits significantly worsen when

exposed to a complex environment with an increased perceptual load. We propose that such an environment imposes greater demands on the perceptual-attentional resources compared to the uncluttered environment. Our findings may explain the difficulties individuals with chronic USN experience on daily basis in real-world situations where cluttered environment are encountered, such as mobility within the community that requires goal-directed locomotion [71, 77], obstacle avoidance [74], wheelchair navigation skills [32], street crossing [288], or performing instrumental activities of daily living [289]. These tasks may not only be lengthier to perform for those with post-stroke USN, but also more demanding, tiring, and possibly leading to difficulty in maintaining a given level of performance over an extended period of time. This could also explain the behavior of busy environment avoidance so often present in individuals with post-stroke neglect in chronic stages [26]. Our results are also consistent with the view that the quantity and allocation of attentional resources available alter performance such that true deficits can be revealed when one can no longer effectively allocate his/her attentional resources in instances of increased perceptual or cognitive load of the task [279]. Specifically, multiple studies found that increased task demands negatively affect the performance and result in the emergence of signs and symptoms of neglect in chronic stages that were otherwise not detected using conventional methods [74, 290-292].

Spatially lateralized and non-lateralized USN related deficits

Findings of this study further revealed the presence of lateralized and non-lateralized deficits in individuals with USN, notably in detection time and time to target outcomes on the detection time and navigation tasks, and in maximal mediolateral deviation from the ideal path outcome on the navigation task. These findings may be explained by attentional mechanisms underlying USN. Firstly, time-related performances (detection time, navigation time to target) of USN+ vs. USN- group, in general, were worsened in a “gradient manner” from the ipsilesional/right (+20°) to contralesional/left periphery (-40°). This demonstrates that time-related outcomes can identify spatially-lateralized loss of attentional capacity. These findings are in accordance with two models of USN attentional theory: the hemispheric imbalance model, namely its *opponent processor*; and the disengagement deficit/attention shift model. The *opponent processor* hypothesis stipulates that there are two opponent processors (in the left/right hemispheres) that control attention towards the contralateral portion of the visual hemispace and inhibit one

another via collasal connections [107]. Neglect is viewed as the result of the hypoactive ipsilesional hemisphere and hyperactive contralesional hemisphere following a stroke. This interhemispherical imbalance causes a decrease from center to periphery of the left/contralesional visual hemispace attention gradient, and an increase of the right/ipsilesional visual hemispace attention gradient [107]. Similar to the results obtained using EVENS, a previous study on the gradient of attention deployment evidenced that all patients with right hemisphere stroke and USN showed reduced response accuracy and increased reaction times to contralateral vs. ipsilateral targets in comparison to individuals with left hemisphere stroke and healthy controls [110].

The *disengagement deficit/attentional shift* model is viewed as a sequence of three internal mental operations including disengagement of attention from current stimulus; moving attention towards a new stimulus; and engagement of attention on the new stimulus. Previously, USN+ individuals with right hemisphere parietal lesions were found to have a deficit in disengagement of attention from ipsilesional targets in response to contralesional targets [134-136]. Similarly, our results could be associated with a deficit in moving attention from ipsilesional to contralesional targets in an activity reflecting real-world attentional demands. In addition, a related meta-analysis deduced that the disengagement deficit is in fact larger in individuals with USN+ individuals a right hemisphere lesion (especially with parietal lobe damage) than in USN- individuals with a left hemisphere stroke [137]. Nearly 60% of our sample of USN+ individuals presented with lesion to the right parietal lobe, supporting the evidence for possible disengagement difficulties.

Secondly, current findings, however, also revealed the presence of non-lateralized deficits, as demonstrated by the outcome of maximum mediolateral deviation from an ideal path in the navigation experiment which was found to be altered both for the left/“neglected” and right/“non-neglected” visual hemispaces in USN+ individuals. Such bilateral deficit in USN+ individuals was also recently observed by our team in the context of goal-directed walking [249]. Goal-directed navigation and locomotion both require space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85], which are processes that involve a complex brain network that transforms perception into goal-directed action and which includes the parietal area [293, 294]. The latter area, which is largely involved

in post-stroke USN, is also known to have non-lateralized functions [267], which may explain the presence of non-lateralized deficits observed in this study during goal-directed navigation. Findings are further consistent with the growing evidence that the persistence of neglect into chronic stages of stroke recovery is likely to be accompanied by widespread non-lateralized attentional deficits, unconfined to one region of space, in addition to the unilateral imbalance of attention to the contralesional space (reviewed in [99, 106]). Collectively, present findings suggest that behavioral performance in post-stroke USN cannot be solely explained by lateralized deficits, but rather by combination of spatially lateralized and non-lateralized impairments.

The initial search and endpoint adjustments noted among individuals with USN in the present study is analogous to those found by Berti et al. (2002) [61], where the walking trajectories to a far space target were not corrected as the patient was approaching the target that was becoming a near vs. a far space one. The patients thus followed a path that was related to the first computation of space carried out at the starting point and failed to remap and readjust the heading direction. Accordingly, present findings could indicate non-lateralized deficits in online control and heading present in individuals with neglect post-stroke.

Severity of USN and EVENS' sensitivity

The navigation task outcome “time to target”, and to a lesser extent the detection task outcome “detection time” in the complex scene evidenced a gradient of responses according to USN severity. Thereby, individuals showed worsened performance with an increase in USN severity, as assessed with clinical tests ranging from mild USN to severe USN. The nature of the navigation task, requiring space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85] to transform perception into action, could account for these findings. In addition, it emerges that time-related outcomes in both tasks are more predictive of USN severity. However, the single-case analyses revealed that the navigation performance does not seem to be dependent on the ability to detect the object, further supporting the usefulness and advantages of EVENS vs. traditional and existing VR-based methods. Indeed, 5 participants (3 USN+, 2 USN-) demonstrated worsened time to target performance (navigation task), despite a normal object detection time (detection task). Several current VR-based USN evaluations employ solely a visual search/object-detection paradigm (e.g. [184, 185, 190, 295,

296]). Our results suggest that a performance-based component of navigation is potentially beneficial for a comprehensive and sensitive assessment. In line with this, EVENS demonstrated promising preliminary sensitivity, as it identified considerably worse performance in 3 USN-individuals vs. HCs (2/3 on the navigation task only), that were otherwise left undetected using traditional tests. Nonetheless, it should also be mentioned that it failed short in identifying performance alterations in those with history of USN vs. USN+ group. Therefore, additional research, including patients with different USN severities, is required to make more concrete inferences as to its usefulness and clinical applicability.

Benefits of a VR-based assessment such as EVENS

In this study, a VR-based assessment revealed the presence of deficits i) that varied depending on the nature of task to be performed (detection vs. navigation); ii) that were modulated according to target location and environment complexity; iii) which could be either lateralized or non-lateralized; and iv) that become apparent despite normal performance on traditional USN tests. Together, these findings support EVENS's usefulness in detecting USN-related deficits in object detection and goal-directed navigation. These findings further emphasize that the nature of the tasks (detection vs. navigation) and the environmental complexity are crucial factors to consider when designing assessment and treatment tools for post-stroke neglect. These factors, as well as other aspects such as target location and the inclusion of a static and dynamic environments, are difficult to control in a real world setting and not accounted for in currently employed clinical assessments for USN. We further propose that EVENS is more ecological in comparison to traditional USN cancellation tests with distractors (paper-and-pencil test [e.g. Bells' Test [297]] or computerized tests [e.g. Star Cancellation Test [184]]) EVENS imposes greater demands on attentional resources as it displays a setting in which we aim to mirror a real grocery shopping aisle. Considering this, further empirical research is needed to determine its relevance and clinical usefulness for evaluating and predicting the impact of USN on real-life functional performance.

Additionally, the significant correlations between USN clinical tests and VR task performance refer to the adequate concurrent criterion validity of EVENS. However, the low magnitude correlations may indicate that the functionality of the VR task, the realism and complexity of the VR scene and EVENS' immersiveness is likely more sensitive in detecting deficits experienced

by individuals with post-stroke USN on daily basis. In addition, EVENS' applicability and suitability for busy rehabilitation settings are supported by the current study, as the setup, running, and scoring of the entire evaluation took under 30 minutes; in comparison to the administration and scoring of all clinical tests which took 40-60 minutes.

Limitations

It is acknowledged that only participants with left USN (i.e. right hemisphere stroke) were included, limiting the generalizability of results to the left hemisphere stroke population. In addition, EVENS incorporates navigation tasks that did not include a locomotor component. While the performance could worsen during actual locomotion, EVENS presents with the advantage of minimizing the contribution of gait and balance impairments while allowing the examination of attentional-perceptual deficits. Moreover, the motor function of the non-paretic upper extremity used in EVENS was not objectively evaluated in the present study using standardized measures. Thus, one could argue that post-stroke, subtle but documented changes in the non-paretic upper extremity function explain the results observed in our group of USN individuals. All participants of this study, however, were able to hold and successfully use a pencil with their right non-paretic hand in cancellation tests and in writing/drawing (e.g. consent form, Clock Drawing/Trail Making/Spatial Construction subtests of the MOCA) and presented with no apparent deficits in the non-paretic upper extremity that would prevent them from using the joystick correctly. Most importantly, the performance of the post-stroke USN individuals in this study was significantly altered compared to that of the post-stroke individuals without USN who also performed the task with the non-paretic upper extremity. Furthermore, no significant differences in performance were observed between our group of USN- individuals and healthy controls, a finding that is consistent with previous studies where the non-paretic hand was employed for similar tasks (e.g. target detection [185] and obstacle avoidance [298]), and which shows that potential sensorimotor post-stroke deficits in the upper extremity did not affect the responses provided with the joystick.

General conclusion and future directions

There are important advantages of the VR design developed in the present study. EVENS offers the potential to assess more functional and complex tasks in individuals with neglect; thus, addressing crucial limitations of the currently available traditional methods and responding to the needs of clinicians for diagnosis, treatment planning, and rehabilitation purposes. Future studies could focus on incorporating an assessment of the feeling of presence, adverse effects and satisfaction. Further, we aim to bring additional adjustments to EVENS using knowledge translation approach where clinicians and experts in the field were interviewed [299] and an in depth assessment of its psychometric properties (e.g. predictive validity and reliability).

Table 5.1A Description of study participants

Participant	Sex (M:F)	Age (years)	Stroke Chronicity (years)	Type of Stroke (Ischemic/Hemorrhagic)	Stroke Location
USN+ (n=12)					
S1	M	53.5	4.1	Ischemic	P-T
S2	M	72.3	2.7	Ischemic	Sylvian
S3	M	45.7	1.6	Hemorrhagic	P
S4	M	57.2	3.5	Hemorrhagic	P-T
S5	F	69.0	0.9	Hemorrhagic	Subarachnoid hemorrhage grade 3, common right artery
S6	M	67.7	1.3	Ischemic	Pontocerebellar fibers
S7	F	50.8	2.5	Ischemic	P-T
S8	M	61.6	0.9	Ischemic	P-O
S9	M	67.6	1.5	Ischemic	F-P
S10	M	73.1	0.3	Ischemic	P-O + midline shift
S11	F	56.5	1.3	Ischemic	Sylvian
S12	M	53.7	0.9	Ischemic	F-T-Ins
Mean ± SD					
Range (-)	9:3	60.7 ± 9.09	1.7 ± 1.1	9/3	-
Ratio (:)					
USN- (n=15)					
S13	M	50.6	0.5	Ischemic	P-O
S14	F	81.1	1.7	Ischemic	F-P
S15	F	43.0	1.7	Ischemic	Globus pallidus, putamen, anterior limb of internal capsule, caudate nucleus, cortical F-P-T
S16	M	58.0	1.4	Ischemic	Lateral medulla
S17	M	57.0	0.6	Ischemic	Sylvian: corona radiata, internal capsule, subcortical center
S18	M	40.8	4.0	Hemorrhagic	Basal ganglia and external capsule
S19	M	68.2	8.8	Ischemic	MCA territory
S20	M	51.5	1.3	Ischemic	Cerebellar, right lateral medullary
S21	M	54.0	1.2	Ischemic	Internal capsule, globus pallidus, lacunar corona radiata, F
S22	M	75.5	0.8	Ischemic	F + MCA territory
S23	M	46.7	1.1	Ischemic	Sylvian
S24	M	52.1	2.3	Ischemic	Posterior limb of right internal capsule
S25	M	73.8	0.7	Ischemic	Internal capsule
S26	M	77.3	2.9	Ischemic	MCA territory
S27	M	48.3	1.3	Hemorrhagic	Brainstem, periaqueductal
Mean ± SD					
Range (-)	13:2	58.5 ± 13.2	2.0 ± 2.1	13:2	-
Ratio (:)					
HC (n=9)					
Mean ± SD					
Range (-)	4:5	56.3 ± 11.2	NA	NA	NA
Ratio (:)					

Table 5.1A Description of study participants. Unilateral spatial neglect (USN); Standard Deviation (SD); Frontal (F); Parietal (P); Middle cerebral artery (MCA); Temporal (T); Occipital (O); Insular (Ins); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Healthy Controls (HC); Not applicable (NA);

Table 5.1B Results of USN clinical tests

Participant	LBT near deviation (cm)	LBT near deviation (%)	LBT far deviation (cm)	LBT far deviation (%)	SCT near	SCT near time (mins)	SCT far	SCT far time (mins)	APT total	APT time (mins)	APT allocentric	APT egocentric	Type of USN	Severity
USN+ (n=12)														
S1	0.5	3.5	3.1	3.1	1.0	2.1	1.0	1.4	0.92	2.5	0	1	Hx	Hx
S2	0.3	2.2	2.0	2.0	1.0	1.5	1.0	1.3	0.92	2.3	0	2	Hx	Hx
S3	0.2	1.6	2.0	1.9	1.0	2.1	1.0	2.1	0.98	3.4	0	1	Hx	Hx
S4	0.4	2.7	1.6	1.6	1.0	1.2	1.0	1.0	0.98	2.2	0	1	Hx	Hx
Mean ± SD														
Range (-)	<i>0.4±0.1</i>	<i>2.5±0.8</i>	<i>2.2±0.6</i>	<i>2.2±0.7</i>	<i>1.0±0.0</i>	<i>1.7±0.4 *</i>	<i>1.0±0.0</i>	<i>1.5±0.5</i>	<i>0.95±0.0</i>	<i>2.6±0.5 *</i>	<i>0.0±0.0</i>	<i>1.3±0.5</i>	NA	NA
SI-S4	<i>(0.2-0.5)</i>	<i>(1.6-3.5)</i>	<i>(1.6-3.1)</i>	<i>(1.6-3.1)</i>	<i>(1.0-1.0)</i>	<i>(1.2-2.1)</i>	<i>(1.0-1.0)</i>	<i>(1.0-2.1)</i>	<i>(0.2-0.98)</i>	<i>(2.2-3.4)</i>	<i>(0-0)</i>	<i>(1-2)</i>		
S5	1.2	8.4	3.6	3.5	1.0	1.1	1.0	1.3	0.88	1.3	0	4	Near, egocentric	Mild
S6	2.6	18.2	21.0	20.8	1.0	2.0	1.0	2.1	1	3.3	1	0	Far > near	Mild
S7	0.8	5.9	3.7	3.6	1.0	1.2	1.0	1.1	1	3.2	3	0	Near, allocentric	Mild
S8	1.1	7.8	4.4	4.3	1.0	2.5	0.9	4.5	0.88	8.1	10	2	Near, allocentric	Mild
S9	1.2	8.6	13.1	13.0	1.0	1.5	1.0	2.2	0.78	4.4	3	2	Far > near, allocentric	Moderate
S10	2.2	15.3	17.9	17.7	0.9	3.2	0.9	2.5	0.94	14.6	7	3	Far > near, allocentric, egocentric	Moderate
S11	1.1	7.8	6.6	6.6	0.7	2.0	0.9	2.3	0.82	3.5	35	7	Near > far, allocentric, egocentric	Severe
S12	0.4	2.8	5.3	5.3	0.6	1.5	0.7	1.4	0.76	3.0	7	1	Near > far, allocentric	Severe
Mean ± SD														
Range (-)	<i>1.0 ± 0.7 **</i>	<i>7.0 ± 5.2 **</i>	<i>7.0 ± 6.6 **</i>	<i>6.9 ± 6.5 **</i>	<i>0.9 ± 0.1 **</i>	<i>1.8 ± 0.6 **</i>	<i>0.9 ± 0.0 *</i>	<i>1.9 ± 0.9 *</i>	<i>0.8 ± 0.08 **</i>	<i>4.3 ± 3.5 **</i>	<i>5.5 ± 9.9 **</i>	<i>2.0 ± 1.9 *</i>	NA	NA
SI-S12	<i>(0.2-2.6)</i>	<i>(1.6-18.2)</i>	<i>(1.6-21.0)</i>	<i>(1.6-20.8)</i>	<i>(0.7-1)</i>	<i>(1.1-3.2)</i>	<i>(0.7-1)</i>	<i>(1-4.5)</i>	<i>(0.7-1)</i>	<i>(1.3-14.6)</i>	<i>(0-35)</i>	<i>(0-7)</i>		
USN- (n=15)														
Mean ± SD	<i>0.2 ± 0.1</i>	<i>1.4 ± 0.8</i>	<i>2.0 ± 0.6</i>	<i>2.05 ± 0.8</i>	<i>1.0-1.0</i>	<i>1.1 ± 0.4</i>	<i>1.0-1.0</i>	<i>1.1 ± 0.6</i>	<i>0.9-1.0</i>	<i>1.9 ± 0.6</i>	<i>0.06 ± 0.6</i>	<i>0.5 ± 0.8</i>	NA	NA
Range (-)	<i>(0.03-0.1)</i>	<i>(0.2-3.2)</i>	<i>(0.8-3.2)</i>	<i>(1.2-4.3)</i>	<i>(0.9-1)</i>	<i>(0.4-1.3)</i>	<i>(0.9-1)</i>	<i>(0.4-1.3)</i>	<i>(0.9-1)</i>	<i>(1.1-3.4)</i>	<i>(0-1)</i>	<i>(0-2)</i>		

Table 5.1B Results of the USN clinical tests. Unilateral spatial neglect (USN); Participants with post-stroke USN (USN+); Participants without post-stroke USN (USN-); Not applicable (NA); Line bisection test (LBT); Star Cancellation Test (SCT); Apples Test (APT); minutes (mins); History of USN: Hx; Numbers in bold correspond to values above or below (where applicable) cut-off values; Star symbols (*, **, ***) represent p-value <0.05, 0.01, 0.001, respectively (USN+ vs. USN- group); USN overall severity is delineated by shades ranging from white (those with history of USN) to dark grey (those with severe USN).

Table 5.2 Single-case analysis

Complex Scene Left target (-40°)												
Detection Task (detection time)				Navigation Task (time to target)				Navigation Task (mMLD)				
USN+ vs. USN- group												
Subject	<i>t</i> -value	Two-tailed probability (<i>p</i> -value)	Z score (effect size)	95% Confidence Interval	<i>t</i> -value	Two-tailed probability (<i>p</i> -value)	Z score (effect size)	95% Confidence Interval	<i>t</i> -value	Two-tailed probability (<i>p</i> -value)	Z score (effect size)	95% Confidence Interval
S1 (Hx)	-0.16	0.87	-0.16	-0.67-0.34	1.0	0.31	1.07	0.42-1.70	-0.19	0.84	-0.20	-0.71-0.31
S2 (Hx)	0.16	0.87	0.16	-0.34-0.67	0.17	0.86	0.17	-0.33-0.68	-0.15	0.87	-0.15	-0.66-0.35
S3 (Hx)	0.89	0.38	0.92	0.30-1.52	-0.06	0.94	-0.06	-0.57-0.43	-0.88	0.39	-0.90	-1.50- -0.2
S4 (Hx)	1.46	0.16	1.51	0.75-2.25	-0.29	0.77	-0.30	-0.81-0.21	-0.48	0.63	-0.50	-1.03-0.04
S5 (MI)	-0.31	0.76	-0.32	-0.83-0.20	0.07	0.94	0.07	-0.43-0.58	0.20	0.84	0.20	0.30-0.71
S6 (MI)	-0.07	0.94	-0.07	-0.58-0.43	4.28	<0.0001	4.42	2.7- 6.11	0.33	0.74	0.34	-0.17-0.86
S7 (MI)	0.24	0.80	0.25	-0.26-0.76	1.58	0.05	1.63	0.83-2.40	1.28	0.11	1.32	0.61- 2.01
S8 (MI)	18.93	<0.0001	19.55	12.3-26.7	3.77	0.002	3.89	2.37-5.39	-0.27	0.39	-0.27	-0.79- 0.24
S9 (Mod)	-0.05	0.96	-0.05	-0.55-0.45	2.73	0.016	2.82	1.66-3.96	1.84	0.04	1.90	1.03-2.75
S10 (Mod)	-0.81	0.24	-0.84	1.42- -0.24	5.28	<0.001	5.46	3.39-7.51	4.93	<0.001	5.09	3.15-7.0
S11 (Sev)	11.96	<0.0001	12.35	7.80-16.90	2.07	0.05	2.14	1.19-3.06	-0.22	0.82	-0.23	-0.74-0.28
S12 (Sev)	3.50	0.003	3.61	2.19-5.02	13.46	<0.0001	13.90	8.79-19.02	1.41	0.08	1.46	0.71-2.19
USN- vs. HC group												
S13	-0.33	0.74	0.34	1.01-0.33	0.52	0.06	0.55	0.16-1.24	0.53	0.60	0.56	1.55-1.26
S14	0.39	0.35	0.42	-0.27-1.09	4.29	0.002	4.53	2.25-6.79	3.41	0.009	3.59	1.74-5.42
S15	1.70	0.12	1.79	0.65-2.86	0.64	0.53	0.67	-0.06-1.39	0.02	0.98	0.02	0.62-0.68
S16	0.89	0.39	0.94	0.12-1.71	-1.2	0.24	1.30	-2.19- -0.3	-1.17	0.27	-1.24	2.10- -0.33
S17	0.60	0.56	0.63	-0.10-1.34	0.00	1.00	0.00	0.65-0.65	0.07	0.94	0.08	-0.57-0.73
S18	-0.45	0.66	0.47	1.16-0.28	1.66	0.13	1.75	0.66-2.80	0.56	0.58	0.59	0.13-1.29
S19	-0.89	0.39	-0.94	-1.71-0.12	-1.21	0.25	-1.28	-2.16- -0.3	-0.89	0.39	-0.94	-1.72- -0.1
S20	-1.08	0.30	-1.14	-1.98-0.27	-0.58	0.57	-0.61	-1.32-0.11	-1.02	0.33	-1.08	-1.89- -0.2
S21	0.79	0.44	0.84	0.05-1.59	0.36	0.72	0.38	-0.30-1.05	0.28	0.78	0.29	-0.38-0.95
S22	-0.27	0.79	-0.29	-0.94-0.38	3.13	0.01	3.30	1.58-5.01	1.59	0.15	1.67	0.61-2.69
S23	-0.09	0.92	-0.10	-0.75-0.55	-0.17	0.86	-0.18	-0.83-0.48	-0.10	0.92	-0.10	-0.76-0.55
S24	0.46	0.65	0.49	-0.21-1.17	-0.35	0.73	-0.37	-1.03-0.31	0.15	0.88	0.16	0.50-0.81
S25	3.03	0.01	3.2	1.52-4.86	0.19	0.39	-0.95	-1.72- -0.1	0.61	0.55	0.64	-0.09-1.35
S26	0.75	0.47	0.79	0.02-1.53	0.59	0.56	0.63	-0.10-1.33	0.82	0.43	0.86	0.07-1.62
S27	-0.72	0.48	-0.76	-1.50-0.00	-0.07	0.94	-0.07	-0.72-0.58	0.07	0.94	0.08	-0.57-0.73

Table 5.2 Single-case analyses of single USN+ participants vs. USN- group (as control data); and single USN- participants vs. HC group (as control data) on the performance of the detection time and navigation tasks for the outcomes related to responses to leftmost target (-40°) in the complex scene. History (Hx); Mild (MI); Moderate (Mod); Severe (Sev); Subject (S). Light grey selections represent individual cases whose performance is considerably worse than the comparison group ($p < 0.05$).

Figure 5.1 Simple and complex virtual scenes



Figure 5.1 Simple (left) and complex (right) virtual scenes. In the detection task, the participant was asked to press the joystick button in response to the appearing target (blue cereal box with “Pop Start” sign) or refrain from clicking in null trials. In the navigation task, the participant was asked to navigate to the object in the most direct way possible using the joystick.

Figure 5.2 Detection time results

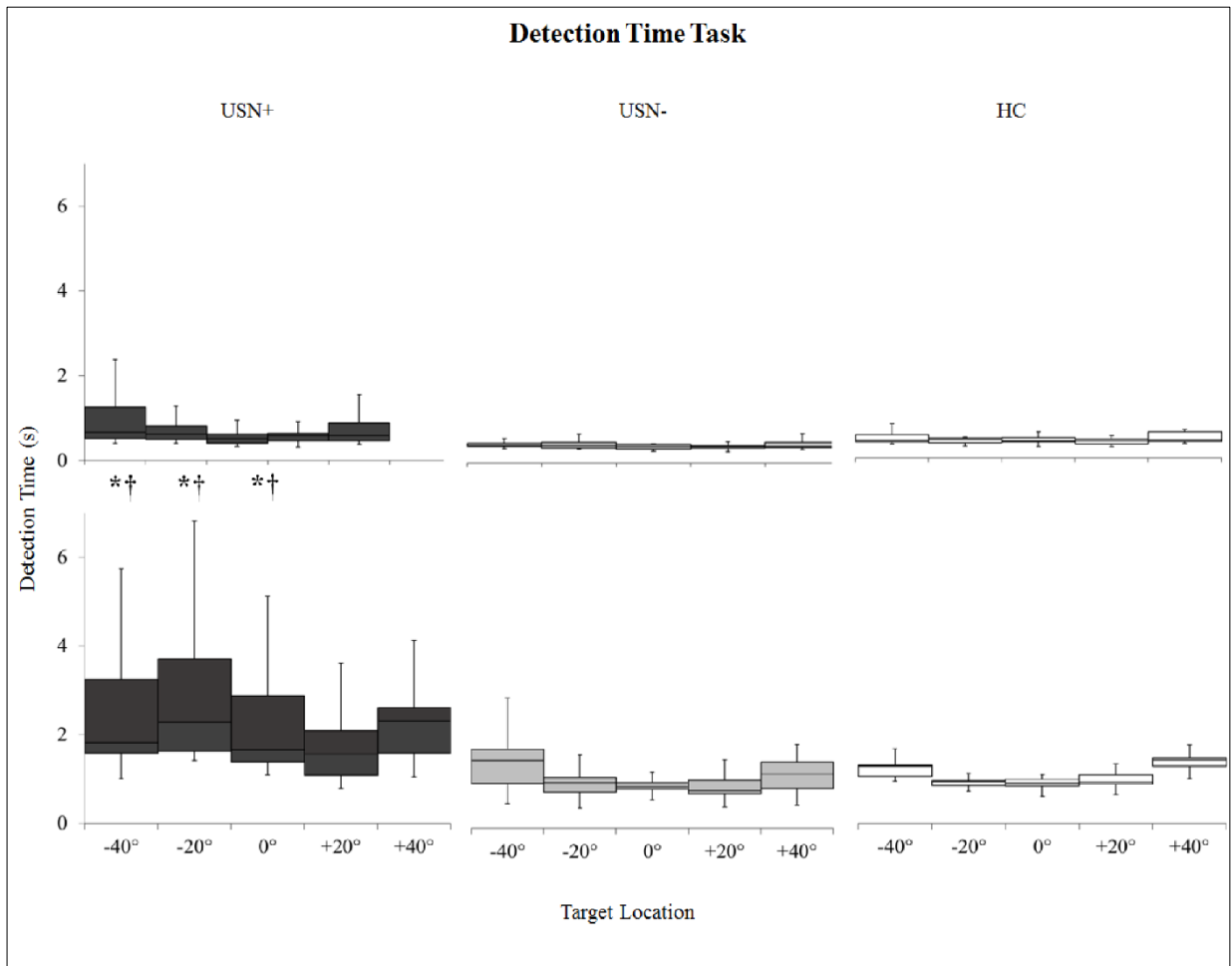


Figure 5.2 Detection time (s) for the simple (A) and complex (B) scenes and the 3 study groups. Black boxes and whiskers for USN+ group, grey for USN- group, white for HC group. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). Statistically significant differences between groups are indicated by: * for USN+ vs. USN- groups; † for USN+ vs. HC groups) at $p \leq 0.05$ for specific target locations.

Figure 5.3 Displacement traces

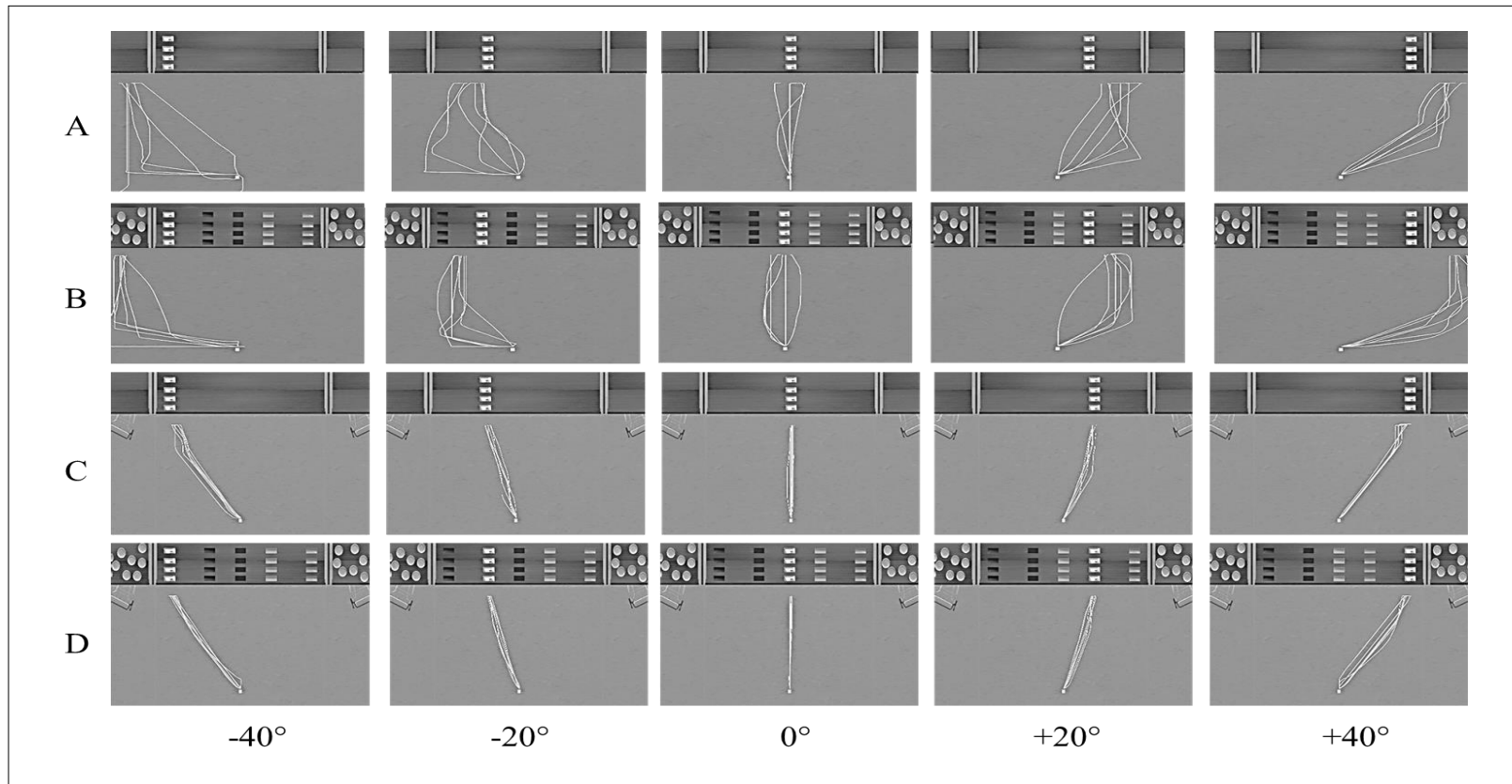


Figure 5.3 Bird's-eye view of the virtual environment and displacement traces (y =anteroposterior displacement; x =mediolateral displacement) during the navigation task towards targets of different eccentricities (from -40° to $+40^\circ$). Performance for one individual with (USN+, A & B) and one individual without (USN-, C & D) USN is illustrated for the simple (A & C) and complex (B & D) virtual scenes. The scale in X-axis refers to the mediolateral (left and right) space. The scale in the Y-axis refers to the anterior-posterior (front and back) space. The participant always starts at coordinate 0, 0 along both axes.

Figure 5.4 Navigation task results

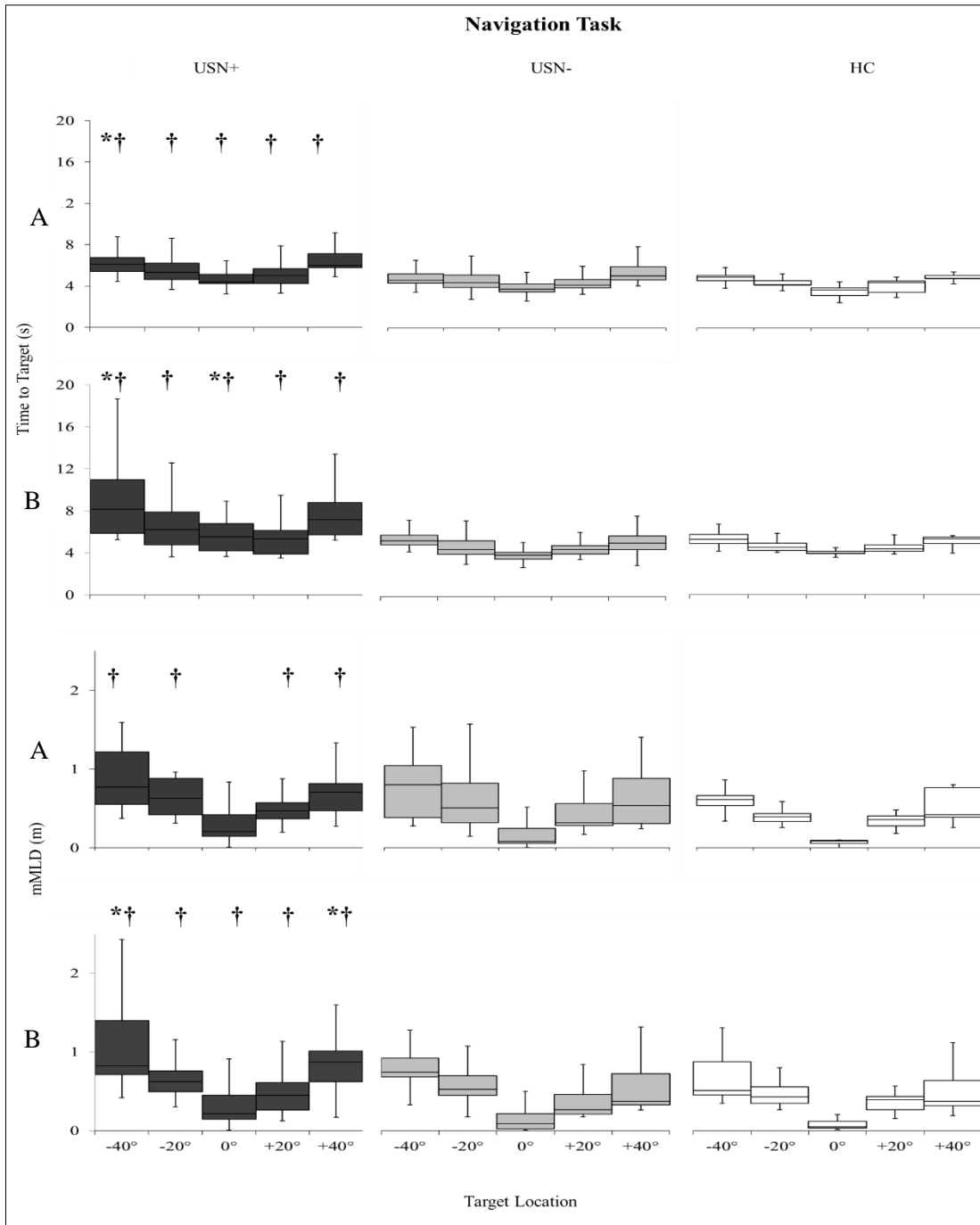


Figure 5.4 Navigation time to target (s) and maximal mediolateral deviations from the ideal path (mMLD, m) for the simple (A) and complex (B) scenes and the 3 study. Black boxes and whiskers for USN+ group, grey for USN- group, white for HC group. Box and whiskers description: minimal and maximal values shown by the whiskers, the bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median). Brackets indicate statistically significant differences between groups (solid brackets for USN+ vs. USN- groups; dashed brackets for USN+ vs. HC groups) at $p \leq 0.05$.

CHAPTER 6

6.1 PREFACE

In the previous Chapter, we presented a novel VR-based assessment tool for post-stroke USN, called EVENS. In the last decade, other VR-based USN assessments have been proposed (reviewed in [36]), and some, as EVENS, were found to be more sensitive in detecting the presence of deficits in cases where conventional USN assessment was negative [31, 33, 34, 184-186, 295, 296]. However, the application of EVENS or any other VR-based tool in clinical settings remains limited and confined to research departments. Despite their promising results over conventional methods, the acceptance and future use of these technologies in clinical practice depends on barriers and facilitators perceived by the end-users (i.e. clinicians). When facilitators are minimized and barriers are not addressed, the acceptance of technology declines and end-users renounce its clinical application [300]. In addition, as per Graham et al., 2006 [8], the barriers and facilitators need to be identified and subsequently included in the ensuing knowledge translation (KT) intervention geared towards increasing the use of evidence-based practice. To the best of our knowledge however, no previous study has evaluated support needs and modifiable barriers that could influence the application and use of VR specifically for post-stroke USN management. In relation to this, having already conducted a systematic literature review and developed a VR-based USN assessment and treatment toolkit [36], as well as preliminary testing of EVENS [301], there was a need to refine our understanding of the barriers and facilitators to the use of VR for USN management. Further, to promote its application and usage adherence in clinical practice, we seek to tailor VR-based USN assessment to clinicians' needs, while also considering the opinions of experts as to the tool's optimal features.

Chapter 6 of this PhD dissertation addresses **general objective 5** and **specific objectives 5.1** and **5.2** of my PhD research agenda. This chapter includes **Manuscript №5** of this dissertation, entitled “*Exploring barriers and facilitators to the clinical use of virtual reality for post-stroke unilateral spatial neglect assessment*”.

MANUSCRIPT № 5

EXPLORING BARRIERS AND FACILITATORS TO THE CLINICAL USE OF VIRTUAL REALITY FOR POST-STROKE UNILATERAL SPATIAL NEGLECT ASSESSMENT

Tatiana OGOURTSOVA^{1,2*}, Philippe S. ARCHAMBAULT^{1,2}, Anouk LAMONTAGNE^{1,2}

¹School of Physical and Occupational
Therapy,
McGill University,
3654 Promenade Sir-William-Osler
Montreal, Quebec, Canada
H3G 1Y5

²Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital,
Site of Centre for interdisciplinary Research
in Rehabilitation of Greater Montreal
3205 Place Alton-Goldbloom
Laval, Quebec, Canada
H7V 1R2

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DECLARATION OF INTEREST

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6.2 ABSTRACT

Background: Hemineglect, defined as a failure to attend to the contralesional side of space, is a prevalent and disabling post-stroke deficit. Conventional hemineglect assessments lack sensitivity as they contain mainly non-functional tasks performed in near-extrapersonal space, using static, 2-dimensional methods. This is of concern given that hemineglect is a strong predictor for functional deterioration, limited post-stroke recovery and difficulty in community reintegration. With the emerging field of virtual reality, several virtual tools have been proposed and have reported better sensitivity in neglect-related deficits detection than conventional methods. However, these and future virtual reality-based tools are yet to be implemented in clinical practice. **Objectives:** The present study aimed to explore the barriers/facilitators perceived by clinicians in the use of virtual reality for hemineglect assessment; and to identify features of an optimal virtual assessment. **Methods:** A qualitative descriptive process, in the form of focus groups, self-administered questionnaire and individual interviews was used. **Results:** Two focus groups (n=11 clinicians) were conducted and experts in the field (n=3) were individually interviewed. Several barriers and facilitators, including personal, institutional, client suitability and equipment factors, were identified. Clinicians and experts in the field reported numerous features for the virtual tool optimization. **Conclusion:** Factors identified through this study lay the foundation for the development of a knowledge translation initiative towards an implementation of a virtual assessment for hemineglect. Addressing the identified barriers/facilitators during implementation and incorporating the optimal features in the design of the virtual assessment could assist and promote its eventual adoption in clinical settings.

Keywords: knowledge translation, qualitative research, hemineglect, evaluation, technology, cerebrovascular accident.

6.3 BACKGROUND

Stroke is the leading cause of adulthood disability as it frequently results in residual motor, sensory, perceptual and/or cognitive impairments [302]. Unilateral spatial neglect (USN) is a common sequela of stroke characterized by the inability to orient, respond, or report to the stimuli present on the contralesional side [43]. It is known to seriously affect patient-related outcomes such as functional independence, community reintegration and quality of life [63, 64]. Given that the global annual incidence of stroke is nearly 15 million [303], and that up to 48% of those with a right hemisphere stroke will experience USN and its devastating effects [10], the use of sensitive USN detection and effective therapy is crucial.

Despite these alarming numbers, research has shown that clinicians do not consistently use the available standardized USN assessments. For instance, surveys indicate that only 13% to 27% of clinicians in acute and subacute care facilities respectively use a standardized USN assessment tool, and that only the near-extraperosnal space USN is evaluated [173, 179]. Inefficient USN detection, or lack thereof, is a significant issue, given that USN is associated with greater risk for falls, functional deterioration, difficulty performing activities of daily living and instrumental activities of daily living [10, 43, 63, 64]; therefore, posing an important hazard when discharging these individuals home and to community-living activities such as driving, going to back to work, caring for family, and community ambulation.

Unfortunately, sensitive detection using the currently available conventional methods is limited given that these tools do not grasp all the facets of USN's multimodal and heterogeneous presentation. In fact, despite an extensive body of research on USN standardized assessment tools, there is currently no gold-standard. The commonly employed paper-and-pencil evaluations can result in misdiagnosis of subjects with mild USN [10]. To exemplify, the large range of USN incidence that is commonly reported in the literature (i.e. 13% to 81% [304]) is suggested to be a result of the different evaluation methods used and of the paper-and-pencil tools' low sensitivity and ecological validity [304]. This lack of sensitivity is demonstrated by studies that reported participants with recovered USN based on conventional paper-and-pencil tests showing residual deficits when more complex, challenging and/or functional tasks are employed. For example, Berard et al., (2012) reported that patients who were classified as recovered, based on paper-and-pencil USN tests, were found to have altered walking trajectory adjustments in response to

changes in visual motion stimuli presentation in far space [270]. Other studies found that paper-and-pencil USN tests failed to predict functional performance in various mobility tasks such as wheelchair navigation [33, 34] and in an obstacle avoidance task performed while walking [248]. Likewise, patients who demonstrated absence of USN on conventional tests exhibited clear perceptual deficits in a virtual reality (VR) 3-dimensional detection time task [185]. Such findings lead to speculate that the conventional paper-and-pencil tests are limited in their ability to pick up milder USN cases, predict functional performance in daily life, and are highly bounded by assessing USN within the near-extrapersonal space only, using static, 2-dimensional methods. With the rapidly growing field and industry of virtual reality (VR), these USN diagnostic techniques could be enhanced and augmented to include 3-dimensional images or stereovision, far space targets and functional everyday tasks.

VR is a computer-based, multisensory, stimulating, and interactive environment that occurs in real time; where the individual is engaged in activities that appear similar to real-world objects and/or events [305-307] and has a strong “sense of presence” [308]. In the last decade, different VR-based USN assessments have been proposed (reviewed in [36]), and some were found to be more sensitive in detecting the presence of deficits in cases where conventional USN assessment was negative [31, 33, 34, 184-186, 295, 296]. However, the application of these tools in clinical settings remains limited. Despite their promising results over conventional methods, the acceptance and future use of these technologies in clinical practice depends on barriers and facilitators perceived by the end-users (i.e. clinicians). When facilitators are minimized and barriers are not addressed, the acceptance of technology declines and end-users renounce its clinical application [300]. In addition, as per Graham et al., 2006 [8], the barriers and facilitators need to be identified and subsequently included in the ensuing knowledge translation (KT) intervention geared towards increasing the use of evidence-based practice. For instance, a multifaceted KT intervention, recently designed by Levac et al., (2016), was shown to increase clinicians’ self-efficacy, perceived behavioral control and facilitating conditions in the use of VR for post-stroke rehabilitation: the GestureTek Interactive Rehabilitation Exercise (IREX, GestureTek, Toronto, ON, Canada) software platform providing interactive games that address various upper extremity and full body movement goals [309]. Similarly, other studies examining clinical barriers/facilitators outside of research context focused on VR for physical impairments post brain injury in adults [310] and children [311], post-traumatic stress disorder among

returning veterans [312], and for burn-related pain control [313]. To our knowledge however, no studies have evaluated support needs and modifiable barriers that could influence the application and use of VR specifically for post-stroke USN management. In relation to this, having already conducted a systematic literature review and developed a VR-based USN assessment and treatment toolkit [36], as well as preliminary testing of a novel VR-based USN functional assessment tool evidencing its superior detection sensitivity in comparison to conventional methods [301], there is a need to refine our understanding of the barriers and facilitators to the use of VR for USN management. Further, to promote its application and usage adherence in clinical practice, we seek to tailor VR-based USN assessment to clinicians' needs, while also considering the opinions of experts as to the tool's optimal features.

Thus, the objectives of this study were to: (1) identify the facilitators and barriers that affect the use of VR for post-stroke USN assessment by clinicians; and (2) identify the features of an optimal VR-based USN assessment that could be implemented and used by clinicians in the management of post-stroke USN.

6.4 METHODS

6.4.1 Study design

A qualitative descriptive approach, in the form of triangulation research strategy, was employed in the present study. More precisely, a focus group methodology and a self-administered paper-based questionnaire were used to explore clinicians' perceptions of the barriers and facilitators to the use of VR for post-stroke USN assessment. A focus group approach was selected with the clinicians given that it can promote the creation and sharing of ideas amongst participants, possibly leading to insights beyond those obtained through individual interviews [315, 316]. For clinicians, we also added self-administered questionnaires as individual's responses or opinions may be influenced by other participants' statements during focus groups; thus, allowing to express personal and anonymous opinions without the possible "peer-influence". The use of multiple methods or data sources is reported to support the developmental of a comprehensive understanding of a phenomena [314]. In addition, clinicians were asked to identify what would be the features of an optimal VR-based USN assessment tool. This latter information was then complemented with individual interviews with experts in the field. Experts in the field were

individually interviewed to accommodate for their different geographical locations around the world and their schedule constraints. The study was approved by the Centre de Recherche Interdisciplinaire en Réadaptation (CRIR, Quebec, Canada) Institutional Review Board and all participants provided their informed consent.

6.4.2 Participants

Purposive sampling was used to identify key informants with insights into the subject of interest [317] and to ensure a broad representation of topics. Given that Occupational Therapists are involved in the assessment and treatment of signs and symptoms of post-stroke USN [173, 179], participants were selected from the pool of Occupational Therapists working with stroke patients in two rehabilitation centers providing in- and out-patient rehabilitation services in the Greater Montreal area (Quebec, Canada). Occupational Therapists were eligible if they were registered with the provincial licensing body, had at least three months of experience working with a stroke clientele in a rehabilitation setting, currently treated a minimum of two adults with stroke per month, and were fluent in English and/or in French. Therapists could participate in the study regardless of their gender, age, and experience with the use of VR. Experts in the field were also recruited based on purposive sampling and were eligible if they held a graduate degree (i.e. MSc or PhD) and conducted research and/or educational activities pertaining to at least one of the following subjects: VR, stroke rehabilitation, post-stroke USN. A deliberate effort was undertaken to recruit experts from different geographical locations to provide an international perspective.

6.4.3 Sample size consideration

In the qualitative research literature, the number of focus groups and sample size within focus groups vary significantly [318]. Several guidelines, however, recommend to include a minimum of four and a maximum of twelve participants per group to optimize individual participation and generate rich discussions [319-321]. It was also reported that conducting two focus groups with fewer participants instead of one focus group with more participants would limit the bias that might be seen in a single group or site and allow to examine more themes across groups [322]. It was thus decided to recruit four to twelve clinicians per focus group and to conduct a minimum of two focus groups until saturation of ideas was reached (i.e. until no new themes emerged).

Transcripts and self-administered questionnaire responses from the first focus group were thus reviewed to reflect on that session before conducting the second focus group, thereby enabling initially identified concepts to be examined in the second session and promote data saturation. Data saturation was further ensured by using a second coder for thematic analysis and the usage of diverse methods (focus groups, individual interviews, self-administered questionnaires) [323]. In addition, all discussion points were noted on the screen viewed by participants and focus groups were ended with the moderator providing a summary of the discussed points. Participants were asked then if the summary is reflective of what was discussed and if they can think of other elements. The focus group was terminated when no new ideas emerged following the summary/closing remarks statement.

6.4.5 Data collection

Focus groups

According to guidelines on the organization of focus groups [319], a plan was developed to assist with the running of the groups. To begin, a fifteen minutes presentation on general information about post-stroke USN and VR was provided. Following this, four open-ended discussion questions were conversed among the participants for forty-five to sixty minutes. Those questions were pre-determined, reviewed and agreed upon by the authors of the manuscript: “1. *How do you feel about using virtual reality in your practice to evaluate and/or treat post-stroke USN?*; 2. *What do you like best about the idea of using virtual reality to evaluate and/or treat post-stroke USN?*; 3. *What are your concerns with using a virtual reality tool for post-stroke USN assessment and treatment?*; 4. *According to you, what would an optimal virtual reality assessment tool for post-stroke USN look like/include/be comprised of?*”. The last question (4), was not directed towards a specific evaluation tool (e.g. EVENS [269]) not to bias the participating clinicians. Finally, participants completed a self-administered questionnaire that took five to ten minutes. All questionnaires were completed privately, anonymously, without peer/investigator influence. The entire process lasted 1 to 1.5 hours. A moderator (T.O.) and one assistant (external to the study and whose role was to note discussion points on slides visible to the group participants) were present at all times. The groups were conducted in French and/or in English as per participants’ preference. Participants received no monetary reward for their participation; however, a catered lunch was offered during the initial informative presentation.

Questionnaire

The self-administered paper-based questionnaire (7-point Likert scale, ranging from “strongly disagree” to “strongly agree”) on institutional and personal barriers was developed with guidance from the Unified Theory of Acceptance and Use of Technology (UTAUT) Model [324]. The UTAUT model proposes that four out of seven constructs are significant, direct determinations of behavioral intention to use the system and include: (1) *Performance Expectancy*: the degree to which the individuals believe that the use of the technologies will result in performance gains; (2) *Effort Expectancy*: the ease of use of the technologies; (3) *Social Factors/Influence*: the extent to which the individuals believe that important others believe that they should use the technologies; and (4) *Facilitating Conditions*: the perceived extent to which the organisational and technical infrastructure exists to support use of the system. On the other hand, the remaining three constructs of (5) *Self-efficacy*; (6) *Attitudes towards Technology*; and (7) *Anxiety towards Technology Use* were shown to neither be direct determinants nor have a significant role in affecting behavioral intention to use the system. As a result, we chose to exclude these last three constructs from our questionnaire.

The reliability and validity of questionnaires using UTAUT model have been previously explored [325, 326]. The questionnaire in this study was reviewed for face validity by all authors of the manuscript, initially developed in English and then translated from English to French. Translation was verified for its accuracy by four individuals (two authors of this article (T.O. and A.L.) and two individuals which were not part of the study development or participation). The questionnaire also included a section (Part I) on the information about clinicians’ demographic factors and professional characteristics including age, gender, time spent on continuing education, degree, work schedule, experience with stroke clientele, specialty certification, teaching activities, and work environment (Appendix 4).

Individual interviews

The individual interviews with experts in the field were conducted following the focus group analysis. Interviews were conducted via Skype® or telephone and the audio of the conversation was recorded. Participants were given an overview of post-stroke USN and VR, as well as preliminary results of the focus group analysis. They were then asked to discuss what would an

optimal VR-based post-stroke USN assessment tool include. The interviews lasted 20 to 60 minutes and were all conducted in English.

6.4.6 Data analysis

Descriptive statistics were used to summarize demographic data of the focus group participants and experts in the field. For the questionnaire, data was summarized by frequency counts in each question/category (barrier/facilitator). The focus groups were videotaped and the audio data were transcribed. The verbatim transcription was then imported into the NVivo software (QSR International, Australia) for data management. The French statements from both groups were translated into English following the verbatim transcription using a back-translation method. Triangulation methods were used for analysis of the data [327]. More specifically, the first author (T.O.) read the entire transcript to gain a general sense of the content's meaning. The transcript's content was then analysed by generating initial codes for all meaningful ideas emerging from the data, using a directed content-based analysis technique [328]. Following this, and a second coder (M.B. – a clinician with research experience who was not a study participant nor assisted with the focus groups in any way) coded the entire transcript using the coding grid. Codes that emerged from the data during the second coding procedure that could not be categorized using the existing grid were further discussed among both raters to explore their meaning and/or relationship to other codes, and a consensus was reached. A final round of analysis was then performed by the first author (T.O.) to ensure that all relevant statements were coded and that agreement between raters was at 100%. The recorded interviews with experts in the field were analysed separately from the focus groups. The interviews were transcribed verbatim and emergent themes, optimal features of a VR-based USN assessment, were selected from the discussion by the first author (T.O.). In the event of inconsistencies between the information from the self-administered questionnaire vs. focus group verbal reports (e.g. an institutional barrier that was identified in the questionnaire, but not mentioned by participants in the focus groups), emergent ideas were coded as initially intended (barrier/facilitator) and within their respective theme (e.g. institutional, equipment, personal factors, etc.).

6.5 RESULTS

6.5.1 *Descriptive variables*

The two focus groups included eleven (n=11) Occupational Therapists: four (n=4) in the group held in French (Group 1 at clinical site 1), and seven (n=7) in the group held in English/French (Group 2 at clinical site 2). Table 6.1 presents the clinician's personal and professional characteristics. Participants were aged 31.3 ± 4.5 years old, with a Bachelor or Professional Master's degree obtained anytime from 1995 to 2013. Most of the participants were full time clinicians with one to more than ten years of experience with stroke patients. Eight participants spend two hours or less per month on self-educational activities (e.g. reading articles, conferences, searching evidence-based engines, etc.) and only two had previous experience with VR.

Seven (n=7) experts in the field were originally contacted for interview. Two (n=2) declined to participate and no response was obtained from two (n=2) other candidates; therefore three (n=3) individuals were included in the study and interviewed (Table 6.2). All experts in the field had previous exposure (active research, presentations, and conferences) to USN, and 2 of the 3 had previous active research experience with VR.

6.5.2. *Barriers and facilitators*

Self-administered questionnaire: All clinician participants completed the self-administered questionnaire without any missing data. Table 6.3 shows the overall perception of therapists about VR for the use of post-stroke USN assessment according to UTAUT constructs. The questionnaire responses demonstrate that: (1) clinicians agreed that their work goals and patients' outcomes can be augmented through the use of VR for post-stroke USN assessment (*Performance Expectancy*); (2) clinicians slightly agreed that VR for post-stroke USN could be easy to use or not complicated to use (*Effort Expectancy*); (3) clinicians tended to be neutral with their perception that the intention to use the VR assessment for post-stroke USN is positively influenced by the opinions and perceptions of other therapists in their workplace (*Social Influence*); (4) clinicians disagreed that they have the available resources and knowledge necessary to use such a tool; and almost all reported the need for a resource person to assist in its

use (*Facilitating Conditions*); and lastly (5) clinicians showed a strong trend in behavioral intentions to use VR for post-stroke USN assessment (*Behavioral Intention to Use the System*).

Overall, the following facilitators emerged from the answered questionnaire: personal (performance and effort expectancy, positive attitude, no fear/anxiety towards VR, intention of use), institutional organization (support, resource person, built-in help facility). On the other hand, the questionnaire unfolded the following barriers: personal (lack of knowledge) and institutional organization (necessary resources).

Focus groups: Thematic analysis of the clinicians' comments on facilitators and barriers to the use of VR for post-stroke USN assessment revealed several natural groupings under barriers (n=5) and facilitators (n=7). The key themes voiced by the group were abstracted and are described below, as are salient comments ascribed to the various themes.

Barriers - client suitability

Four different themes emerged around client suitability as a barrier: old age, infection control, functional level, and deficits that may impact participation in VR:

P1a: The older clients, they are afraid of computers, they have a lot of anxiety: "I never used that, I would not use that" (quoting a client). This [anxiety] could affect their results. We won't of course use it [VR] only in evaluation. But, it is one of the preoccupations that older persons can express.

P4b: For patients with MRSA [Methicillin-resistant staphylococcus aureus], can we use it [VR]?

Barriers - equipment

Several topics emerged around the barriers related to equipment: availability, cost, lack of generalization, side effects, and space/training requirements:

P3b: There is also an aspect of generalization. Are the results of it [VR] are transferrable to real-life functioning?

P2a: Maybe I am afraid to have aftereffects following its [VR] use. I have apprehensions towards this. I don't want my patient to be nauseous or to vomit after the therapy session. It is this kind of things on a practical level that makes me say that I don't really want to use that [VR].

P4b: [I have preoccupations towards] the time to get to know it [VR], for us - the clinicians.

Barriers - personal

Personal barriers included anxiety, lack of VR experience and resources, lack of knowledge about VR and/or USN, unwillingness to use VR or other standardized measure, and time:

P1a: I have hard time to understand how it [VR] can be used as an assessment, given that we already have a very functional and ecological environment to evaluate our patients, we have the grocery store. So I don't think that I would tend to use it [VR] for evaluation.

P2a: It is certainly what we will do with this information knowing that he [patient] has no difficulties in daily activities, if we do not see it in daily activities. Therefore, at this moment, I do not know what I will do with this information [coming from VR assessment]. We have short hospital stays, so when the patient is independent in self-care activities, we send him [patient] home.

P2a: I understand that it [VR] could be more sensible than the line bisection test, but it cannot measure USN in the personal space. When a patient is shaving on one side, it is not with VR that I will assess or treat that. Even on extrapersonal level, I do not know at which point VR is really for extrapersonal space. It could be more fun since we have less tools, but it remains that it [USN of extrapersonal space] is very specific {...} so there are not that many patients per year. If I have one patient per year with this [USN of extrapersonal space], even that - I find is a lot.

Facilitators - client suitability

The point that VR might be suitable for the younger individuals with stroke given their drive for technology and previous exposure to technology came out on several occasions:

P5b: It [VR] would be good for our young clients. They are already attracted to technology.

Facilitators – equipment

Facilitators related to equipment such as precision, sensitivity, variability, accessibility, generalizability, training, versatility and built-in help were reported:

P5b: It [VR] can give us more tools, and tools that would allow us to evaluate things outside of the near space, without necessarily going in the real environment.

P3b: To have access to higher level activities because it [VR] is very multimodal. It [VR] is more visual, the client moves, there is more stimuli so it makes it more interesting. It [VR] could allow to detect more problems than we would see with our conventional evaluation tools.

Facilitator – institutional organization

Institutional organization facilitators such as resource person/assistance were discussed for overall management including assessment and treatment using VR:

P7b: I will use it [VR] as long as there is a resource or assistant person.

In fact, if there is a resource/assistant person, he [assistant] can write a journal reflecting the activities of the person – what they did in treatment, how he [patient] performed. In this way, us as therapists, we can see the feedback and the evolution of the patient.

Facilitator – personal

Several facilitators on the personal level emerged and included: knowledge of importance of USN assessment using sensitive methods, willingness or interest towards VR use for USN (intention of use), positive attitudes towards VR, time, performance and effort expectancy:

P1b: For my part, for USN evaluation, we [clinicians] are in lack of assessment for USN since a long time. I remember we had students that came in early 2000's presenting that the BIT [Behavioral Inattention Test] was the best that we have at the moment. We use it very rarely, given that we see that the patient has USN; however, patients tend to do well on those tests [BIT subtests], and it [BIT] doesn't necessarily measure the change.

Epecially, for the out-patients, there are patients that I follow until the driving assessment stage, and I do not have tools that inform me of their improvements or lack of thereof of the USN. So for the tasks that are paper and pencil, it [their performance] is not bad, but we see them [patients] from time to time neglecting obstacles in their space, bumping into left-sided obstacles. So, it would be very interesting to have sensible tools.

P6b: I like that it [VR for USN assessment] can be repeated in time, for example in in-patient, then in out-patient, to see the evolution/progression, rather than just evidencing it [USN of extrapersonal space] by walking for example. We are currently very limited in conventional extrapersonal-space USN assessment.

6.5.3 Optimal features of VR-based USN assessment

Optimal features of a VR-based post-stroke USN assessment were identified. Clinicians reported that they would be open to use an immersive, 3-dimensional tool that has a simple/intuitive start up system, with individual files saving options and that can print out reports of performance/progress. They conveyed that performed tasks should be client-centered and functional, including activities centered around leisure, instrumental and self-care activities of daily life, near and far-extrapersonal USN assessment, and having an option of different tasks to perform as per the patient's preference. Clinicians would like to complete the VR USN assessment in thirty to sixty minutes and they expressed an interest in receiving training on the device and running of the system.

Experts reported the following additional features: presence of attentional distractors, ability to adjust the attentional load of the task, eye tracking during tasks, gaze and movement coordination tasks (e.g. transfer from near- to far-extrapersonal space through navigation), goal-directed space navigation (e.g. following the principles of the zoo map subtest of the Behavioral Assessment of Dysexecutive Syndrome [329]) and locomotor tasks within limited space (e.g. using treadmill or stationary robotics that can change directions), a VR version of conventional tests (e.g. VR-based line bisection and cancellation tasks in near and far space), targets placed in space using polar coordinates, and symmetrically-designed environments. The common features to those reported by clinicians included functional tasks in 3D immersive environments with an adjustable level of difficulty, near and far space tasks, simple start up and analysis of results, and clear guidelines and training. The latter two factors were expressed not only as optimal features of a tool by experts in the field, but also as facilitators (equipment/personal) for its implementation and adherence to its use.

6.6 DISCUSSION

To our knowledge, this study is the first to highlight the barriers and facilitators to the clinical use of a VR-based assessment tool for post-stroke USN. The key barriers that were identified, including personal, institutional, equipment, and client suitability, will help optimize the design and implementation of future VR-based USN tools in clinical practice. A multimodal and active KT intervention can now be designed (e.g. [309]) according to the identified support needs and modifiable barriers. For instance, addressing factors of lack of knowledge about VR use and importance of USN-sensitive assessments as well as lack of resources in the clinical setting could influence VR adoption and its sustainable use for USN management. The personal barrier of lack of knowledge about USN and the importance of USN-sensitive assessment (e.g. please refer to comment of *P2a* under that category) is highly concerning, demonstrating that a clinician, working full-time on a stroke rehabilitation ward, does not see the need for a sensitive post-stroke USN assessment of peripersonal space (near and far extrapersonal space) that in fact is known to be greatly prevalent among those with right hemisphere stroke and often left undetected using conventional methods or observation. Based on this study, we propose the following interventions and elements geared towards increasing the knowledge-base of scholarly practitioners about post-stroke USN, its assessment, and the VR technology: the addition of a

specialized course in visual-perception and related-technologies in the current OT educational curriculum, multifaceted KT interventions for clinicians including hands-on workshop experiences, e-learning modules, case studies, experts' panel discussions, a designated expert clinician (champion or mentor) or resource person in each targeted setting, training and ongoing support in the use of chosen technologies, and evaluation of change in practice following the KT interventions.

The finding that most of the participating clinicians were open to the use of VR and had a positive attitude towards its use for post-stroke USN indicates that there is a potential in continuing to pursue the knowledge to action model cycle with the aim of improving current practices as described by Graham et al., 2006 [8]. Specifically, present results could be employed to plan for a future implementation of a VR-based USN assessment tool in a clinical setting, monitor its use and evaluate what changes it brings to the clinical post-stroke USN management. To tackle most of the representative population (individuals with post-stroke UNS), we propose that the implementation of a VR-based USN assessment tool should initially occur in rehabilitation centers providing stroke rehabilitation services, and be integrated with other occupational therapy evaluation procedures. This would complement existing findings and provide data on concurrent validity and sensitivity with respect to the conventional methods employed in that setting. Thereafter, a broader implementation could be foreseen to private, community and acute-care settings.

The results of the self-administered questionnaire in our study are consistent with previously published reports on behavioral intention to use technologies in healthcare settings. For instance, our results, showing an agreement among clinicians that a VR-based USN assessment can enhance their performance and ensuring patients' outcomes (i.e. performance expectancy) are in accordance with a larger cross-sectional exploratory study by Liu et al., (2015) [326]. Using the UTAUT-based questionnaire, they found that performance expectancy was the most significant factor in determining Occupational and Physical therapists' acceptance and use of technology in rehabilitation [326]. Similarly to the responses of clinicians' in the present study, effort expectancy [326, 330-332] and social influence [326] were not found to be salient factors influencing behavioral intention to use technologies in studies using the UTAUT-based questionnaires with different health professionals including medical doctors, health educators,

nurses, as well as Occupational and Physical Therapists. Promisingly, participants in the present study, similar to those in Liu et al., (2015) study, expressed their intention to use the newly available technology, confirming previously found clinicians' positive attitudes towards VR

The findings of the present study offer multiple practical implications. First, the identified factors that influence clinicians' acceptance and adoption of VR for post-stroke USN assessment can inform future research on priorities for the planning of training programs and of the resources needed for the effective acquisition and implementation of such technology. The interviewees in the present study were critical regarding barriers related to VR equipment in terms of possible side effects and generalizability, time and training demands, and costs of implementation; as well as client suitability barriers such as age, functional status, and infection control. It demonstrates that despite increasing evidence for the effectiveness of VR in post-stroke USN assessment and treatment, health care professionals are still grappling with those core issues and they are imperative to be addressed in future KT resources to support VR clinical integration outside of a research context. Similarly, the collaborative results from focus group and experts in the field on the optimal features of a VR-based USN assessment can serve to adapt current tools or to guide the development of a new tool that better suits different clients' functional capabilities and deficits (e.g. aphasic, wheelchair-bound), as well as end-users/clinicians needs (e.g. easy application/start up, print out reports, progress reports, resource/assistance, time constraint, 3-dimensional immersive environment, tasks options, etc.). We suggest future presented tools to incorporate these findings which in turn could promote its adherence and satisfaction with its use in clinical settings among practicing rehabilitation professionals.

The current study also has its limitations. First, clinicians' perceptions were determined at one point in time by using a cross-sectional exploratory study design. Although we consider that it is appropriate given the exploratory nature of this project, future longitudinal designs that would study these perceptions in time would be beneficial. Moreover, a true collaborative approach by including clinicians and experts in the field in the same focus groups would have been advantageous, but this was not possible given the different geographical locations and schedule conflicts. Nevertheless, individual interviews have also proven to be effective methods in gathering information and mixing qualitative methods (focus groups, interviews, surveys) as used in the present study is suggested to provide broader understanding of the phenomenon of

interest that may be otherwise overlooked if a single method is used [333]. Lastly, another limitation is that the evidence behind VR assessment for post-stroke USN is still limited and exploratory at the moment [36]. This implies that it may be challenging to implement practice changes in the future. Yet, the results of the present study offer preliminary steps by including the end-users/clinicians early in the process of the knowledge to action model [8], possibly facilitating forthcoming implementation of this type of system in clinical practice.

Conclusion

The present study explored the facilitators and barriers to the clinical use of VR for post-stroke USN assessment and identified features for an optimal VR-based USN assessment tool through mixed qualitative methods including focus group, self-administered questionnaires and individual interviews. Findings show that clinicians are open to the idea of using VR for post-stroke USN assessment. Facilitators such as knowledge of the importance of USN assessment, equipment usability, client suitability and institutional organization support can be emphasized during an implementation phase. However, therapists also identified several personal, institutional, equipment usability and client suitability barriers that should be addressed in designing a future knowledge translation intervention prior to and during an implementation phase. The reported features of an optimal VR-based USN assessment tool by a collaborative effort of end-users and experts in the field offer invaluable concepts for the modification of already-existing tools or the development of new tools. Considering those features should lead to a more effective clinical implementation of a tool while promoting its use and adherence among rehabilitation professionals.

Table 6.1 Personal and professional characteristics of focus groups' participants

Variable	Group 1 (n=4; P1a-4a)	Group 2 (n=7 P1b-7b)
Age at evaluation (mean ± SD)	29.1 ± 3.8	33.4 ± 5.2
Gender ratio (M:F)	0:4	0:7
Degree and year of graduation (range)	BSc or MSc (Applied)/ 2008-2012	BSc or MSc (Applied)/ 1995-2013
Work schedule	Full time* (n=4)	Full time * (n=6) Part time** (n=1)
Experience with stroke rehabilitation (years)	4-10	1 - >10
Number of patients per day (range)	2-5 (n=4)	6-10 (n=4) 2-5 (n=3)
Evaluation vs. treatment time per day (hours, range)	1-2: 4-6	.75-3: 3-7
Continuing education in stroke rehabilitation (hours/month)	≤ 2 (n=4)	≤ 2 (n=4) 2-5 (n=3)
Clinicians with University teaching experience (n)	1	4
Clinicians having experience with VR (n)	0	2 [†]

Table 6.1 Personal and professional characteristics of focus groups' participants. Legend: Standard deviation (SD); Male (M); Female (F); Bachelor in Science (BSc); Masters in Science (MSc); number (n); Virtual reality (VR); Participant (P); * Full time = ≥35 hours/week; **Part time = <35 hours/week; † presentations, conferences and research.

Table 6.2 Characteristics of experts in the field

Variable	Participant 1	Participant 2	Participant 3
Gender	M	F	M
Degree & year of graduation	PhD (2004)	MSc Thesis (2012)	MD (1986) - Specialist in Physical Medicine, Rehabilitation & Neuropsychiatry
Expertise areas	Brain Injury; Movement Control; Neuropsychology; Neuroscience; Rehabilitation/Therapy; Stroke; Virtual Reality	USN; Stroke Rehabilitation; Knowledge Translation; Traumatic Brain Injury; Cognition	Stroke rehabilitation; Neurorehabilitation; Motion Analysis; Motor Cognition and Learning; Perception; Neurodegenerative Disorders
University teaching experience	Yes	Yes	Yes
VR experience	Yes *	Yes [†]	Yes *
USN experience	Yes * [†]	Yes * [†]	Yes * [†]

Table 6.2 Characteristics of experts in the field. Legend: Male (M); Female (F); Masters in Science (MSc); Doctor of Philosophy (PhD), Doctor of Medicine (MD); Virtual reality (VR); Unilateral spatial neglect (USN) [†] presentations, conferences, * active research area.

Table 6.3 Response frequencies by Unified Theory of Acceptance and Use of Technology Model constructs

	Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<i>Performance expectancy</i>							
I will find virtual reality (VR) for post-stroke unilateral spatial neglect (USN) assessment useful in my job	1				3	4	3
Using VR for post-stroke USN assessment will enable me to accomplish tasks more quickly				2	3	6	
Using VR for post-stroke USN assessment will increase my productivity			1	3	5	2	
<i>Effort expectancy</i>							
My interaction with VR for post-stroke USN assessment would be clear and understandable				1	6	3	1
It would be easy for me to become skillful at using VR for post-stroke USN assessment					4	5	2
<i>Social influence</i>							
People who influence my behavior at work think that I should use VR for post-stroke USN assessment		1		9	1		
People who are important to me think that I should use VR for post-stroke USN assessment		1		10			
The senior management of this institution would be helpful in the use of VR for post-stroke USN assessment	1	1		7	2		
In general, I feel that the organization will support me in the use of VR for post-stroke USN assessment			1	1	5	4	
<i>Facilitating conditions</i>							
I have resources necessary to use VR for post-stroke USN assessment	1	4	3	2	1		
I have the necessary knowledge to use VR for post-stroke USN assessment	2	3	3	1	2		

I would like a specific person (or group) would be available for assistance with VR for post-stroke USN assessment difficulties							1	10
I think I could complete a job or a task using VR for post-stroke USN assessment if there was no one around to tell me what to do as I go	3	2	2	1	3			
I think I could complete a job or a task using VR for post-stroke USN assessment if I could call someone for help if I get stuck					1	6	4	
I think I could complete a job or a task using VR for post-stroke USN assessment if I had a lot of time to complete the job for which the software was provided	1	1	1	4	1	2	1	
I think I could complete a job or a task using VR for post-stroke USN assessment if I had just the build-in help facility for assistance	2	1	3		3	1	1	
<i>Behavioral intention to use the system</i>								
If made available to me, I intend to use VR for post-stroke USN assessment in the next 12 months							7	4
If made available to me, I predict I would use VR for post-stroke USN assessment in the next 12 months					2	6	3	
If made available to me, I plan to use VR for post-stroke USN assessment in the next 12 months					2	6	3	

Table 6.3 Response frequencies by Unified Theory of Acceptance and Use of Technology Model constructs. The highlighted boxes indicate to the response category chosen by most of the focus group participants; Virtual reality (VR); Unilateral spatial neglect (USN).

CHAPTER 7: GENERAL DISCUSSION

7.1 Summary of Results

The general aim of this PhD dissertation was to investigate perceptuo-motor control in post-stroke USN during goal-directed locomotion and navigation, and thereby to work towards improving current clinical practices in post-stroke USN management, mainly in the development and implementation of a functional VR-based USN assessment tool. To that end, effects of USN, its severity, underlying visual perceptual skills, and the effects of conditions of variable cognitive-perceptual demands on goal-directed locomotion and navigation were examined. A novel, ecological, VR-based evaluation of neglect symptoms, EVENS was developed and tested. This was followed by the identification of barriers and facilitators to the clinical use of VR for post-stroke USN management, and identification of additional features to be incorporated in VR-based USN assessment tool as per clinicians and experts in the field.

In Manuscript № 1 (Chapter 2), objectives were to determine: 1) the extent to which goal-directed locomotion performance towards actual vs. remembered vs. shifting targets is affected in participants with post-stroke USN as compared to those without USN and age-matched healthy control individuals; 2) the extent of the association between goal-directed locomotion performances with USN severity in near and far space; and 3) the preliminary sensitivity of the goal-directed VR locomotion task in detecting deficits in patients with history of USN and in those with mild USN as per conventional evaluation methods. It was hypothesized that post-stroke USN alters goal-directed locomotion abilities to left-located target to a larger extent than a stroke without USN, with alterations to be observed possibly in all conditions. We expected to find greater association between USN severity in far vs. near space and alterations in goal-directed walking performance to the left target. Further, we anticipated that goal-directed locomotion performance to the left target in the remembered condition would be sensitive in detecting deficits otherwise left undetected using conventional assessments. These hypotheses were largely confirmed in Manuscript №1, where participants with post-stroke USN showed altered locomotion abilities (end-point measures) in actual and remembered conditions to left and right targets; and a delayed onset of reorientation to the left and right shifting targets vs. other two study groups ($p < 0.05$). Goal-directed locomotion performance was associated mostly with

USN in near-space (and not far space as initially hypothesized) but only to a low-moderate degree. The goal-directed locomotion task was also sensitive in detecting deficits in participants with “recovered” USN as per the conventional paper-and-pencil tests vs. those without post-stroke USN on testing or history of USN, supporting the evidence of conventional tools failing to predict performance in more functional tasks.

The main objective of Manuscript №2 (Chapter 3) was to further our understanding of the role of post-stroke USN in the control of mobility/navigation, where we aimed to ascertain the contribution of USN related attentional-perceptual deficits vs. stroke-related sensorimotor deficits. Hereby, we proposed to examine USN effects in a joystick-driven goal-directed navigation task which is analogous to the goal-directed locomotion paradigm used in Manuscript № 1. The objectives were to: 1) estimate the extent to which post-stroke USN affects goal-directed navigation abilities in actual, remembered and shifting conditions; and 2) estimate the extent to which post-stroke USN affects target detection abilities as well as the relationship of navigation abilities with measures of detection abilities and clinical measures of USN. We hypothesized that post-stroke USN would affect navigation and detection abilities, such that greater end-point accuracy errors, longer re-orientation of navigation trajectories and greater detection times would be observed for the group with vs. those without USN and healthy controls, possibly in all conditions. We also hypothesized that clinical USN measures would be minimally associated with navigation outcomes. These hypotheses were confirmed in Manuscript №2, where navigation performance alterations were observed in remembered and shifting conditions in individuals with USN vs. the other 2 study groups. Furthermore, this manuscript also confirmed that the ability to detect objects is altered across the visual field (i.e. not limited to the “neglected”/left visual space) as individuals with post-stroke USN presented with longer detection times compared to the other two study groups for all target locations. Overall, and in agreement with the locomotor experiment findings, the present study show both lateralized and non-lateralized deficits in object detection and navigation behavior, as well as alterations in memory-guided condition and in task requiring representational updating. However, discrepancies between locomotion vs. navigation experiments were noted in the direction of deviation towards the left target (under vs. overshooting, respectively); and performance alterations in the actual condition (deficits present vs. absent, respectively).

In Manuscript №3 (Chapter 4), objectives were to estimate: 1) the extent to which visual-perceptual abilities, including: contrast sensitivity, optic flow direction and coherence, and shape discrimination in bilateral (left/right) visual hemispaces, are affected in individuals with and without post-stroke USN and in healthy control individuals; 2) the relationship between USN clinical tests and psychophysical tests of visual perceptual abilities; 3) the preliminary sensitivity of psychophysical tests in detecting deficits that were otherwise left undetected using conventional USN clinical tests; and 4) the extent to which visual-perceptual abilities contribute to goal-directed locomotion impairments in individuals with post-stroke USN. It was hypothesized that individuals with vs. those without USN and healthy controls would present with higher thresholds in all psychophysical tests, indicating worse behavior, possibly in both visual hemispaces. Moreover, we hypothesized to find significant but low-magnitude correlations between USN clinical tests and psychophysical measures. Further, we speculated that psychophysical measures would be sensitive in detecting deficits in those with history of USN and potentially in those without post-stroke USN as assessed by traditional paper-and-pencil tests. Finally, we hypothesized that visual-perceptual abilities, specifically those related to optic flow processing, would significantly contribute in explaining impairments found in goal-directed locomotor behavior. These hypotheses were confirmed in Manuscript №3, where higher discrimination thresholds were found for all tested visual-perceptual abilities in the USN+ group compared to USN- and HC groups ($p < 0.05$). Low to moderate association between clinical assessments of USN and the majority of the tested higher-order perceptual abilities were unveiled. Psychophysical tests were sensitive in detecting deficits in individuals with history of USN or with no USN on traditional assessments, and were found to be significantly correlated with goal-directed locomotor impairments.

Further, we developed and examined the feasibility of a newly created USN assessment tool, the Ecological VR-based Evaluation of Neglect Symptoms (EVENS). EVENS consists of two ecological scenes with variable perceptual-attentional demands (simple vs. complex) where functional tasks of object detection and goal-directed navigation are performed. In Manuscript №4 (Chapter 5), objectives were to estimate: 1) the effects of post-stroke USN on functional VR tasks; and 2) the preliminary sensitivity of EVENS in detecting deficits that were otherwise left

undetected using conventional USN clinical tests. We hypothesized that the presence of post-stroke USN would alter functional object detection and navigation performances, more so in the complex vs. simple VR scene. We also hypothesized that EVENS would identify deficits in individuals with history of USN (i.e. during acute stages of stroke recovery) but presenting no USN on testing using conventional methods during the present study, and possibly in some individuals with undiagnosed USN. These hypotheses were confirmed in Manuscript №4, where we found: altered performances on both the detection and navigation tasks in the USN+ individuals compared to individuals without USN; presence of detection and navigation deficits that varied as a function of environment complexity and which could present either unilaterally (lateralized) or bilaterally (non-lateralized); presence of detection and navigation deficits consistent with the USN presentation in individuals that otherwise show no sign of neglect using traditional clinical measures.

Subsequently, we worked towards promoting the development and future clinical implementation of a VR-based USN assessment tool such as EVENS. In Manuscript №5 (Chapter 6), objectives were to identify: 1) the facilitators and barriers that affect the use of VR for post-stroke USN assessment by clinicians; and 2) the features of an optimal VR-based USN assessment that could be implemented and used by clinicians in the management of post-stroke USN. We expected clinicians to identify various barriers and facilitators to VR use in post-stroke USN assessment. We hypothesized that clinicians and experts in the field would identify several features of an optimal VR USN assessment tool. These expectations were confirmed in Manuscript №5, where findings showed that clinicians are open to the idea of using VR for post-stroke USN assessment. Facilitators such as knowledge of the importance of USN assessment, equipment usability, client suitability and institutional organization support can be emphasized during an implementation phase. However, therapists also identified several personal, institutional, equipment usability and client suitability barriers that should be addressed in designing a future knowledge translation intervention prior to and during an implementation phase. The reported features of an optimal VR-based USN assessment tool were as follow: an immersive, 3-dimensional tool that has a simple/intuitive start up system, with individual files saving options and that can print out reports of performance/progress; a tool that contains client-centered, functional tasks, including activities centered around leisure, instrumental and self-care

activities of daily life, near and far-extrapersonal USN assessment, and options of different tasks to perform as per the patient's preference; presence of attentional distractors, ability to adjust the attentional load of the task, eye tracking during tasks, gaze and movement coordination tasks (e.g. transfer from near- to far-extrapersonal space through navigation), goal-directed space navigation and locomotor tasks within limited space, a VR version of conventional tests, targets placed in space using polar coordinates, and symmetrically-designed environments.

7.2 General Discussion

This dissertation offers many novel and pioneering findings in the field of post-stroke USN; consequently, five main themes emerged, and are discussed below.

7.2.1 POST-STROKE NEGLECT AFFECTS MOBILITY, BUT THE MODE OF DISPLACEMENT MODIFIES DEFICITS PRESENTATION

Only a handful of studies examined the influence of post-stroke USN on mobility. While these studies found larger deviation in the walking trajectories of individuals with post-stroke USN as compared to comparison groups without USN, the results were not consistent in terms of the direction of the mediolateral deviation, where some reported rightward deviations [61, 72, 77], but also deviations to both the left and the right sides [71, 73]. In Manuscript №1 and №2, we confirmed, in a fully powered study, the earlier findings that post-stroke USN negatively impacts goal-directed locomotion and goal-directed navigation. We also identified that the type of mobility task performed affects the direction of the deviation. Namely, the responses in the joystick task differed from the locomotion task in terms of the direction of the endpoint trajectory deviation in relation to the target, as individuals predominantly overshoot left-sided targets in the navigation task vs. undershot that same target in the locomotor task.

We propose that factors such as the differences in the mode of displacement in the walking vs. the joystick navigation tasks as well as the influence of walking dysfunctions could explain this discrepancy in findings between two studies. To clarify, the joystick mode of control allowed the participants to make trajectory adjustments that are not limited in magnitude and not restricted by one's walking capacity, as opposed to what is experienced during locomotion. For this reason, participants with USN, who also presented with a reduced walking ability, may have undershot

the left (neglected) target in the walking task, while they overshoot that same target during joystick navigation. The joystick-driven task may thus reflect more accurately the perceptuomotor abilities of individuals with post-stroke USN, but falls short in estimating the impact of USN on actual locomotion. Another difference between joystick navigation and walking is that the former did not allow bodily horizontal rotation, such that the only way to align with a target located on the side is to terminate the trial while being in front of it. In contrast, locomotor steering is achieved through both, body displacement and reorientation [254], such that while the endpoint trajectory ‘apparently undershoots’ the target in terms of MLD, it may still be ‘on target’ when considering the body orientation with respect to that target [255].

Discrepancy in the direction of deviation have also been reported in previous studies. Turton and colleagues (2009) [77] observed leftward vs. rightward deviations in individuals with post-stroke USN heading towards a centrally located target in a wheelchair (n=9) vs. while walking (n=5), although it should be mentioned that only two participants performed the two tasks. In addition, Huitema et al., (2006) [71], in an experiment that involved walking to a centrally located target, reported that USN+ individuals, who were also slow walkers (n=3), deviated to the ipsilesional/right side; and those who are fast walkers (n=3), deviated to the contralesional/left side. The authors concluded that walking trajectory deviation in individuals with USN may depend on the walking ability. Results from our studies, where the same individuals performed both tasks of navigation and locomotion support the presence of an interaction between USN and walking ability, which is otherwise not present during joystick navigation. Thus, while similarities exist between the tasks and results evidenced through the navigation and locomotor experiments, important differences were also revealed, which need to be considered in the design of USN-related evaluation/treatment methods using a VR setup.

In addition, our team previously conducted a systematic review examining the effects of post-stroke USN on goal-directed upper extremity movements performed within the near-space [65]. The findings were consistent with the hypothesis that there are two different types of action control, processed via distinct visual streams, ventral and dorsal [66]. More precisely, impairments among individuals with post-stroke USN were found mostly during perceptual, memory-guided or delayed tasks (e.g. delayed pointing to remembered target location – ventral

stream processing/offline movements); but not in immediate tasks (e.g. pointing to an actual target – dorsal stream processing/online movements). We propose that the conditions used in the *joystick experiment* could tap into ventral vs. dorsal stream hypothesis such that i) the actual condition is visually-guided/online as it requires a quick joystick response; ii) the remembered condition is memory-guided/offline and; iii) the shifting condition is visually-guided, but since it also necessitates representational updating, it could include an offline component. On one hand, the proposed ventral vs. dorsal stream hypothesis which explains goal-directed arm movement deficits in post-stroke USN may potentially hold for far-space exploration in *navigation (joystick-driven task)*, given that significant between-group differences were shown in offline conditions (i.e. remembered and shifting), but not in the actual/online condition. On the other hand, this hypothesis fails to explain far-space exploration in *locomotion*, given that significant between-group differences were shown in both online (actual) and offline (remembered) conditions. We argue that as opposed to joystick navigation, goal-directed locomotion requires additional space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85] to transform perception into action. It is also a longer task to perform as opposed to joystick navigation, and is more physically demanding. As a result, the actual condition in the locomotor experiment is potentially no longer a clear-cut “online” condition, but rather incorporates both, online and offline components. These additional demands on the visual-perceptual, attention, and sensorimotor systems during walking vs. navigation could account for these differences in findings between the two experiments. Overall, rather than fully supporting the ventral stream hypothesis in USN proposed by Milner and Goodale [6], our results of the locomotion vs. navigation experiment align with the model proposed by Rizzolatti & Matelli (2003) who suggested that a system encompassing both ventral and dorsal streams is underlying USN, such that action control in the dorsal system is affected by the disruption of visuospatial information from ventral regions (temporal-parietal) [257].

7.2.2. MODIFICATIONS IN COGNITIVE CONDITIONS AND PERCEPTUAL DEMANDS WORSEN OBJECT DETECTION, GOAL DIRECTED LOCOMOTION AND NAVIGATION IN POST-STROKE USN

We live in busy, cluttered, and constantly dynamic environments, where we profoundly rely on all our senses and functions, including vision and cognition, to function safely and to

successfully perform everyday life activities. The findings in Manuscripts №1, №2, and №4 evidence that the presence or history of post-stroke USN negatively and significantly impacts functional performance in goal-directed locomotion, navigation and object detection. This is especially the case when more challenging perceptual-cognitive demands involving spatial memory and representational updating are introduced (Manuscripts №1 and №2), and when perceptual-attentional demands of the scene is heightened by making the environment more ‘cluttered’, as experienced in conditions of daily living (Manuscript № 4).

In Manuscripts №1 and №2, we employed three different conditions: *actual* (i.e. goal-directed locomotion and navigation to one visible and stationary target); *remembered* (i.e. goal-directed locomotion and navigation to the remembered location of one target, involving a spatial memory component); and *shifting* (i.e. goal-directed locomotion and navigation to a target that could shift its location and necessitate trajectory readjustment, involving a representational updating component). Although the remembered and the shifting conditions vs. actual condition involved supplementary cognitive components of spatial memory and representational updating, the environment remained very simple and free of clutter and distractions that would normally be present in real daily life. Even so, only individuals with post-stroke USN and those with history of post-stroke USN demonstrated greater difficulties not only when these supplementary cognitive components were introduced (during goal-directed locomotion and navigation), but also in the actual condition (during goal-directed locomotion). We propose that far-space exploration requiring goal-directed locomotion, and to a lesser extent navigation, imposes greater demands on vestibular and proprioceptive systems that inform the person about environmental features and that of the goal, allowing to subsequently adapt the locomotor behavior [211]. Correspondingly, the nature of the locomotor and navigation tasks, requiring space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85] to transform perception into action, could explain the findings.

Similarly, Manuscript №4 found that while USN negatively affects perceptual and navigational abilities to targets located predominantly on the neglected side, deficits significantly worsen when exposed to a “complex” (yet, realistic) environment with an increased perceptual load. We propose that such an environment imposes greater demands on the perceptual-attentional resources compared to the uncluttered environment. Our findings may explain the difficulties

individuals with chronic USN experience on daily basis in real-world situations where cluttered environment are encountered, such as mobility within the community that requires goal-directed locomotion [71, 77], obstacle avoidance [74], wheelchair navigation skills [32], street crossing [288], or performing instrumental activities of daily living [289]. These tasks may not only be lengthier to perform for those with post-stroke USN, but also more demanding, tiring, and possibly leading to difficulty in maintaining a given level of performance over an extended period of time. This could also explain the behavior of avoiding busy environments so often present in individuals with post-stroke neglect in chronic stages [26]. Our results are also consistent with the view that the quantity and allocation of attentional resources available alter performance such that true deficits can be revealed when one can no longer effectively allocate his/her attentional resources in instances of increased perceptual or cognitive load of the task [279]. Specifically, multiple studies found that increased task demands negatively affect the performance and result in the emergence of signs and symptoms of neglect in chronic stages that were otherwise not detected using conventional methods [74, 290-292].

In addition, goal-directed locomotion performance in the remembered condition (Manuscript №1) and navigation in the complex environment (Manuscript №4) were more sensitive in detecting deficits in participants with “recovered” USN as per the conventional paper-and-pencil tests vs. those without post-stroke USN on testing or history of USN, supporting the evidence of conventional tools failing to predict performance in visually-guided functional tasks [33, 34, 248, 270]. These findings demonstrate that although individuals may appear “recovered” or free of USN on paper-and-pencil tests in static, two-dimensional environments, perhaps their deficits become more apparent and severe exposed to a three-dimensional environment or to a more functional task. It can be speculated that a real environment would add even greater demands on the attention resources, thus leading to difficulties in performing the self-care and instrumental activities as so often encountered by individuals with post-stroke USN in the chronic phase [49].

7.2.3 LATERALIZED AND NON-LATERALIZED DEFICITS IN POST-STROKE USN

In Manuscripts №1, №2, №3, and №4, we consistently found that post-stroke USN influences performance on a wider visual space spectrum that is not limited to the left/ “neglected” visual hemispace. In other words, lateralized and non-lateralized performance alterations were observed.

For example, in Manuscript №1, end-point measures (MLD and HEs) were significantly affected by presence of post-stroke USN when individuals were walking towards both left and right sided targets. In addition, the temporal measure of the onset of reorientation was evidenced to be altered in post-stroke USN participants when walking to left and right sided targets. Similarly, the detection task in Manuscript №2 identified USN-related deficits in the detection time of left-sided (i.e. contralesional) and right-sided (ipsilesional) targets. Previous studies have also reported presence of non-lateralized deficits in individuals with post-stroke USN [103, 162]. Functional imaging studies reported the intraparietal sulcus and the frontal cortex to play a role in non-lateralized visual processing [258, 259]. In relation to that, our sample of individuals with post-stroke USN was constituted of nearly 70% of those with parietal and/or frontal lesions [249] further indicating that the presence of non-lateralized deficits could be accounted for by the lesion areas involved.

Furthermore, Manuscript №3 also identified both lateralized and non-lateralized visual-perceptual deficits in individuals with post-stroke USN. For instance, contrast sensitivity was found to be more severely affected by USN in the left/ “neglected” visual hemispace, indicating to a decreased ability detecting lower thresholds in the left/contralesional visual hemispace. This finding is consistent with previous research [14, 21-24], indicating lateralized contrast sensitivity deficits. Contrast sensitivity is known to be dynamically modulated by eye saccades (e.g. [262]), predominantly in connection with the frontal eye fields (e.g. [263]) and the superior colliculi (e.g. [14, 15]), receiving retinal input predominantly from the contralateral hemifield [264]. As the sample of USN+ individuals in the present study constituted only those with right hemisphere lesions, the influence of disrupted right hemisphere contrast sensitivity networks most likely account for the observed left/contralesional visual hemispace deficits.

On the contrary, shape discrimination and optic flow direction discrimination abilities were found to be considerably worse in USN+ vs. the other two study groups in both the left/ “neglected” and right/ “non-neglected” hemispaces. These non-lateralized deficits could potentially be explained by the involved networks. The ventral visual stream (occipito-temporal-frontal areas) is proposed to play a crucial role in processing perception of objects’ shape, color, texture, location, size and orientation constancy [334], while the dorsal stream (occipito-parietal-frontal) is suggested to incorporate motion processing areas responsible for optic-flow and self-

motion (reviewed in [335]). Recent evidence, however, suggests that processing functions of the ventral vs. dorsal streams are not as clear cut. For instance, Van de Winckel et al., (2012) evidenced activations in the anterior intraparietal sulcus and premotor area (i.e. dorsal stream) during shape discrimination in persons with stroke [265]. In addition, the V5/MT complex, with projections to the medial superior temporal area (i.e. ventral stream) and the parietal cortex (i.e. dorsal stream) is found to process optic flow information [266]. It emerges that the parietal cortex or projections to the parietal cortex represent a common network involved in processing abilities of shape discrimination and optic flow. The parietal lobe, known to be typically associated with neglect and spatial functions, is thus involved in non-lateralized functions [267, 268] that can co-exist and worsen spatial deficits in USN [99, 106].

However, optic flow coherence ability was found to be affected by USN in the right/ “non-neglected” visual hemispace only. Visual motion in one hemifield is suggested to activate the contralateral primary visual cortex and to suppress activation in the ipsilateral brain region [336]. However, hemispheric asymmetry in the MT complex was also identified, where right hemisphere dominance for motion processing has been found [336, 337]. Specifically, visual motion processing from the right visual hemifield resulted in stronger activations of the right MT complex compared to the left MT complex following visual motion stimulation in the left visual hemifield. This also indicates to the fact that it is the non-crossed fibers from the ipsilateral hemisphere that play the predominant role in processing of optic flow [337]. This latter notion can be considered in arguing the observed worse performance in right visual hemispace in optic flow coherence processing. We can speculate that when an individual with left post-stroke USN is exposed to visual motion coming from the left visual hemispace, the left/not-lesioned hemisphere is stimulated and results in normal processing of information. However, when the same person is viewing visual motion coming from the right visual hemispace, the right hemisphere fails to process the information given the right hemisphere lesion. We further propose that in optic flow direction discrimination experiment, perception of distance/location of central vs. lateral focus of expansion was necessary; therefore, imposing greater demands on the attentional/perceptual networks involving the ventral stream. On the other hand, in optic flow coherence testing, distance/location judgement was no longer necessary. Thus, it was possibly recruiting only the ipsilateral MT complex, without projections to the ventral stream, leading to deficits observed in the ipsilesional hemifield only.

Lastly, Manuscript №4 similarly revealed the presence of lateralized and non-lateralized deficits in individuals with USN, notably in detection time and time to target outcomes on the detection time and navigation tasks, and in maximal mediolateral deviation from the ideal path outcome on the navigation task. These findings again may be explained by attentional mechanisms underlying USN. Firstly, time-related performances (detection time, navigation time to target) of USN+ vs. USN- group, in general, were worsened in a “gradient manner” from the ipsilesional/right (+20°) to contralesional/left periphery (-40°). This demonstrates that time-related outcomes can identify spatially-lateralized loss of attentional capacity. These findings are in accordance with two models of USN attentional theory: the hemispheric imbalance model, namely its opponent processor; and the disengagement deficit/attention shift model. The opponent processor hypothesis stipulates that there are two opponent processors (in the left/right hemispheres) that control attention towards the contralateral portion of the visual hemispace and inhibit one another via collasal connections [107]. Neglect is viewed as the result of the hypoactive ipsilesional hemisphere and hyperactive contralesional hemisphere following a stroke. This interhemispherical imbalance causes a decrease from center to periphery of the left/contralesional visual hemispace attention gradient, and an increase of the right/ipsilesional visual hemispace attention gradient [107]. Similar to the results obtained using EVENS, a previous study on the gradient of attention deployment showed that all patients with right hemisphere stroke and USN have a reduced response accuracy and increased reaction time to contralateral vs. ipsilateral targets in comparison to individuals with left hemisphere stroke and healthy controls [110].

The disengagement deficit/attentional shift model is viewed as a sequence of three internal mental operations including disengagement of attention from current stimulus; moving attention towards a new stimulus; and engagement of attention on the new stimulus. Previously, USN+ individuals with right hemisphere parietal lesions were found to have a deficit in disengagement of attention from ipsilesional targets in response to contralesional targets [134-136]. Similarly, our results could be associated with a deficit in moving attention from ipsilesional to contralesional targets in an activity reflecting real-world attentional demands. In addition, a related meta-analysis deduced that the disengagement deficit is in fact larger in individuals with USN+ individuals a right hemisphere lesion (especially with parietal lobe damage) than in USN- individuals with a left hemisphere stroke [137]. Nearly 60% of our sample of USN+ individuals

presented with lesion to the right parietal lobe, supporting the evidence for possible disengagement difficulties.

Manuscript №4, however, also revealed the presence of non-lateralized deficits, as demonstrated by the outcome of maximum mediolateral deviation from an ideal path in the navigation experiment which was found to be altered both for the left/ “neglected” and right/ “non-neglected” visual hemispaces in USN+ individuals. Goal-directed navigation (similar to goal-directed locomotion) requires space computation and re-adjustments of self with respect to target location [256] and perceived optic flow direction [85], which are processes that involve a complex brain network that transforms perception into goal-directed action and which includes the parietal area [293, 294]. The latter area, which is largely involved in post-stroke USN, is also known to have non-lateralized functions [267], which may explain the presence of non-lateralized deficits observed in this study during goal-directed navigation. Findings are further consistent with the growing evidence that the persistence of neglect into chronic stages of stroke recovery is likely to be accompanied by widespread non-lateralized attentional deficits, unconfined to one region of space, in addition to the unilateral imbalance of attention to the contralesional space (reviewed in [99, 106]). Collectively, present findings suggest that behavioral performance in post-stroke USN cannot be solely explained by lateralized deficits, but rather by combination of spatially lateralized and non-lateralized impairments.

7.2.4. POST-STROKE NEGLECT AFFECTS VISUAL-PERCEPTUAL ABILITIES AND TOGETHER THEY CONTRIBUTE TO MOBILITY DYSFUNCTION

In Manuscript №3, we identified that the presence of post-stroke USN significantly affects all tested visual-perceptual abilities, including contrast sensitivity, shape discrimination and optic flow direction and optic flow coherence. Most of these psychophysical measures only modestly correlated to USN clinical assessment outcomes. Moreover, for the first time, we showed that measures of visual perceptual abilities are highly sensitive in detecting deficits consistent with the presence of USN and which were otherwise left undetected using conventional USN paper-and-pencil tests. All psychophysical tests were identified as being distinctly sensitive, where individuals with history of neglect in the acute phase of stroke recovery (i.e. no neglect on conventional tests during study) performed considerably worse in comparison to those without post-stroke neglect or without history of post-stroke neglect. More importantly, the testing

paradigm used in Manuscript №4 unveiled worse performance in several individuals without post-stroke USN on the traditional evaluation tools (USN-) vs. healthy controls. This critical result points to a promising sensitivity of the psychophysical measures vs. traditional paper-and-pencil USN clinical tests in unveiling visual-perceptual deficits. Visual-perceptual psychophysical testing could thus be an advantageous, affordable, simple, complementary and potentially sensitive diagnostic method for post-stroke USN.

Our findings also confirm the initially stated hypothesis in relation to the effects of these visual-perceptual abilities on goal-directed locomotion dysfunction, where, in combination with USN in near space and walking speed, they justify nearly 70% of the observed locomotor deficits. This is in line with former studies showing for example that optic flow is an essential source of visual information that is used in functional activities such as the control of heading direction during locomotion [83-85]. Moreover, in accordance with two earlier studies providing preliminary evidence of USN affecting the use of optic flow information while walking [88, 270], Manuscript №3 now offers leading evidence that 1) USN+ individuals are severely affected in the processing of optic flow (direction and coherence) and 2) deficits in optic flow processing in USN+ individuals explain, to some extent, their locomotor impairments.

Additionally, our findings can be supported by functional neuroanatomy of the use of optic flow in heading estimation. For instance, Peuskens et al., 2001 [271] used positron emission tomography and functional magnetic resonance imaging to examine human cerebral activation pattern elicited when perceiving a ground plane optic flow pattern and arbitrating heading directions. The MT/V51 complex, including an inferior satellite, and dorsal intraparietal sulcus area, predominantly in the right hemisphere, and the dorsal premotor region bilaterally were found to be actively involved. Different brain areas such as the right parietotemporal junction [272], the angular gyrus, the right inferior parietal lobe, the parahippocampal region [69], and the right superior temporal cortex [70] have all been implicated in USN. It has been proposed that visual attention is mediated through a number of interconnected, yet functionally independent neuroanatomical networks, with the posterior parietal lobe being crucial for spatial attention and orienting [273, 274]. Therefore, the anatomical substrates of USN and those of optic flow processing in heading estimation are concurrent and underpin our findings.

7.4.5 OPEN TO THE IDEA, YET HAVING GENUINE CONCERNS: WHAT CLINICIANS THINK OF VR FOR POST-STROKE NEGLECT ASSESSMENT AND HOW WE CAN FURTHER BUILD ON THESE FINDINGS

Manuscript №5 is essential to this dissertation and ties up the “stopper” knot to the string of included studies. Although previous manuscripts offer valuable and novel information that could greatly serve the development and refinement of a VR-based assessment tool for post-stroke neglect, all these efforts could be in vain if end-users/clinicians who are dealing with stroke patients on everyday basis are unwilling to implement and use such a tool in their practice.

The key barriers that were identified, including personal, institutional, equipment, and client suitability, will help optimize the design and implementation of future VR-based USN tools in clinical practice. A multimodal and active KT intervention can now be designed (e.g. [309]) according to the identified support needs and modifiable barriers. For example, addressing factors of lack of knowledge about VR use and importance of USN-sensitive assessments as well as lack of resources in the clinical setting could influence VR adoption and its sustainable use for USN management. The personal barrier of lack of knowledge about USN and the importance of USN-sensitive assessment is highly concerning, demonstrating that a clinician, working full-time on a stroke rehabilitation ward, does not see the need for a sensitive post-stroke USN assessment of peripersonal space (near and far-extrapersonal space) that in fact is known to be greatly prevalent among those with right hemisphere stroke and often left undetected using conventional methods or observation. Based on this study, interventions and elements geared towards increasing the knowledge-base of scholarly practitioners about post-stroke USN, its assessment, and the VR technology could be proposed, including: the addition of a specialized course in visual-perception and related-technologies in the current OT educational curriculum, multifaceted KT interventions for clinicians including hands-on workshop experiences, e-learning modules, case studies, expert panel discussions, a designated expert clinician (champion or mentor) or resource person in each targeted setting, training and ongoing support in the use of chosen technologies, and evaluation of change in practice following the KT interventions.

The finding that most of the participating clinicians were open to the use of VR and had a positive attitude towards its use for post-stroke USN indicates that there is a potential in continuing to pursue the knowledge to action model cycle with the aim of improving current

practices as described by Graham et al., 2006 [8]. Specifically, present results could be employed to plan for a future implementation of a VR-based USN assessment tool in a clinical setting, monitor its use and evaluate what changes it brings to the clinical post-stroke USN management. To tackle most of the representative population (individuals with post-stroke UNS), we propose that the implementation of a VR-based USN assessment tool should initially occur in rehabilitation centers providing stroke rehabilitation services, and be integrated with other occupational therapy evaluation procedures. This would complement existing findings and provide data on concurrent validity and sensitivity with respect to the conventional methods employed in that setting. Thereafter, a broader implementation could be foreseen to private, community and acute-care settings.

The results of the self-administered questionnaire in our study are consistent with previously published reports on behavioral intention to use technologies in healthcare settings. For instance, our results, showing an agreement among clinicians that a VR-based USN assessment can enhance their performance and ensuring patients' outcomes (i.e. performance expectancy) are in accordance with a larger cross-sectional exploratory study by Liu et al., (2015) [326]. Using the UTAUT-based questionnaire, they found that performance expectancy was the most significant factor in determining Occupational and Physical therapists' acceptance and use of technology in rehabilitation [326]. Similarly to the responses of clinicians' in the present study, effort expectancy [326, 330-332] and social influence [326] were not found to be salient factors influencing behavioral intention to use technologies in studies using the UTAUT-based questionnaires with different health professionals including medical doctors, health educators, nurses, as well as Occupational and Physical Therapists. Promisingly, participants in the present study, similar to those in Liu et al., (2015) study, expressed their intention to use the newly available technology, confirming previously found clinicians' positive attitudes towards VR

Manuscript №5 offers multiple practical implications. First, the identified factors that influence clinicians' acceptance and adoption of VR for post-stroke USN assessment can inform future research on priorities for the planning of training programs and of the resources needed for the effective acquisition and implementation of such technology. The interviewees in the present study were critical regarding barriers related to VR equipment in terms of possible side effects and generalizability, time and training demands, and costs of implementation; as well as client

suitability barriers such as age, functional status, and infection control. It demonstrates that despite increasing evidence for the effectiveness of VR in post-stroke USN assessment and treatment, health care professionals are still grappling with those core issues and they are imperative to be addressed in future KT resources to support VR clinical integration outside of a research context. Similarly, the collaborative results from focus group and experts in the field on the optimal features of a VR-based USN assessment can serve to adapt current tools (e.g. EVENS) or to guide the development of a new tool that better suits different clients' functional capabilities and deficits (e.g. aphasic, wheelchair-bound), as well as end-users/clinicians needs (e.g. easy application/start up, print out reports, progress reports, resource/assistance, time constraint, 3-dimensional immersive environment, tasks options, etc.). We suggest that future tools should incorporate those findings, in order to promote adherence and satisfaction with its use in clinical settings among practicing rehabilitation professionals.

7.3 Limitations

Studies included in this dissertation have limitations. Manuscript №1, 2, 3 and 4 did not examine eye movements during the experiments that could offer valuable information on gaze shifts, spatial fixations and re-fixations, possible remapping and gaze shifting impairments underlying USN. We also recognize that only participants with left USN (i.e. right hemisphere stroke) were included, limiting the generalizability of results to the left hemisphere stroke population. Another limitation is that the navigation task (Manuscript №2 and 4) did not allow rotations along the vertical axis to mimic head and body horizontal rotation strategies as used in goal-directed locomotion [254]. Moreover, the motor function and recovery of the non-paretic upper extremity used in the joystick experiment was not objectively evaluated in the present study using standardized measures and one could argue that a unilateral hemisphere stroke could possibly result in subtle impairments to the non-paretic upper extremity, as documented in the literature. Nevertheless, we believe that the paradigm used in this study allowed, to the best possible, to minimize the contribution of post-stroke sensorimotor impairments. Further, no significant differences between USN- and HC participants were observed in any of the outcome measures, suggesting that sensorimotor deficits of the non-paretic upper extremity, if any, did not affect the joystick task performance. In addition, different VR technologies (2-D desktop systems, 3-D HMDs, multi-screen cave systems, etc.) entail different affordances in terms of immersiveness,

feeling of presence, field of view, etc. Also, they all present with their own advantages (e.g. 2D desktop display cost-effectiveness and easy of application) and shortcomings (e.g. 3D HMDs side-effects, cumbersomeness, lack of proper disinfection procedures from one use to another). In this PhD, the 3D NVisor HMD was chosen as the viewing media, in spite of its possible shortcomings, to enhance and promote the feeling of presence due to its full immersion and prevent possible real-world attention shifts (that could occur in patients with USN). Therefore, its use allowed us to better identify the effects of USN on the performed tasks. In addition, the application of such HMDs is currently on the rise as they are becoming more affordable/cost-effective and user-friendly. Most importantly, clinicians expressed that they are keen and open to the use of a 3D HMD (in contrast to the 2D desktop screen) as the viewing media for USN assessment, showing to its future promising use adherence.

In relation to that, Manuscript № 5 also has its limitations. Clinicians' perceptions were determined at one point in time by using a cross-sectional exploratory study design. Although we consider that it is appropriate given the exploratory nature of this project, future longitudinal designs that would study these perceptions in time would be beneficial. Moreover, a true collaborative approach by including clinicians and experts in the field in the same focus groups would have been advantageous, but this was not possible given the different geographical locations and schedule conflicts. Individual interviews, however, have also proven to be effective methods in gathering information. Combining qualitative methods (focus groups, interviews, surveys) as in Manuscript № 5 was further suggested to provide a broader understanding of the phenomenon of interest compared to when a single method is used [333]. Lastly, another limitation is that the evidence behind VR assessment for post-stroke USN is still limited and exploratory at the moment [36]. This implies that it may be challenging to implement practice changes in the future. Yet, the results of this manuscript offer preliminary steps by including the end-users/clinicians early in the process of the knowledge to action model [8], possibly facilitating forthcoming implementation of this type of system in clinical practice.

7.4 Future Directions

In order to increase USN detection sensitivity and treatment effectiveness, I suggest that future assessment and treatment tools for post-stroke USN should incorporate features of spatial memory, representational updating, increased perceptual demands within the near and far-space

exploration, psychophysical testing of visual perception abilities, and include functional activities such as locomotion, navigation and object detection. VR, as used in most of manuscripts of this dissertation, permits the integration of these components. Future research can also incorporate eye tracking and brain imaging techniques to better define the involvement of implicated brain networks and mechanisms. Further research on EVENS for post-stroke USN could focus on incorporating an assessment of the feeling of presence, adverse effects and satisfaction. Moreover, the identified factors that influence clinicians' acceptance and adoption of VR for post-stroke USN assessment can inform future research on priorities for the planning of training programs and of the resources needed for the effective acquisition and implementation of such technology.

As a closing remark, I would like to emphasize the need to work towards a better, more representative and unified operational definition of neglect. As shown in most of manuscripts, deficits related to neglect are not necessarily lateralized, unilateral or spatial, but rather can affect performance on a wider spectrum of visual space and be influenced by non-spatial factors such as memory, representational updating, visual perception, arousal, detection/reaction time, etc. Perhaps, this calls for building a collaborative, international network composed of experts in the field who can work collectively towards a more refined definition and standardization of related terminology.

CHAPTER 8: REFERENCES

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APPENDICES

APPENDIX 1: Consent Forms

INFORMED CONSENT FORM

Effects of unilateral spatial neglect on goal-directed walking: a pilot study

Investigators:

Tatiana Ogourtsova, MSc., BSc., OT(c), erg.
PhD student in Rehabilitation Science,
School of Physical and Occupational Therapy,
McGill University, Montreal.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Anouk Lamontagne, PhD, PT
Associate Professor
School of Physical and Occupational therapy,
McGill University, Montreal.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Phillipe Archambault, PhD, OT
Associate Professor
School of Physical and Occupational therapy,
McGill University, Montreal.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Foreword

This consent form is addressed to healthy control participants. We are inviting you to participate in a research that is aimed to understand how visual neglect influences the reaching and walking of persons who had a stroke. In the context of this study, participants will be evaluated while reaching and walking to targets located at different places while being immersed in a virtual environment. Before agreeing to participate in this project, please take time to read and carefully consider the following information.

This consent form explains the aim of this study, the procedure, advantages, risks and inconvenience as well as the persons to contact, if necessary.

This consent form may contain words that you do not understand. We invite you to ask any questions that you deem useful to the researcher and the other members of the staff assigned to the research project and ask them to explain any work or information which is not clear to you.

Goals of the study: One of the most common and complex deficit after stroke is visual neglect.

Visual neglect is the inability to pay attention to people and/or things on the side that is affected

by the stroke. For example, someone with left-sided paralysis may also have left-sided visual neglect. Visual neglect can negatively affect efficient participation in everyday activities (e.g. those requiring reaching to or walking towards an object). Unfortunately, current rehabilitation approaches for visual neglect often lead to modest improvements. Thus, there is a need to explore new intervention strategies by further investigating the effects of visual neglect. In this project, we will evaluate the impact of visual neglect, its characteristics and its impact on reaching and walking movements. The data collected in this project will be later used as a basis to design a novel rehabilitation intervention.

Objectives:

- (1) Characterize visual-perceptual abilities in participants with post-stroke USN as compared to those without USN and healthy control individuals;
- (2) Examine reaching and walking abilities in the same groups of participants;
- (3) Examine the relationships between performances on reaching and walking tasks and i) neglect severity; and ii) visual perceptual abilities.

Nature of your participation: Your participation will consist of 2 separate sessions of 1.5 to 2 hours each, including the preparation time. The evaluation will be conducted at Jewish Rehabilitation Hospital (Laval). Ideally, the 2 sessions will take place within the same week. The first session (~1.5 hours) will consist of clinical tests to assess your walking function (Rivermead Mobility Index and 10 meters walking speed). Your vision (Snellen Chart), and your cognitive functions (Montreal Cognitive Assessment) will also be evaluated to ensure that you can properly see, and understand the visual information during the investigation. Following, different images will be presented on the screen and you will be asked to determine their characteristics (e.g. direction, orientation, etc.). You can wear your glasses for all the tests if needed.

The second session (~2 hours) will consist of an evaluation of your reaching and walking abilities to a target while immersed in the virtual environment. This session will require 30 minutes of preparation/calibration time, and approximately 1.5 hours of actual evaluation. You should be dressed in sportswear for this session.

Preparation: In order to collect information on your eye movements during this session, a small camera will be set up within the head mounted display (see picture below) that will allow you to

view the virtual environment. The eye tracker will be calibrated where you will be asked to look at different points on the screen. To collect information on your movements during reaching and walking, small sphere-shaped markers will be attached to you at different locations (e.g. head, trunk, arm, and legs) using double-sided hypo-allergic adhesive tape. All hygiene measures will be followed when placing those markers.



Evaluation: You will be evaluated on your abilities to reach for an object or walking to an object located in different places. This virtual object will be viewed through the head-mounted display that you will wear on your head. A therapist will also remain next to you throughout the experiment. You will be able to rest as much as needed between trials.

Personal advantages: This study does not provide you any direct benefit. However, the results from this study will be later used to design an intervention that uses virtual reality to improve the effects of visual neglect in stroke survivors.

Risks and inconveniences: Risks (e.g. fatigue, dizziness, falls) associated with your participation in this study are minimal. A therapist will always be present to provide any assistance, as needed. You may however feel tired following the evaluation and you may also experience slight nausea, dizziness or eye strain due to the virtual environment. However, these are temporary feelings and will completely subside with rest. In addition, the habituation session will further minimise the possibility of it occurring during the actual evaluation.

Confidentiality: Any personal information collected during this study will be codified to ensure confidentiality. Only members of the research team will have access to this information. For monitoring purposes, however, research documents could be accessed by a representative of the REB of CRIR or of the Ethics Unit of the Ministry of Health and Social Services of Quebec, which adhere to a strict privacy policy. Data will be kept locked up for a duration of 5 years

following project termination, after which they will be destroyed. If research findings are presented in the form of scientific presentations or publications, nothing will identify you. Should your withdrawal from the study, all data collected will be destroyed if you request so.

Voluntary participation: You can be assured that the information that you have received about this project is accurate and complete. Your participation in this project is entirely voluntary. Your refusal to participate would in no way affect the treatment you receive in this hospital, if applicable. In addition, you may withdraw from the study at any time. If you withdraw your participation from this project, all the research data collected will be destroyed.

Responsibility clause: In accepting to participate in this study, I shall not relinquish any of my rights and I shall not liberate the researchers or their sponsors or the institutions involved from any of their legal or professional obligations.

Financial compensation: Transportation and parking costs incurred through my participation in this project will be reimbursed, up to a maximum of \$30.00 per visit, upon presentation of receipts.

Resource persons: Should you have any questions or require further information regarding the study, you can contact Tatiana Ogourtsova, PhD Candidate (phone number 450-688-9550 ext. 4823; e-mail tatiana.ogourtsova@mail.mcgill.ca or Anouk Lamontagne, Ph.D (phone number 450-688-9550 ext. 531; e-mail anouk.lamontagne@mcgill.ca). If I have any questions regarding your rights and recourse concerning your participation in this study, you can contact Ms. Anik Nolet, Research Ethics Co-ordinator of the CRIR establishments: 514-527-4527 ext 2643 or by e-mail at: anolet.crir@ssss.gouv.qc.ca. You can also contact the Commissioner of complaints of the Institution.

CONSENT:

My signature indicates that I have read this document that I understand the purpose of the research, the nature of and extent of my participation as well as the benefits and risks/inconveniences to which I will exposed to as presented in this form. I have been given the opportunity to ask questions concerning any aspects of the study and have received answers to my satisfaction.

I, the undersigned, voluntary agree to take part in this study. I can withdraw from the study anytime without prejudice of any kind. I certify that I have had sufficient time to consider my decision to participate in this study.

A signed copy of this consent form will be given to me.

Participant: _____ Date: _____

(Participant)

_____ Contact No. _____

(Name)

Responsibility of the principal investigator:

I, the undersigned, _____ certify that I have explained to the participant their involvement in this project, I have responded to all the questions posed to me and I have clearly indicated that the participant is free to leave the study described above at any time and have provided a signed and dated copy of this consent document to the participant.

Name and Signature of the investigator: _____

Date: _____ Contact No.: _____

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Les effets de la négligence spatiale unilatérale sur la navigation et la marche dirigées vers un but: une étude pilote

Chercheurs au projet:

Tatiana Ogourtsova, MSc., BSc., OT(c), erg.
Doctorante en Sciences de réadaptation,
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Anouk Lamontagne, PhD, PT
Professeure agrégée
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Phillipe Archambault, PhD, OT
Professeur agrégé
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Préambule

Ce formulaire de consentement s'adresse aux participants sains. Nous vous invitons à participer à une recherche qui vise à comprendre comment la négligence visuelle influe l'atteinte et la marche orientées vers un but chez des personnes qui ont eu un accident vasculaire cérébral (AVC). Dans le cadre de cette étude, les participants seront évalués en fonction de leur capacité à atteindre un objet et à marcher vers cet objet qui sera localisé à différents endroits tout en étant immergé dans un environnement virtuel.. Avant d'accepter de participer à ce projet de recherche, veuillez prendre le temps de comprendre et de considérer attentivement les renseignements qui suivent. Ce formulaire de consentement vous explique le but de cette étude, les procédures, les avantages, les risques et inconvénients, de même que les personnes avec qui communiquer au besoin. Le présent formulaire de consentement peut contenir des mots que vous ne comprenez pas. Nous vous invitons à poser toutes les questions que vous jugerez utiles au chercheur et aux autres membres du personnel affecté au projet de recherche et à leur demander de vous expliquer tout mot ou renseignement qui n'est pas clair.

But de l'étude:

Un des déficits les plus fréquents et complexes après un AVC est la négligence visuelle. La négligence visuelle est l'incapacité d'une personne à porter attention aux choses sur le côté affecté par l'AVC. Par exemple, une personne ayant une paralysie du côté gauche suite à un AVC peut aussi avoir la négligence visuelle du côté gauche. La négligence visuelle peut négativement affecter la participation efficace dans les activités de la vie quotidiennes (ex. celles qui nécessitent d'atteindre à un objet ou à marcher vers un objet). Malheureusement, les méthodes de réadaptation actuelles de négligence visuelle conduisent souvent à des améliorations modestes. Ainsi, il est nécessaire d'explorer de nouvelles stratégies d'intervention en enquêtant davantage les effets de la négligence visuelle. Dans ce projet, nous allons évaluer l'impact de la négligence visuelle, ses caractéristiques et son impact sur les mouvements d'atteinte du bras et la marche. Les données recueillies dans ce projet serviront de base pour le développement de nouvelles interventions en réadaptation.

Objectifs:

- (1) Caractériser la perception visuelle chez les participants avec la négligence visuelle ayant subi un AVC par rapport à ceux sans la négligence visuelle et les participants sains;
- (2) Examiner les mouvements d'atteinte du bras et la marche chez ces mêmes groupes de participants;
- (3) Examiner les relations entre les performances de mouvement d'atteinte du bras et de la marche et i) la sévérité de la négligence visuelle; et ii) les capacités de la perception visuelle.

Nature et durée de votre participation: Votre participation à ce projet s'effectuera sur 2 sessions individuelles d'une durée d'une heure et demie à deux heures chacune, incluant le temps de préparation. Ces évaluations se tiendront à l'Hôpital juif de réadaptation à Laval et, idéalement, se feront au cours de la même semaine.

La première session (~1h30m) consistera en des tests cliniques servant à évaluer votre démarche (Indice de Mobilité de Rivermead, vitesse de marche sur 10m). Votre vision (le Test de Snellen), et vos fonctions cognitives (Évaluation Cognitive de Montréal) seront également évaluées pour s'assurer que vous pouvez bien voir et comprendre l'information visuelle lors des tests. Des images vous seront également présentées sur un écran d'ordinateur et vous devrez déterminer les

caractéristiques de celles-ci (e.g. direction, orientation, etc). Au besoin, vous pouvez porter vos lunettes pendant les tests.

La deuxième session (~2 heures) consistera en l'évaluation de vos mouvements d'atteinte du bras et de votre démarche, tout en étant immergé dans l'environnement virtuel. Cette session demandera 30 minutes de préparation et environ une heure et demie d'évaluation. Vous devrez être vêtu(e) de vêtements de sport pour cette session.

Pour recueillir des informations sur les mouvements de vos yeux lors de cette session, une caméra miniature sera installée dans le casque de réalité virtuelle (voir image ci-dessous) vous permettant de visualiser l'environnement virtuel. Pour recueillir des informations sur vos mouvements lors de mouvements d'atteinte et de la marche, de petits marqueurs en forme de sphère vous seront attachés à différents endroits (tête, thorax, bras et jambes) avec du ruban adhésif hypo allergène à double face. Toutes les mesures d'hygiène seront respectées pour poser ces marqueurs.



Évaluation: Vous allez être évalué sur votre façon d'atteindre un objet ou en marchant vers cet objet virtuel localisé à différents endroits. Cet objet virtuel sera perçu grâce à un casque de réalité virtuelle que vous allez porter sur votre tête. Un thérapeute restera à côté de vous tout au long de l'expérience. Vous allez pouvoir vous reposer autant que nécessaire entre les essais.

Avantage personnel: Vous ne retirerez aucun bénéfice direct de votre participation à cette étude. Toutefois les résultats de cette étude donneront des informations pouvant aider au développement d'interventions se servant de la réalité virtuelle pour améliorer la négligence visuelle des personnes ayant subi un AVC.

Risques et inconvénients: Les risques (ex. fatigue, étourdissements, chutes) reliés à votre participation à cette étude sont minimes. Pendant l'évaluation, un thérapeute sera toujours présent pour vous assister au besoin. Vous pourriez par contre ressentir de la fatigue suite à l'évaluation et aussi avoir de légères nausées ou étourdissements causés par le visionnement des images. Ces sensations sont temporaires et se résorberont avec un peu de repos.

Confidentialité: Les renseignements personnels recueillis au cours de cette étude, seront codifiés pour en assurer la confidentialité. Seuls les membres de l'équipe de recherche auront accès à l'information. Cependant, à des fins de contrôle, les documents de recherche pourraient être consultés par une personne mandatée par le comité d'éthique de la recherche des établissements du CRIR (Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain) ou par l'Unité d'éthique du Ministère de la Santé et des services sociaux du Québec. Ces personnes adhèrent à des politiques strictes de confidentialité. Les données de recherche seront conservées sous clé au Centre de recherche de l'HJR pour une période de cinq (5) ans suivant la fin de l'étude après quoi elles seront détruites. Les données du projet ne seront dévoilées que sous forme de présentations scientifiques ou de publications, sans que votre nom ou toute autre information pouvant révéler votre identité n'y apparaisse.

Participation volontaire et retrait de l'étude: Nous vous assurons que l'information que vous avez reçu à propos de cette étude est exacte et complète. Votre participation à cette étude est volontaire. Si vous êtes traité dans cet hôpital, votre refus de participer n'aura aucun effet sur les traitements que vous y recevez. De plus, vous pouvez vous retirer en tout temps, sans avoir à donner de raisons, en faisant connaître votre décision à un membre de l'équipe de recherche. Advenant votre retrait de l'étude et si vous en faites la demande, toutes les données vous concernant seront détruites.

Clause de responsabilité: En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, le commanditaire ou les institutions impliquées de leurs obligations légales et professionnelles envers vous.

Indemnité compensatoire : Des frais de déplacement encourus pour votre participation vous seront remboursés jusqu'à concurrence de \$30.00 par visite, sur présentation de reçus.

Personnes ressources: Si vous avez des questions ou désirez plus d'information concernant cette étude, vous pouvez contacter, Tatiana Ogourtsova, Doctorante, numéro de téléphone 450 - 688-9550 poste 4823, adresse courriel tatiana.ogourtsova@mail.mcgill.ca ou Anouk Lamontagne, Ph.D numéro de téléphone: 450-688-9550 poste 531; adresse courriel anouk.lamontagne@mcgill.ca).

Si vous avez des questions sur vos droits et recours ou sur votre participation à ce projet de recherche vous pouvez communiquer avec Me Anik Nolet, coordonnatrice à l'éthique de la recherche des établissements du CRIR au 514-527-4527 poste 2643 ou par courriel à: anolet.crir@ssss.gouv.qc.ca. Vous pouvez également contacter Monsieur Michael Greenberg, commissaire aux plaintes et à la qualité des services de l'HJR au (450) 688-9550 poste 232.

CONSENTEMENT:

Je déclare avoir lu et compris le présent projet, la nature et l'ampleur de ma participation, ainsi que les risques auxquels je m'expose tels que présentés dans le présent formulaire. J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses à ma satisfaction.

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans préjudice d'aucune sorte. Je certifie qu'on m'a laissé le temps voulu pour prendre ma décision.

Une copie signée de ce formulaire d'information et de consentement doit m'être remise.

Participant: _____ Date: _____

(Signature)

_____ Téléphone: _____

(Nom)

ENGAGEMENT DU CHERCHEUR:

Je, soussigné(e) _____, certifie :

avoir expliqué au signataire les termes du présent formulaire;

avoir répondu aux questions qu'il m'a posées à cet égard;

lui avoir clairement indiqué qu'il reste, à tout moment, libre de mettre un terme à sa participation au projet de recherche décrit ci-dessus; et

confirmé que je lui remettrai une copie signée et datée du présent formulaire.

Nom et signature du chercheur: _____

Date: _____ Téléphone: _____

INFORMED CONSENT FORM

Determining the barriers and facilitators to adopt virtual reality for the assessment of unilateral spatial neglect and development of a virtual reality assessment tool for unilateral spatial neglect

Investigators:

Tatiana Ogourtsova, MSc., BSc., OT, erg.
PhD student in Rehabilitation Science,
School of Physical and Occupational Therapy,
McGill University, Montreal, Quebec.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Anouk Lamontagne, PhD, PT
Associate Professor
School of Physical and Occupational therapy,
McGill University, Montreal, Quebec.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Anita Menon, PhD, OT
Academic Associate
School of Physical and Occupational therapy,
McGill University,
Montreal, Quebec.

Phillipe Archambault, PhD, OT
Associate Professor
School of Physical and Occupational therapy,
McGill University, Montreal, Quebec.
Feil-Oberfeld Research Centre
Jewish Rehabilitation Hospital (site of CRIR),
Laval, Quebec.

Olga Overbury, PhD
School of Optometry,
Department of Ophthalmology
University of Montreal, McGill University,
Montreal, Quebec.

Foreword

This consent form is addressed to clinicians working in the field of stroke rehabilitation. We are inviting you to participate in a research that aims to understand the barriers and facilitators that are foreseen in implementing the use of virtual reality in the management of post-stroke unilateral spatial neglect (USN); and also, to identify the features of an optimal virtual reality-based USN assessment tool. In the context of this study, participants will be asked to fill out an online or paper-based questionnaire and to participate in one focus group session. Before agreeing to participate in this project, please take time to read and carefully consider the following information.

This consent form explains the aim of this study, the procedure, advantages, risks and inconvenience as well as the persons to contact, if necessary.

This consent form may contain words that you do not understand. We invite you to ask any questions that you deem useful to the researcher and the other members of the staff assigned to the research project and ask them to explain any work or information which is not clear to you.

Goals of the study: One of the most common and complex deficit after stroke is USN. USN is the inability to pay attention to people and/or things on the side that is affected by the stroke. For example, someone with left-sided paralysis may also have left-sided USN. USN can affect efficient participation in everyday activities. Unfortunately, current assessments for USN are not highly sensitive to detect deficits and to encompass its heterogeneity. Thus, there is a need to explore new assessment strategies such as the use of virtual reality.

Objectives:

- (1) To determine the barriers and facilitators faced by clinicians in using virtual reality for post-stroke USN management.
- (2) To identify the features of an optimal virtual reality-based USN assessment tool.

Nature of your participation: Your participation will consist of 2 separate sections.

The first section (~2 hours) will consist of a focus group, where the features of an optimal virtual reality-based USN assessment will be discussed among other clinicians. Prior to the focus group, information about USN, and virtual reality will be provided in a lecture format. The focus group will be conducted at the Jewish Rehabilitation Hospital (Laval) and at the Institut de Réadaptation Gingras-Lindsay de Montréal (Montreal).

The second section (~20-30 minutes to complete) will consist of answering a questionnaire that will contain sociodemographic questions (e.g. age, gender, education, experience as clinician, etc.); and questions pertaining to the facilitators and barriers in implementing the use of virtual reality in post-stroke USN management.

Preparation: no preparation is required for the participation in this study.

Evaluation: during the focus group, your responses will be recorded on tape (audio and video) for later analysis.

Personal advantages: This study does not provide you any direct benefit. However, the results from this study will be later used to design comprehensive virtual reality-based USN assessment that will enhance the management of post-stroke USN.

Inconveniences: Inconveniences associated with your participation in this study are minimal. Please note that the focus group will be conducted outside of working hours.

Confidentiality: Any personal information collected during this study will be codified to ensure confidentiality. Only members of the research team will have access to this information. For monitoring purposes, however, research documents could be accessed by a representative of the REB of CRIR or of the Ethics Unit of the Ministry of Health and Social Services of Quebec, which adhere to a strict privacy policy. Data will be kept locked up for a duration of 5 years following project termination, after which they will be destroyed. If research findings are presented in the form of scientific presentations or publications, nothing will identify you.

Should your withdrawal from the study, all data collected will be destroyed if you request so. We are asking you to remain discrete with respect to the identity of other participants of the focus group, as well as the issues that will be discussed during the group.

Voluntary participation: You can be assured that the information that you have received about this project is accurate and complete. Your participation in this project is entirely voluntary. In addition, you may withdraw from the study at any time.

Responsibility clause: In accepting to participate in this study, I shall not relinquish any of my rights and I shall not liberate the researchers or their sponsors or the institutions involved from any of their legal or professional obligations.

Financial compensation: Catered lunch/dinner and a parking pass (if needed) will be provided during the focus group.

Resource persons: Should you have any questions or require further information regarding the study, you can contact Tatiana Ogourtsova, PhD Candidate (phone number 450-688-9550 ext. 4823; e-mail tatiana.ogourtsova@mail.mcgill.ca or Anouk Lamontagne, Ph.D (phone number 450-688-9550 ext. 531; e-mail anouk.lamontagne@mcgill.ca). If I have any questions regarding

your rights and recourse concerning your participation in this study, you can contact Ms. Anik Nolet, Research Ethics Co-ordinator of the CRIR establishments: 514-527-4527 ext 2643 or by e-mail at: anolet.crir@ssss.gouv.qc.ca. You can also contact the Commissioner of complaints of the Institution at the JRH, Mr. Michael Greenberg, at (450) 688-9550 poste 232, or the Commissioner of complaints of the Institution at the IRGLM at (514) 345-5225.

CONSENT:

My signature indicates that I have read this document that I understand the purpose of the research, the nature of and extent of my participation as well as the benefits and risks/inconveniences to which I will be exposed to as presented in this form. I have been given the opportunity to ask questions concerning any aspects of the study and have received answers to my satisfaction.

I, the undersigned, voluntarily agree to take part in this study. I can withdraw from the study anytime without prejudice of any kind. I certify that I have had sufficient time to consider my decision to participate in this study.

A signed copy of this consent form will be given to me.

Participant: _____ Date: _____
(Participant)

_____ Contact No. _____
(Name)

Responsibility of the principal investigator:

I, the undersigned, _____ certify that I have explained to the participant their involvement in this project, I have responded to all the questions posed to me and I have clearly indicated that the participant is free to leave the study described above at any time and have provided a signed and dated copy of this consent document to the participant.

Name and Signature of the investigator: _____

Date: _____ Contact No. : _____

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Déterminer les obstacles et les facilitateurs en lien avec l'utilisation de la réalité virtuelle pour l'évaluation de la négligence spatiale unilatérale (NSU) et développement d'un outil d'évaluation basé sur la réalité virtuelle pour la NSU.

Chercheurs au projet:

Tatiana Ogourtsova, MSc., BSc., OT, erg.
Doctorante en Sciences de réadaptation,
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal, Québec.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Anouk Lamontagne, PhD, PT
Professeure agrégée
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal, Québec.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Anita Menon, PhD, OT
Associée Académique
École de physiothérapie et d'ergothérapie de
l'Université McGill,
Montréal, Québec.

Phillipe Archambault, PhD, OT
Professeur agrégé
École de physiothérapie et d'ergothérapie de
l'Université McGill, Montréal, Québec.
Centre de Recherche Feil-Oberfeld
Hôpital Juif de Réadaptation (site du CRIR),
Laval, Québec.

Olga Overbury, PhD
École d'optométrie,
Département d'ophtalmologie
Université de Montréal, Université McGill,
Montréal, Québec.

Préambule

Ce formulaire de consentement s'adresse aux cliniciens travaillant dans le domaine de la réadaptation suite à un accident vasculaire cérébral (AVC). Nous vous invitons à participer à une recherche qui vise à comprendre les obstacles et les facilitateurs à l'utilisation de la réalité virtuelle dans l'évaluation de la négligence spatiale unilatérale (NSU) post-AVC; et d'identifier les caractéristiques d'un outil d'évaluation optimale, basée sur la réalité virtuelle, pour la NSU. Dans le cadre de cette étude, les participants seront invités à remplir un questionnaire en ligne ou sur papier et à participer à une séance de groupe de discussion. Avant d'accepter de participer à ce projet de recherche, veuillez prendre le temps de comprendre et de considérer attentivement les renseignements qui suivent.

Ce formulaire de consentement vous explique le but de cette étude, les procédures, les avantages, les risques et inconvénients, de même que les personnes avec qui communiquer au besoin.

Le présent formulaire de consentement peut contenir des mots que vous ne comprenez pas. Nous vous invitons à poser toutes les questions que vous jugerez utiles aux chercheurs et aux autres membres du personnel affecté au projet de recherche et à leur demander de vous expliquer tout mot ou renseignement qui n'est pas clair.

But de l'étude:

Un des déficits les plus fréquents et complexes après un AVC est la négligence spatiale unilatérale (NSU). La NSU est l'incapacité d'une personne à porter attention aux choses sur le côté affecté par l'AVC. Par exemple, une personne ayant une paralysie du côté gauche suite à un AVC peut aussi avoir la NSU du côté gauche. La NSU peut affecter la participation efficace dans les activités de la vie quotidiennes. Malheureusement, les évaluations actuelles pour la NSU ne sont pas très sensibles pour détecter les déficits et pour décrire ses différentes facettes. Ainsi, il est nécessaire d'explorer de nouvelles stratégies d'évaluations telles que l'utilisation de la réalité virtuelle.

Objectifs:

- (1) Déterminer les obstacles et les facilitateurs en lien avec l'utilisation de la réalité virtuelle, rencontrés par les cliniciens dans l'évaluation de la NSU post-AVC.
- (2) Identifier les caractéristiques optimales d'un outil d'évaluation qui utilise la réalité virtuelle pour mesurer la NSU post-AVC.

Nature et durée de votre participation: Votre participation comprendra deux étapes.

La première étape (~2 heures) consiste d'un groupe de discussion, où les caractéristiques d'une évaluation optimale utilisant la réalité virtuelle pour la NSU seront discutées entre plusieurs cliniciens. Avant le groupe de discussion, des informations sur la NSU et la réalité virtuelle seront fournies. Le groupe de discussion aura lieu à l'Hôpital Juif de Réadaptation (Laval) ou à l'Institut de Réadaptation Gingras-Lindsay de Montréal (Montréal).

La deuxième étape (~20-30 min) consiste à répondre à un questionnaire qui contiendra des questions sociodémographiques (âge, sexe, éducation, expérience en tant que clinicien, etc.); et les questions concernant les facilitateurs et les obstacles dans la mise en œuvre de l'utilisation de la RV dans la gestion de la NSU post-AVC.

Préparation: aucune préparation n'est nécessaire pour la participation à cette étude.

Évaluation: au cours du groupe de discussion, vos réponses seront enregistrées (audio et vidéo) pour une analyse ultérieure.

Avantage personnel: Vous ne retirerez aucun bénéfice direct de votre participation à cette étude. Toutefois, les résultats de cette étude donneront des informations pouvant aider au développement d'évaluation utilisant la réalité virtuelle pour évaluer la NSU des personnes ayant eu un AVC.

Inconvénients: Les inconvénients reliés à votre participation à cette étude sont minimes. SVP, notez que la participation au projet sera en dehors des heures de travail.

Confidentialité: Les renseignements personnels recueillis au cours de cette étude seront codifiés pour en assurer la confidentialité. Seuls les membres de l'équipe de recherche auront accès à l'information. Cependant, à des fins de contrôle, les documents de recherche pourraient être consultés par une personne mandatée par le comité d'éthique de la recherche des établissements du CRIR (Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain) ou par l'Unité d'éthique du Ministère de la Santé et des services sociaux du Québec. Ces personnes adhèrent à des politiques strictes de confidentialité. Les données de recherche seront conservées sous clé au Centre de recherche de l'HJR pour une période de cinq (5) ans suivant la fin de l'étude après quoi elles seront détruites. Les données du projet ne seront dévoilées que sous forme de présentations scientifiques ou de publications, sans que votre nom ou toute autre information pouvant révéler votre identité n'y apparaisse. Nous vous demandons de demeurer discret relativement à l'identité des autres personnes participant au groupe de discussion ainsi qu'à l'égard des propos qui y seront tenus.

Participation volontaire et retrait de l'étude: Nous vous assurons que l'information que vous avez reçue à propos de cette étude est exacte et complète. Votre participation à cette étude est volontaire. De plus, vous pouvez vous retirer en tout temps, sans avoir à donner de raisons, en faisant connaître votre décision à un membre de l'équipe de recherche.

Clause de responsabilité: En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, le commanditaire ou les institutions impliquées de leurs obligations légales et professionnelles envers vous.

Indemnité compensatoire : Un déjeuner / dîner traiteur et un coupon de stationnement (au besoin) seront fournis au cours du groupe de discussion.

Personnes ressources: Si vous avez des questions ou désirez plus d'information concernant cette étude, vous pouvez contacter, Tatiana Ogourtsova, Doctorante, numéro de téléphone 450 - 688-9550 poste 4823, adresse courriel tatiana.ogourtsova@mail.mcgill.ca ou Anouk Lamontagne, Ph.D numéro de téléphone: 450-688-9550 poste 531; adresse courriel anouk.lamontagne@mcgill.ca).

Si vous avez des question sur vos droits et recours ou sur votre participation à ce projet de recherche vous pouvez communiquer avec Me Anik Nolet, coordonnatrice à l'éthique de la recherche des établissement du CRIR au 514-527-4527 poste 2643 ou par courriel à: anolet.crir@ssss.gouv.qc.ca. Vous pouvez également contacter Monsieur Michael Greenberg, commissaire aux plaintes et à la qualité des services de l'HJR au (450) 688-9550 poste 232, ou le commissaire aux plaintes et à la qualité des services de l'IRGLM au (514) 345-5225.

CONSENTEMENT:

Je déclare avoir lu et compris le présent projet, la nature et l'ampleur de ma participation, ainsi que les risques auxquels je m'expose tels que présentés dans le présent formulaire. J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses à ma satisfaction.

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans préjudice d'aucune sorte. Je certifie qu'on m'a laissé le temps voulu pour prendre ma décision.

Une copie signée de ce formulaire d'information et de consentement doit m'être remise.

Participant: _____ Date: _____

(Signature)

_____ Téléphone. _____

(Nom)

ENGAGEMENT DU CHERCHEUR:

Je, soussigné(e) _____, certifie :

Avoir expliqué au signataire les termes du présent formulaire;

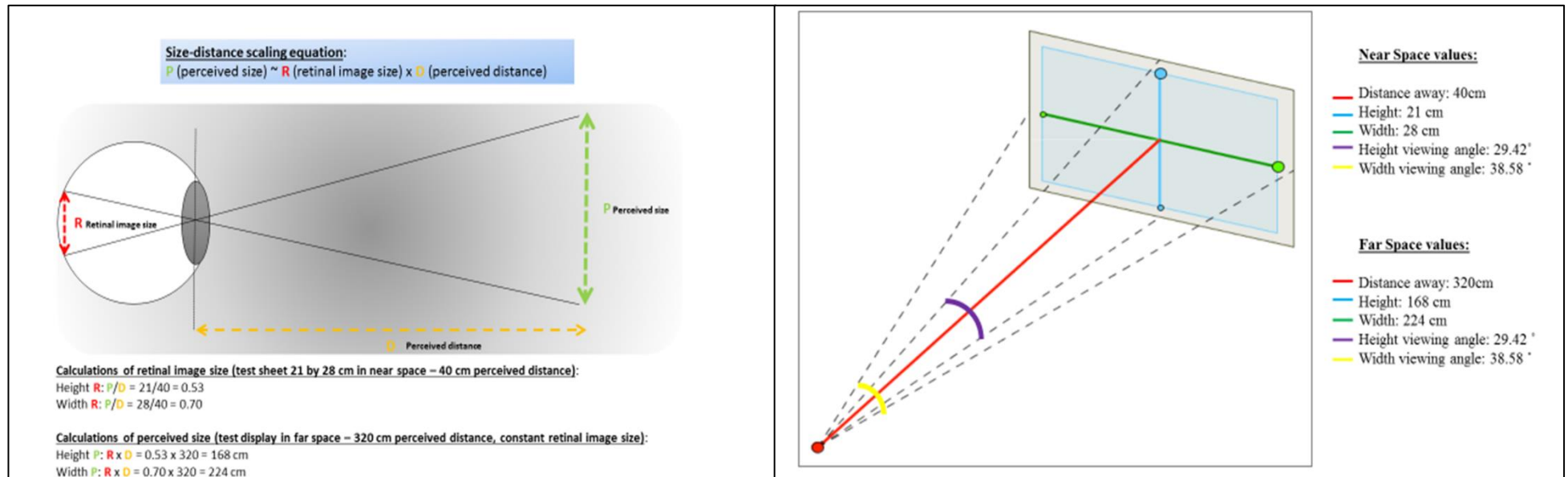
Avoir répondu aux questions qu'il m'a posées à cet égard;

Lui avoir clairement indiqué qu'il reste, à tout moment, libre de mettre un terme à sa participation au projet de recherche décrit ci-dessus; et confirmé que je lui remettrai une copie signée et datée du présent formulaire.

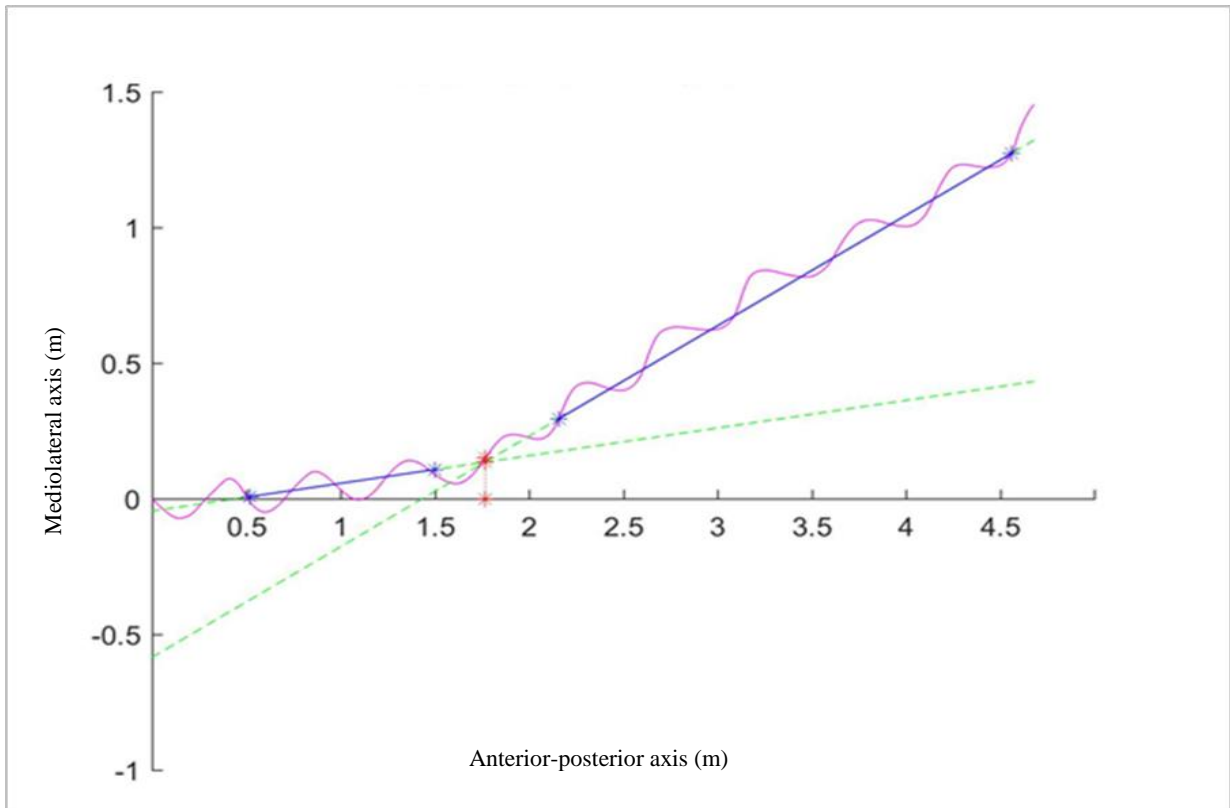
Nom et signature du chercheur: _____

Date: _____ Telephone: _____

APPENDIX 2: Calculations related to near vs. far space USN tests presentations



APPENDIX 3: Calculations related to onset of reorientation strategy



Appendix 3 Calculation method for the onset of reorientation strategy during the shifting condition. The displacement trajectory of the individual is shown in purple, with target shifting condition to the right. The result (time of onset of re-orientation) is illustrated by the red star. This point is found by fitting the displacement trajectory lines pre- and post-target shift point (that occurs at 1.5 meters of forward displacement, illustrated by blue lines) and determining the intercept point of these two lines (i.e. red star).

APPENDIX 4: Questionnaire used in focus groups

PREAMBLE

Virtual reality (VR) is defined as the “use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real-world objects and events”¹. Current assessment of post-stroke unilateral spatial neglect (USN) consists of different paper-and-pencil tools that are limited in their ability to pick up milder USN cases, predict functional performance in daily life, and are highly bounded by assessing USN within the near-extrapersonal space only, using static, 2-dimensional methods.

With the rapidly growing field of VR, USN diagnostic techniques could be enhanced and augmented beyond the conventional methods to include 3-dimensional images or stereovision, and evaluation of functional activities within the far space.

QUESTIONNAIRE

We are interested in learning about your views on the use of virtual reality (VR) in the assessment of post-stroke unilateral spatial neglect (USN). By completing this questionnaire you will contribute to the knowledge about the emerging field of VR and its future implementation in clinical practice.

The present questionnaire consists of *two* parts. In the *first* section, you will be asked socio-demographic questions. Please choose one response for each question by marking the corresponding checkbox or fill in the answer.

In the *second* section, you will be asked questions regarding the implementation of VR in the assessment of post-stroke USN. Please choose one response that best reflects to your views on the 7-point Likert scale by marking the corresponding checkbox.

References:

- (1) Weiss, P.L., et al., *Video capture virtual reality as a flexible and effective rehabilitation tool*. J Neuroeng Rehabil, 2004. **1**(1): p. 12.

Section I

1. Date of birth (dd/mm/yy): [Click]
2. Gender:
 - Female
 - Male
3. Specify the degree of your professional training:
 - Diploma entry level
 - Bachelors
 - Masters
 - PhD
4. Year of graduation of the latest degree: [Click]
5. Your current work schedule is:
 - Full time (≥ 35 hours/week)
 - Part time (< 35 hours/week)
6. How many years of clinical experience do you have with stroke clientele?
 - < 1 year
 - 1-3 years
 - 4-10 years
 - > 10 years
7. Do you have a specialty certification or advanced training in stroke rehabilitation?
 - Yes
 - No

8. Do you provide lectures at a university?

Yes

No

9. Is your institution affiliated with a university?

Yes

No

10. Do you have access to new information at work (e.g. library, search engines)?

Yes

No

11. How much time per month do you spend on continuing education related to stroke rehabilitation (e.g. reading articles, conferences, courses, etc.)?

<2 hours

2-5 hours

>5 hours

12. Are there funds available for continuing education in your setting?

Yes

No

13. On a typical day, approximately how many clients with stroke do you see?

<2

2-5

6-10

>10

14. On a typical day, how much time do you spend assessing clients with stroke (hours)?
[Click]

15. On a typical day, how much time do you spend treating clients with stroke (hours)?
[Click]

16. On average, how many new clients with stroke are admitted per month to your setting?

0-10

11-20

21-30

31-40

>40

17. What is the typical length of stay/rehabilitation for clients with a stroke at your setting?

<1 day

1-5 days

6-9 days

10-15 days

16-25 days

>25 days

18. What is the source of funding for your setting?

Private for profit

Private not for profit

Public

Veterans Administration

Other [Click]

19. Is your setting a teaching institution (defined as an institution that hosts medical students and student therapists for their clinical rotations/training)?

Yes

No

20. If yes, about how many students do you personally supervise per year?

0

1-2

3-5

<5

21. Is stroke rehabilitation research conducted in your setting?

Yes

No

Don't know

22. How many therapist(s) from your field including you work in your setting?

1

2-4

5-10

>10

23. Do you work in a team that includes professionals from other disciplines?

Yes

No

If the answer in 23 is yes, continue to next questions. If the answer is no, skip to Section II.

24. Is the team a stroke team (or neuro-rehabilitation team), specifically, a team that focuses primarily on the assessment and treatment of individuals with stroke?

Yes

No

25. Which professionals work in your team?

- Physical Therapists
- Occupational Therapists
- Speech Therapists
- Family Physician
- Psychologist
- Dietician
- Neuropsychologists
- Neurologists
- Psychiatrist
- Case manager
- Physiatrist
- Social Worker
- Nurse
- Other: [Click]

26. Do you have previous experience with virtual reality?

- Yes
- No

27. If yes, in what context?

- Clinical work
- Research (as participant, research assistant, or investigator)
- Education (rounds, in-services, conference presentations, reading articles, courses, etc.)
- Other: [Click]

Section II

Performance expectancy

1. I will find virtual reality (VR) for post-stroke unilateral spatial neglect (USN) assessment useful in my job:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Using VR for post-stroke USN assessment will enable me to accomplish tasks more quickly:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Using VR for post-stroke USN assessment will increase my productivity:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. If I will use VR for post-stroke USN assessment, I will increase my chances of getting a raise:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Effort expectancy:

1. My interaction with VR for post-stroke USN assessment would be clear and understandable:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. It would be easy for me to become skillful at using VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Attitudes towards technology

1. Using VR for post-stroke USN assessment is a good idea:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. VR for post-stroke USN assessment will make work more interesting:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Working with VR for post-stroke USN assessment would be fun:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. I would like to work with VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Social influence

1. People who influence my behavior at work think that I should use VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. People who are important to me think that I should use VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. The senior management of this institution would be helpful in the use of VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. In general, I feel that the organization will support me in the use of VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Facilitating conditions

1. I have resources necessary to use VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. I have the necessary knowledge to use VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. VR for post-stroke USN assessment would not be compatible with other methods I use:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. I would like a specific person (or group) would be available for assistance with VR for post-stroke USN assessment difficulties:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Self-efficacy

1. I think I could complete a job or a task using VR for post-stroke USN assessment if there was no one around to tell me what to do as I go:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. I think I could complete a job or a task using VR for post-stroke USN assessment if I could call someone for help if I get stuck:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. I think I could complete a job or a task using VR for post-stroke USN assessment if I had a lot of time to complete the job for which the software was provided:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. I think I could complete a job or a task using VR for post-stroke USN assessment if I had just the build-in help facility for assistance:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Anxiety

1. I feel apprehensive about using VR for post-stroke USN assessment:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. I would hesitate to use VR for post-stroke USN assessment for fear of making mistakes I cannot correct:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. VR for post-stroke USN assessment is somewhat intimidating me:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Behavioral intention to use the system

1. If made available to me, I intend to use VR for post-stroke USN assessment in the next 12 months:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. If made available to me, I predict I would use VR for post-stroke USN assessment in the next 12 months:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. If made available to me, I plan to use VR for post-stroke USN assessment in the next 12 months:

Strongly disagree	Quite disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Quite agree	Strongly agree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

END OF QUESTIONNAIRE

THANK YOU

PRÉAMBULE

La réalité virtuelle (RV) est définie comme étant « l'utilisation de simulations interactives créées avec le matériel et les logiciels informatiques qui offrent aux utilisateurs la possibilité d'interagir dans des environnements qui sont perçus comme étant semblables à des objets et des événements du monde réel »¹. L'évaluation actuelle de la négligence spatiale unilatérale (NSU) suite à un accident vasculaire cérébral (AVC) comprend différents outils d'évaluation de type 'papier-crayon' qui sont limités dans leur capacité à détecter les cas légers de la NSU et à prédire la performance fonctionnelle dans la vie quotidienne. Ces outils sont restreints à l'évaluation de la NSU dans un espace extra-personnel rapproché et utilisent des méthodes statiques en deux-dimensions.

Avec la croissance rapide du domaine de la RV, les techniques d'évaluation de la NSU pourraient être améliorées au-delà des méthodes traditionnelles afin d'inclure des images en trois-dimensions ou de la stéréovision, de même que l'évaluation d'activités fonctionnelles réalisées dans l'espace éloigné

QUESTIONNAIRE

Nous sommes intéressés à connaître votre point de vue sur l'utilisation de la réalité virtuelle dans l'évaluation de la négligence spatiale unilatérale post-AVC (NSU). En remplissant ce questionnaire, vous contribuerez à l'avancement des connaissances dans le domaine émergent de réalité virtuelle et de son utilisation future dans la pratique clinique.

Le questionnaire se compose de deux parties. Dans la première section, on vous posera des questions sociodémographiques. Se il vous plaît, choisissez une réponse pour chaque question en cochant la case correspondante ou en écrivant votre réponse.

Dans la deuxième partie, il vous posera des questions concernant l'utilisation de la réalité virtuelle dans l'évaluation de l'USN. Se il vous plaît choisir une réponse qui reflète le mieux votre point de vue sur l'échelle de Likert (7 points) en cochant la case correspondante.

Références:

(2) Weiss, P.L., et al., *Video capture virtual reality as a flexible and effective rehabilitation tool*. J Neuroeng Rehabil, 2004. 1(1): p. 12.

Section I

26. Date de naissance (jj/mm/aa): [Click]

27. Sexe:

Femme

Homme

28. Indiquez votre degré de formation professionnelle:

Diplôme niveau d'entrée

Baccalauréat

Maîtrise

Doctorat

29. Année d'obtention du dernier diplôme: [Click]

30. Votre horaire de travail actuel est:

Temps plein (≥ 35 heures/semaine)

Temps partiel (< 35 heures/semaine)

31. Combien d'années d'expérience clinique avez-vous avec la clientèle AVC?

< 1 an

1-3 ans

4-10 ans

> 10 ans

32. Avez-vous un certificat de spécialité ou une formation avancée en réadaptation post-AVC?

Oui

Non

33. Offrez-vous des cours dans une université?

Oui

Non

34. Est-ce votre institution est affiliée à une université?

Oui

Non

35. Avez-vous accès à de nouvelles informations au travail (ex: bibliothèque, moteurs de recherche)?

Oui

Non

36. Combien de temps par mois consacrez-vous à l'éducation continue liée à la réadaptation post-AVC (ex. la lecture des articles, des conférences, des cours, etc.)?

<2 heures

2-5 heures

>5 heures

37. Y at-il des fonds disponibles pour la formation continue dans votre établissement?

Oui

Non

38. Dans une journée typique, combien de clients ayant subi un AVC voyez-vous?

<2

2-5

6-10

>10

39. Dans une journée typique, combien de temps passez-vous à l'évaluation des clients ayant subi un AVC (heures)? [Click]

40. Dans une journée typique, combien de temps passez-vous à traiter des clients ayant subi un AVC (heures)? [Click]

41. En moyenne, combien de nouveaux clients ayant subi un AVC sont admis par mois dans votre établissement?

0-10

11-20

21-30

31-40

>40

42. Quelle est la durée typique de séjour / réadaptation pour les clients subi un AVC dans votre établissement?

<1 jour

1-5 jours

6-9 jours

10-15 jours

16-25 jours

>25 jours

43. Quelle est la source de financement dans votre établissement?

Privé pour profit

Privé non pour profit

Publique

Administration de vétérans

Autre [Click]

44. Est-ce que votre établissement est une institution d'enseignement (définie comme une institution qui accueille des étudiants en réadaptation pour leurs stages cliniques / formation)?

Oui

Non

45. Si oui, combien d'étudiants supervisez-vous par année?

0

1-2

3-5

<5

46. Est-ce qu'il y a de la recherche en réadaptation post-AVC menée dans votre milieu?

Oui

Non

Je ne sais pas

47. Combien de thérapeute(s) de votre domaine, y compris vous, travaillent dans votre milieu?

1

2-4

5-10

>10

48. Travaillez-vous dans une équipe qui comprend des professionnels d'autres disciplines?

Oui

Non

Si la réponse est oui à 23, continuer aux questions suivantes. Si la réponse est non, passez à la Section II.

49. Mon équipe est une équipe spécialisée qui se concentre principalement sur l'évaluation et le traitement des personnes ayant subi un AVC :

Oui

Non

50. Quelles sont les professionnels qui travaillent dans votre équipe?

Physiothérapeute

Ergothérapeute

Orthophoniste

Médecin de famille

Psychologue

Diététicien (ne)

- Neuropsychologue
- Neurologue
- Psychiatre
- Gestionnaire de cas
- Physiatre
- Travailleur(se) social(e)
- Infirmier (ère)
- Autre: [Click]

51. Avez-vous une expérience antérieure avec la réalité virtuelle?

- Oui
- Non

52. Si oui, dans quel contexte?

- Travail clinique
- Recherche (en tant que participant, assistant de recherche, ou chercheur (se))
- Éducation (conférences, présentations, articles, cours, etc.)
- Autre: [Click]

Section II

Attentes par rapport au rendement

1. Je trouve que la réalité virtuelle (RV) pour l'évaluation de la NSU post-AVC serait utile dans mon travail:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. L'utilisation de RV pour l'évaluation de la NSU post-AVC me permettrait d'accomplir des tâches plus rapidement:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. L'utilisation de RV pour l'évaluation de la NSU post-AVC augmenterait ma productivité:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Si je vais utiliser la RV pour l'évaluation de la NSU post-AVC, je vais augmenter mes chances d'obtenir une augmentation de salaire:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Attentes par rapport à l'effort

3. Mon interaction avec la RV pour l'évaluation de la NSU post-AVC serait claire et compréhensible:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Il serait facile pour moi de devenir habile à utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Attitudes envers la technologie

5. L'utilisation de la RV pour l'évaluation de la NSU post-AVC est une bonne idée:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. La RV pour l'évaluation de la NSU post-AVC rendrait mon travail plus intéressant:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. Travailler avec la RV pour l'évaluation de la NSU post-AVC serait amusant:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. J'aimerais travailler avec la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Influences sociales

5. Les personnes qui influencent mon comportement au travail pensent que je devrais utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Les personnes qui sont importantes pour moi pensent que je devrais utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. La direction de mon établissement pense que ça serait utile d'utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. En général, je pense que l'organisation me supportera dans l'utilisation de la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Conditions facilitatrices

5. J'ai les ressources nécessaires pour utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. J'ai les connaissances nécessaires pour utiliser la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. La RV pour l'évaluation de la NSU post-AVC ne serait pas compatible avec d'autres méthodes que j'utilise présentement:

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. J'aimerais qu'une personne spécifique (ou un groupe) soit disponible pour porter assistance avec les difficultés envisagées lors de l'utilisation de la RV pour l'évaluation de la NSU post-AVC :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Auto-efficacité

1. Je pense que je pourrais compléter un travail ou une tâche en utilisant la RV pour l'évaluation de la NSU post-AVC s'il n'y avait personne à l'entour pour me montrer ce qu'il y a faire.

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Je pense que je pourrais compléter un travail ou une tâche en utilisant la RV pour l'évaluation de la NSU post-AVC s'il y avait quelqu'un que je peux appeler si je suis mal pris(e).

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Je pense que je pourrais compléter un travail ou une tâche en utilisant la RV pour l'évaluation de la NSU post-AVC si j'avais beaucoup de temps à compléter le travail pour lequel un logiciel est fourni.

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Je pense que je pourrais compléter un travail ou une tâche en utilisant la RV pour l'évaluation de la NSU post-AVC si j'avais seulement accès au centre d'aide pour assistance :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Anxiété

1. Je me sens inquiet(ète) envers l'utilisation de la RV pour l'évaluation de la NSU post-AVC

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. J'hésiterais à utiliser la RV pour l'évaluation de la NSU post-AVC parce que j'ai peur de faire des erreurs que je ne peux pas corriger :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. La RV pour l'évaluation de la NSU post-AVC est quelque peu intimidante pour moi :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Intention comportementale envers l'utilisation du système

1. Si disponible, j'aurais l'intention d'utiliser la RV pour l'évaluation de la NSU post-AVC dans les prochains 12 mois :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Si disponible, je prévois utiliser la RV pour l'évaluation de la NSU post-AVC dans les prochains 12 mois :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Si disponible, je planifie utiliser la RV pour l'évaluation de la NSU post-AVC dans les prochains 12 mois :

Fortement en désaccord	Assez en désaccord	Légèrement en désaccord	Ni d'accord ni en désaccord	Plutôt d'accord	Tout à fait d'accord	Fortement d'accord
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

FIN DU QUESTIONNAIRE

MERCI

END OF DISSERTATION