The Involvement of the Superior Colliculi in Post-Stroke Unilateral Spatial Neglect: A Pilot Study

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ABSTRACT

The underlying mechanisms of the unilateral spatial neglect (USN), a highly prevalent and disabling consequence of stroke that often responds poorly to existing interventions, remain unclear. Animal research suggests that post-stroke USN may be related in part to a disruption of visual attention mediated through the midbrain superior colliculi (SC). However, little attention has been placed on studying this mechanism in humans with post-stroke USN.

The first manuscript of this thesis presents a literature review on the implications of the SC in USN and reviews the rationale and potential for USN treatments aimed at involving the SC. Overall, 21 animal research studies and 24 human research studies were retrieved. Animal studies suggest a direct involvement of the SC in USN presentation and alleviation through a number of interconnections. It proposes that when the ipsilateral SC is deactivated, the animal presents with USN of the contralesional hemispace where the ipsilateral SC is found to be hypoactive, and the contralateral SC is hyperactive. This activity imbalance is restored after the contralateral SC is also deactivated, leading to USN alleviation. Nonetheless, given the paucity of human studies that were found, the contribution of the SC in USN, while plausible, remains to be confirmed. While intervention studies were retrieved where eye patching, with SC activity rationale, was used as a treatment for USN, several methodological issues were identified for future research in his area. Overall, it is suggested that further exploration of the mechanisms involved and their impact on USN in humans will help develop theoretically based intervention strategies tailored to USN type.

The implication of the collicular pathway has been studied using the spatial summation effect (SSE), where response to bilateral presentations is significantly faster that to unilateral presentations. It has never been directly analyzed in those with post-stroke USN. The objectives of the second manuscript, in which the thesis related study was conducted were twofold: 1. to determine the feasibility of investigating SC contribution using the SSE and, 2. to compare the SC contribution in three groups - individuals with

left USN of the near extrapersonal space following right hemisphere stroke, those without USN following a right hemisphere stroke and healthy normal controls. This pilot study included individuals with (n=7) and without (n=10) right hemisphere post-stroke USN and individuals with no history of previous stroke and USN (n=10). All participants were tested on a computer reaction time test under two conditions: using both eyes and using a right monocular eye patch while responding to unilateral and bilateral achromatic stimuli presentations. An eye tracker device was used to control for fixation ability. It was found that the SSE was present in controls under binocular and monocular conditions. In individuals without post-stroke USN, SSE was found abnormal (under binocular and monocular conditions) where reaction times to bilateral stimuli were faster than to the unilateral left stimuli only and not to the unilateral right stimuli presentations. As for the participants with USN, we found that they had poor fixation ability by demonstrating either failure to fixate or several missed fixations (i.e. loosing fixation). Overall, the feasibility of using SSE to investigate the contribution of the SC in post-stroke USN is challenging with this population given poor fixation. Interestingly, the SC are connected to the frontal eye field in directing spatial attention and controlling voluntary and reflexive saccade eye movements that are involved in fixation. This suggests that inability to properly fixate may be associated with SC impairment in individuals with post-stroke USN. Further research is needed to investigate this mechanism and to develop innovative treatment techniques for USN that could potentially involve training of fixation.

RÉSUMÉ

Les mécanismes neuronaux sous-jacents de la négligence spatiale unilatérale (NSU), une conséquence répandue et invalidante d'un accident vasculaire cérébral (AVC) qui répond pauvrement aux traitements, sont encore mal connus. Des travaux récents sur des animaux suggèrent que la NSU peut être liée en partie à une rupture du contrôle de l'attention visuelle médiée par les collicules supérieurs (CS) du mésencéphale. Toutefois, peu d'attention a été mise sur l'étude de ce mécanisme chez l'homme avec la NSU suite à un AVC.

Le premier manuscrit présente une revue de littérature sur les implications des CS dans la NSU et examine la justification et le potentiel, et vise à associer les CS à des traitements pour NSU. Au total, 21 études sur les animaux et 24 études sur l'homme étaient récupérées Les études chez l'animal suggèrent une implication directe des CS dans la présentation et l'allégement de la NSU. Principalement, lorsque la CS ipsilatérale est désactivé, l'animal présente la NSU de l'hémiespace contralésionnelle. Le CS ipsilatéral se trouve être hypoactif, et le CS contralatéral est hyperactif. Ce déséquilibre dans les activités des CS est rétabli suite à la désactivation du CS contralatéral mènant à l'allégement de la NSU. Néanmoins, étant donné la rareté des études sur l'homme qui ont été trouvées, la contribution des CS dans la NSU, tandis que plausible, reste à confirmer. Des études basées sur les connaissances des activités des CS chez l'homme ont été trouvées – dans lesquelles la patche de l'œil a été utilisée comme un traitement pour la NSU. Néanmoins, plusieurs questions doivent être abordées dans les futures études analysant l'effet de la patche de l'œil sur la NSU. Dans l'ensemble, il est suggéré que l'exploration additionnelle et directe des mécanismes en jeu et leur impact sur la NSU chez l'homme contriburent au développement des stratégies d'intervention adaptées aux plusieurs types de NSU.

L'implication des parcours rétino-colliculaires a été étudiée en utilisant l'effet de la sommation spatiale (ESS), mais n'a jamais été directement analysé chez cieux avec de la NSU suite à un AVC. Les objectifs du deuxième manuscrit étaient de déterminer la faisabilité d'enquêter sur l'implication des CS en utilisant l'ESS et d'analyser la

contribution des CS chez les individus présentant une NSU gauche de l'espace extrapersonnel près suite à un AVC de l'hémisphère droit (n=7), les personnes sans NSU suite à un AVC de l'hémisphère droit (n=10), et chez des individus sains (n=10). Les participants ont été testés sur une tâche de temps de réaction sur l'ordinateur en utilisant les deux yeux et en utilisant une patche monoculaire sur l'œil droit tout en répondant à des présentations achromatique unilatérales et bilatérales. Un dispositif oculomètre a été utilisé pour measurer de la capacité de fixation. Par conséquent, l'ESS était présent chez les individus sains sous conditions binoculaire et monoculaire. Chez les personnes sans NSU, l'ESS était anormal (sous conditions binoculaire et monoculaire), dans lesquelles les temps de réaction aux présentations bilatérales étaient plus rapides qu'aux présentations unilatérales gauches, et pas droites. Les participants avec NSU ont démontré une capacité de fixation faible en démontrant soit une incapacité totale de fixer ou plusieurs pertes de fixation. En conclusion, la possibilité d'utiliser l'ESS pour enquêter sur la contribution des CS dans la NSU suite à un AVC est difficile étant donné une pauvre capacité de fixation. En effet les CS sont liés au domaine œil frontal à diriger l'attention spatiale et le contrôle des mouvements oculaires volontaires et réflexes. Nous pouvons donc spéculer que l'incapacité à fixer indique une insuffisance des activités des CS chez des individus avec NSU suite à un AVC. D'autres recherches sur ce sujet sont nécessaires afin de développer des techniques thérapeutique innovantrices qui pourraient impliquer un entraînement à la fixation.

ACKNOWLEDGMENTS

The experience leading to this thesis was a very gratifying, enjoyable and challenging one. I would like to thank all those people who contributed, each in their own ways, to make this journey a possible and pleasurable one for me.

First and foremost, I would like to express profound gratitude and appreciation to my supervisor, Dr. Nicol Korner-Bitensky, for her invaluable support, encouragement, supervision, and expertise provided throughout my studies. Her insight, patience, critical and creative thinking; as well as continuous professional and personal guidance enabled me to initiate, carry out and complete my work successfully. This allowed me to also grow on many personal levels and as a health care professional.

I would also like to acknowledge the endless help and support received from my co-supervisor, Dr Alain Ptito. His clinical and research experience, generosity throughout every stage of this thesis and many other contributions made this project into a possible and an exciting experience for me and my supervisory committee. I also wish to express sincere gratitude to all the member of my research committee, Dr. Gail Eskes & Dr. Lesley Fellows for their insights, suggestions, and support provided throughout my studies that assisted me in achieving my goals, and beyond. A special thanks to Dr. Sandra Leh for her provided support throughout the development of the study and numerous valuable insights.

Finally, my acknowledgments would be incomplete without thanking my dear family and friends for their constant multi-faceted support throughout all the steps of this master completion. To my departed father, Ogourtsov Oleg Vladimirovich, to whom I dedicate my success, who first encouraged me to enroll into the degree and until his last day, believed in me. To my mother, Elena Tesler, thank you for supporting me with encouragement, smiles, endless kindness, patience, and love. To my brother, Roman Ogourtsov, thank you for your insights and support. To my treasured friends, thank you for your compassion, understanding, and endless encouragements throughout my journey.

A genuine thank-you goes out to all these people for their unique contribution and guidance that allowed and assisted me to complete this thesis.

CONTRIBUTION OF AUTHORS

The literature review of this thesis was, in part, a manuscript send and accepted for publication on September 22, 2009 to the Neuropsychologia journal, entitled, "Contribution of the Superior Colliculi in Post-Stroke Unilateral Spatial Neglect and Recovery". It was mainly written by myself and Dr. Nicol Korner-Bitensky. I conducted the literature search and review under Dr. Nicol Korner-Bitensky supervision and guidance. As a co-author, Dr. Alain Ptito provided us with insightful suggestions and comments on the content, clearness and arrangement of the manuscript. Dr. Gail Eskes and Dr. Lesley Fellows also gave valuable suggestions on the content and structure of the manuscript.

The second manuscript of this thesis entitled, "The Involvement of the Superior Colliculi in Post-Stroke Unilateral Spatial Neglect: Pilot Study", was mainly written by myself and Dr. Nicol Korner-Bitensky, and was sent for publication in March 2010 to Neuropsychologia journal. Co-authors, Dr. Alain Ptito, Dr. Sandra Leh and Dr. Gail Eskes again gave us valuable insights into the content and presentation of the article. In conjunction with Dr. Sandra Leh, the testing paradigm that was used in the present study was modified from the testing paradigm used by Dr. Sandra Leh in her previous study. I have developed the letters of recruitment and consent forms in conjunction with Dr. Nicol Korner-Bitensky, submitted the study for ethics approval, requested permission for changes in the protocol, recruited all study participants, collected socio-demographic data, performed all the testing, and analyzed the data under the supervision of Dr. Nicol Korner-Bitensky. Dr. Lesley Fellows also have valuable suggestions on the content of the manuscript.

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PREFACE

This thesis consists of a collection of two manuscripts. As per McGill University requirements, these papers have a cohesive, unitary character making them a report of a single program of research. The first manuscript has been sent for publication. The second manuscript is being prepared to be sent for publication in a scientific journal. It is required by the Graduate and Postgraduate Studies (GPS) at McGill University, that the thesis incorporates a literature review and conclusion that is separate from that included in the manuscripts. Thus, it is unavoidable to have material duplication throughout this report. Tatiana Ogourtsova wrote this thesis with editing by Dr. Nicol Korner-Bitensky.

This thesis is organized in 8 chapters. Chapter 1 is an introduction to the topic of unilateral spatial neglect (USN) and the superior colliculi (SC). Chapter 2 is a review of literature that covers the following areas: 1. USN: Definition and Prevalence; 2. USN: Consequences and Effectiveness of Treatment; 3. USN: Mechanism – the Ultimate Search; 4: USN – Superior Colliculi (SC). Chapter 3 provides the thesis objectives. Chapter 4 consists of the first manuscript entitled, “Contribution of the superior colliculi in post-stroke unilateral spatial neglect and recovery”. Chapter 5 offers a bridge between the conclusion of the first manuscript and the objectives of the second manuscript. It is followed by Chapter 6 that incorporates the second manuscript entitled, “Superior Colliculi Involvement in Post-Stroke Unilateral Spatial Neglect: Pilot Study”. Chapter 7 and 8 summarize the findings and provide a conclusion incorporating both manuscripts.

1. INTRODUCTION

Stroke is the third leading cause of death in Canada where more than 50,000 strokes occur each year. 75% of individuals with stroke are left with severe to minor impairments following their stroke. Presently, about 300,000 Canadians are leaving with the effect of stroke ("Heart and Stroke Foundation", 2009). Among the post-stroke impairments, spatial-perceptual disorders are found to be common and disabling clinical consequences of stroke. One of the most serious, unilateral spatial neglect (USN), is experienced by 23% to 46% of individuals with stroke (Jutai et al., 2003). USN is defined as the inability to orient to, respond to, or report stimuli occurring in the contralesional visual hemispace, when such failure cannot be attributed to sensory or motor deficits (Heilman & Valenstein, 1979). USN is found to be associated with an increased risk of falls (Jutai et al., 2003), poor rehabilitation outcomes and worse independence in everyday life tasks such as dressing, bathing, eating and mobility; and a higher risk of functional deterioration at one-year (Paolucci et al., 2001). Given that after age 55, the risk of stroke doubles every 10 years ("Heart and Stroke Foundation", 2009), and this segment of the population continues to grow, so does the concern for their post-stroke rehabilitation outcomes.

The role of rehabilitation professionals working with this population is to objectively assess for USN and provide evidence-based treatment strategies in attempt to alleviate this disorder. Nonetheless, despite active research in USN interventions, none of the strategies available to date are effective in reducing functional disability (see Cochrane, 2007 for a review; Bowen & Lincoln, 2007). The lack of clear evidence supporting treatment efficacy has lead to a call for the development of more theoretically targeted treatments for USN (i.e. based on underlying mechanisms and understanding of subtypes) (Bowen & Lincoln, 2007). In order to generate new and more effective treatment techniques, the underlying mechanism(s) of USN need to be researched. Currently, the neurophysiology and neuroanatomy of USN remain unclear. Through numerous animal studies, it has been suggested that the SC, a midbrain structure, is involved in USN

presentation and alleviation. To date, no human studies have analyzed this mechanism directly. Therefore, in order to explore the role of the SC in post-stroke USN, a pilot project was initiated. More specifically, the objectives of this thesis were to (1) A. review the existing literature on SC involvement and USN including animal and human intervention studies; and B. to identify gaps in the scientific literature that will guide future research; (2) A. to determine the feasibility of investigating SC contribution using the Spatial Summation Effect (SSE) and, B. to compare SC contribution in three groups - individuals with left USN of the near extrapersonal space following right hemisphere stroke, those without USN following a right hemisphere stroke and healthy normal controls.

2. REVIEW OF LITERATURE

2.1. USN: Definition and Prevalence

Visual-perceptual disorders are highly prevalent and disabling clinical consequences of stroke. One of the most serious being USN; experienced by 23% to 46% of individuals with stroke. USN is characterized by the inability to orient, respond, or report to the stimuli appearing on the contralesional side when such failure cannot be attributed to sensory nor motor deficits (Jutai et al., 2003).

While USN can occur following left hemisphere lesions it is most common following right hemisphere lesions. More specifically, the reported incidence of USN among individuals with right-hemisphere stroke ranges from 13% to 81% (Pierce & Buxbaum, 2002). It is known that the right hemisphere attends to both visual hemispaces; while the left hemisphere attends predominantly to the right visual hemispace (Refer to Figure 2.1). Thus, following a stroke in the right hemisphere, a left USN is commonly present. USN is less probable to occur following a left lesion since the right hemisphere attends to both, right and left visual hemispaces (Swan, 2001).

Twenty to 45 percent of USN resolves spontaneously within the acute post-stroke period. For the remainder, USN can become long-standing and introduces major disability and activity restrictions (Paolucci et al., 2001).

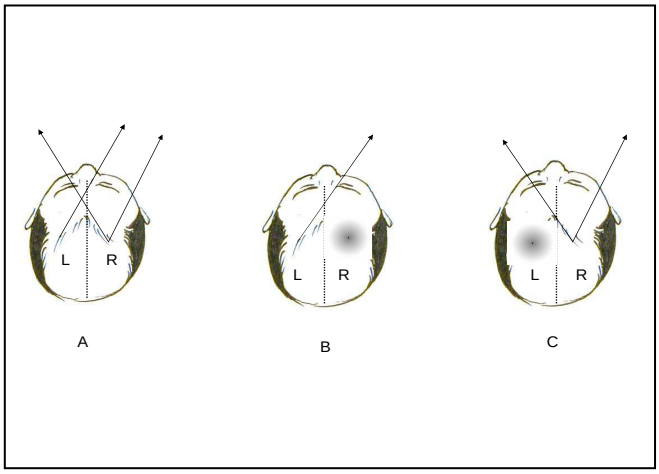

Figure 2.1: Attention Hemispaces of the Right and Left Hemispheres of the Brain

A. The right hemisphere of the brain attends to both the left and right visual hemispaces. However, the left hemisphere of the brain attends only to the right visual hemispace.

B. When a right hemisphere cerebrovascular accident occurs, only the left hemisphere is attending to the right visual hemispace, and left visual neglect is likely to occur.

C. When a left hemisphere cerebrovascular accident occurs, the right hemisphere is attending to both, the right and left visual hemispaces, and visual neglect is less likely to occur.

Recent studies have isolated three hemispaces in which USN can occur and for which different neural mechanisms are responsible: *personal* (the person fails to attend to contralesional side of his/her body), *near extrapersonal* (the person fails to attend to contralesional space within the reaching distance) and *far extrapersonal* (the person fails to attend to contralesional space beyond the reaching distance). USN can occur in any one of, or in a combination of these hemispaces (Bisiach et al., 1986; Piere & Buxbaum, 2002). In the literature several terms for USN are used interchangeably such as hemi-inattention, visual neglect, unilateral neglect, hemineglect, and hemispatial neglect.

2.2. USN: Consequences and Effectiveness of Treatment

Clinically, a severe USN is easily observable. For example, an individual with left USN following a right hemisphere lesion may shave only the right side of his face, eat food from the right side of his plate only or, when moving through space, bump into obstacles on the left. Mild or moderate USN is less easily observable and often goes undetected (Menon-Nair et al., 2006). This is a serious given that it is associated with significant post-stroke disability and poor rehabilitation outcomes. The literature on stroke indicates that individuals with USN, when compared 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 (Paolucci et al., 2001), and are more prone to frequent falls (Jutai et al., 2003). Results from such studies suggest that those with USN respond poorly to intensive cognitive rehabilitation programs. In addition to its obvious burden on the individual, USN also places a major burden on the family and the caregivers (Paolucci et al., 2001 & Buxbaum et al., 2004).

To counteract these substantial disabling effects and thereby reduce the associated burden and costs to the health care system, it is critical that rehabilitation professionals develop and implement effective intervention strategies aimed at reducing USN and its sequelae.

To date, approximately 18 different treatment strategies have been put forward (Refer to Figure 2.2). The earliest were proposed in the 1950's (Luaute et al., 2006) with the most recent innovations such as the use of virtual reality proposed in 2005 (Katz et al., 2005) The efficacy and effectiveness of these rehabilitation strategies are subject to debate. In fact, as suggested by a recently completed meta-analysis, most interventions are not highly effective in improving functional outcomes (Luaute et al., 2006). For instance, visual scanning training is a popular method of choice amongst therapists. Yet, the scientific literature regarding this method is not definitive on whether its beneficial effects are maintained post rehabilitation and whether this strategy really improves functional skills. Studies on other treatment strategies such as limb activation, mental imagery and feedback training are similarly inconclusive (Luaute et al., 2006). Indeed an October 2007 Cochrane review (n=12 randomized clinical trials) of the effectiveness of interventions for USN summarized the situation very succinctly indicating that there is some direct effect of treatment on the task being investigated but that there is currently insufficient evidence to support or counter the effectiveness of USN treatment approaches at reducing disability (i.e. activity restrictions) (Bowen & Lincoln, 2007).

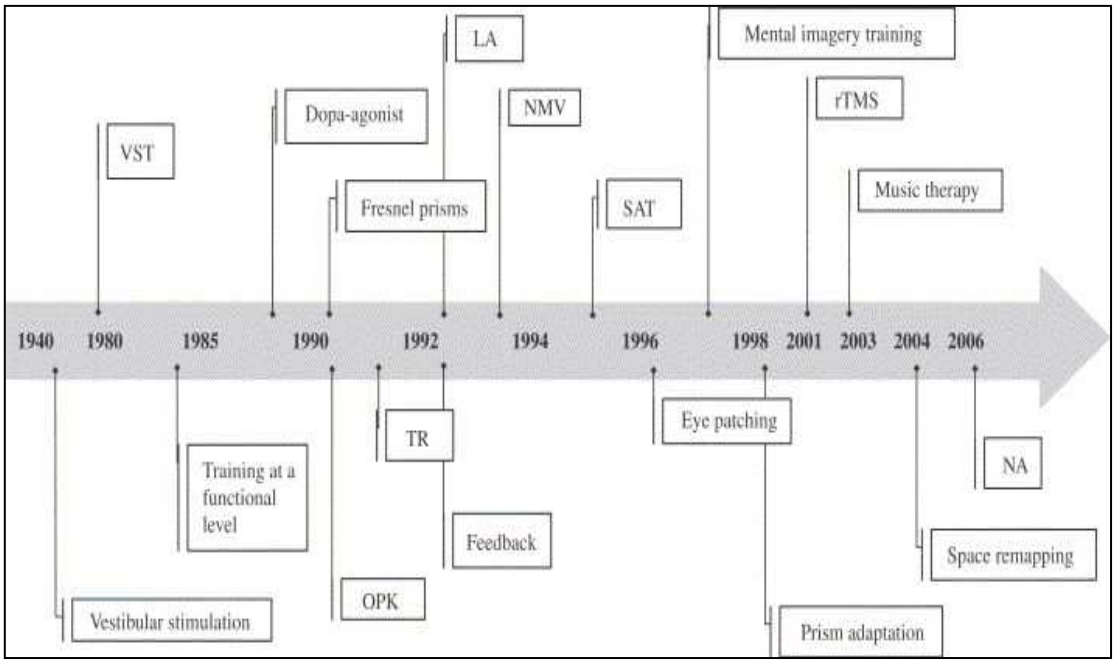

Figure 2.2: USN Treatment Strategies Timeline

"Time-line of the first publications for the 18 different attempts to remediate visuo-spatial neglect. *Abbreviations*: VST: visual scanning training; LA: limb activation; rTMS: repetitive transcranial magnetic stimulation; SAT: sustained attention training; OPK: optokinetic; NMV: neck muscle vibration; TR: trunk rotation; NA: noradrenergic agonist".

(Luaute et al., 2006: with permission from author)

USN: Mechanism – The Ultimate Search

The above section suggests that development of new and effective treatment methods is imperative (Luaute et al., 2006). Indeed, rehabilitation professionals need to partner with experts in the basic cognitive neurosciences to identify the areas of the brain and the mechanism(s) that are responsible for the disabling effects of USN. In this manner, effective intervention strategies can be generated using a strong neurological basis.

The search for brain areas responsible for USN has produced intense debate amongst researchers. Damage to the right parieto-temporal junction is most frequently reported in individuals with visual neglect (Bartolomeo et al., 2007). Mort et al. (2003) suggest that the most critical brain regions responsible for USN when the stroke occurs in the region supplied by the middle cerebral artery are the angular gyrus and the right inferior parietal lobe. Furthermore, they also indicate that damage to the parahippocampal region is critical for USN presentation when stroke occurs in the region supplied by the posterior cerebral artery. Another recent study of 140 individuals with right hemisphere lesions identified the right superior temporal cortex as the critical brain area responsible for USN (Karnath et al., 2004).

Why is there such disagreement on the location of the lesion? One possible explanation may be that USN has been recognized as a multi-component, heterogeneous disorder. As mentioned earlier, USN can be seen in various hemispaces. A recent study on USN examined the neural bases of *personal* and *extrapersonal* visual neglect using modern methodological accuracy made possible with high-resolution anatomical imaging (Committeri et al., 2007). By studying a fairly large and homogeneous sample of 88 individuals with stroke, the researchers came to the conclusion that the neural bases of *personal* and *extrapersonal* USN are in fact considerably different. More specifically, they found that critical regions responsible for *personal* USN are in the post-central and supramarginal gyri (parietal lobe subspaces). In contrast, for *extrapersonal* USN, critical regions are located in the frontal lobe (ventral premotor and dorsolateral prefrontal cortex) and in the temporal lobe (middle and anterior superior temporal gyrus, and the superior temporal sulcus) (Committeri et al., 2007).

The disagreement on the universal basic neuroanatomy of USN may, in part, explain the rather ineffective range of USN interventions in as that they may not be specifically directed to the responsible brain structure(s). Thus, generating knowledge on the anatomical substrate of this disorder is not only of theoretical value, but also of great clinical importance.

In addition, different theories of USN have been proposed. The attention deficit theory has been introduced to justify the behavioral outcomes associated with USN. More specifically, five potential attentional deficits have been described in relation to visual neglect. First, a right hyper-capture of attention hypothesis suggests that USN is a result of highly attracted attention towards the stimuli presentation to the ipsilesional side in individuals with USN (Gianotti et al., 1991). Moreover, a disengage deficit premise has been proposed implying that individuals with USN demonstrate marked difficulty in disengaging their attention from ipsilesional stimuli presentations to contralesional stimuli presentation (Posner et al., 1987); and re-engaging attention (e.g., a reduction in inhibitory processes that slow return to a previously engaged location/object, termed inhibition of return, or IOR). Also, a generalized attentional deficit supposition argues that with a right hemisphere lesion, USN is present and more prominent because the right hemisphere is suggested to be responsible for global features of visual input rather than the details that are suggested to be mediated by the left brain hemisphere (Lamb & Robertson, 1990). Lastly, a more general model has been put forward and is called the opponent–processor model. As mentioned previously, a hemisphere mainly attends to the contralateral visual hemispace. This model argues that each hemisphere attends to the contralateral visual hemispace by inhibiting the other hemisphere. It goes on to propose that with a right hemisphere lesion the left hemisphere is not inhibited, and this results in exaggerated attentional shift to the right (i.e. left USN). Cortical mechanisms that mediate such interactions have been examined in animals. For instance, the superior colliculi (SC) is likely to be the neurobiological basis behind the opponent-processor theory of USN (Bartolomeo et al., 2007). Interestingly, the SC's involvement in USN has been demonstrated in several animal studies (Lomber et al., 2001 & Rushmore et al., 2006).

Thus, it is very likely that an understanding of how the control of orienting/selection is implemented and how it is impaired in neglect is central to the design of effective interventions. In fact, the SC in animals have been found to play an important role in attention orienting mechanisms described above.

2.4. USN: Superior Colliculus (SC)

To understand the importance of examining the SC in relation to USN, it is first necessary to recognize what a SC is, along with its properties with regards to USN. There are two SC, right and left, located in the dorsal midbrain and along with other midbrain structures, they are involved in the mediation of saccadic eye movements, fixation (Schneider & Kastner, 2005), and control of spatial attention during visual search (Himmelbach & Karnath, 2007). Each colliculus is composed of three layers - superficial, intermediate, and deep (Lomber et al., 2001) and receives retinal input predominantly from the contralateral visual hemifield (Swan, 2001).

The superficial layer is mainly responsible for processing visual input, and the deeper section assists in orienting head and eye movements in response to visual stimuli (Schneider & Kastner, 2005). More specifically, the superficial layer receives input from the reticotectal pathway, and is influenced by the projections from the striate and extrastriate cortices to the geniculostriate pathway (Fries, 1984). The deep layer receives input from the prefrontal cortex, frontal eye field (FEF), and parietal cortex. It has been suggested that spatial attention is a result of balance between these cortical and subcortical circuits. For example, the projections from the superficial layer to the pulvinar, which is in turn connected to the parietal, prefrontal and cingulate cortical areas, assist in mediating spatial attention (Romanski et al., 1997) while the intermediate (Facteau et al., 2004) and deep layers (Bell et al., 2004) participate in the capture of attention, at least in monkeys.

The SC have been implicated in different attentional mechanisms that can be related to USN presentation and alleviation. These include the promising ‘opponent-processor’ model of attention, the inhibition of return effect (Bartomeo & Chokron, 2002), and its

connection to the FEF (Heide & Kompf, 1998). They will be discussed in more detail in the first manuscript presented below.

3. THESIS OBJECTIVES

- **Manuscript 1:** To review the existing literature on SC involvement and USN including animal and human intervention studies; and to identify gaps in the scientific literature that will guide future research.

- **Manuscript 2:** To determine the feasibility of investigating SC contribution using the SSE and to compare SC contribution in three groups - individuals with left USN of the near extrapersonal space following right hemisphere stroke, those without USN following a right hemisphere stroke and healthy normal controls.

In this study we hypothesized that the SSE would be present in healthy controls and in those without USN post-stroke and that the SSE would be seen under both binocular and monocular conditions. In contrast, we hypothesized that the SSE would be absent or abnormal in those with USN under the binocular condition, but present, or at least improved, under the monocular condition

4. CONTRIBUTION OF THE SUPERIOR COLLICULI IN POST-STROKE UNILATERAL SPATIAL NEGLECT AND RECOVERY: A COMPREHENSIVE LITERATURE REVIEW

4.1 MANUSCRIPT 1

Contribution of the Superior Colliculi in Post-Stroke Unilateral Spatial Neglect and Recovery

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Word Count: Review excluding references: 7887 words
Abstract: 163 words

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ABSTRACT

Unilateral spatial neglect (USN) is a highly prevalent and disabling consequence of stroke that often responds poorly to existing interventions. Its underlying neural mechanisms are still unclear. Recent work suggests that post-stroke USN may be partly related to a disruption of top-down and bottom-up control of visual attention mediated in part through the midbrain superior colliculi (SC). With mounting evidence from animal and human research, our objectives were: 1) to synthesize the literature implicating the SC in USN; 2) to review the rationale and potential for eye patching and prism adaptation as USN treatments aimed at involving the SC; and 3) to provide recommendations for research on the potential of therapeutic interventions that involve and/or target the retino-collicular pathway. Given the paucity of human studies, the contribution of the SC in USN, while plausible, remains to be confirmed. Further exploration of the mechanisms involved and their impact on USN in human subjects will help develop theoretically based intervention strategies tailored to USN type.

KEY WORDS

Unilateral spatial neglect, attention, stroke, superior colliculi, eye patching, prisms adaptation, frontal eye field, temporo-nasal asymmetry.

INTRODUCTION

Visual-spatial disorders are highly prevalent and disabling clinical consequences of stroke. One of the most serious, unilateral spatial neglect (USN), has been defined as the inability to orient to, respond to, or report stimuli occurring in the contralesional visual hemispace, when such failure cannot be attributed to sensory or motor deficits (Heilman & Valenstein, 1979).

While USN can occur following left hemisphere lesions, it is most commonly seen following right hemisphere lesions with an estimated incidence ranging from 13% to 81% (reviewed in Pierce & Buxbaum, 2002). Clinically, severe left USN is easily observable as the patient may only eat food from the right side of the plate or bump into obstacles in the left hemispace. In mild or moderate cases it is less discernable and may go undetected (Menon-Nair et al., 2006) creating an increased risk of falls (Jutai et al., 2003), poor rehabilitation outcomes and worse independence in everyday life tasks such as dressing, bathing, eating and mobility, and a higher risk of functional deterioration at one-year (Paolucci et al., 2001).

Since the 1950's (reviewed in Luauté et al., 2006) more than 18 treatment strategies have been proposed for USN, ranging from visual scanning training (Weinberg et al., 1977) to the use of virtual reality (Katz et al., 2005). Despite the amount of research, however, there are few recognized standard treatments for neglect, and recent reviews of treatment efficacy have concluded that there is insufficient evidence to support or counter the effectiveness of current USN treatment approaches at reducing disability (see Cochrane, 2007 for a review; Bowen & Lincoln, 2007). The lack of clear evidence supporting treatment efficacy has lead to a call for the development of more theoretically targeted treatments for USN (e.g., based on underlying mechanisms and understanding of subtypes) (Bowen & Lincoln, 2007).

Neglect has been widely regarded as a disorder of the spatial orienting system and a number of different deficits related to the control of orienting have been reported (Posner, 1984; Siéroff, 2007). Orienting can be defined as a set of processes designed to select a region of space, or an object or event within it, for further perceptual and cognitive processing. Orienting can involve overt eye movements to align the fovea with

the target object or event, or covert internal shifts of attention to the space/objects without an overt eye movement. Neglect has been associated with deficits in a variety of processes that underlie the overt or covert shifting of attention, including the initial engagement of attention (e.g., described as a hyper-reflexive capture of attention by stimuli on the right side, termed the spatial bias), the disengagement of attention to produce another shift (e.g., the slowed disengagement from right-sided stimuli in order to shift attention leftward, termed the disengage deficit) and the re-engagement of attention (e.g., a reduction in inhibitory processes that slow return to a previously engaged location/object, termed inhibition of return, or IOR). Thus, an understanding of how the control of orienting/selection is implemented and how it is impaired in neglect is central to the design of effective interventions.

A greater appreciation of the heterogeneity of USN symptoms and an understanding of its underlying mechanism(s) linking animal and human studies will improve treatment success. A strong partnership between rehabilitation professionals and experts in cognitive neuroscience is needed to take this new knowledge and translate it into highly effective and targeted USN interventions. With this ultimate goal in mind, this article presents an overview of the mechanisms underlying USN that involve the superior colliculus (SC). We also examine the implications of SC involvement for designing more effective treatment strategies for those with post-stroke USN, with an emphasis on eye patching and prism adaptation, interventions that have been promising.

METHODS

A comprehensive literature search was performed covering the time period ranging from 1969 to 2008 using the following electronic databases: Medline, PsychINFO, and PubMED to identify animal and human studies that implicate the SC in USN. Observational and intervention studies were included, particularly human studies that investigated the effect of eye patching and prism adaptation on USN. The following key terms were used: visual neglect, neglect, hemi-inattention, unilateral spatial neglect, opponent-processor, exogenous, inhibition of return, stroke, cerebrovascular accident, superior colliculi (us), eye patch(ing), prism adaptation, frontal eye field; and visual perceptual. The Cochrane library was also reviewed using the same key words. In

addition, reference sections of all the retrieved articles were perused in search of other relevant articles. The works of all main authors specializing in this area were searched via the ISI Web of Science database. 45 articles were retrieved fitting the criteria. Out of these, 21 are animal studies, and 24 are human studies. The following section will review the animal and human work on the neural mechanism of USN presentation and recovery with an emphasis on the role of the SC. Finally, the intervention studies focusing on eye patching and prism adaptation as interventions were reviewed.

RESULTS

The Neural Substrates of USN

Debate about which damaged brain regions are critical for USN is ongoing. Different brain areas such as the right parieto-temporal junction (Bartolomeo et al., 2007), the angular gyrus, the right inferior parietal lobe, the parahippocampal region (Mort et al., 2003), and the right superior temporal cortex (Karnath et al., 2004) have all been implicated suggesting substantial heterogeneity in the component processes that, when disrupted, result in USN. It has been proposed that visual attention is mediated through a number of interconnected, yet functionally independent neuroanatomical networks (reviewed in Mesulam, 1999; Posner & Petersen, 1990) with the posterior parietal lobe being crucial for spatial attention and orienting. For instance, deficits in two fronto-parietal networks are found to be involved in neglect: 1. the dorsal network (i.e. intraparietal sulcus and the frontal eye field (FEF)); and 2. the ventral network (i.e. temporo-parietal junction and ventral frontal cortex) (for review see Corbetta & Shulman, 2002). More precisely, ventral network is found to be structurally damaged in individuals with post-stroke neglect (Corbetta et al., 2005). Even if structurally intact, the dorsal network is found to have functional imbalance of evoked potentials such that the left dorsal parietal cortex is hyperactive, and the right one is hypoactive in individuals with post-stroke USN (Corbetta et al., 2005).

In its role at mediating visual scanning, the posterior parietal cortex outputs information to the FEF and adjacent premotor areas (Mesulam, 1999; Mesulam, 1981; Mesulam, 1990). In addition, there are direct interconnections between the FEF and subcortical structures such as the superior colliculi (SC). In fact, the SC play an important

role in directed attention (Facteau et al., 2004; Mesulam, 1999) as illustrated by the Sprague Effect whereby USN in cats (induced by experimentally lesioning the contralateral striate and extrastriate visual cortices) can be abolished by a second lesion to the contralateral SC (Sprague, 1966). This effect suggests that a better understanding of the role of the SC in USN may provide a rational route to effective treatment of this disorder in humans.

Neuroanatomy and general function of the SC

Before appraising the intervention studies, we will review the basic functions and neuroanatomy of the SC. The SC are located in the dorsal midbrain and along with other midbrain structures, they are involved in the mediation of saccadic eye movements, fixation (Schneider & Kastner, 2005), and control of spatial attention during visual search (Himmelbach et al., 2007). Each colliculus is composed of three layers - superficial, intermediate, and deep (Lomber et al., 2001) and receives retinal input predominantly from the contralateral visual hemifield (Swan, 2001). The superficial layer is mainly responsible for processing visual input, and the deeper section assists in orienting head and eye movements in response to visual stimuli (Schneider & Kastner, 2005). More specifically, the superficial layer receives input from the reticotectal pathway, and is influenced by the projections from the striate and extrastriate cortices to the geniculostriate pathway (Fries, 1984). The deep layer receives input from the prefrontal cortex, FEF, and parietal cortex. It has been suggested that spatial attention is a result of balance between these cortical and subcortical circuits. For example, the projections from the superficial layer to the pulvinar, which is in turn connected to the parietal, prefrontal and cingulate cortical areas, assist in mediating spatial attention (Romanski et al., 1997) while the intermediate (Facteau et al., 2004) and deep layers (Bell et al., 2004) participate in the capture of attention, at least in monkeys.

The SC have been implicated in different attentional mechanisms that can be related to USN presentation and alleviation. These include the promising 'opponent-processor' model of attention, the inhibition of return effect (Bartolomeo & Chokron, 2002), and its connection to the FEF (Heide & Kompf, 1998). They will be discussed in more detail in below animal and human studies sections.

The Role of SC in USN – Evidence from Animal Studies

Opponent-Processor Model

The 'opponent-processor' model proposes that each cerebral hemisphere mainly attends to the contralateral visual hemispace while simultaneously inhibiting the attentional effects from the ipsilateral hemisphere (Kinsbourne, 1970). Thus, damage to the right hemisphere will reduce attention to the left hemispace both by impairing attentional processing in the right hemisphere, and by disinhibiting attentional mechanisms in the left hemisphere, resulting in an exaggerated attentional shift to the right (i.e. left USN). Indeed, the neural mechanisms that mediate the 'opponent-processor' model have been examined in animals, with mounting evidence suggesting that the SC is likely to form at least part of the neurobiological mechanism behind it (Lomber et al., 2001; Payne et al., 1996; Lomber et al., 1996; Rushmore et al., 2006).

For instance, early studies by Foreman (1983); Overton, Dean & Redgrave (1985); Overton & Dean (1988); Kirvel (1975); and Flandrin & Jeannerod (1981) all found that unilateral lesions of the animal's (cats and rats) SC resulted in neglect of the contralateral hemispace. More recent behavioral studies in cats have used a perimetry task to test for USN presence or absence. This task consists of placing the animal in a semi-circular arena containing openings across the wall to permit stimulus presentation. Orientation is assessed by the turning of the head and/or body towards the stimulus. In general, all the studies we have retrieved demonstrate that unilateral lesions in a variety of areas such as the SC alone (Lomber et al., 2001; Payne et al., 1996; Lomber et al., 1996), the middle suprasylvian sulcus (Payne et al., 1996; Lomber et al., 1996), the posterior-middle suprasylvian sulcus (Lomber et al., 2002), the occipito-temporal cortical region as well as the SC (Sherman, 1977), the occipito-parieto-temporal cortical region and the SC (Wallace et al., 1989), create a contralateral deficit in orienting. All show that impairment in orienting is reversed by a second lesion (either permanent or reversible) on the side opposite the original lesion, in a variety of areas but predominantly in the SC (Lomber et al., 2001; Payne et al., 1996; Lomber et al., 1996; Lomber et al., 2002; Sherman, 1977; Wallace et al., 1989).

It is important to note that control of orienting by these circuits seems to depend upon the task that is used. Following unilateral muscimol injection into the SC, cats demonstrated profound visual neglect of the contralateral hemispace during the perimetry

task while preserving visuomotor accuracy in foot placement while walking in a cluttered alleyway (Wilkinson et al., 2007). This finding supports the notion that, at least in cats, vision to guide walking compared to vision to orient to stimuli in the perimetry task can operate independently. From this study it can be speculated that the SC is not solely involved in mediating attention, but also appears to be implicated in regulating attentional processes during higher level cognitively demanding tasks.

In addition, further evidence from animal models suggests that USN may result from structural brain damage as well as from the ensuing pathological state of inhibition of the lesioned hemisphere by the contralateral hemisphere. Thus, an induced USN is not simply the result of a disruption of the circuitry of the affected hemisphere, but it may alternatively be an imbalance of left and right collicular activity. For example, Hovda & Villablanca (1990) demonstrated that in USN in cats the ipsilesional SC has significantly lower oxidative metabolism than the contralesional SC. More recently, Rushmore et al. (2006) reported that in cats with USN (induced by cooling deactivation of the posterior parietal cortex or by a unilateral lesion of all visual cortical areas), the ipsilateral SC is hypoactive whereas there is hyperactivity in the deep and intermediate levels of the contralateral SC. When recovery from USN took place (by cooling of the contralateral SC while the initial cooling of the ipsilateral SC or posterior parietal cortex was still present), a reduction in the activity of the contralateral SC was observed. These findings suggest that a modification in the activity level of the SC is likely the means through which USN appears and resolves, implying that the treatment of USN in humans should aim at modulating contralateral SC excitability.

To summarize, animal studies suggest that the SC with their interconnections to the posterior parietal cortex region, play a major role in visual attention. The studies support the opponent-processor model of USN (e.g. Rushmore et al., 2006) whereby, when the ipsilesional SC is hypoactive, the left SC is disinhibited (hyperactive) and an exaggerated attentional shift to the right visual hemispace (i.e. left USN) is engendered. When the imbalance between collicular activities is counteracted by a second lesion to the opposite SC, USN is alleviated suggesting that there are both cortical and subcortical circuits involved in orienting that work in a mutually inhibitory network.

Inhibition of Return Effect (IOR)

In contrast, the 'inhibition of return' effect (IOR) refers to the notion that during visual exploration one inhibits attention to already seen events thus facilitating processing of novel information during visual search. IOR was first demonstrated using reaction time tests where reaction time to an initially attended stimulus (exogenous orienting) is faster than the reaction time to the same stimulus presented more than once (endogenous orienting) (Posner & Rafal, 1985). It is proposed that following a right hemisphere lesion, IOR is impaired in patients with left USN (Bartolomeo et al., 1999; Bartolomeo et al., 2001) making them unable to disengage their attention from the right visual hemifield and to orient their attention leftwards exogenously. Interestingly, the SC have been implicated as the potential neural mechanism behind impaired exogenous orienting and IOR (Sapir et al., 1999). For instance, Gottlieb et al. (1998) examined the role of the parietal cortex in exogenous and endogenous orienting with physiological neural recordings and magnetic resonance imaging of the lateral intraparietal area in rhesus monkeys. The majority of tested neurons showed significantly greater responses during reflexive/immediate/exogenous orienting than during voluntary/goal-driven/endogenous orienting to visual stimuli. Given that the intraparietal fissure is one of the main sources of cortical projection to the intermediate and deep layer of the SC (Fries, 1984; Pare & Wurtz, 1997), one can speculate that the SC, with its interconnections to the parietal cortex, is involved in this effect.

Frontal Eye Field (FEF)

The SC are also found to be interconnected with FEF, a region involved in the control of voluntary and reflexive saccadic reactions that influence shifts of visual attention. FEF neurons responsible for voluntary saccadic activity have two main connections to the SC: 1. a direct fronto-tectal pathway; and, 2. an indirect connection through the caudate nucleus and the substantia nigra (Heide & Kompf, 1998). The FEF neurons that are involved in mainly reflexive saccades are also interconnected with the posterior parietal cortex with outputs to the SC through the mediodorsal nucleus of the thalamus (Fries, 1984; Stanton et al., 1988; Lynch et al., 1994; Sommer & Wurtz, 1998; Crapse & Sommer, 2009; Barbas & Mesulam, 1981; Goldman-Rakic & Porrino, 1985). In fact, this connection of the SC with the FEF (directly and indirectly) is found to be important for the spatial attention network influencing saccade-related activity. For

example, in monkeys, FEF cooling results in profound neglect while deactivation of the right SC causes longer saccadic reaction time and a decrease in amplitude (Keating & Gooley; 1988). Neuroanatomical animal studies also provide evidence for a role of the SC in generating reflexive saccades (McPeek & Keller, 2004; Paus, et al., 1995; Petit & Beauchamp, 2003 Keating & Gooley, 1988). More recently, Neggers et al., (2005) found a negative correlation between SC activity and speed of saccades such that increased SC activity was associated with increase in saccade latency. These studies support the involvement of the SC with their connections to the FEF in attention orienting responses and they suggest that similar mechanisms may be at play in humans.

The Role of SC in USN – Evidence from Human Studies

Opponent-Processor Model

When it comes to the evidence for the opponent-processor model in USN and activity imbalance in the cerebral hemispheres, a single case report has been published (Vuilleumier et al., 1996). A 74 year-old man with a right posterior parietal infarct exhibited post-stroke left USN. Ten days later, he experienced a second stroke in the left dorsolateral frontal lobe and recovered suggesting that left visual neglect is not simply the result of structural damage to the right posterior parietal cortex, but rather an imbalance in the activity of the cerebral hemispheres; the right disinhibiting the left leading to an exaggerated attentional shift to the right (i.e. left USN). The authors speculated that the second stroke restored the balance of cerebral activity and caused the orienting attention to return to normal.

With respect to the Sprague Effect, to date only one human case report has been published. Weddell (2004) reported on a 34 year-old man with a midbrain tumor that left both SC intact. The patient later developed left USN after experiencing a right frontal lesion secondary to interventions for hydrocephalus. Interestingly, resolution of the USN seven months later was explained when MRI findings showed new left SC damage caused by the recurring tumor. Seventeen months later the patient experienced a new right USN when additional tumor growth extended to the right SC. To our knowledge, this report is the only human case demonstrating the Sprague effect whereby visual orientation in the affected field was restored after contralesional collicular damage. Weddell (2004) argued that the right frontal lesion decreased the functioning of the right cortical-subcortical

circuits, including connections to the right SC, resulting in left USN. The subsequent left SC lesion resolved the activity imbalance and visual neglect was thus alleviated. Further, Weddell (2004) argued that the right USN was observed after the right SC lesion due to newly disrupted activity balance. He concluded that cortical and subcortical hemispheric balance is imperative for preservation of spatial attention, and that visual neglect is likely present upon disequilibrium between the cerebral hemispheres. This tantalizing demonstration of the Sprague Effect in humans has yet to be taken further in terms of defining the role of the SC in the manifestation of USN and its treatment.

Inhibition of Return Effect (IOR)

IOR impairment has been described in patients with post-stroke USN (Bartolomeo et al., 1999; Bartolomeo et al., 2001; Siéroff et al., 2007). Healthy controls and individuals without post-stroke USN demonstrate slower response time to an already explored visual stimulus for both right and left sided targets, while those experiencing post-stroke USN respond faster to a second stimulus than to a first for right sided targets. This finding is in keeping with an inability to inhibit attention to already explored visual stimuli in the right hemifield. As for left-sided targets, some subjects with USN show IOR while others demonstrate facilitation by responding faster to the second stimulus. Bartolomeo and colleagues (1999) propose that individuals with right hemisphere stroke may show facilitation rather than inhibition to return to previously explored objects on their right side. They exhibit left USN by maintaining their attention to the right visual hemispace with difficulty attending to new object/events in the contralesional hemispace (exogenous orienting). These findings speak to the complexity and heterogeneity of USN, lend a potential explanation for the inconsistency in effectiveness of current treatment strategies and, are further evidence that, at least for some patients, information from the "unaffected hemifield" is abnormally processed.

The SC play an important role in IOR. This was demonstrated by Sapir et al. (1999) who performed a reaction time test to nasal and temporal hemifield presentations, with or without cueing, in a subject who had experienced a right posterior midbrain hemorrhage. No IOR was observed for stimuli mediated through the right damaged SC (temporal hemifield of the left eye and nasal hemifield of the right eye). In contrast, IOR

was present for stimuli mediated by the left SC (temporal hemifield of the right eye and nasal hemifield of the left eye). While this single subject study points to the implication of the SC in IOR, the subject was not tested for presence of USN, leaving the role of the SC in USN unclear.

Frontal Eye Fields (FEF)

The contribution of the parietal cortex to the control of saccadic eye movements has also been examined in humans with brain lesions (Pierrot-Deseilligny et al., 1991; Braun et al., 1992). In general, there is an increase in saccade latency in those with posterior parietal lesions. For example, a study by Heide & Kömpf (1998) examined saccadic eye movements in individuals post-stroke who exhibited focal lesions in the posterior parietal cortex, FEF, supplementary motor area and dorsolateral prefrontal cortex. Only those with right parietal lesions demonstrated considerably lengthened saccadic latencies which correlated significantly with USN severity. In addition, the same group demonstrated rightward lateralization of visual search, which also was significantly associated with USN severity. The FEF lesion group also showed a rightward bias and a deficit in visual exploration. These data support the notion that the posterior parietal cortex and FEF are critical structures for contralateral hemifield exploration but leaves the contribution of the SC unclear, at least in humans, since only animal studies have shown SC to be imperative for saccade-related activity.

Further attempts at relating IOR to FEF functioning have been made by Ro et al. (2003) using transcranial magnetic stimulation (TMS) of the FEF in healthy adults performing a computerized visual exploration task. When TMS was applied to the right FEF (temporarily interfering with functioning of the region) between the presentation of a cue and the target, IOR to ipsilateral targets was eliminated. In addition, another study looking at IOR and S-cone stimuli (i.e. stimuli invisible to SC) found that this type of stimuli can evoke IOR. However, no IOR was observed for S-cone stimuli when saccadic movements were required in the task (Sumner et al., 2004). This suggests that there is separate collicular and cortical mechanisms for IOR and that the SC may play a role in IOR mediation with FEF interconnection.

Intervention in humans - Does eye-patching for USN tap into the Sprague effect?

Researchers and clinicians have attempted to alleviate USN with visual occlusion, the rationale being to decrease visual input to the ipsilesional hemisphere (Beis et al., 1999; Butter & Kirsch, 1992; Walker et al., 1996; Zeloni et al., 2002; Barrett et al., 2001; Serfaty et al., 1995; Soroker et al., 1994). Visual occlusion of the right eye is based on findings that visual fields are mediated mainly by the contralateral superior colliculus, as determined first by Hubel et al. (1975) in animals. Posner and Rafal (1987) first proposed that visual occlusion should be attempted in patients with USN. They reasoned that if, in a person with left USN, the right eye is patched, the input from the left visual field would stimulate/converge mainly on the right superior colliculus; and less would converge on the left superior colliculus. They went on to postulate that this decrease in left superior colliculus activity would lead to a reduction of the exaggerated attentional shift to the right, thereby alleviating left USN (Fig. 1; Swan, 2001). When eye patching was first proposed, collicular activity and its role in USN had not been investigated. Today, with the knowledge gained from animal studies, the mechanism behind eye-patching and its effect on USN is clearer, but still speculative, as SC activity in relation to post-stroke USN is yet to be investigated in humans.

In the past two decades a number of research teams have attempted to investigate the impact of eye patching in humans with post-stroke USN. Our search revealed four pre-post studies (Butter & Kirsch, 1992; Walker et al., 1996; Serfaty et al., 1995; Soroker et al., 1994), one single subject study (Barrett et al., 2001), and two randomized control trials (RCTs) (Beis et al., 1999; Zeloni et al., 2002). Out of these, one looked at only right eye patching, four at right and left eye patching, and two at half-eye patching.

Briefly, patching the right eye seems to improve performance on USN testing in some studies, but the effects are not consistent across patients or outcomes. Butter and Kirsch (1992) indicated that right eye patching was effective in reducing USN in 11 out of 13 participants. Patients with post-stroke left USN improved on a line bisection test during eye patching and they benefited from a combination of eye patching and left visual stimuli presentations (Butter & Kirsch, 1992). One can surmise that eye occlusion and left visual stimuli presentations amplify the processing of visual stimuli by the right cerebral

hemisphere while reducing the activity of the left thereby alleviating USN symptoms. Overall, however, although promising, these results only provide limited information on the effectiveness of eye patch wear in activities of daily living.

We hypothesize that the benefit of eye patching to alleviate USN can be justified using the temporo-nasal asymmetry of the retino-collicular projections. More precisely, an early neuroanatomical study in cats suggests that the nasal hemiretina, which processes the temporal hemifield, has a stronger input to the contralateral SC than the temporal hemiretina, which receives input from the nasal hemifield (Sherman, 1974). This biased representation favoring the temporal hemifield of the SC has been well documented in different populations such as in newborns (Lewis & Maurer, 1992) and in hemianopic individuals (Rafal et al., 1990). Given that the geniculostriate pathway (through the lateral geniculate nucleus (LGN)) is not yet fully developed in infants, and is inhibited in hemianopic individuals, the retinotectal pathway (through the SC) is the only fully functional visual pathway found responsible for this behavioral asymmetry. More recently, a fMRI study by Sylvester and colleagues (2007) confirmed a strong SC activation during temporal hemifield stimuli presentation compared to nasal hemifield stimuli presentation, although the LGN did not show any significant activation. Another study analyzed temporo-nasal asymmetry and the role of the SC using the redundant target effect (RTE) and color. The RTE is defined as a faster reaction time to two bilaterally presented visual stimuli in comparison to a unilateral presentation and the SC have been identified as its neural mechanism (Bertini et al., 2008; Savazzi & Marzi, 2004). Because the SC are “color-blind” (i.e. do not process S-cone dependent stimuli), a positive RTE is observed only for monochromatic stimuli and it is greater for temporal hemifield conditions in comparison to nasal hemifield stimuli presentations (Dacey & Lee, 1994). Those studies are suggesting that SC are strongly implicated into processing temporal hemifield stimuli presentations.

A study with normal healthy individuals using right and left eye patches in order to isolate the functioning of each SC (Rafal et al.; 1991) demonstrated that reflexive orienting of covert attention was strongly influenced by temporal hemifield stimuli presentations. Because visual information uses both crossed and uncrossed pathways to project to the striate cortices, a right eye patch causes the left SC to receive most afferents

from the left temporal visual hemifield (left nasal hemiretina), and fewer afferents from the left nasal hemifield (left temporal hemiretina).

As for the monocular patching technique, complete occlusion of the right eye in the presence of left USN entails that the left eye processes visual inputs into the temporal hemiretina, projecting to the ipsilesional (possibly hypoactive) SC, as well as in the nasal hemiretina, projecting to the contralateral SC (possibly hyperactive). Consequently, since both SC receive visual inputs, this technique is deemed inappropriate to eliminate competition between the SC and to stabilize SC activity levels. This could explain the low efficacy of monocular eye patching in alleviating post-stroke USN (e.g. Butter and Kirsch, 1992; Walker et al., 1996).

Left eye compared to right eye patching and USN

Patching the left eye may have an impact on left USN severity, although this would not be predicted based on the initial reasoning of Posner & Rafal (1987). Three pre-post studies have explored this question in humans. Serfaty et al. (1995) analyzed the effect of monocular patching in 26 patients with right hemisphere stroke experiencing left USN of near extra-personal space. Half of the participants demonstrated significantly greater scores on the star-cancellation subtest when wearing the right eye patch compared to no eye patch. Eleven did not show any improvement with either patch, while two showed significant improvement with the left eye patch. Similarly, Walker et al. (1996) studied the effects of no eye occlusion versus a monocular right eye patch or a left eye patch in 9 individuals with post-stroke left USN. Only three showed a decrease in neglect when wearing the right eye patch. Soroker et al. (1994) found that only one out of six subjects demonstrated significantly better results on a line bisection task using the right eye patch compared to the left eye patch or no eye patch conditions. Interestingly, three subjects showed significantly better outcomes when the left eye patch was used compared to right eye or no patch conditions.

It is important to note that these studies (Walker et al., 1996; Serfaty et al., 1995; Soroker et al., 1994) have small sample sizes and that the testing of USN related impairment was performed only during a brief period of eye patch wear. It could be that any beneficial effect of eye patching may be cumulative and not immediate. Studies with

prolonged eye patch wear and more promising results are described later in this paper. Moreover, all studies are only testing impairment (i.e. USN presence versus absence) and not analyzing the effect of eye patching on function. They have also used different tests with questionable sensitivity. More specifically, Serfaty et al. (1995) only used the star-cancellation subtest of the Behavioral Inattention Test (BIT) (Wilson et al., 1987) and may have failed to find differences because of a lack of sensitivity of the tool. The BIT is a reliable and valid tool if used and analyzed as a whole (Menon-Nair & Korner-Bitensky, 2004) but the line bisection task used by Soroker et al. (1994) is not standardized and has no known psychometric properties. Given that USN is a complex and heterogeneous disorder, the use of standardized tools with strong psychometric properties is warranted in order to accurately assess the change in USN under different conditions.

Interestingly, a study by Roth et al. (2002) looked at eye patch wear and the effect of eye dominance on spatial attention in nineteen normal individuals. The right eye dominant group demonstrated less far bias when using the left eye patch and the left eye dominant group showed similar results when using a right eye patch. In addition right eye dominant individuals showed significantly fewer bisection errors when performing the task in the right hemispace. The exact opposite was found for the left eye dominant group. In both groups, the non-dominant eye occlusion enhanced performance during midline placement. The authors propose that patching the non-dominant eye seems to amplify the functioning of the dominant attention systems in the contralateral cerebral hemisphere. In other words, if the left eye is patched in a person who is right eye dominant, the attentional system of the left hemisphere is stimulated and the activation system of the right hemisphere is suppressed. With this in mind, right eye occlusion in a person with a right hemisphere stroke and left neglect may inhibit the contralesional brain hemisphere and stimulate the ipsilesional one, creating an activity balance and alleviation of USN symptoms. However, if this person is left eye dominant, occluding the left eye may not provide the same effect, if any at all. When considering these findings in relation to the other findings mentioned earlier, Serfaty et al. (1995) found no relation between eye dominance and eye patch use; Soroker et al. (1994) only used right eye dominant subjects and Butter & Kirsch (1992) did not control for this variable. Given the methodological

limitations of the cited studies, the effect of eye dominance on eye patching and USN is still poorly understood and is calling for further research.

Does the effect of eye patching depend upon the nature of the USN?

Some researchers have suggested that the effects of patching the eye might depend upon neglect symptomatology (i.e. inattention versus action-intentional neglect; Barrett et al., 2001). A single case study (Barrett et al., 2001) of a 49 year-old woman with a right hemisphere stroke and left USN supports the benefit of left, but not right, monocular eye patch wear. In this study, the patient was tested on a computerized line bisection task while wearing either a right or left patch, or no patch. Interestingly, her performance on the task significantly improved with the left patch in comparison to the other testing conditions. Surprisingly, her results were significantly worse with the right patch than with no patch, a contradiction to the initial hypothesis that decreased errors would occur with the right eye patch. It may be that the ratio of contralateral versus ipsilateral visual input to the SC differs from one individual to another or that improvement with left eye patching is indicative of motor-intentional neglect (i.e. not sensory neglect) whereby the left eye patch decreased rightward bias. A very interesting link can be made here with Wilkinson's et al. (2007) study where cats showed only visual/sensory neglect and not motor-intentional neglect in association with SC damage. The rationale behind using the eye patching technique is therefore that an effect on contralesional SC functioning will occur but that the selection of participants with motor-intentional USN, rather than sensory USN, could explain inconsistent findings.

Half-eye patching and USN

Two randomized clinical trials have looked at the effect of half eye patching. The first used randomized controlled trial to explore the effects of monocular and right half eye patch (Beis et al., 1999) with the hypothesis that the latter would result in greater reduction of the USN than the former given that half eye patching eliminates all visual stimuli to the left cerebral hemisphere. With right half eye patching, the right cerebral hemisphere would be stimulated and be more prone to inhibit the left, resulting in a decrease of exaggerated attentional shifts to the right (i.e. left USN). Twenty-two

individuals presenting with left USN in the sub-acute phase post-stroke were tested following a period of eye patch wear on average 12 hours a day for 3 months. At 3 months, only those using the right half patch showed significantly better Functional Independence Measure (FIM) (Granger et al., 1993) scores and more efficient displacement of the right eye into the left visual field than the control group. Based on animal work these results suggest that in situations where only glasses with right half patches are worn, only the ipsilesional SC is receiving retinal input. As suggested by Rushmore et al.'s work (2006), the ipsilesional SC (hypoactive) is stimulated via the right half eye patch wear and the contralesional SC (hyperactive) is inhibited. This results in activity modulation of both SC and assists in alleviating visual neglect.

The efficacy and long term effect of right half eye patch wear for 1 week in patients with left post-stroke USN of the near-extrapersonal space has been investigated by Zeloni et al. (2002). USN symptoms were substantially reduced in the treatment group. Given the design limitations of the studies (e.g. small sample size) the evidence for using a using right eye patch for the treatment of USN is limited, with very little information on carry-over effects in functional tasks. Yet, the findings warrant exploration of this approach since they point to modulated activity of the SC which contributes to the extent of USN symptoms. Moreover, temporo-nasal asymmetry could also explain the positive effect of half eye patching in comparison to monocular eye patching for treating USN. The occlusion of the right half of each eye (i.e. the temporal hemiretina of the right eye and the nasal hemiretina of the left eye) prevents visual inputs from reaching the right SC; the reverse holds, when occluding the left part of each eye. For this reason, the half-eye patching technique appears more appropriate to eliminate competition between the SC and to restore post-stroke activity imbalance. However, when using half-eye patching, a role for the retino-geniculo-striate pathway cannot be excluded since information from the left nasal hemifield is processed via this route. In fact, it is the striate cortex contralateral to the occluded right nasal and temporal hemifields that does not receive visual inputs. Therefore, the beneficial effects of eye patching on USN may be due to imbalanced activation in the SC and/or in the cortex.

It can be speculated that individuals with purely parietal lesions (not involving the extrastriate areas) or those with occipital lesions (not involving striate areas) would

benefit from this treatment strategy given that one of the visual pathways is preserved (i.e. retino-tectal versus geniculostriate). We expect individuals with both pathways impaired to show less USN alleviation with the half eye patching technique. In fact, Beis et al., (1999) and Zeloni et al., (2002) included participants with right cerebral vascular lesions only (i.e. spared extrastriate areas) and showed a positive effect of the half eye patching. In contrast, the eye patching studies (Butter & Kirsch, 1992; Walker et al., 1996; Serfaty et al., 1995; Soroker et al., 1994, Barrett et al., 2001) that included individuals with temporal-parieto-occipital lesions with both visual pathways compromised showed limited improvements in USN following monocular eye patching.

It can also be hypothesized that half eye patching influences IOR and this may explain why in those individuals showing disruptions in IOR, half eye patching reduces or alleviates USN. If a patient with a right-hemisphere lesion is unable to disengage attention from right sided stimuli in order to attend to left sided stimuli, then blocking the right visual hemifield using right-sided half eye patching should inhibit attention towards the right visual hemifield. This can potentially stimulate IOR and alleviate the USN. Furthermore, if the SC are strongly involved in mediating IOR (Sapir et al., 1999), right half eye patching will increase left collicular function and by doing so enhance IOR to right-sided events during visual search. Until the role of the SC in USN is clearly defined, these are exciting but untested assumptions.

Prisms Adaptations and USN – Is the SC implicated?

Prism adaptation is another treatment strategy for USN that has yielded some success. The use of prisms results in an optical deviation of the visual field to the right side; such that the observed objects appear further to the individual's right side than they really are. For example, in a pseudorandomized study, Serino et al. (2009) applied prismatic goggles deviating visual field 10° rightwards (2 weeks for 30 minutes) to participants with left post-stroke USN. The treatment group significantly improved from baseline on USN testing compared to the control group who was treated with neutral goggles. The experimental group of the Nys et al. (2008) RCT (4 days for 30 minutes) also showed improvement; however, this was not seen in all outcome measures. Interestingly, Rossi et al. (1990) intervention group (4 weeks wear during all daily activities) showed improvement as compared to the control group on USN impairment

outcome measures but not in activities of daily living performance. Rossetti et al. (1998) intervention group (5 minutes while performing a repetitive reaching-to-target task) also demonstrated significant improvements as compared to the control group on USN outcome measures immediately after and two hours post-testing.

The mechanisms underlying the effect of the prism adaptation are not yet clearly defined. It is proposed that patient's subjective notion of "straight ahead" is shifted after the use of prisms (Redding and Wallace, 1996). However, despite having an effect on the exploratory upper extremity motor behaviors (Rossetti et al, 1998), and shift in exploratory eye movements (Ferber et al., 2003); the use of prisms adaptations do not change the perceptual bias or the lack of awareness for the right sided hemispace (Ferber et al., 2003). We suggest that use of prisms as treatment strategy for USN is more of a compensatory method rather than a remediation/recovery strategy. When using prisms for left post-stroke USN, the left SC is stimulated and right SC is understimulated leading to no changes in levels of activity and USN alleviation by that mechanism. More precisely, given that visual field is displaced to the right side, the individual mostly perceives right temporal and right nasal fields. In terms of the temporo-nasal asymmetry, it means that the left superior colliculus is strongly stimulated and the right is understimulated. This might explain the persisting perceptual bias despite the changes in motor behaviors. In addition, it is proposed that prism adaptation may have more effect on the dorsal network (visually guided behavior) than the ventral network (perceptual processing) (Danckert & Ferber, 2006). Given that the dorsal network is structurally intact but presents with changes in evoked potentials, and the ventral network is structurally damaged in individuals with post-stroke left USN (Corbetta et al., 2005), the prisms adaptation may influence the dorsal network functioning to some extent; but have no effect on the ventral structurally damaged network. Therefore, one possibility might be that individuals with post-stroke USN are compensating for their deficit using the prisms, rather than showing recovery of perceptual processing. This is also reflected in the above presented intervention studies where results are not consistent across all neglect tests, no significant functional improvement is noted (e.g. Rossi et al. (1990)), and little long-term effects of the prisms adaptation use are described.

DISCUSSION

Three to five million new patients with stroke will suffer from neglect each year worldwide. Given the magnitude, persistence, heterogeneity, and disabling effects of this disorder, a better understanding of the underlying mechanisms of USN is critical for diagnostic purposes and for enhancing intervention effectiveness. The brain mechanisms of spatial inattention need to be clearly identified as many questions remain unanswered. There are now excellent opportunities for interdisciplinary collaborations to help achieve a better understanding of USN and to develop individualized treatment strategies suited to the symptoms observed. This paper reviewed the work on the role of the SC in USN drawing from animal and human research and an attempt was made to pave the way for future research in that area.

The SC are anatomically connected to the posterior parietal cortex. This pathway is clearly involved in USN presentation and alleviation following a brain lesion in animals. Attention in humans is mediated, at least partly, by this pathway as well. Most human imaging studies indicate the temporal-parietal junction as the critical lesion site for USN. One can speculate that the neural projections from the parietal area to the SC are disrupted in post-stroke USN; resulting in the well known clinical presentation. The opponent-processor theory and the animal work behind it support the implications of the parietal cortex and the SC in USN. Similarly, exogenous orienting deficit and the lack of IOR appear to be a result of the same parieto-collicular/temporo-parieto-collicular pathway disruption. In addition, the interconnection of the FEF and the SC, mediating saccadic eye movements and IOR are also suggested to be implicated in the USN presentation. These theories are not necessarily mutually exclusive and can co-exist. For instance, the collicular imbalance in the opponent-processor theory can very well inhibit the parieto-collicular pathway and result in absence of IOR and exogenous orienting deficits seen in USN. The common features remain the implication of the parietal cortex and the SC. Given the abundant literature on the role of the SC in animal USN, and lack of studies directly linking SC activity to USN using the opponent-processor theory, the IOR effect and the FEF connection, the present review suggests that SC involvement in human USN post-stroke needs to be investigated.

In spite of significant progress in the development of new and more effective interventions in the past ten years, the evidence regarding long term stability and functional outcomes is still unclear. Overall, the human work on eye patching and USN recovery suggests that half eye patching may be beneficial to alleviate visual neglect. The hypothesis that with half eye patching the ipsilesional SC is stimulated and the contralesional SC is inhibited given the temporo-nasal asymmetry in the retino-collicular projections is certainly a reasonable one. If parallels can be drawn between the animal studies on SC activity levels, right half eye patching likely blocks all visual input to the left brain hemisphere and the left SC. In this case, the ipsilesional right SC is stimulated and the contralesional left SC is under-stimulated, creating an activity balance between both, hence leading to reduced USN. However, eye patching as an intervention strategy needs to be studied in greater detail with focused attention on the following issues: 1) neglect subtypes and benefits of patching; 2) differential effects of patient characteristics (e.g. presence versus absence of IOR); 3) therapy refinement according to eye dominance and other patient-specific variables; 4) main outcome measures to be used initially to identify USN accurately followed by assessments that have an ability to detect change in USN severity; 5) optimal duration and intensity of treatment; and, 6) influence of treatment on the parieto-collicular pathway of attention (i.e. use of temporal field presentations instead of nasal field presentations during treatment).

Similarly, the prisms adaptation intervention strategy appears promising. However, we suggest that it is a compensatory technique rather than a remediation strategy with little effect on SC pathway rehabilitation for USN. Overall, the underlying mechanism of this method is still unclear and more research is indicated to improve the use of this technique. Currently, rehabilitation professionals are lacking USN remediation strategies. It is worthwhile to advance stroke rehabilitation research beyond compensatory techniques and focus on brain mechanisms recovery for optimal and more efficient rehabilitation results.

Most importantly, what remains to be studied is SC activity levels in humans with and without USN and how to use this information to design effective treatment methods to address various USN types. These new research directions will help refine

rehabilitation strategies aimed at reducing the negative effects of post-stroke neglect by taking into account the attentional impairment and its pathophysiology.

In conclusion, modern technology enables the study of the influence of the SC in USN as never before. This provides researchers and clinicians with an exciting opportunity to examine the fundamental mechanism of SC in patients with post-stroke USN. Ultimately, a clearer understanding of the mechanisms behind various forms of post-stroke USN will lead to more effective interventions and a better understanding of why current treatments work for some patients and not others.

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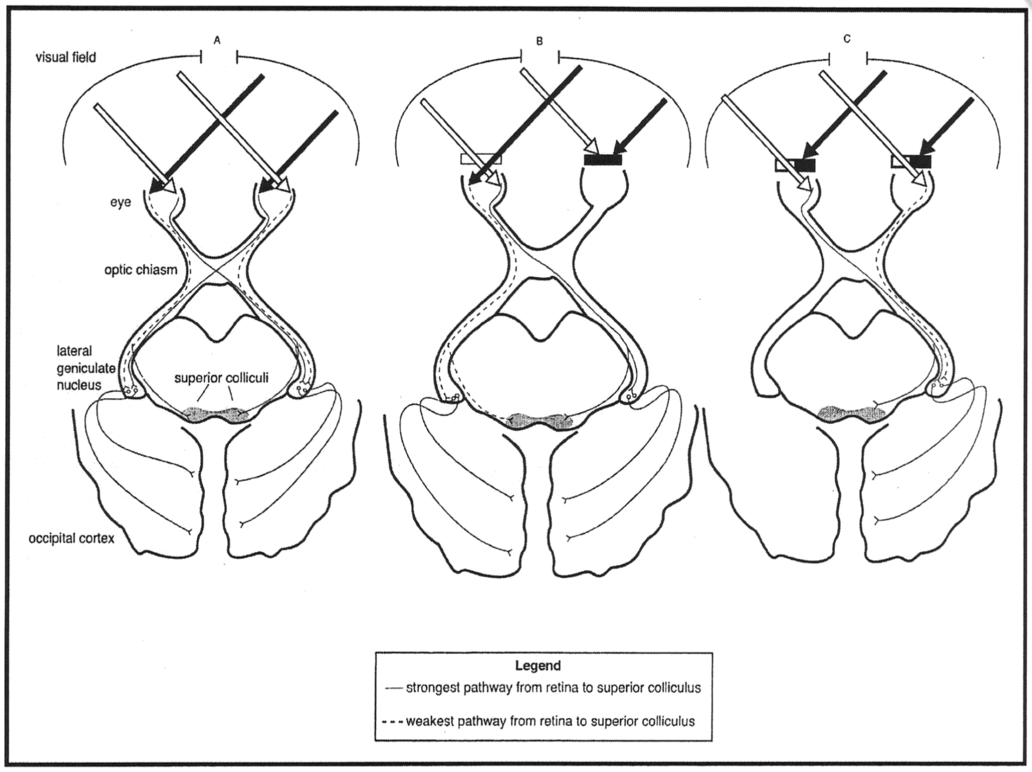

Figure 4.1: SC Activity and Eye Patching

A. In normal healthy individuals, the visual input from the retina mainly converges on the contralateral superior colliculus.

B. When the right eye is covered with an eye patch, it is the right superior colliculus that receives most of the retinal input. In a stoke individual with left USN (right brain hemisphere lesion), the right superior colliculus is more stimulated than the left, generating mostly leftward eye saccades.

C. When the right half of each eye is occluded, all the visual retinal input is converging on the right superior colliculus. In a stoke individual with left USN (right brain hemisphere lesion), the right superior colliculus is stimulated, generating only leftward eye saccades.

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5. INTEGRATION OF MANUSCRIPT 1 AND 2

The very recent and novel information gleaned from the animal models should be used to test hypotheses and further expand our knowledge base regarding USN in humans. While SC activities in orienting attention have been analyzed in animals, clearly, there is a gap in the literature on the involvement of the SC in humans with USN due to stroke. The animal research on this topic is extensive and as identified in the first manuscript, it suggests that the activities of the SC, in connection with different brain areas such as the parietal cortex and the frontal eye field, play an important role in USN presentation and alleviation. Ultimately, a clearer understanding of the mechanisms behind various forms of post-stroke USN will lead to more effective interventions and a better understanding of why current treatments work for some individuals with stroke and not others. With this goal in mind, the second study was designed. The study described below attempts to draw parallels and clarify, in humans, some of the findings that arise from the animal work as well as studies on the SC in brain disorders other than stroke. Using available technologies, researchers and clinicians have an exciting opportunity to examine the fundamental mechanism of SC in individuals with post-stroke USN. More precisely, the Spatial Summation Effect (SSE) paradigm, in conjunction with achromatic (i.e. black/white stimuli) presentations has been used in the past to analyze SC activity in individuals with other conditions than stroke. Using this paradigm will allow a better understanding of the brain structures and mechanisms important to visual attention in the hemisphere contralateral to the lesion. This should assist in sorting out mechanisms underlying various forms of neglect, which in turn could lead to rational therapy development based on plausible neurobiological mechanisms that can account for numerous USN subtypes.

6. SUPERIOR COLLICULI INVOLVEMENT IN POST-STROKE UNILATERAL SPATIAL NEGLECT

6.1: MANUSCRIPT 2

Superior Colliculi Involvement in Post-Stroke Unilateral Spatial Neglect: A Pilot Study

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ABSTRACT

Background: The neural mechanism of unilateral spatial neglect (USN) is unclear. The superior colliculi (SC) are suggested to be involved in USN presentation. The spatial summation effect (SSE), where reaction times to bilateral stimuli are faster than to unilateral, is a behavioral index of SC function. We determined the feasibility of investigating SC contribution in post-stroke USN using SSE in three groups.

Methods: Seven participants with left near-extrapersonal space USN (USN+) following right hemisphere stroke, 10 without (USN-) and 10 controls were tested under binocular/ monocular (right eye patched) conditions while responding to unilateral/bilateral stimuli.

Results: Control and USN- groups completed the SSE paradigm. Most USN+ participants were unable to initiate the SSE paradigm due to poor visual fixation and demonstrated higher contrast sensitivity for left-sided stimuli. Controls showed SSE (under both viewing conditions), the USN- showed abnormal SSE: reaction times to bilateral stimuli were faster than to unilateral-left, but not to unilateral-right, stimulus (under both binocular/monocular conditions).

Conclusion: This first study investigating SC contribution in post-stroke USN using the SSE identified higher contrast sensitivity to left-sided stimuli and poor fixation in the USN+ group. These findings suggest avenues for future research leading to novel interventions.

KEY WORDS

Unilateral spatial neglect, spatial summation effect, stroke, superior colliculi, eye patching, fixation.

INTRODUCTION

Visual-spatial disorders are common following a stroke. One of the most serious is unilateral spatial neglect (USN) experienced by 23% to 46% of individuals with stroke (Jutai et al., 2003). USN is defined as the inability to orient to, respond to, or report stimuli occurring in the contralesional visual hemispace, when such failure cannot be attributed to sensory or motor deficits (Heilman & Valenstein, 1979). USN can lead to significant disability and activity restriction (Paolucci et al., 2001) such as an increased risk of falls (Mackintosh et al., 2006), long rehabilitation stays, low levels of independence post discharge, and a high risk of poor functional outcomes (Paolucci et al., 2001). Unfortunately, despite over 60 years of research on treatment techniques, there remains limited evidence for the effectiveness of USN intervention strategies in terms of improving functional outcomes and reducing disability (Luaute et al., 2006; Bowen & Lincoln, 2007). This failure may be explained in part by the fact that USN is a heterogeneous disorder and that its neurophysiology and neuroanatomy remain unclear. For instance, different brain areas such as the right parieto-temporal junction (Bartolomeo et al., 2007), angular gyrus, right inferior parietal lobe, parahippocampal region (Mort et al., 2003), and right superior temporal cortex (Karnath et al., 2004) have all been implicated in post-stroke USN. Thus, while most of the intervention literature treats USN as a single global disorder (Pierce & Buxbaum, 2002) its heterogeneity may require selective treatment approaches according to lesion location and clinical presentation.

To generate new and more effective treatment strategies that take USN heterogeneity into consideration requires an in-depth understanding of the underlying mechanism(s). To date, basic neuroscience research using animal models has provided mounting evidence that the superior colliculi (SC), with their interconnections to the posterior parietal region, are critical for processing directed attention (Facteau et al., 2004; Mesulam, 1999; Lomber et al., 2001; Payne et al., 1996; Lomber et al., 1996; Lomber et al., 2002; Sherman, 1977; Wallace et al., 1989; Wilkinson et al.; 2007; Rushmore et al. 2006). Many of these animal studies have demonstrated that a unilateral SC lesion causes USN of the contralesional hemispace and that introducing an additional lesion in the remaining intact SC leads to USN alleviation, suggesting USN was the result of an imbalance in

SC/parietal activity that was normalized by the subsequent lesion. This contribution of the SC in USN has been further substantiated in animal studies by Rushmore et al., 2009 who found an imbalance in neural activity between the colliculi following posterior parietal lobe cooling deactivation. After parietal cooling, the ipsilesional SC was hypoactive and the contralesional SC showed hyperactivity, thereby suggesting that there are both cortical and subcortical circuits involved in orienting that appear to work in a mutually inhibitory network. In addition, the SC are found to be interconnected with the frontal eye fields (FEF), a region involved in the control of voluntary and reflexive saccadic eye movements (Fries, 1984; Stanton et al., 1988; Lynch et al., 1994; Sommer & Wurtz, 1998; Crapse & Sommer, 2009; Barbas & Mesulam, 1981; Gold-man-Rakic & Porrino, 1985). This interconnection is also thought to influence shifts in visual attention in monkeys (Keating & Gooley; 1988; Munoz & Istvan, 1998). Further, the involvement of the SC in USN is suggested by a case studies of the Sprague effect in which USN due to brain damage in a person was ameliorated following an additional midbrain/superior colliculus lesion (Weddell, 2004). While SC involvement thus appears plausible in humans post-stroke, further systematic investigation of the SC contribution to USN presentation and alleviation is needed.

The Spatial Summation Effect (SSE) in combination with eye patching can be used as a simple technique to provide new insights into SC activity in post-stoke USN. The SSE is a phenomenon in which the reaction time to two bilaterally presented stimuli is faster than the reaction time to a single stimulus (also called the “redundant target effect”; Savazzi & Marzi, 2004; Leh et al., 2006). One model (based on the cumulative frequency distribution of reaction times (RTs)) proposes that the SSE reflects the convergence of processing from both stimuli, resulting in neural co-activation and a speeded response as determined using the Miller’s Inequality Test (Miller, 1992). Using this model, the involvement of the SC in this neural summation was supported by Savazzi & Marzi (2004) who compared the performances of healthy young adults (n=8) to those of individuals with complete sections of the corpus callosum (n=2). Using a computer-based reaction time test, the participants were asked to respond to a seen stimulus (small squares shown 5.5° to the right and/or left of the middle fixation point) as quickly as possible by

pressing a computer button with their dominant hand. Because achromatic (i.e. black/white) stimuli are visible to the SC while short wave sensitive cones (S-Cones) that are responsible for chromatic (i.e. color) perception in the short wave (e.g., purple) range do not project to the SC, the investigators compared RTs that contained a pair of purple stimuli to those containing either a pair of white stimuli or a mixed pair of white and purple stimuli. In healthy individuals, RTs to bilateral stimuli presentations were significantly faster than to unilateral presentations with both white and purple stimuli. However, the neural co-activation effect (based on frequency of distribution of RTs) was only seen with white stimuli, suggesting that SC involvement was required for the effect. In addition, the same pattern of results as in normals, was seen in individuals with callosotomy, suggesting that hemispheric connections were not required. Thus, since neural co-activation is eliminated when visual input to the SC is minimized by the use of short wave monochromatic stimuli; these results suggest that the neural summation of bilateral stimuli presentations in individuals without a corpus callosum and in healthy controls can be mediated subcortically through the SC.

A similar study design investigated the SSE with presentations of achromatic and chromatic stimuli in hemispherectomized subjects with and without blindsight (i.e. the ability to respond to visual stimuli without having any conscious visual experience), and normal age-matched healthy individuals (Leh et al., 2006a). In the control participants, the SSE was observed for either bilateral achromatic and chromatic (short wave) stimuli presentations. However, hemispherectomized individuals with blindsight showed the spatial summation effect with achromatic stimuli only. No effect was observed with chromatic stimuli. These findings are in keeping with the possibility that visual information from the blind hemifield is processed via the SC as the hemispherectomized individuals demonstrated the SSE only with achromatic stimuli. The hemispherectomized individuals without blindsight did not demonstrate the SSE with either achromatic or chromatic bilateral stimuli. A subsequent study by Leh et al., (2006b) used diffusion tensor imaging (DTI) tractography on the same individuals as in the earlier study. Hemispherectomized individuals with blindsight showed an ipsilateral and contralateral connection from the SC to the visual association areas, primary visual areas, prefrontal

areas and to the posterior part of the internal capsule. In contrast, those without blindsight did not show any projections from the SC on the hemispherectomized side (Leh et al., 2006b).

A recent study by Müller-Oehring and colleagues (2009) provides some of the first evidence that individuals with USN exhibit the SSE. Eleven individuals with acute near extrapersonal USN and 11 with hemianopsia following a stroke, tumor resection, head injury, or aneurysm were studied. The SSE paradigm consisted of green circle presentations in 9 blocks of 50 trials each. Stimulus conditions included single (left or right), bilateral (left and right), and paired (two left or two right) visual field presentations. Individuals with hemianopsia did not demonstrate the SSE. In contrast, individuals with USN did show the SSE with faster reaction times to paired bilateral presentations (481ms $\pm$ 99ms) compared to unilateral single presentations (489ms $\pm$ 97) (SSE=7.5 ms, Z=-2.3, $p<0.02$). These results suggest that processing of contralesional stimuli is present even in the neglected field. While this study provides interesting information on the SSE in those with USN, the contribution of the SC to USN remains unclear as only green color long-wave (520-570 nanometers) stimuli were used.

The SSE paradigm with achromatic versus S-cone stimuli presentations is an interesting avenue by which an estimate of the contribution of the SC to visual processing in individuals with USN can be attempted. In addition, monocular eye patching can serve to isolate the contribution of the SC. Specifically, it is now generally well accepted that visual input to the SC comes mainly from the contralateral visual field. Thus it is proposed that when using a right monocular eye patch, the input from the left peripheral visual field would stimulate/converge mainly on the right SC with considerably less information reaching the left SC (Posner & Rafal, 1987) (Swan, 2001). If, as suggested by Rushmore (2009), the ipsilesional SC is hypoactive and the contralesional SC is hyperactive following a stroke in the posterior parietal lobe that causes neglect, one can speculate that when the right eye is patched, the activity of the contralesional (i.e. left) SC would decrease, allowing for relatively increased activity of the ipsilesional (i.e. right) SC, resulting in a reduction in symptoms of neglect (Swan, 2001). Given that the SC are

involved in the SSE effect with achromatic stimuli, if the SC activity is abnormal or absent after a stroke, it is speculated that no SSE will be observed using achromatic stimuli. However, if SC activity is hypothesized to balance out with eye patching, it is also hypothesized that applying a right eye patch may lead to normal SSE with achromatic stimuli. In fact, visual occlusion using eye patching can improve USN severity (Beis et al., 1999; Butter & Kirsch, 1992; Walker et al., 1996; Zeloni et al., 2002; Barrett et al., 2001; Serfaty et al., 1995; Soroker et al., 1994).

We hypothesize that with a right monocular eye patch and a SSE paradigm, it is possible to identify the contribution of the SC in mediating visual information from the neglected and the non-neglected hemifields. Therefore, a paradigm including no eye occlusion (binocular viewing condition) and right eye patching (monocular viewing condition), combined with testing for the presence of the SSE using achromatic presentations should provide insights to further clarify the involvement of the SC in post-stroke USN. To our knowledge, this paradigm has never been used in this patient population. Therefore, this pilot study explored the mechanisms behind post-stroke USN, with an emphasis on the contribution of the SC. The specific objectives were: (1) to determine the presence of and compare the SSE effect and presumed SC involvement in 3 groups: a) individuals with left USN of near extrapersonal space following right hemisphere stroke; b) subjects without USN of near extrapersonal space following a right hemisphere stroke; and, c) healthy individuals with no history of stroke using the SSE and achromatic (black/white) stimuli; and, (2) to examine the effects of monocular patching on the SSE in these groups. In the course of the study it became clear that individuals with USN+ had extreme difficulties controlling their eye movements. Thus, a secondary analysis of eye movement control during the fixation tasks was conducted.

METHODS

Participants

The goal was to accrue three groups of individuals as described above. Presence of right hemisphere middle cerebral artery stroke was based on the brain imaging report, neurological examination, and/or medical chart. Inclusion criteria for all groups were:

being 18 years of age or older; English and/or French speaking; right-handed and able to use their right hand to press a mouse button; sufficient cognitive status (Mini-Mental State Examination (MMSE) score of 23/30 or more (Lopez et al., 2005), and comprehension sufficient to understand testing instructions as determined by the treating occupational therapist. Potential participants with a history of other neurological diseases including a brain tumor, Parkinson's disease, Multiple Sclerosis, or previous stroke (as determined by a review of the medical chart for those with stroke and an interview for the control individuals), were not eligible. Also, individuals with any primary visual impairment (e.g. disease of optic nerve, retina or ocular media) that impedes normal or corrected-to-normal acuity and/or presence of visual field deficit, as determined by interview, were excluded.

Sample Size Consideration

To address the main objective, that is, to analyze within subject variations in response time according to bilateral versus unilateral stimuli, and monocular versus binocular viewing conditions, a sample size formula for matched pairs was used (Dupont & Plummer, 1990) with a difference score of 75 ms, a within group standard deviation of 40 ms and a Type 1 error of p=.05. These estimates were generated based on the few existing studies that used the SSE paradigm with other neurological patients (Savazzi & Marzi, 2004; Leh et al., 2006). With 4 individuals per group it is possible to reject the hypothesis that this response difference is zero with probability (power) of 0.8. However, given that there were two experimental groups in the present study (i.e. USN- and USN+ groups), that there is a possibility of potentially larger within stroke variations in response time as compared to healthy controls, it was deemed prudent to recruit 10 individuals per group.

Measures and Instrumentation

Socio-demographic and Stroke-related Variables Measurement

A chart review and short interview with the participants from the USN- and USN+ groups were used to collect the socio-demographic data (age, sex, level of education) and stroke-related variables (lesion location, time since stroke and type (hemorrhagic or ischemic). Socio-demographic information from the control participants was elicited during pre-assessment interviews.

USN Measurement

USN of near extrapersonal space was measured using the Line Bisection Test (LBT) (Schenkenberg et al., 1980) and the Star Cancellation Test (SCT) (Wilson et al., 1987) given their strong psychometric properties (Jehkonen et al., 1998; Bailey et al., Menon-Nair & Korner-Bitensky, 2004). Two USN tests were administered given research studies indicating improved detection of USN when more than one test is used (Lindell et al., 2007). Classification of USN was determined as a positive score (indicative of USN) on one or both of the tests. A positive score on the LBT corresponds to a right deviation equal or more than 0.6 millimeters (Schenkenberg et al., 1980). A positive score on the SCT corresponds to a star detection ratio (i.e. number of cancelled small stars on the left side of the page over the total number of cancelled stars) of equal or less than 0.46 (Wilson et al., 1987).

Pre-Testing Feasibility Assessment

Computerized tasks were generated using an Intel Pentium M processor 1500MHz with 1024 by 768 pixels spatial resolution. Gamma correction of the images and display contrast was performed using an Eye-One Display2 colorimeter (from Gretagmacbeth). The following requirements were evaluated pre SSE testing as these skills were needed to apply the SSE paradigm:

1. ability to achieve sufficient eye movement control to be able to follow a moving target in order to calibrate the right and left pupil position with the point of gaze using the TM3 (Eye Tech Digital Systems) eye tracker device. A 16-point calibration was used and involved a single circle moving to 16 different positions on the screen. The device ends the task automatically when the participant's gaze at each of the circles is captured. When the participant fails to direct his/her gaze to the appearing circles, the task is interrupted by the program. During assessment, when this occurred, the instructions were repeated and calibration was restarted. This process was performed up to 3 times, after which a "failure to calibrate" was given.
2. ability to complete the contrast sensitivity task in order to obtain contrast sensitivity scores for stimuli presentations to the right and left of midline in order to equate the achromatic contrast of the right and left stimuli presented during the SSE testing. This task was included in the protocol based on findings that contrast sensitivity for

stimuli presented in the hemispace contralateral to the lesion is decreased in individuals with post-stroke USN (Angelelli et al., 1998). Given that only right-handed individuals were recruited for this study, contrast sensitivity for the dominant, right-sided stimuli was set to 50. The contrast sensitivity for the left stimuli was calculated using a task where two gabor patches of different contrast intensities were presented at 5° to the right and 5° to the left of the midpoint of the screen. The participant was asked to select which stimulus was darker using a mouse button. Stimulus contrast was decreased after two accurate responses and increased after one wrong response. This corresponded to one reversal. The contrast was decreased by 50% upon the first reversal and by 25% thereafter. The task was terminated after 6 reversals and the contrast for the left stimulus was calculated as the mean contrast of the last five reversals. Failure to accomplish the contrast sensitivity task was determined when the participant gave only "right-sided" responses repeatedly until the end of the task, and/or reported "not seeing the left-sided figure" when he/she was queried regarding why the response was always "right-sided". It is to be noted that even if the participant provided only one left response, the contrast sensitivity score was still computed for the left-sided stimulus. If the participant was unable to complete the contrast sensitivity task, the testing session was terminated, that is, the SSE paradigm was not initiated.

3. ability to fixate a midpoint on the screen *prior* to initiation of the SSE testing paradigm. This is defined as the participants' ability to control their eye movements in order to fixate inside a clearly delineated circle (11.5 centimetres in diameter) located in the middle of the computer screen for a 2-second period. As shown in Figure 6.1, a white cross that moves in unison around the screen with the participant's eye movements was used in this task. If the participant was able to complete the task, the SSE paradigm was initiated automatically by the software program. If the participant was unable to focus inside the circle area, he/she was given a 10 minute fixation training session and encouraged to fixate on the 11.5 cm in diameter circle using the white cross.
4. extent of fixation on a midpoint on the screen *during* the SSE testing paradigm. This was measured quantitatively by the software program that recorded the number of

missed fixations to the left, right and bilateral stimuli during the SSE testing. A missed fixation is defined as the individual's gaze being outside of the 11.5 cm circular central area during the actual response to the stimulus. If during a response to the stimulus there was a missed fixation, this trial was not replaced by a new trial. During administration of the SSE paradigm, a static black cross (0.5cm by 0.5 cm) indicated the midpoint of the screen and was present during the entire testing. As shown in Figure 6.2, the white cross that moved with the individual's eye movements was also present so as to provide a cue to the participant to remain focused on the midpoint of the screen. If an individual missed 40% or more of the trials within the run, this run was excluded for the analysis.

Measurement of the SSE under Monocular and Binocular Viewing Conditions

To compare SC contribution using the SSE paradigm and the effect of binocular versus monocular viewing conditions on SC activity, the presence versus absence of the SSE under both binocular and monocular conditions was determined. The presence of the SSE was defined as statistically significant faster reaction times to bilateral stimuli than to unilateral left and right stimuli. The SSE paradigm was adapted from the protocol used by Leh et al., (2006). The SSE was initiated automatically when the individual completed the fixation task described above. In the SSE task, the stimuli consisted of achromatic black/white gabor patches with a right stimulus contrast sensitivity set constantly at 50% and left stimulus contrast sensitivity as determined by the contrast sensitivity task (see above). One SSE testing session consisted of 12 runs where 6 runs were performed under the binocular viewing condition and 6 runs were performed under the monocular viewing condition; order of conditions was randomized. Each run consisted of 60 trials with visual stimuli and 20 trials with null presentations (exactly the same procedure except no stimulus is presented) in random order as predetermined by the computer program (Leh et al., 2006): 20 stimuli at 5^o to the right of the midpoint on the screen; 20 stimuli at 5^o to the left of the midpoint; 20 bilaterally at 5^o to the right and to the left of the midpoint simultaneously and 20 null presentations was presented with a randomized inter-trial interval to either 2000, 2500 or 3000 ms. The stimuli(us) on each trials were presented for 250 ms. Each trial with null presentation also lasted 250 ms.

Procedures

Ethics approval was obtained from the Institutional Review Boards of the McGill University Health Center (MUHC) and from the *Centre de recherche interdisciplinaire en réadaptation* (CRIR), Montreal, Quebec, Canada. Participants with stroke were recruited from a multi-site acute care university teaching hospital in Montreal, Quebec, Canada and an inpatient post-stroke rehabilitation site. Control individuals were recruited from other sources including a community residence for autonomous older individuals and word of mouth.

Testing Procedures

Testing lasted 60 to 90 minutes and most often was completed in one session. For individuals with stroke, the data collection began with the administration of the LBT (Schenkenberg et al., 1980) and SCT (Wilson et al., 1987) to identify presence of USN. Next, the pre-SSE paradigm tasks were administered including the eye tracker calibration task and contrast sensitivity task. The participant was positioned in front of a table and aligned with respect to a midpoint using his/her sternum as the reference point. During testing the computer screen was located approximately 70 cm from the upper body with the mouse positioned for right hand use. Standardized verbal instructions were provided. To begin, the eye tracker was calibrated as described earlier. Next, the contrast sensitivity task was completed, with the participant indicating whether the right or left stimuli (i.e. achromatic gabor patches) was darker. Finally, the fixation screening task was administered. If the participant was able to keep both eyes focused inside the clearly illustrated 11.5 cm circle for 2 seconds, the SSE task was automatically initiated. If the participant was unable to fixate, he/she was given a 10-minute fixation training session with the evaluator providing verbal and visual feedback and encouragement.

During the SSE task, the participant was given standardized instructions to respond by pressing the mouse button with the right hand as quickly as possible to the stimuli, either one or two round figures, that appeared on the screen while focusing on the middle of the screen by maintaining the white cross as close as possible to the black cross (Figure 2). A short practice session under the binocular condition was initiated in which 10

presentations of all possible combinations of stimuli (i.e. right, left, bilateral) were shown. If the participant was unable to follow the instructions, still did not understand the procedures following the practice session, or could not fixate to criterion following fixation training, the session was terminated.

DATA ANALYSIS

Statistical computations were carried out using SPSS 17.0.3 (SPSS for Windows, 2001; Levesque, 2007).

Comparing Main Outcomes on the SSE paradigm

Within group analysis was carried out to determine presence versus absence of SSE where the mean reaction times and standard deviations were calculated for the 120 left, 120 right, and 120 bilateral stimuli presentations first for the 6 runs under the monocular condition, and then for the 6 runs under binocular conditions. These results were then entered into two (one for controls and one for the USN- group) separate 3 x 2 repeated-measures analyses, the Generalized Estimating Equations (GEE) using the type of stimulus (right, left or bilateral) and viewing condition (binocular or monocular) as within subject factors (Ballinger, 2004). The GEE analysis was used because the assumptions for the use of a repeated-measures ANOVA were violated. It is important to note that it was not possible to analyze the SSE data using GEE for the USN+ group given that only 2 individuals with USN completed the SSE testing. Rather, the data for these 2 participants are discussed using descriptive statistics.

Comparing Prerequisite skills (Feasibility) on the SSE paradigm

To compare the proportions per group who were able to successfully complete the calibration task, the contrast sensitivity task, and the pre-SSE fixation task, the Mann-Whitney U test (Corder & Foreman 2009) was performed to compare performance for control vs USN-; control vs USN+; and USN- vs USN+. Between groups differences in the number of missed fixations were computed as follows: the number of missed fixations for binocular and monocular conditions each was computed for each individual and categorized according to the following: the number of missed fixations under binocular condition is greater than the number of missed fixations under monocular condition; the

number of missed fixations under binocular condition is smaller than the number of missed fixations under monocular condition; and, the number of missed fixation under binocular condition is equal to the number under monocular condition. Given that only 2 USN+ participants completed the SSE paradigm, their results regarding number of missed fixations are presented using the raw data.

RESULTS

Within the study time frame (from March 2008 – September 2009), 9 USN+, 10 USN– participants, and 10 healthy control individuals who met the inclusion/exclusion criteria were recruited. Of these, only two potential USN+ participants (as indicated by the medical chart and treating therapist) refused to participate prior to the scheduled testing session. Therefore, the final group sizes were: 7 USN+, 10 USN- and 10 control individuals: 17 males and 10 females. The mean age of control participants was 74.00 ± 8.86 years, 58.29 ± 11.20 years for the USN+ group; and, 61.10 ±17.51 for the USN- group. The educational level of the study groups ranged from 10.90 years to 13.30 years. In addition, the cognitive status of the USN- and the USN+ groups, as per the MMSE score, was 28.40 ± 2.22 and 27.14 ± 2.19, respectively. The mean time since stroke in the USN+ group was 23.43 ± 18.28 days and 37.70 ± 28.61 days for the USN- group. In terms of lesions locations, the USN- group included 4 individuals with fronto-parietal lesions, 2 individuals with frontal lesions, 1 individual with right thalamic lesion, and 3 individuals with right lacunar lesions. In the USN+ group, 6 out of seven individuals presented with right fronto-patietal lesions, and 1 individual with a parietal lesion.

During testing of the first two control participants (ZT and KZ), the SSE paradigm was attempted with each run including 10 presentations of each stimulus, rather than 20, and participants were asked to complete 10 binocular and 10 monocular runs (rather than 6 and 6). However, given that prior to each run there is a delay while the program is set up, the testing was found to be burdensome for the participants. Thus, in subsequent testing the number of presentations per run was increased leading to less waiting time for participants and more efficient testing. Therefore, participants ZT and KZ were included

into the demographic data analysis and in the analyses of the pre-testing feasibility, but excluded from the analyses related to SC contribution.

Overall, six out of 7 USN+ individuals completed the calibration task compared to the 100% of the control (Z=0.488, p=0.313) and 100% of the USN- participants (Z=0.488, p=0.313). Five out of 7 USN+ individuals completed the contrast sensitivity task compared to the 100% of the control (Z=0.976, p=0.165) and 100% of the USN- participants (Z=0.976, p=0.165) (see Table 6.1).

The mean contrast sensitivity to left stimuli was 49.18 ± 3.9% for the controls, 52.74 ± 3.85% for the USN- group, and 72.30 ± 26.63% for the 5 in the USN+ group who completed the task. A score higher than 50% indicates that stimulus presented on the left needs to be darker for the individual to perceive it as being equal to that on the right.

The following results address the primary study objective comparing the SC contribution using the SSE paradigm with achromatic stimuli and the effect of binocular versus monocular viewing conditions on SC activity in three groups. The response times for the control and USN- groups under binocular and monocular conditions are shown in Table 6.2. In the control group, there was a significant main effect of type of stimulus but not of viewing condition such that mean reaction time to bilateral stimuli, under both binocular and monocular conditions, was significantly faster ($p<0.001$), than to unilateral left stimuli and unilateral right stimuli confirming the presence of a SSE in this group. In addition, the overall reaction times were similar under the monocular (916.57 ± 34.05) and binocular (871.59 ± 20.56) conditions (p=0.449); no interaction between viewing condition and reaction times to the three stimulus types (i.e. no interaction between viewing condition and SSE) was noted.

In the group with USN- a main effect of type of stimulus as well as a main effect of viewing condition was observed such that under both binocular and monocular conditions the mean reaction time to bilateral stimuli was significantly faster ($p<0.001$) than to left unilateral stimuli, but not significantly faster than to the right unilateral stimuli (p=0.981).

Given that presence of SSE is defined as faster reaction times to bilateral stimuli than to right and left unilateral stimuli, the SSE was uncharacteristic in this group. Overall reaction times were significantly slower under the monocular (966.81 ± 34.65) versus binocular condition (874.65 ± 31.68) (Wald Chi-Square: 26.25; df: 3; $p<0.001$); however, no interaction between viewing condition and reaction times to the three stimuli types was noted

In terms of fixation ability prior to SSE paradigm testing, the proportion of those with USN+ who passed the fixation task was 2 out of 7 or 28.5% as compared to the 100% of the control group ($Z=-2.315$, $p=0.021$) and 90% of the USN- groups' participants ($Z=-2.098$, $p=0.018$): USN- and control group success rates did not differ significantly ($Z=0.378$, $p=0.353$). In terms of the extent of fixation during the SSE paradigm testing, the USN- and the control group did not differ significantly in the number of missed fixations under binocular versus monocular condition ($Z=-0.289$, $p=0.396$). The extent of fixation during the SSE paradigm testing could not be analyzed for the USN+ group given that only 2 individuals passed the fixation task prior SSE testing.

As for the USN+ participants**,** the mean response times and the number of missed trials for the 2 individuals (PO and BI) in the USN+ group who went on to carry out the SSE paradigm are presented in Figures 6.3 and 6.4. PO was able to complete the SSE paradigm testing under the binocular condition only: he was unable to fixate under the monocular condition. His mean reaction time to bilateral stimuli was faster than to unilateral left, but not to the unilateral right stimuli, suggesting abnormal SC involvement. The difference in reaction time was larger between bilateral and right-sided presentations (63 ms) than between bilateral and left-sided presentations (24 ms) (Figure 6.3a). As for the extent of his fixation ability during binocular testing of the SSE paradigm, he missed 7 out of 120 or 5.8% of left-sided presentations, 9 out of 120 or 7.5% of right-sided presentations, and 18 out of 120 or 15% of bilateral presentations (Figure 6.3b).

BI was able to complete testing under both binocular and monocular conditions. As was in the case for PO, under binocular viewing condition, BI demonstrated faster mean

reaction times to bilateral presentations than to left-sided presentations only. In fact, his mean reaction time to right-sided presentations was faster than to bilateral presentations (Figure 6.4a). As for the extent of his fixation during binocular testing, he missed 11 out of 120 or 9.1% of left-sided presentations, 15 out of 120 or 12.5% of right-sided presentations, and 10 out of 120 or 8.3% of bilateral presentations. Under the monocular condition, a similar pattern in reaction times was observed where reaction time to bilateral stimuli was faster only in comparison to the left-sided presentations, and slower in comparison to right-sided presentations (Figure 6.4a). However, these data should be interpreted with caution given the considerable number of missed fixations by BI in the monocular condition; 17 out of 120 or 14.6% of left-sided presentations, 75 out of 120 or 62.5% of right-sided presentations, and 76 out of 120 or 63.3% of bilateral presentations.

DISCUSSION

In this study, we hypothesized that the SSE would be present in healthy controls and in those without USN post-stroke under both binocular and monocular conditions. In contrast, we expected the SSE to be absent or impaired in those with USN in the binocular condition, and present, or at least improved, under the monocular condition. In the control and USN- individuals, the testing paradigm was successfully completed by all participants except one who may, according to the experimenter, have had an attentional problem.

With regard to our first hypothesis, the SSE was obtained in the healthy controls and it did not differ under binocular or monocular conditions. This finding suggests that in normal individuals, even if monocular patching affects the balance of activity in the SC, cortical pathways are available for neural summation and apparently are not affected by any changes in subcortical activity. In contrast to our initially stated hypotheses, however, the USN- individuals did show an abnormal SSE whereby reaction times to bilateral presentations were not faster than to unilateral right-sided presentations. The absence of the SSE suggests that the location of the lesion in the right hemisphere of these individuals may have led to abnormal neural summation due to disturbances in the

subcortical – cortical network affecting the interaction between the SC and the parietal and frontal regions. It is also plausible that the altered balance between the two SC is insufficient to produce contralesional hemispace neglect. Given that the response time to the left-sided stimulus was considerably longer than to unilateral right-sided and bilateral stimuli, we can surmise that the USN in these individuals was so mild that the tools we used were not sensitive enough to detect its presence. These results are consistent with earlier findings by Kaizer et al.(1988) showing that individuals with post-stroke left USN have longer reaction times to left-sided stimuli compared to right-sided and middle situated stimuli. In addition, given that monocular eye patching was used in the present study, the contralesional (left) SC still had access to information from the left temporal hemiretina. Therefore, we speculate that the hyperactivity of the left SC was not totally suppressed. In future studies, it will be interesting to analyze the effect of blocking right visual field information through patching of the right half of each eye on reaction times to left-sided and bilateral stimuli presentations given that half-eye patching will block visual input to the left SC.

As for the individuals with post-stroke USN, we found that this paradigm is challenging for them because of their poor fixation ability with this method. It is possible that the poor fixation of the USN+ group results from disturbed SC contribution to the frontal eye field (FEF), a region involved in the control of voluntary and reflexive saccadic reactions that influence shifts of visual attention (Heide & Kompf, 1998). In fact, 6 out of 7 USN+ individuals had documented fronto-parietal lobe lesions. Moreover, a recent study has confirmed that the SC are involved in controlling microsaccadic movements which are exhibited during fixation (Hafed et al., 2009). In monkeys, FEF cooling results in USN while deactivation of the right SC causes longer saccadic reaction times and a decrease in saccadic amplitude (Keating & Gooley; 1988). Animal research has also shown that the SC play an important role in directing and initiating saccades (Hafed & Krauzlis, 2008; Port & Wurtz, 2009; Munoz & Istvan, 1998). In humans, there is an increase in saccade latency in those with posterior parietal lesions. For example, Heide & Kömpf (1998) found that individuals with right parietal lesions demonstrated considerably lengthened saccadic latencies and rightward lateralization of visual search that correlated

significantly with USN severity. This localization can be related to our results given that all the USN+ individuals presented with lesions that comprised to some extent the parietal lobe. In addition, in the present study, the USN + individuals who completed the paradigm, demonstrated an abnormal SSE whereby reaction times to bilateral stimuli were faster only compared to unilateral left-sided stimuli but not to unilateral right-sided stimuli. Interestingly, monocular eye patching had no effect on reaction times.

To our knowledge this is the first study that attempted to evaluate the SSE in combination with eye patching and achromatic stimuli in individuals with post-stroke USN. The only other study on SSE in individuals with USN used sporadic brief color-changes of 150 ms duration to which the participants were asked to respond with a mouse-click as a control for fixation (Müller-Oehring et al., 2009). A rigorous evaluation of fixation ability was not used. Our results strongly support a potential involvement of eye movement control deficits in USN+ individuals and they underline the need to evaluate systematically this aspect in unilateral spatial neglect. In addition, the Müller-Oehring et al. (2009) study used a heterogeneous sample of USN of different origins that could have influenced the nature and presentation of USN. In the present study, USN was determined using standardized tools and only those with a right middle cerebral artery stroke were included. Moreover, the use of the eye tracker system enabled the measurement of fixation ability that we have demonstrated to be a critical component in the evaluation process. Lastly, the study by Müller-Oehring et al. (2009) used color stimuli presentations; therefore SC functioning could not be derived from their data given that the SC appear most sensitive to processing black/white visual information (Savazzi & Marzi, 2004). This may explain why the reaction times they obtained were shorter than ours. Also the utilization of color stimuli reinforces the possibility that the normal SSE observed was mediated through other pathways left undisturbed in those individuals with USN.

The limitations of the present study include a sample size that may have been small but nevertheless appropriate for a pilot phase. In future studies, we will be need to achieve a better understanding of the stroke-specific sequelae that differentiate those who can from those who cannot carry out the SSE paradigm. We are hopeful that the present study

furnishes an impetus to carry out further studies with a greater patient sample. In addition, it should be noted that this study earmarked only those individuals experiencing near extrapersonal USN leaving the investigation of far extrapersonal and personal space USN and the contribution of the SC to be done. Further research that investigates patients with various types of USN will provide additional insights into collicular involvement in USN that should, in turn, lead to an improved understanding of the neural mechanisms of unilateral spatial neglect and more efficient treatment approaches.

Finally, what might be considered a limitation of this study namely that those with USN could not complete the SSE paradigm because of difficulty with fixation, suggests in fact that eye movement control in those with USN warrants further study. Indeed, to our knowledge, studies investigating the effectiveness of training fixation have not been attempted. As previously mentioned, numerous interventions have been proposed for the treatment of post-stroke USN with relatively little impact on functional outcome (Luaute et al., 2006; Bowen & Lincoln, 2007). Given our results, training of fixation using eye patching and different types of achromatic stimuli presentations (e.g. unilateral versus bilateral) may be a promising avenue.

In addition, the finding that the contrast sensitivity to left sided stimuli is high in those with USN also offers valuable suggestions to clinicians who attempt retraining. If, for those with USN, visual information needs to be darker before it is detected, one simple form of intervention would be to have left-sided objects, such as written text, made darker. A high-resolution functional magnetic resonance imaging study in healthy adults has found that the SC respond to low stimulus contrasts and are weakly activated by changes in stimulus contrast (Shneider & Kastner, 2005). Given that individuals with USn in the present study demonstrated higher left-sided stimuli contrast sensitivity suggests right SC dysfunction.

While SSE testing was challenging for those with post-stroke USN, there is the potential to continue the exploration of SC activity by other means. For example, functional magnetic resonance imaging with its high spatial resolution can be used to study SC

neural activities (Iacoboni et al., 2000) and to evaluate plastic changes in the human brain. This tool is providing new insights into stroke and stroke recovery (Hodics & Cohen, 2005). Also, diffusion tensor imaging (DTI) tractography has recently been used to describe SC connectivity in hemispherectomized individuals with blindsight (Leh et al., 2006b) and thus offers another avenue for future studies.

CONCLUSION

The SSE can be used to evaluate the neural integration of visual processing between the right and left visual fields. Results from the utilization of the SSE paradigm suggest that even individuals with undetected USN show disturbances in neural integration, potentially involving the SC. While healthy controls and stroke victims without USN were able to complete the SSE paradigm, the majority of those with USN demonstrated difficulty with fixation that prohibited testing. One plausible explanation is that fixation deficits in post-stroke USN could be related to a disruption of SC-FEF interaction. This speculation opens exciting avenues for future research centered on the identification of the mechanisms involved in post-stroke USN. This in turn will lead to a greater refinement of interventions to alleviate this disabling condition.

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Figure 6. 1: Example of the Fixation Task prior SSE Paradigm Testing

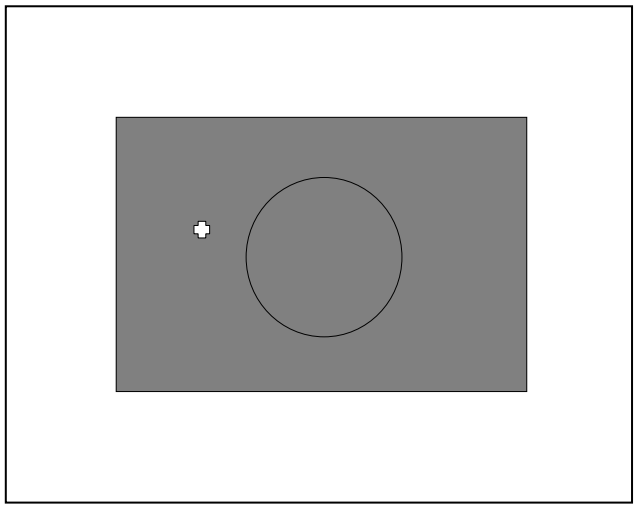


Figure 6.2: Example of the SSE Paradigm Testing

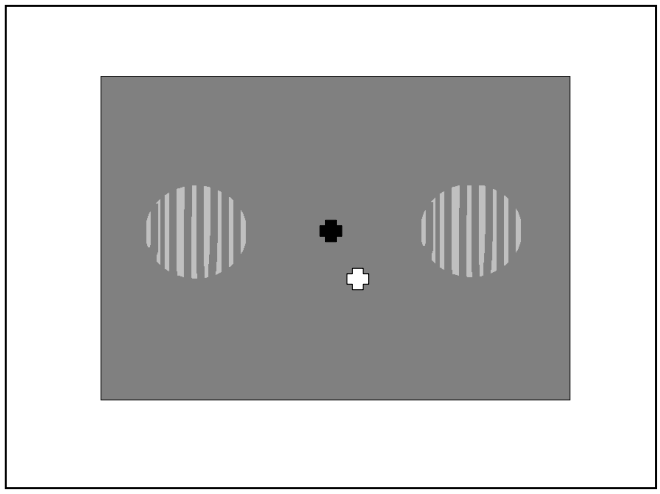
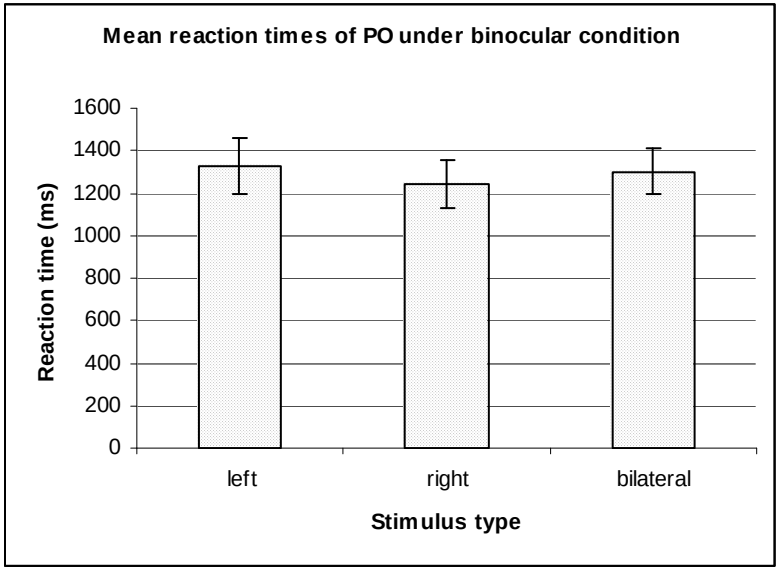


Figure 6.3: PO Participant (USN+) Results

A.



B.

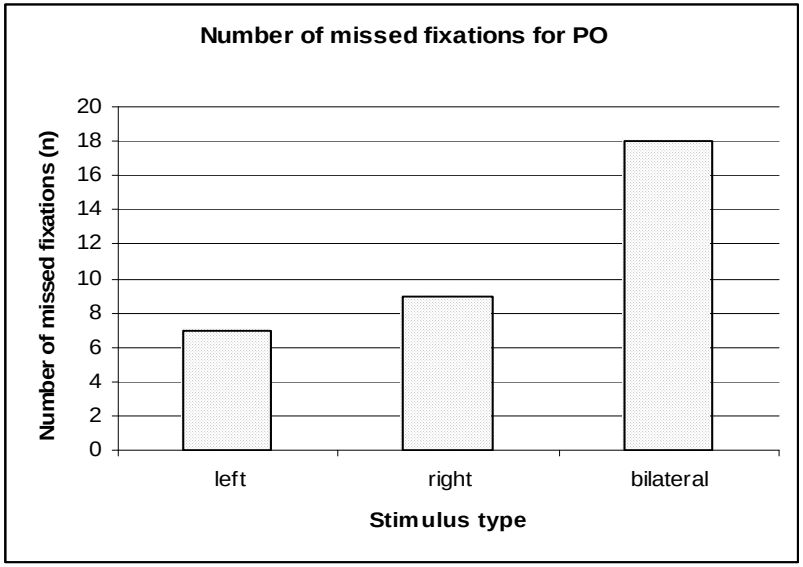
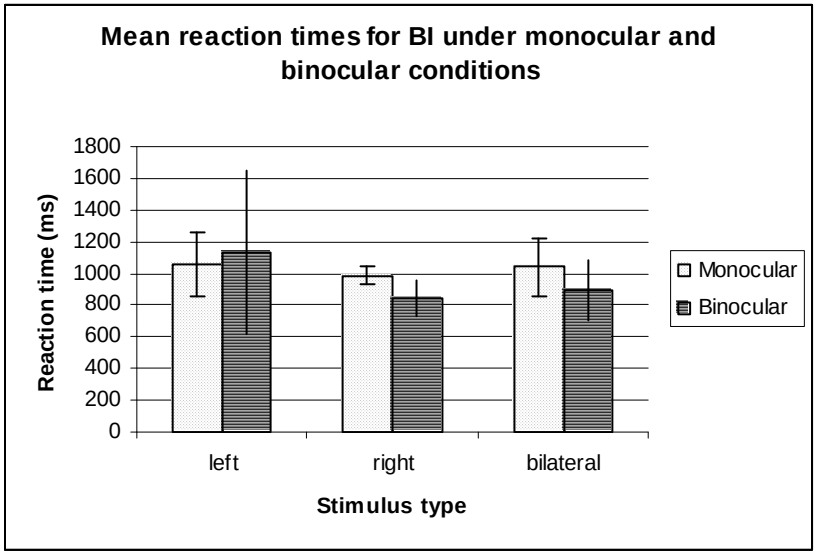


Figure 6.4: BI Participant (USN+) Results

A.



B.

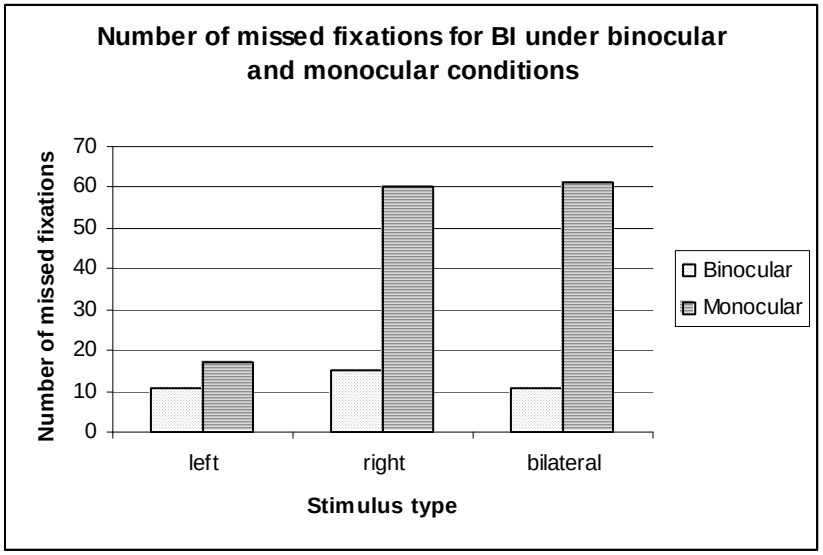


Table 6.1: Feasibility measures of the study groups

Subject	Fixation Ability	Calibration Ability	Calibration Scores (Right & Left)		Contrast Sensitivity Task	Contrast Sensitivity Scores (Left)
Controls						
ZM	1	1	8.7	6.9	1	47.7
DU	1	1	106.3	121.2	1	44.4
MU	1	1	23.1	17.6	1	47.6
JA	1	1	16.5	15.8	1	51.6
TK	1	1	113.8	176.4	1	52.9
VE	1	1	60.7	48.8	1	53.4
YV	1	1	158	144	1	53.2
ZT	1	1	114.3	104.3	1	52.3
KZ	1	1	11.8	28.9	1	44.9
ET	1	1	49.2	38.8	1	43.8
USN -						
HA	1	1	77.1	133.8	1	47.3
BB	1	1	13.5	11.6	1	51.5
MO	1	1	79.9	80	1	51
KJ	1	1	15.1	21.6	1	54.5
PB	1	1	130.5	60.9	1	53
ML	1	1	6.8	12.3	1	48.7
LL	1	1	4.6	35.9	1	59.8
CO	1	1	87.6	126.5	1	52.6
BW	1	1	8.1	8.9	1	52.6
HB	0	1	113.6	101.6	1	46.4
USN+						
DB	0	0	N/A	N/A	0	N/A
DS	0	1	16	9	0	N/A
TA	0	1	10.7	16.5	1	68.5
BI	1	1	6.9	6.1	1	40.3
BO	0	1	87.4	84.4	1	99.2
GR	0	1	115.0	129.1	1	99.5
PO	1- binocular only	1	135.6	59.3	1	54.0

Legend 1: Presence of ability to complete the task; 0: Absence of ability to complete the task

Table 6.2: Results of mean reaction times and mean number of missed fixations for healthy control and USN-groups

Group	Viewing Condition		Side	Median	Mean ± SD
Controls	Binocular	Reaction time (ms)	Left	907.5	887.58 ± 73.16
			Right	883	895.56 ± 79.21
			Bilateral	821	834.29 ± 76.99*
		Number of missed fixations	Left	0	1.37 ± 2.27
			Right	0	1.72 ± 2.71
			Bilateral	0	1.72 ± 2.72
	Monocular	Reaction time (ms)	Left	918	941.52 ± 114.64
			Right	915	922.9 ± 105.54
			Bilateral	865.5	887.94 ± 114.36*
		Number of missed fixations	Left	0	0.41 ± 0.76
			Right	0	0.47 ± 0.89
			Bilateral	0	0.62 ± 1.14
USN-	Binocular	Reaction time (ms)	Left	930	927.8 ± 128.51
			Right	842	861.08 ± 106.31
			Bilateral	828	832.57 ± 114.73§
		Number of missed fixations	Left	1	3.23 ± 4.38
			Right	1	3.39 ± 4.67
			Bilateral	1	3.80 ± 4.94
	Monocular	Reaction time (ms)	Left	1004	1007.25 ± 119.70
			Right	950	960.16 ± 108.08
			Bilateral	937	930.53 ± 108.73§
		Number of missed fixations	Left	2	2.50 ± 3.25
			Right	1	2.58 ± 3.62
			Bilateral	1	2.56 ± 3.50

Legend

***** Significant at 0.05 for bilateral stimuli being faster than to unilateral left and right stimuli

§ Significant at 0.05 for bilateral stimuli being faster than to unilateral left stimuli only

SD: Standard Deviation

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7. THESIS SUMMARY

The results of the studies presented in the two preceding manuscript provide valuable information for rehabilitation professionals, experts in neuroscience and researchers focusing their work towards developing and evaluating new and more effective treatment techniques for USN based on plausible underlying mechanisms. This section summarizes and discusses the main finding from these studies.

The first manuscript reviewed the work on the role of the SC in USN drawing from animal and human research and an attempt was made to pave the way for future research in that area. Overall, 45 articles were retrieved for this review where 21 were animal studies, and 24 were human studies. Animal research confirms that the anatomical pathway between the SC and the posterior parietal cortex is clearly involved in USN presentation and alleviation following a brain lesion. The opponent-processor theory and the animal work behind it support the implications of the parietal cortex and the SC in USN; where the ipsilesional SC is found to be hypoactive and the contralesional SC is hyperactive, leading to an exaggerated attentional shift to the right hemispace (i.e. left USN). Similarly, deficits in exogenous orienting and inhibition of return (IOR) effect leading to USN appear to be a result of the same parieto-collicular/temporo-parieto-collicular pathway disruption. In addition, the interconnection of the frontal eye field (FEF) and the SC, mediating saccadic eye movements and IOR are also suggested to be implicated in USN presentation. Attention in humans is mediated, at least partly, by these pathways as well. Nonetheless, as the manuscript suggests, this is only a speculation given that there is no clear evidence directly linking SC involvement in USN presentation and alleviation following a stroke. Given the abundant literature on the role of the SC in animal USN, and lack of studies directly linking SC activity to USN using the opponent-processor theory, the IOR effect and the FEF connection, the present review suggests that SC involvement in human USN post-stroke needs to be investigated.

In addition, the first manuscript explored the rationale behind the eye patching and prisms adaptations use as USN treatment strategies, with a focus on the SC implications. Overall, the human work on eye patching and USN recovery suggests that half eye patching may be beneficial to alleviate visual neglect. If parallels can be drawn between the animal studies on SC activity levels, right half eye patching likely blocks all visual input to the left brain hemisphere and the left SC. In this case, the ipsilesional right SC is stimulated and the contralesional left SC is under-stimulated, creating an activity balance between both, hence leading to reduced USN. However, eye patching as an intervention strategy needs to be studied in greater detail with focused attention on the following issues such as neglect subtypes and benefits of patching, differential effects of patient characteristics (e.g. presence versus absence of IOR), etc. On the other hand, prisms adaptations for USN are speculated to be an adaptive rather than a remediation strategy for USN alleviation, with little effect on the retino-collicular pathways.

This review suggest that a better understanding of the mechanisms behind various forms of post-stroke USN will lead to more effective interventions and a better understanding of why current treatments work for some patients and not others. With this goal in mind, the second study was designed.

The second manuscript presents a study with the objectives to (1) determine the feasibility of investigating SC contribution using SSE, achromatic stimuli and monocular eye patching method; and (2) estimate the SC contribution in individuals with left USN of near extrapersonal space following right hemisphere stroke (n=7), those without USN following a right hemisphere stroke (n=10) and healthy control individuals (n=10). This is the first study to use the SSE in combination with eye patching and achromatic stimuli in individuals with post-stroke USN.

In terms of feasibility of using the SSE in those with post-stroke USN, we found that this paradigm is challenging with those individuals, mainly given that most of the participants presented with poor fixation ability. This difficulty in fixating leads to speculate that their SC activities are disturbed in comparison to controls and post-stroke individuals without

USN. This effect could be explained by the fact that the SC are also found to be interconnected with FEF, a region involved in the control of voluntary and reflexive saccadic reactions that influence shifts of visual attention in humans and animals (Heide & Kompf, 1998; Keating & Gooley; 1988; Hafed & Krauzlis, 2008; Port & Wurtz, 2009). The SC are found to be impaired in USN+ group likely due to the fact that that the SC with their interconnections to the posterior parietal cortex region, play a major role in visual attention, as clearly confirmed by numerous animal studies (Facteau et al., 2004; Mesulam, 1999; Lomber et al., 2001; Payne et al., 1996; Lomber et al., 1996; Lomber et al., 2002; Sherman, 1977; Wallace et al., 1989; Wilkinson et al.; 2007; Rushmore et al. 2006). In the control and USN- individuals, the feasibility of using the testing paradigm was determined to be adequate where 90% to 100% of group participants completed the prerequisite tasks.

Overall, the control group demonstrated SSE under binocular and monocular conditions. In contrast, the USN- group demonstrated SSE under binocular and monocular conditions where reaction times to bilateral stimuli presentations were faster than to unilateral left presentations only, and not unilateral right presentations. We can speculate that in those with right hemisphere stroke, the right SC is hypoactive and the left SC is hyperactive, leading to a longer response time to left sided stimuli. Nonetheless, it is likely that this misbalance between SC activities is perhaps not substantial enough for the person to present with contralesional hemispace neglect.

In conclusion, the results of the present study have important clinical relevance. While healthy controls and individuals with stroke without post-stroke USN were able to complete the SSE paradigm, the majority of the group with USN demonstrated difficulty with fixation and thus could not initiate the paradigm. One plausible explanation is that fixation deficits in post-stroke USN could be related to a disruption of SC functioning. This speculation opens exciting avenues for future research that should lead to a better understanding of the mechanisms that are affected in post-stroke USN and ultimately to targeted interventions aimed at reducing post-stroke USN.

8. CONCLUSIONS

Three to five million new patients with stroke will suffer from neglect each year worldwide. Given the magnitude, persistence, heterogeneity, and disabling effects of this disorder, a better understanding of the underlying mechanisms of USN is critical for diagnostic purposes and for enhancing intervention effectiveness. The brain mechanisms of spatial inattention need to be clearly identified as many questions remain unanswered. The interdisciplinary collaboration allowed us to achieve a better understanding of SC mechanism in USN presentation and alleviation, using the SSE paradigm, achromatic stimuli and monocular eye patching method. We have found that our study participants with post-stroke USN have difficulty completing the SSE paradigm due to poor fixation ability. Poor fixation ability may indicate altered SC functioning. It is suggested that studying fixation in post-stroke USN, and training of fixation in individuals with post-stroke USN may be the research agenda aimed at refining rehabilitation strategies to reduce the negative effects of post-stroke neglect by taking into account the attentional impairment and its pathophysiology. Overall, the information gathered from the literature review and the pilot study has great potential in advancing stroke rehabilitation research and improving the rehabilitation outcomes for this population.

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