Towards culturally adapted virtual reality exposure therapy for Inuit in Quebec

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Table of Contents

Abstract

Suicide rates amongst Indigenous communities are 6-11 times higher than the Canadian average. Access to mental health resources in remote parts of Canada is limited. Although virtual reality (VR) is well validated as an exposure component to cognitive behavioral therapy (CBT) in anxiety disorders, including post-traumatic stress disorder, its acceptance and cultural safety among Indigenous individuals remains unknown. VR treatments that incorporate biofeedback as a way to regulate autonomic functioning may increase efficacy and in the future, could guide the process of treatment. This thesis is comprised of two major parts and is the basis for a protocol design for a future clinical trial aimed at targeting emotion regulation (ER) through a culturally adapted VR-assisted, individual CBT for Inuit of Nunavik. The first portion consists of a pilot study for this future clinical trial. Data collected to assess the feasibility of this approach was primarily through qualitative methods, from health care professionals (N=14) and key Inuit community workers. These findings confirmed that VR is readily accepted and feasible. The second part of this thesis is, through a systematic review, to determine which outcome measures are valid for the future trial. We conducted a systematic review on the utility of psychophysiological metrics as trauma intervention outcomes in order to validate the use of objective outcome measures free of cultural and linguistic elements. The findings of this review suggested that changes observed in psychophysiological measures were closely correlated to changes in the Clinician-Administered PTSD Scale (CAPs) questionnaire, a gold standard assessment of PTSD symptom severity and now the primary outcome in the protocol of the clinical trial.

Résumé

Les problèmes mentaux et les taux de suicide parmi les communautés autochtones sont de 6 à 11 fois plus élevés que la moyenne canadienne. L'accès aux ressources en santé mentale dans le nord du Canada est limité. Bien que la réalité virtuelle (RV) soit bien validée en tant que composante de l'exposition à la thérapie cognitivo-comportementale (TCC) dans les troubles anxieux, y compris le trouble de stress post-traumatique (TSPT), elle n'a pas été testée ni adaptée culturellement aux personnes autochtones. Les traitements VR qui intègrent le biofeedback comme moyen de réguler le fonctionnement autonome peuvent augmenter l'efficacité et, à l'avenir, pourraient guider le processus de traitement. Cette thèse comprend deux parties principales et constitue la base d'une conception de protocole pour un futur essai clinique visant à cibler la régulation des émotions (ER) par le biais d'une TCC individuelle assistée par la réalité virtuelle et adaptée à la culture pour les Inuits du Nunavik. La première partie consiste en une étude pilote pour ce futur essai clinique. Les données recueillies pour évaluer la faisabilité de cette approche ont été principalement obtenues à l'aide de méthodes qualitatives auprès de professionnels de la santé (N = 14) et de travailleurs communautaires Inuits. Ces résultats ont confirmé que la RV est facilement acceptée et réalisable. La deuxième partie de cette thèse est, à travers une revue systématique, de déterminer quelles mesures de résultats sont valables pour la future étude. Nous avons effectué une revue systématique de l'utilité des paramètres psychophysiologiques en tant que résultats d'une intervention en traumatologie afin de valider l'utilisation de mesures de résultats objectifs sans éléments culturels et linguistiques. Les résultats de cette revue suggèrent que les changements observés dans les mesures psychophysiologiques étaient étroitement corrélés aux changements dans le questionnaire de l'échelle du SSPT administré par le clinicien (CAP), une évaluation de référence de la gravité des symptômes du SSPT et maintenant le principal résultat du protocole de l'essai clinique.

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Contribution of Authors

Noor Mady and Dr. Outi Linnaranta designed this thesis project. Noor Mady conducted the full literature review and writing of the thesis. Qualitative data collection was conducted by Noor Mady, Dr. Outi Linnaranta and Dr. Liliana Gomez Cardona. The systematic review (manuscript to be submitted) was conducted collaboratively. Noor Mady and Michelle Yang conducted systematic searches, screened articles (both independently of each other), assessed quality of studies, extracted and validated data. Noor Mady contributed to creating and editing all the tables included in the systematic review. Michelle Yang wrote the first draft of the manuscript, however, all authors contributed to the writing process (see Appendix 1). The protocol (second manuscript to be submitted) was written by Noor Mady as first author (see Appendix 2). Quinta Seon contributed to the background research of Emotion Regulation assessments for the protocol. Dr. Linnaranta critically reviewed this thesis.

1 CHAPTER I: INTRODUCTION

1.1 Mental health of Inuit in Quebec

1.1.1 Inuit health and trauma

In Canada, suicide rates among some Indigenous people (First Nations, Métis, and Inuit) have been higher than the general population, most commonly in those younger than 25 years old (Chachamovich et al., 2015). Often, suicide and self-inflicted injuries are among the top causes of death. Research shows that suicide has increased severalfold in the past decades in Inuit communities (Chachamovich et al., 2015). In a cross-sectional study of young Inuit (N=305, M_{age}= 19, Range=15-24 years old) living in Nunavik (northern Quebec), Inuit males reported lifetime suicide attempts ten times more often than males across Canada, and Inuit females reported six times greater (Fraser et al., 2015).

It has been widely documented that Indigenous peoples are one of the most vulnerable to mental health problems (Fraser, Geoffroy, Chachamovich, & Kirmayer, 2015). Some of the reasons include intergenerational trauma, lack of access to medical services and lifestyle (Anderson, 2015, Chachamovich et al., 2015; Quebec, 2012). These factors contribute to the challenges psychiatric health care professionals in Quebec face when providing treatment for those who are in remote areas and in need. Other factors may include forced assimilation (residential schools) and economic and political marginalization, which may have placed heavy burdens on these communities (Fraser et al., 2015).

Indigenous individuals have experienced trauma throughout colonialist history. Residential schools were implemented and funded by the government of Canada, from 1831-1996, where students were not encouraged to freely express their identity (Marsh, Coholic, Cote-Meek, & Najavits, 2015). The resulting internalized oppression has led some survivors to express their grief through violence, often towards family and community members (Marsh, 2015). Many believe a key to healing historical trauma, such as abuse experienced through residential schools, is through a process of reclaiming identity and revitalizing the culture and language as resources for narratives of self-identity and healing (Kirmayer et al., 2011; Marsh, 2015).

Within the province of Quebec, there are approximately eleven Indigenous groups (see Figure 1, Indigenous and Northern Affairs Canada, & Communications Branch 2013). Among those groups, over 100,000 individuals identify as Inuit. Historically, suicide was less common among Inuit living in northern Canada, and rates were as low as 5.2 per 100,000 in mid 19th century (Fraser et al., 2015). According to the latest reports, suicide rates in Nunavik are six to eleven times larger than the Canadian average (Anderson, 2015, Chachamovich et al. 2015; Wexler et al., 2016). There are various risk factors related to suicide among Inuit. For example, researchers found that the risk factors for Inuit in Nunavut who died by suicide (N=120, between 2003-2006) were similar to those observed in studies within the general population (Chachamovich et al., 2015). More specifically, these researchers found an association between both psychopathology (family history of major depressive disorder and suicide completion, have had major depressive disorder, alcohol or cannabis dependence) and early life adversity (childhood abuse) and suicide, among Inuit. Strikingly, even controls (sex-matched Inuit community members, randomly selected) in this study presented with a high prevalence of psychiatric illnesses (25% with history of Major Depressive Disorder and >33% with cannabis use disorder; Chachamovich et al., 2015).

Protective factors may impact suicide rates among Inuit. In a more recent study of Inuit in Nunavut, Beaudoin and colleagues (2018) found that participants who never attempted suicide (N=30, Males=25, M_{age}=27.9) had more protective factors (e.g. use of services, environmental stability, relationships, etc.) than those who died by suicide (N=30, Males= 25, M_{age}= 23.9) and those who had made a suicide attempt (N=30, Males=25, M_{age}=27.1; p <0.05). These researchers found among the three groups in their study, individuals who had made a suicide attempt consulted health services more than those who never made an attempt and to an even greater extent than the group who died by suicide. This may be of interest for future research with regards to the outcome of service use. Specifically, in addition to improving current treatments, future research may also target treatment access and methods of reaching populations that may not necessarily seek services, as shown through this study. In another study, researchers assessed the life trajectories of Inuit (*N*=184) who died by suicide (*N*=92, M_{age}=23.2) and found that compared to controls (M_{age}=27.8), they had a more significant burden from adversity creating a cascading effect (Affleck et al., 2020). The number of suicide attempts between controls and those who died by suicide were similar, however, those with no suicide attempt exhibited more protective variables. According to these researchers, protective variables that were related to the social environment were most impactful (Affleck et al., 2020).

Figure 1. Map of Indigenous Communities in Quebec

[Indigenous and Northern Affairs Canada, & Communications Branch]. (2013, March 1). https://www.aadnc-aandc.gc.ca/Mobile/Nations/NationsAltMap-eng.html

1.1.2 A holistic view on Mental wellbeing of the Inuit

In Quebec, a significant amount of work remains to be done to help Indigenous individuals, especially those who live in urban settings and lack access to appropriate centers for healthcare (Yaphe et al., 2019).Unfortunately, most health care workers in the province of Quebec have limited exposure to Indigenous communities and issues (Yaphe, Richer, & Martin, 2019). In Canada, we only recently began implementing Indigenous curricula in medical student training. British Columbia, Saskatchewan, Manitoba and Ontario have developed cultural safety trainings for health care professionals (Yaphe et al., 2019). Similarly, facilitators developed a cultural safety training for healthcare professionals (N=45) in Quebec. The process included a First Nation's community member, a non-Indigenous public health physician and a medical student with previous exposure to Indigenous populations. Some participants were familiar with the challenges Indigenous people face when accessing health care in Montreal but most were unaware of cultural safety (Yaphe et al., 2019).

A report on the health needs of aboriginals living in Montreal shows the most frequently perceived needs during the previous month were related to trauma: nervousness/anxiety, sadness or low/ depressed mood (All participants= 59.6%, Inuit= 56%), bodily aches or pain (49.4%), and sleep-related issues (49.4%; Montreal urban aboriginal health needs assessment, 2012). Despite the increased need for health services, it remains not optimally met by medical services. Indigenous individuals underutilize healthcare services, including those targeting mental health. Among those who do seek services, many discontinue. In response, recent approaches have emphasized cultural safety and incorporating traditional Indigenous practices (e.g. sweat ceremonies, sharing circles, traditional healers, elder teachings) and research methods (Marsh et al., 2015). This is referred to as *Two-Eyed Seeing*, the process of witnessing the strengths of Indigenous knowledge/ways of knowing through one eye and acknowledging the strengths of western knowledge/ways of knowing through the other (Marsh et al., 2015). This analogy translates into the idea that it is beneficial for all to see through both eyes. In a recent literature review of Aboriginals' mental health in Canada, Marsh and colleagues (2015) concluded that interventions should focus on strengthening cultural identity, community integration and therefore increase connection among individuals and political empowerment. More specifically, these researchers highlighted the importance of studies that encourage Indigenous individuals to explore treatments that could improve health in their communities.

Traditional spiritual and healing methods continue to exist in many communities. Traditional knowledge and healing practices may improve health and empower Inuit communities (Marsh et al., 2015). Indigenous spirituality is also a key component to their holistic view of healing, and it includes beliefs such as: trust, sharing, and respect (Marsh et al., 2015). To heal from the intergenerational trauma and continued hardships experienced within Inuit and other Indigenous communities, a common existing theme is to reclaim identity and culture (Marsh et al., 2015). In a recent report published in Nunavik, Inuit expressed the desire to see a greater incorporation of traditional medicine in their services. Western and traditional medicine could blend well, as previously described, and provide a more holistic response to Inuit needs and wellbeing (Parnasimautik Consultation Report, 2014).

1.1.3 Cultural safety and acceptability of psychiatric care

According to Richer and Martin (2019), cultural safety refers to:

> An environment that is spiritually, socially, emotionally and physically safe for people; where there is no assault or denial of their identity and what they need. It is about shared respect, shared meaning, shared knowledge and experience of learning together (p. 62).

Enhancing cultural safety is essential in research practice. Some have suggested that the goal of cultural safety is for health care professionals and researchers to acknowledge that individuals both perceive and experience the world differently and to use this as a tool to address power relations (Darroch et al., 2017). In other words, cultural safety encourages one to consider various factors that may impact health care: historic, economic and social variables. It is important to incorporate cultural traditions, language, foods and intergenerational dialogue in Inuit suicide prevention programs, as shown through previous reports (Fraser et al., 2015). These are several factors that may enhance cultural safety.

Researchers have concluded that there is a need for culturally safe mental health intervention tools for Inuit populations (Kirmayer & Valaskakis, 2009). For example, by incorporating culture into treatment, an increased success in substance abuse interventions for Indigenous individuals was noticed (Marsh et al., 2015). Enhancing cultural safety includes using language that promotes respect of Inuit beliefs and values and helps to address the health disparities experienced by these communities. When researchers incorporate cultural safety into their work, they show a commitment to decolonization and greater equity in research and its distribution (Darroch et al., 2017). For example, the cultural safety of mental health interventions that have been validated in other populations should be culturally adapted to Indigenous communities.

1.1.4 Barriers to treatment access

Nunavik is located in the northern part of Quebec and Inuit individuals living there rely primarily on air travel to come to southern parts of the province. The Inuit communities in Nunavik have criticized the lack of the region's locally accessible health care services (Parnasimautik Consultation Report, 2014). More specifically, this report highlights the devastation individuals feel when they travel for medical services and must leave their family behind. Specifically, in 2012-2013, almost a third of the population in Nunavik traveled to Montreal for medical appointments. Additionally, overcrowding is common in Nunavik residential housing, and is not helping to improve current substance abuse problems, physical and sexual abuse, violence etc., (Parnasimautik Consultation Report, 2014). The report suggests immediate support post crisis situations (e.g. suicide), where individuals impacted are often left to cope alone. In addition, there are concerns raised about collective traumatic events experienced by the Nunavik community, which continue to have adverse impacts. These are a few barriers to treatment access present among Inuit communities in Quebec.

In another report, participants (*N*=20) from the Inuulitsivik Health Centre (Hudson's Bay) and the Tulattavik Health Centre (Ungava Bay) highlighted that mental health is a priority in Nunavik (Lessard, 2008). They emphasized the increased mental health issues experienced by younger individuals. This report also included that frequently reported disorders among Inuit are: schizophrenia, bipolar disorder, depression, anxiety and related disorders etc. It is suggested that these traumas should be addressed through ongoing programs targeting prevention and wellbeing.

1.2 Emotion Regulation

1.2.1 Definitions

Emotion Regulation (ER) is defined as a "set of mental processes that influences which emotions we have when we have them and how we experience and express them" (p.1, Montana et al., 2020). Contrastingly, emotion dysregulation is defined as "undesired intensification or deactivation given by the person's inability to manage or process emotions effectively" (p.1, Montana et al., 2020). Others have discussed how emotion inflexibility may increase risk for affective disease (Coifman and Summers, 2019). Emotion flexibility refers to an "ability to respond to shifting emotional contexts, including environmental contexts as well as internally elicited emotion" (p.2, Coifman et al., 2019).

When fear is inferred beyond the definite danger it is considered less adaptive, and having high sensitivity to threat and less cognitive regulation is linked to a higher risk of affective disease related symptoms development, such as suicide (Coifman and Summers, 2019). It is understood that poorly regulating positive emotions may also present as a risk factor for affective disorders. However, the mechanism by which symptom development occurs is less understood, for example, whether poor generation of positive emotions adds to certain symptoms more than others (Coifman and Summers, 2019).

Some have studied various ER based models to better understand how they inform VR based strategies. In a meta-analysis of 280 studies, Naragon-Gainey and colleagues (2017) found three dominant factors as common ER strategies, namely: disengagement, aversive cognitive preservation and adaptive engagement. They also discussed various and contrasting approaches through which emotions may be regulated: food restriction, acceptance of emotional experiences, suppression, reaching out to others or isolation. More specifically, these authors discuss several models for ER, the temporal process models, the strategy-based models and the ability-based models (Naragon-Gainey, McMahon, & Chacko, 2017). The temporal process models are based on a four-stage theory by which a given situation elicits an emotion, attention is given to that situation, appraisal of the meaning of that given situation is conducted which leads to an emotional response. The strategy-based models consist of a process of rationalizing an approach. Through strategy-based models, it is ideal to show flexibility to match the context instead of classifying approaches strictly, for example avoiding maladaptive strategies and only using adaptive ones. Finally, the ability-based models suggest that there are certain skills that promote healthy ER, for example successful modification of emotions and acceptance of aversive emotions (Naragon-Gainey, McMahon, & Chacko, 2017).

1.2.2 Emotion Regulation: Clinical implications

Emotion dysregulation is considered a core component of Post-traumatic stress disorder (PTSD), which involves and impairment in distinguishing threat (Fitzgerald, DiGangi & Phan, 2018). In other words, individuals experience an amplified emotional "bottom-up" response to a trigger. The National Institute of Mental Health defines PTSD as a consequence of a shocking or dangerous experience.

In a meta-analytic review of the literature (*N*=35 studies), Schäfer and colleagues (2017) determined that a significant relationship exists also between habitual use of adaptive and maladaptive ER strategies in adolescents who have anxiety and depression. More specifically, it was discovered that more frequent use of maladaptive ER strategies and less reliance on adaptive ones had an impact on the teens' psychopathological outcomes (Schäfer et al., 2017). These authors describe that ER strategies include problem solving and acceptance, whereas emotion dysregulation may involve avoidance or rumination.

Enhancing ER is promising for reducing PTSD related symptoms. In a review for treatments for PTSD, Perlick and colleagues (2017) provide an overview of strategies to target emotions from core PTSD symptoms to lessen their negative impact on veterans and their partners and show evidence to support ER skills training as part of PTSD interventions. It was shown that higher levels of emotion dysregulation are predictive of PTSD symptom severity and interpersonal difficulties in veterans with PTSD (Perlick et al., 2017). Two novel treatments for PTSD, structure approach therapy (SAT) and multi-family group for military couples (MFG-MC) involve ER skills training. SAT places a strong focus on helping partners to enhance ER and reduce avoidance of trauma-related triggers. MFG-MC is an adapted version of multi-family group treatment, previously tested in patients with schizophrenia (McFarlane et al., 1995). MFG-MC seeks to help individuals with serious mental illness using problem solving skills training and support to reduce symptoms (Perlick et al., 2017). In another study, of female adolescents with a history of childhood sexual abuse, difficulties in ER were associated with increased and more severe PTSD and depressive symptoms (Chang, Kaczkurkin, McLean, & Foa, 2018). A recent review of the literature has shown that VR-based ER training can promote wellbeing (Montana et al., 2020). More specifically, improvements in ER were achieved using mindfulness-based stress reduction and meditation, and researchers also used both subjective and objective measures of assessment. ER, a strong target for therapeutic treatment to reduce trauma symptom outcomes, is the chosen target for the future trial to be conducted by our laboratory team.

Some researchers have also studied how emotion dysregulation or negative thoughts may mediate psychological outcomes. For example, emotion dysregulation may underlie the relationship between PTSD symptoms and alcohol misuse, as shown in a sample of Latinx adults (N=238, Male= 11.3%, M_{Age}=38.0; Paulus et al., 2019). PTSD symptoms through emotion dysregulation indicated significant indirect effects in this study, as well as greater chances of screening for hazardous drinking, while having controlled for covariates such as gender, marital status, years of education, years in the U.S. and number of traumatic events endorsed (Paulus et al., 2019). Through a study conducted with a British clinical sample of trauma-exposed patients (N= 171, Male= 51.5%, M_{Age}=49.85), researchers have suggested to target negative thoughts, attachment representations and ER to enhance skills acquisition, in treatment of complex PTSD (CPTSD; Karatzias et al., 2018).

1.3 Virtual Reality

Virtual reality (VR) is a novel, promising technology that provides an interactive computer-generated environment for the user (Riva et al., 2016). It provides the participant with an illusion that they are present in a given environment and may involve other sensory information, such as auditory. It requires a headset (e.g. many available such as Oculus) and appropriate computer software. There are various applications for VR, some are empirically tested such as DEEP VR (Montana et al., 2020). VR may be utilized for simple relaxation, guided relaxation, distraction and exposure, which are all useful complements to psychotherapy like cognitive behavioural therapy (CBT). VR is also a great alternative to in-vivo exposure, which is not always feasible, and may be less suitable for mixed traumas.

1.3.1 Uses of VR

VR has the potential to serve as a complementary tool in therapy and is useful for the treatment of PTSD, other psychiatric disorders and pain reduction (Sharar et al., 2007; Grimmer-Somers, 2009; Riva, Banos, Botella, Mantovani, & Gaggioli, 2016). VR exposure paradigms are also a valid treatment for specific anxiety disorders, including PTSD (Forman-Hoffman et al., 2018; Katzman et al., 2014; Maples-Keller et al., 2017; Rizzo and Shilling, 2017). VR triggers emotional experiences that may lead to valuable changes and provide the user with a sense of being present in that environment (Montana et al., 2020). VR works by increasing the effectiveness of cognitive behavioural therapy (CBT) through exposing patients to a virtual world which evokes emotions related to a traumatic memory. The therapist's role in this scenario is to help the patient control their reaction to the visual stimuli. These exercises are then presumed to generalize to the patient's everyday life. VR may provide support for mental well-being through guided meditation applications or it can be embedded in a traditional psychotherapy session. VR involves various application types, some more passive others game-like.

1.3.2 Clinical use of VR

Researchers have considered the aspects of VR that make it successful. Some commercial VR applications for relaxation and stress relief are available, for example Deep VR (Montana et al., 2020; Lindner et al., 2017). In some cases, guided relaxation treatments using VR, improve coping skills with anxiety and ER (i Badia et al., 2018; Pizezoli et al., 2019; Navarro-Haro et al., 2019). Researchers have shown that nature-based VR scenarios, compared to those without nature sounds, are more effective in reducing stress (Pizzoli et al., 2019). Personalized VR (PVR) has also gained popularity, where a focus is placed on the users' relevant life events, personal memories and experiences. PVR may provide a stronger approach to ER and stress, since it encourages one to rely on several processes including cognitive, behavioral and psycho-physiological responses (Pizzoli et al., 2019).

Researchers have demonstrated that the content of VR matters too. Specifically, Tanja-Dijkstra and colleagues (2018) found that VR with coastal nature had better impact than the one with an urban setting. Another research group found that VR may rely on one's perception of the environment, including minor details such as sounds. With the goal of promoting wellbeing and social connection among the New Zealand Defense Force, researchers conducted semi-structured interviews and collected observations with defence personnel, during and after having used a VR environment meant to simulate New Zealand terrain and vegetation (McIntosh, Rodgers, Marques, & Gibbard, 2019). These researchers used the feedback obtained from the participants to adapt this VR environment and many users even recognized the bird calls. This lead to the conclusion that the ability for a VR experience to elicit emotion depends in part on the users' perception of the designed environments and stimuli and they suggested to not underestimate the usefulness of feedback when it comes to details, as the modeling process can enhance the level of immersion (McIntosh et al., 2019).

Moreover, others have shown that ER may be improved through the selection of incongruent memories, in a group of healthy adults (N=128, Males= 37, M_{age}=24.6), using the MoodAdaptor mobile VR application (Konrad et al., 2016). Some have tested mindfulness-based VR interventions in patients with themes such as a walk in a forest and a river with a mountain landscape (Tong et al., 2015; Cikajlo et al., 2016). More specifically, Tong and colleagues (2015) determined that patients with chronic pain (N=13, M_{age}= 49) showed improved results due to the meditative walk VR with biofeedback intervention. Similarly, Cikajlo and colleagues (2016) established that participants (N=8) had higher satisfaction following their Samsung gear stress-reduction VR intervention.

1.3.2.1 Psychiatric Applications of VR

VR exposure paradigms can apply to treatment of various disorders, including anxiety and related disorders. In a review of reviews on VR, the screened articles (i.e. meta-analyses and systematic reviews) all supported its use in the treatment of certain disorders (Riva et al., 2016). These included anxiety, stress, eating disorders and pain management, but not yet depression or schizophrenia. In a separate randomized clinical trial, researchers examined a self-guided application-based VR cognitive behavior therapy (VR CBT) to treat acrophobia (Donker et al., 2019). These participants (N=193, Women=129, M_{age}=41.33) significantly reduced in acrophobia symptom scores (p <0.01), as measured through the Acrophobia questionnaire over a three-week intervention period where participants were exposed to six sessions. In a cross-sectional design using VR to assess participants' (N=59, Women=51, >4 score on Structured Interview for Anxiety Disorders according to the Fifth Diagnostic and Statistical Manual criteria) with acrophobia, researchers found statistically significant changes reported for their clinical condition (Tardif, Therrien, & Bouchard, 2019). Lindner and colleagues (2019) have examined the effects of a VR therapy for public speaking anxiety, in two formats, with one therapist led session and subsequently four weekly self-led sessions. Participants (N=50, Female=36) showed a statistically significant decrease in public speaking anxiety scores (p< 0.01) and these findings were maintained at six months follow-up (p=.006). In various treatment approaches, VR relies on exposing one to an emotionally triggering environment and then monitoring the user's experience to it (Riva et al., 2016). Contrastingly, in pain or eating related issues, VR may help one by altering how they experience their body and space, through a virtual environment. In both cases, VR shows great potential to promote clinical change and to improve wellbeing (Riva et al., 2016).

1.3.2.2 CBT with VR for trauma patients

Meta-analyses of VR exposure therapy (VRET) for anxiety disorders have promising results (Carl et al., 2019; Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008). Carl and colleagues (2019) included five studies that assessed PTSD and found a medium effect size for VRET (g = 0.59) compared to waitlist conditions. However, when assessing all included studies (*N*=30) for various anxiety disorders, these researchers found a large effect size (g = 0.88) compared to waitlist conditions and a medium one compared to psychological controls (g = 0.78), with results similar at follow-up. In another meta-analysis (*N*=21 studies), researchers determined that VRET interventions in significant declines in anxiety symptoms (Parsons & Rizzo, 2008). Powers and colleagues (2008) found a large mean effect size (Cohen's d = 1.11) for VRET interventions, compared to control conditions (e.g. waitlist) in a meta-analysis. In a study conducted by Bouchard and colleagues (2017), VRET was more effective than in vivo exposure and waitlist for the treatment of social anxiety disorder, as measured using the Liebowitz Social Anxiety Scale-Self Reported version, and outcomes were maintained at 6-month follow-up. Participants (*N*=59, Female=43, M_{age}=34.5) in this study received CBT with VR exposure for 14 weekly 60 minutes sessions. For the purposes of treatment of multi-traumatized Inuit, exposure faces complexity of trauma, and might not be easily accepted nor safe, especially in remote treatment.

1.3.2.3. ER applications of VR

VR applications may be used to target ER in various ways. For example, Marín-Morales and colleagues (2018) showed that immersive virtual environments may elicit different emotional states in healthy participants (N=60, males= 24, M_{age}= 28.9), while monitoring physiological responses like heart rate variability and electroencephalographic potentials. In that study, patients were screened using the patient health questionnaire (PHQ-9) and the Self-Assessment Manikin (SAM). Researchers previously validated the Emotional Labyrinth (3D maze), an emotionally adaptive VR application aimed to promote mental wellbeing in a group of 20 participants (males=11, M_{age}=28.15; i Badia et al., 2018). These researchers used the Visual Analogue Scales (VAS) to quantifying the intensity of emotions and SAM to assess the following factors: arousal, pleasantness and dominance. Physiological responses, namely, electrocardiography, electrodermal activity, respiration and electromyography, showed consistent results with subjective emotion ratings (i Badia et al., 2018).

Others demonstrated corresponding neural activity in a sample of healthy adults (*N*=8) who were exposed to a nature VR environment in the fall season (a landscape of hills and cornfields), using a brain computer interface (Lorenzetti et al., 2018). These researchers also used various psychometrics to assess ER, such as the Emotion Regulation Questionnaire (ERQ) and the Satisfaction with Life Scale (SLS). Furthermore, Weerdmeester and colleagues (2017) exhibited promising results for the use of a biofeedback VR application game called "DEEP VR" in healthy adults (*N*=72, M_{age}=21.5). In their study, ER was assessed through the Trier Social Stress Test, a measure of psychobiological stress (Montana et al., 2020). This application is a great example of the utility of VR as a tool to help individuals better regulate their physiological arousal. Although these and other studies demonstrate the value of VR in improving ER, this approach has yet to be tested and culturally adapted among Inuit communities. ER was considered a holistic target of trauma treatment, safer for remote treatment than direct trauma clues, and thus, VR is the chosen technology to be tested in the future trial.

1.3.2.4. VR and pain

VR has even proven to be useful as complementary treatment among burn victims. In a study with adult outpatients (*N*=10, Males=8, M_{age}=47.1) undergoing routine burn care, VR was helpful as a complementary tool to pharmacological treatments (Ford, Manegold, Randall, Aballay & Duncan, 2018). In a review, researchers demonstrated that VR is effective as complementary to pharmacologic agents, to reduce pain and anxiety in patients with burn injury as they have wound dressing changes and physiotherapy, compared to other forms of distraction or using medications alone (Morris, Louw & Grimmer-Somers, 2009). This confirms VR's utility as an affordable, complementary tool that may be implemented in health care settings where feeling distress or pain is not uncommon. Several reviews of the literature have shown the utility of VR as a distraction approach to patients with pain (Malloy & Milling, 2010; Gupta, Scott & Dukewich, 2018). In addition to working through distraction, Gupta and colleagues (2018) concluded that VR may also be succeeding through neurophysiologic changes related to conditioning and exposure therapies. These researchers stress the promise VR shows in medicine, even in chronic pain conditions such as fibromyalgia, where VR in combination with CBT resulted in significant symptom reductions and increased perceived quality of life (Garcia-Palacios et al., 2015).

1.3.3 Psychophysiological Measures in Trauma

Recording psychophysiological measures provide a manner to safely guide VR based treatments, further inform/automate treatment and may differ among ethnic groups (Martínez et al., 2014). These measures directly assess one's ability to control bodily reactions when exposed to a given environment. By using psychophysiological measures during a session, safety is increased since the therapist is able to monitor a number of given variables (e.g. heart rate, skin conductance etc.) related to emotional triggers. This is especially important when therapy is conducted in remote settings. Montana and colleagues (2020) also stressed the significance of enhancing future study designs by including both subjective and objective outcome measures. Psychophysiological measures are not yet validated to be used as outcome independent treatments, but may provide a less subjective comparative measure in future protocols. Several studies mentioned in this review used physiological markers as an objective measure to compare to subjective report of emotional states, as experienced by the participants during the intervention. In two of the studies mentioned in their review, researchers used biofeedback to enhance ER, a process where individuals receive feedback on their physiological measures when exposed to an intervention (Montana et al., 2020). This set-up allows the therapist to interact with the VR environment and to alter scenarios based on the user's needs. In a study looking participants (N=30, Males= 17, M_{age}=27.5) and the fear of public speaking, researchers exhibited the value of using physiological signals in detecting anxiety, through VR exposure therapy (Šalkevicius, Damaševičius, Maskeliunas & Laukienė, 2019).

Psychophysiological measures may also enable automatized treatments as in adaptive VR and through self-management. *Adaptive VR* is an enhanced way of using VR to improve ER (Pizzoli et al., 2019). Researchers define an adaptive VR an environment that adapts its contents to the users' state in their current state. This is normally achieved dynamically through monitoring of psychophysiological measures to sustain a level of immersion and emotional reaction by the user (Pizzoli et al., 2019).

We conducted a systematic review on the *Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures* (see Appendix 1). The review aims to determine whether emotional processes are accurately characterized in individuals with PTSD and may be characterized with physiological variables (like HR, acoustic startle response, etc.) and which psychometric outcomes showed the greatest concordance to measures based on the literature and to inform the methods of the future validation trial. Through this systematic review, we concluded that psychometric outcomes (namely the Clinician-Administered PTSD Scale, CAPS) remain the gold standard as measures in trauma-focused interventions. However, psychophysiological measures contribute significantly through biofeedback and as a treatment outcome measure, and add to the efficacy of treatment by providing specific knowledge about an individual response. This work may inform future validation trials of psychophysiological measures in PTSD treatment.

1.4 Psychiatric support needed of the Inuit in Quebec

1.4.1 Telepsychiatry

Currently, telemonitoring and biofeedback is not common within the field of psychiatric practice. However, the Mental Health Commission of Canada advocates for the use of e-mental health to provide timely services for individuals with limited access (Schellenberg, Hatcher, Thapliyal, & Mahajan, 2014). Implementing telemonitoring could provide insight to treatment in northern Quebec. Additionally, with a current global pandemic crisis (COVID-19) and a need to maintain social distancing, the value of e-tools is increasing (Liu et al., 2020; Kannarkat, Smith, & McLeod-Bryant, 2020).

In a systematic review of telehealth to manage chronic conditions among Indigenous individuals, researchers found virtual approaches to be effective. Participants had reduced hospitalisations and decreased transfers to city-based health care centers (Fraser, MacKean, Grant, Hunter, Towers, & Ivers, 2017). The researchers emphasized including cultural safety methods in these platforms to increase acceptability of the intervention.

1.4.2 Rationale

Although VR exposure is validated as an exposure component (Katzman et al., 2014), it has not been previously tested or culturally adapted to Inuit in Quebec. To help reduce the significant suicide rates present in Inuit communities, improving emotion regulation through VR may be particularly of interest to their youth, who are severely impacted. Psychophysiological measures are needed to guide VR based treatments and differ between ethnic groups (Martínez et al., 2014). Previously, stimulus-response trials with patients who have PTSD detected distinct startle response, baseline cue-dependent reactivity and habituation compared to healthy individuals (Ramaswamy et al., 2015; Tegeler et al., 2017). Therefore, psychophysiological measures may help monitor treatment-related changes and with longitudinal data, phenotype of the pathology of trauma. Importantly, little is known about these differences in response with Inuit populations, as it relates to VR immersion treatment.

ER fits the holistic view of Inuit on wellbeing as it provides room for cultural adaptation and individualization of treatment through VR exposure. In a recent review of the literature on the use of ER interventions in VR to enhance wellbeing in adults, researchers have concluded that not many applications have been scientifically tested, and only two studies mentioned having tested immersive VR applications in patient populations (Montana et al., 2020). Additionally, no studies have been conducted using VR interventions to target ER among Inuit in Quebec. Therefore, this line of research is novel in addressing the unmet needs of a vulnerable group who continues to experience a mental health crisis surrounding trauma and suicide and cannot access traditional, psychiatric services and therapist-centered psychotherapy (Chachamovich et al., 2015).

This thesis is composed of the various steps taken and data collected so far, leading up to our future validation trial, with a focus on providing a culturally adapted VR treatment using ER for Inuit community members. As part of our plan, we hope to integrate new technology such as wearable sensors, VR headsets and applications, to enhance network connections and therefore provide a high-tech solution to treatment and monitoring of patient progress. Included in this thesis are two manuscripts to be submitted: a systematic review on the *Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures* and the validation study protocol.

2 CHAPTER 2: RESEARCH QUESTION, OBJECTIVES, HYPOTHESIS

2.1 Aims

1. To evaluate factors affecting acceptability, feasibility, and cultural safety of VR applications among the Inuit of Quebec.
2. To conduct a systematic review on the Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures.
3. To test the validity of psychophysiological measures, in a laboratory setting, to potentially act as surrogates to psychometric outcome measures.
4. To use all knowledge obtained from aims 1&2 to plan the clinical trial and write the trial protocol.

2.2 Research Question(s)

1. **Main Question:** Do Inuit accept VR as a tool for psychiatric treatment? (Aim 1)
2. **Feasibility Study:** What are the elements in the landscape and soundscape that Inuit are likely to find relaxing/stressful/relevant for cultural safety? (Aim 1)
3. **Systematic Review:** What is the utility of psychophysiological measures in complementing psychometric scales in longitudinal studies with PTSD patients? (Aim 2)
4. **Physiological Measures Study:** What are the optimal psychophysiological measures that correlate with trauma-related symptoms and stimuli responses (relaxation and stress exposures)? (Aim 3)

2.3 Primary Outcomes

Overall goal:

1. Development of a research protocol for a future clinical trial to be presented to the Inuit advisory group.

Primary outcomes:

1. Feedback from key Inuit informants on the acceptability and utility, ease of use and favored themes of VR applications.
2. Psychometric outcome for the trial with strong concordance to psychophysiological measures in trauma based on systematic review.
3. Optimal measures and potential cut-off points of physiological measures for the trial.

2.4 Hypotheses

Feasibility, acceptability and cultural safety. We hypothesize that culturally adapted VR will be readily accepted and feasible among key Inuit informants and participants, as measured qualitatively through semi-structured interviews and focus groups.

Primary outcome for selection of measures for outcome in the trial. We hypothesize that the psychophysiological measures (electromyography, heart rate, and skin conductance reactivity, blood pressure levels) could reliably complement the CAPS to describe outcome of trauma therapy.

Physiological measures. We hypothesize that the mean psychophysiological (heart rate, heart rate variability, skin conductance, temperature) response between Inuit and healthy and patient control groups will be quantifiably different (see psychometrics Study 3).

3 CHAPTER III: METHODS AND PROCEDURES

My thesis is part of a larger project aiming at validation of a Virtual Reality-Cognitive Behavioural Therapy (VR-CBT) to treat trauma. A protocol called *Use of virtual reality exposure as a component in remote medical treatment among Indigenous populations – a proof of concept study* has been approved by the Douglas Institute Ethics Committee (IUSMD-19-24, Date of letter of approval: October 31, 2019). My thesis includes the feasibility and acceptability of VR (Study 1 of the protocol IUSMD-19-24) and the methods for the validation of the psychophysiological measures (Study 3 of the protocol IUSMD-19-24) and the planning of the future validation study through development of that protocol (see Figure 2). Additionally, we completed a systematic review on the *Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures* (see Appendix 1). Additionally, to plan for the future trial, this thesis includes a second manuscript, the protocol for the validation study which was developed from the aims of this thesis (see Appendix 2).

The selected group of individuals for this study consist of a vulnerable population and are likely to have been exposed to traumatic experiences. Therefore, greater caution will be placed on ethics at every step of the research process to ensure safety in participation. This research is guided by the principles of ownership, control, access and possession (OCAP; Tri-Council Policy Statement 2010). These guidelines apply to Inuit, First Nations and Métis communities across Canada and provide structure for privacy, intellectual property, data custody and secondary use of data. In adherence to these values, respect for persons is necessary and this is achieved through free, informed and continued consent. Additionally, financial compensation and feedback will be provided for all participants involved in the study. There will be co-signing of scientific reports and continuous collaboration throughout the research process with the Inuit community, to promote ownership and access to knowledge.

3.1 Study design and population

Study designs

This thesis summarizes a tripartite study towards a culturally-adapted VR-CBT for Inuit in Quebec (see Figure 2). Firstly, focus groups and community stakeholders were interviewed on the feasibility and acceptability among Inuit in Quebec of components of our proposed VR treatment. Secondly, study 2 is lead and conducted by other members of the laboratory. Thirdly, we systematically reviewed psychophysiological measures tested in PTSD, to guide the selection of appropriate metrics of our proposed VR-CBT (see Appendix 1). Lastly, informed by the previous research works, I prepared a research protocol for a randomized controlled trial of the culturally adapted VR-CBT (see Appendix 2). The proposed protocol for a future trial will be processed with an Inuit advisory group towards the final version.

Populations

During Study 1, our goal was to recruit a total of 15 Inuit, aged 14 years or older and health care professionals working with Inuit patients. Exclusion criteria included any medical history of heart conditions, epilepsy, increased risk for convulsions e.g. acute substance use.

For the Psychophysiological Measures study (Study 3), we will to recruit 20 healthy controls, 20 patients from the Douglas Institute and 20 Inuit with trauma symptoms. The inclusion criteria for the psychophysiological measures study are: current state stable as evaluated by the clinician, 14-60 years of age, ability to tolerate a virtual reality helmet, comprehension of one's role in the study and the risks and possessing a level of English or French that allows one to take informed consent and to understand study instructions. The exclusion criteria for that study include: currently abusing alcohol or drugs (over the last 2 weeks), changes to psychoactive medications (in the past 4 weeks), history of psychosis or schizophrenia, medical history of heart conditions or epilepsy, active suicidal risk, consumption of alcohol/caffeine/stimulants/cannabis within 24 hours prior to the session, and nicotine consumption within 15 minutes of the VR testing session.

Measures

Study 1

Qualitative interview guides (see Appendix 3).

Study 3

PTSD checklist for DSM-5 (PCL-5; Weathers et al., 2013). The PCL-5 is a 20-item validated questionnaire to assess PTSD symptoms based on the DSM-5 over the previous month. Each item is rated on the following five options: “not at all”, “a little bit”, “moderately”, “quite a bit”, “extremely”. It has been previously administered at all assessment time points (i.e., pre-treatment, 6-week post-treatment assignment, post-treatment, 3-month follow-up) as well as across treatment sessions (see Appendix 4).

Patient health questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is a nine item validated measure of general health, including depression and distress (Kroneke et al., 2001). Participants rate frequency of depressive symptoms over the past two weeks as either: 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), or 3 (“nearly every day”). The PHQ-9 has been previously administered at all assessment time points: pre-treatment, 6-week post-treatment assignment, post-treatment, and 3-month follow-up (see Appendix 4).

Childhood trauma questionnaire-short form (CTQ-SF; Bernstein et al., 2003). The CTQ-SF is 28-item retrospective validated measure of childhood and teenaged experiences surrounding topics of varying forms of abuse (physical, emotional, sexual), and physical and emotional neglect. Participants select from the following options to rate each item: 1 (“never true”), 2(“rarely true”), 3 (“sometimes true”), 4 (“often true”) or 5 (very often true; see Appendix 4).

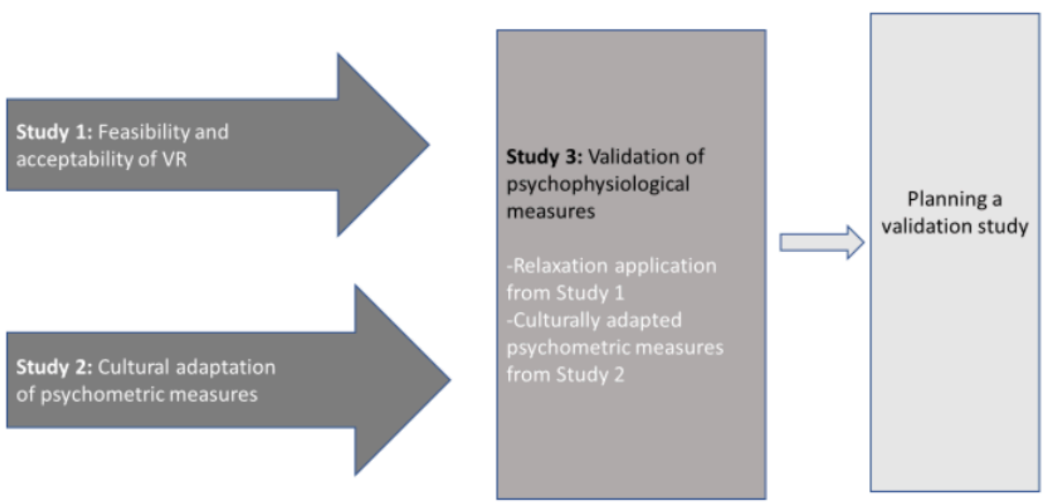
Generalized anxiety disorder 7-item (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006). The GAD-7 is a 7-item validated questionnaire meant to assess symptoms of anxiety in the previous two weeks. Participants rate each item from “not at all sure” to “nearly every day”. This scale has been shown to be reliable and is meant to be used for screening and monitoring of anxiety related symptoms (see Appendix 4).

Visual Analogue Subjective Affect Scales (VAS; Monk, 1989). The VAS is a self-report measure aiming to assess how participants currently feel. It consists of three items and participants are asked to rate on a spectrum where their current emotional state lies on each of the items. The first vector is labeled "not at all anxious" to "very anxious". The second, "very calm" to "very excited" and the third vector measures feeling "very pleasant" to "very unpleasant" (see Appendix 4).

Preparation of the lab

The set-up of the testing lab took several months. This included choosing, purchasing and learning how to use: the necessary computer equipment to run VR technology, the latest VR Oculus Rift S headset, the appropriate wearable finger sensor TPS from Thought Technology and its associated analysis software. Developing this optimal system with sensors, data collection/transfer, data cleaning, processing and user interface for measures is all necessary for a validation trial. Choosing the optimal sensor also meant finding one sensitive enough to changes during and across sessions and this involved comparing with popular alternatives such as the Shimmer GSR+.

Figure 2. Flowchart of the three studies in preparation for the validation study.



Note. This figure is obtained from an approved protocol submitted to the Douglas Institute ethics committee. This thesis includes all aspects of this figure except Study 2. The systematic review is also included (see Appendix 1).

3.2 Procedures

All participants were required to provide informed consent prior to participation.

Study 1

In assessing the cultural acceptance and feasibility of a guided relaxation treatment using virtual reality immersion, the overall steps were the following. Firstly, to choose the optimal tools, including the preferred headset, preferred relaxation application and features etc. Secondly, to determine which elements of the VR exposure improve or decrease its usability. Thirdly, to adjust the necessary VR intervention content to increase cultural safety. Therefore, after training the personnel from Ullivik center (e.g., nurses) to use VR applications in their daily work, qualitative data was collected from them. A semi-structured interview and focus group format was used (see Appendix 3). Each of the interviews were recorded in audio format and transcribed. The transcripts were de-identified and then destroyed. The VR relaxation applications used have been reported to be safe and efficient and last between 9-30 minutes (Lindner et al., 2017). The VR headsets used were wireless: Oculus Go and Oculus Quest. Some participants chose to provide general feedback without using the headset directly. Participants all received financial compensation for their participation in the study.

Study 3

After obtaining informed consent, each VR-CBT session begins with the completion of a Visual Analogue Subjective Affect Scale (VAS) on current affect. Following habituation to the sensors, the participants complete the remaining a set of questionnaires. This habituation also allows for baseline measurement of physiological variables. The therapy then progresses to the first VR stimulus, a relaxation environment for 10 minutes. After they complete this period, participants fill out another VAS. We then begin a culturally safe height-exposure VR paradigm, which was developed by our collaborator's team Dr. Stephane Bouchard. Immediately after this exposure, we record their psychophysiological measures again and we ask participants to complete a subjective report of how they are feeling (VAS). After a spontaneous recovery period, we record their psychophysiological measures again. At post-testing, the results may be discussed with the participants.

3.3 Statistical Analysis

To evaluate the feasibility of VR components for the future intervention study, qualitative methods were used in Study 1 to analyze the semi-structured interviews and observations made. A preliminary thematic and content analysis of the interviews was conducted to identify the different perspectives and opinions of people regarding VR immersion, to determine what elements of the VR exposure influence its usability. The main categories used to organize and analyze the data included relevance and cultural safety of the use of VR. This will allow for making necessary adjustments to the content of the relaxation treatment in the trial, based on the feedback obtained.

In Study 3, the difference in physiological arousal between baseline, relaxation and exposure is measured. As well as detecting any change in subjective affect ratings following VR stimuli and their concordance with objective physiological measures. Additionally, we can assess temporal outcomes, such as the time between baseline and highest peak of amplitude during exposure and the time between highest peak of amplitude during exposure and spontaneous recovery to baseline. This is important since individuals with PTSD tend to have higher resting arousal and delayed recovery to baseline after exposure to stimulating content (Hauschildt, Peters, Moritz & Jelinek, 2011).

4 CHAPTER IV:RESULTS

4.1 Participants

Study 1

The data collected this year from participants involve three different sources (see Appendix 5). Firstly, members of our lab conducted the cultural adaptation of the Growth and Empowerment Measure for Inuit in Quebec. We received comments concerning the general idea of using VR from the members of this committee [GEM comity; composed of Inuit members (*N*=4, Female=3)]. Members of this comity were all social/community workers and one was a director of an association for Inuit. The other two sources of data came from research assistant applicants (*N*=5), which was collected less formally, and the health care personnel working in community centers such as Ullivik (*N*=10). These participants were all adults, living in Montreal and mostly women (Male=2). The health care professionals provided feedback after testing existing relaxation apps. These key informants were from Montreal and Nunavik and have all worked with Inuit for many years.

4.2 Qualitative data

Study 1

Feasibility. Health care professionals (*N*=10, Female=10) who work with Inuit informed us that an application is a great idea, especially for young people in Nunavik. They also confirmed that there is no doubt about the pertinence of the project and were of the opinion that it is easy to use. The GEM comity felt that VR is generally feasible as well.

Acceptability and cultural safety. Based on the preliminary collected data, VR is generally accepted. The GEM comity felt that VR will be accepted and stated that it may be especially popular among the youth. Some favored themes that came up include wintertime, northern landscapes, community, cultural traditions (throat singing, drummers, making of necklaces etc.). A relaxing video was widely accepted as a positive introduction to health treatment using VR.

Feedback for improvements. The health professionals suggested for the team to focus on simple elements. Colors that were mentioned as positive by the GEM comity included: green (nature), orange (growth), pink (seal lover) and purple. It was suggested to incorporate images of water, view of the sea and open spaces (northern landscapes) which all represent healing elements within Inuit culture. Health care workers also appreciated the soothing voice in the meditative application and suggested that participants should be able to select the music of their choice.

4.3 Systematic Review

A systematic review, *Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures: A Systematic Review*, was conducted (see Appendix 1). This review has guided the outcome measures in the planning for the trial protocol. In summary, through this review, it was determined that the primary outcome for the trial will be psychometric. Specifically, changes observed in psychophysiological measures, namely: heart rate, heart rate variability, skin conductance, electromyography and systolic blood pressure, were all statistically significantly correlated to differences in the CAPS questionnaire, a gold standard assessment of PTSD symptoms. However, lacking clear cut-offs for recovery the psychophysiological measures are not suitable to be used as outcome measures as such. Although heart rate was the most frequently used among the various studies to assess PTSD symptom outcomes, results were conflicting. Heart rate variability showed similar contradictory results (see Appendix 1). Nonetheless, biofeedback can be expected to increase efficacy of the trial and to complement psychometrics in predicting outcome and measuring efficacy in specific physiological responses. Therefore, psychophysiological measures will be included in the trial protocol.

4.4 Psychophysiological Measures: Study 3

Data collection to assess psychophysiological response between Inuit and healthy and patient control groups did not take place due to COVID-19. This data collection will take place at a later date when clinical research may be conducted safely. It is expected that varying psychophysiological responses will exist between patients from the Douglas, Inuit with a history of trauma and healthy control.

4.5 Protocol for Intervention Study

A protocol for the intervention study, to provide culturally adapted VR treatments for trauma-related symptoms for Inuit communities in Quebec, was developed to be submitted as a manuscript (see Appendix 2).

5 CHAPTER VI: DISCUSSION

5.1 Key findings

This thesis was aimed at developing a trial protocol for an intervention study (see Appendix 2). The goal of this study is to improve ER related to trauma among Inuit in Quebec. ER as a target is helpful among trauma exposed populations, as it mediates its effect on psychiatric symptoms, anxiety, depression, sexual abuse and substance abuse (Schäfer et al., 2017; Chang et al., 2018; Paulus et al., 2019; Karatzias et al., 2018).

To thoroughly develop this protocol, we strived to evaluate the factors that impact acceptability, feasibility, and cultural safety of VR applications through qualitative approaches. Specifically, VR was readily accepted thus far and is feasible among key Inuit informants and participants, as measured through semi-structured interviews, focus groups and self-report measures. The feedback obtained provide a crucial first step towards cultural adaptation of a future VR intervention.

Additionally, the systematic review on the Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures confirmed our second hypothesis, that the psychophysiological measures may compliment the CAPS assessment to measure outcome of trauma therapy (see Appendix 1). Taken together, all these segments are key pieces of information which helped inform the recently developed protocol. Further, through our systematic review of the literature, it was determined that psychophysiological measures cannot be used as a primary outcome measure for the future trial. However, previous work has shown that individuals with PTSD show elevated heart rate at resting or when exposed to a neutral environment, which the use of psychophysiological measures may help to quantify and monitor (Hopper, Spinazzola, Simpson, & van der Kolk, 2006). Including psychophysiological measures as a secondary outcome in the future protocol will enhance the safety of participants and also provide an objective measure of treatment progress of a trauma exposed group. Additionally, these tools may help us to better identify moments of emotional arousal and changes in cognitive processing among participants with PTSD to enrich our future interventions.

5.2 Study limitations

The collected qualitative data from health care professionals and key informants this year does not go without limitations. Firstly, it is based on a small sample size, with very few men in the sample (*N*=2). However, amongst the feedback collected thus far, none was strongly negative and the informants were either Inuit and/or had direct contact with Inuit communities for many years. Furthermore, the study is cross-sectional in design and therefore is susceptible to recall and responder bias. Nonetheless, the advantages to this design are that it is more feasible and cost-effective.

An additional limitation is that alcohol/substance use is not compatible with VR. As part of safety measures, we have included these specifications in our limitations. Rates of substance use are high in Inuit communities and this means an added barrier with using VR at both a research and clinical level. To mitigate this barrier, we have consulted with other groups who have used VR in populations that also encounter substance use and they have suggested using a device to check alcohol level prior to participation in the study. We plan to also screen for use of illegal drugs and cannabis and to exclude participants who demonstrate a significant level based on pre-set cut-offs (see Appendix 2).

Another present limitation is the translation of questionnaires in Inuktitut in the protocol, which will decrease reliability when comparing to other validated scales. However, the study design does involve testing at several time points, and repeated data collection for the scales included (baseline, at the end of treatment and follow-up). Therefore, we can expect to detect a reliable change. We intended to include the culturally adapted and translated GEM measure (selected by the advisory committee) to assess factors supporting healing, yet, we cannot integrate it into the protocol since it lost necessary scale properties through this adaptation process (e.g. it doesn't produce a quantifiable score).

The largest limitation present in the thesis work this year was the COVID-19 pandemic, which halted clinical research and participant recruitment/testing. There were some items we had planned to research that remained unaddressed due to human research restrictions. This includes the full data collection for the psychophysiological measures study (study 3), through which we aimed to determine the optimal outcome and the validation of the cut-off points for the trial. To account for this, the systematic review conducted was used to determine the optimal primary outcome for the protocol, which is the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) questionnaire. We also hoped to quantify the predicted ethnic differences in response to VR exposures through this study, which lacking this data has not allowed for. Although we were unable to collect data to address the third and final hypothesis of this thesis and to determine whether a difference exists in psychophysiological response between Inuit and healthy and patient control groups based on cut-offs, this study will be conducted at a later date when health officials determine effects of the pandemic are reduced and it is safe to do so. Additionally, we were unable to collect any patient data for the Feasibility study.

As for the systematic review, some of the limitations include that only English publications were considered. Additionally, there was no standard measurement for the biomarkers. The researchers used varying measures in the chosen studies and there is no clear way to account for those variances. This also implies that there may be insufficient quantity of data for some of the measures which makes it difficult to make accurate comparisons between the chosen measures (see Appendix 1).

This line of research has significant strengths as well, since novel tools, such as VR, are promising as complementary to traditional clinic-based psychiatric healthcare. This is the first time VR as a tool is used in Inuit population in Quebec. In addition, we are advocating for the use of psychophysiological measures, which is innovative and yet to be implemented as a gold standard in trials as determined through our systematic review. To our knowledge, this is the first systematic review to address longitudinal studies within our specific focus. Having an objective measure of bodily reaction to an emotionally triggering stimulus may complement self-report measures and maybe even be used as a future surrogate tool. This may also reduce respondent bias. So far, we have not received any significant negative feedback from key Inuit informants and health care professionals involved with Inuit communities. A true strength of our line of research is also the involvement of key Inuit informants at every stage of the research process. We value inclusiveness and engagement in an enriched learning environment for our team and a culturally safe space for all. Through our research work, we hope to increase knowledge of factors affecting cultural safety of VR and about acceptance of technology to improve mental wellbeing.

6 CHAPTER VI: FUTURE DIRECTIONS

6.1 Conclusions and future directions

Psychiatrists and other mental health care professionals are faced with various barriers when providing treatment to remote communities. Novel tools, such as VR, are promising as complementary to traditional clinic-based psychiatric healthcare. This work has contributed to increasing knowledge of the factors that impact acceptability, feasibility and cultural safety of VR to improve mental wellbeing among Inuit in Quebec. The goal is for this developed protocol, for a future validation study, is to test a culturally adapted VR treatment for trauma-related symptoms, targeting emotion dysregulation among Inuit communities in Nunavik.

The next step of this process is to finalize the protocol with the advisory committee, composed of Inuit members, to ensure cultural safety and maintain OCAP principles. With their support, the laboratory will be able to begin the project in the coming months. Our ultimate goal through the trial is to provide culturally safer psychometric treatment. However, in the long term, we hope this treatment approach reaches populations who cannot access traditional, therapist-centered psychotherapy. Using VR assisted CBT in other populations has increased efficacy of therapy, has made cultural adaptation of landscapes and soundscapes possible, and will hopefully increase acceptance of the therapy in this population.

If the trial is successful, there may be some associated risks. For example, remote treatment will only be possible if we are successful in real-time data transfer to the therapist's location to maintain continued engagement in therapy. This enhances the safety of the process as psychophysiological measures make it possible to adapt the type, intensity and duration of exposure to a given environment based on the needs of the patient. To facilitate this method, our team has partnered with the National Research Council to develop an interface to manage this data, called bConnected. This research platform is currently being designed by a team composed of health care professionals, developers and researchers. bConnected will be adapted to the specific needs of the project by ensuring that technological tools have enough bandwidth to transfer sufficient data in real time which will optimize remote treatment.

In order to succeed in the implementation of the trial, cultural safety needs to be maintained throughout every stage. To accomplish this objective, we plan to continue to engage with Inuit collaborators in the research process to confirm technological feasibility, ethical viewpoints and confidentiality. This enhanced engagement may lead to general shift in the unmet needs to support mental health services. Additionally, we have recruited a diverse team to conduct this study, with a strong representation of women, several members are Inuit and/or Indigenous and several others are immigrant researchers. This will help to mitigate any cultural or language barriers encountered, including having individuals who can formally translate validated psychometric scales to Inuktitut, a principal language of Inuit in Canada. In addition, we are currently working with a team of researchers to design the VR-CBT therapy manual that will be implemented in the future trial (see Appendix 2). To enhance cultural safety, we also plan to assess the therapists' cultural competence.

In the future, the best correspondence could be based on individual needs and treatment modules automatized by psychophysiological measures. This would involve the therapist using a telemonitoring format, with psychophysiological biofeedback and the adaptive VR treatment using automatized treatment modules. If the trial is successful, this will allow for a low cost but high-quality VR exposure therapy for enhancing ER among Inuit. If this VR-CBT treatment is successful, there may be less need to travel to the Montreal for therapy and this may help reduce some of the cultural shock experienced each time members of Nunavik have to commute for health care services. As well as to reduce individuals needing to leave family and friends behind at times when traveling to Montreal for health-related services. This will also help in reducing transport costs and to target crisis situations faster, such as suicide and decrease risk related to these circumstances. These were all mentioned barriers by the community about the current health services situation in Nunavik (Parnasimautik Consultation Report, 2014). In addition, if therapy is more accessible and shows positive results, this may increase levels of engagement by the Inuit community. This means that our VR-CBT treatment may also be widely applied to other Indigenous populations that live remotely and may benefit from this service. These teletherapy tools may also translate to other trauma settings where they can also be useful, for example, among humanitarian workers, police or firemen, or military personnel and members of the space program. Additionally, with a current global pandemic, e-health tools and services have become invaluable (Liu et al., 2020; Kannarkat, Smith, & McLeod-Bryant, 2020).

We hope that our VR-CBT intervention will be a successful tool targeting ER to heal trauma and mitigate the consequences of the current Inuit mental health crisis in Quebec. We hope that through this work and collaboration with Inuit communities, we are able to strengthen our ties and build rapport with Inuit communities in Quebec by increasing their involvement in their health care. The sustainability of this project was ensured from the start. Upon completion of the study described through the presently developed protocol, similar services will be integrated into the Douglas Institute. These services will be managed by Dr. Gustavo Turecki and Dr. Eduardo Chachamovich through the Réseau Universitaire Intégré de Santé et Services Sociaux (RUISSS).

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6.3 Appendices

6.3.1 Appendix 1: Systematic Review

Utility of Psychophysiological Metrics as Trauma Intervention Outcome Measures: A Systematic Review

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Abstract

The reliability of standard subjective symptoms assessments of post-traumatic stress disorder (PTSD) can be compromised by memory, emotional, cultural and linguistic biases. Comparatively, dynamic emotional changes may be objectively indicated by physiological responses. We examine in this systematic review the clinical utility of psychophysiological markers of trauma responses and their longitudinal changes during treatment. Here, 20 articles were identified that reported the magnitude of treatment response through the amplitude of electromyography, heart rate, and skin conductance reactivity, blood pressure levels, and elapsed time from peak trauma-cued arousal to baseline levels. Physiological measures were found to be useful to personalize the type and strength of stimuli in exposure therapies, as an indicator of reduced dysfunctional coping strategies, and as biofeedback. Psychophysiological sensors could capture some otherwise undetected characteristics, such as the most effective components of treatment. However, psychometrics remain the most reliable outcome measure of treatment for post-traumatic stress. Given the sensitivity of psychophysiological markers to changes in trauma symptoms, the effects of trauma interventions on emotional processing may be phenotyped with physiological measurements. The current findings could provide opportunities for the development of wearable sensing technology that can be used in-vivo during experimental and clinical procedures. As available data is limited, further research is needed to confirm clinical utility of psychophysiological measures and provide valid response cut-offs. Future work could complement psychometrics with psychophysiological assessment, and integrate ambulatory psychophysiological systems into testing protocols.

Keywords:

heart rate, skin conductance, blood pressure, electromyography, treatment, longitudinal, Clinician-Administered PTSD Scale

1. Introduction

The autonomic responses of patients with post-traumatic stress disorder (PTSD) to stressors may be heightened or dampened in comparison to that of the general population. In experimental settings, a dysregulated dynamic between the sympathetic and parasympathetic nervous system during fear conditioning paradigms has characterized PTSD-related responses (Campbell, Wisco, Silvia, & Gay, 2019; Sack, Hofmann, Wizelman, & Lempa, 2008). In cross-sectional studies, individuals with PTSD have a higher resting physiological arousal, such as higher resting heart rate (HR) and skin conductance (SC), show heighted reactivity to startling sounds and trauma cues, and delayed recovery from cue-activated startle to baseline levels (Campbell et al., 2019; Hauschildt, Peters, Moritz, & Jelinek, 2011; Kibler & Lyons, 2004; Nachar, Lavoie, Marchand, O'Connor, & Guay, 2014; Park et al., 2019; Volchan et al., 2011). Dysregulated physiological responses are seen not only in response to external stimuli such as trauma cues, but also to internal stimuli, such as intrusive thoughts about trauma (Sherin & Nemeroff, 2011; Williamson, Porges, Lamb, & Porges, 2015). Furthermore, there is some evidence that this abnormal response might characterize response to a variety of anxiety or stress-provoking stimuli, such as height exposure (Norton & Paulus, 2017). Because these emotional processes have been experimentally phenotyped in real-time using wearable devices (Fletcher, Tam, Omojola, Redemske, & Kwan), it is possible that they may have utility in the assessment of trauma severity.

To date, psychometric scales (F. W. Weathers, Keane, & Davidson, 2001) have been the gold standard of trauma assessment. However, several factors have limited the reliability of traditional psychometric across experimental and clinical settings. In trauma patients, it is common to encounter recall bias when administering psychometric tests, either due to retrospective reporting, or as part of the trauma- and anxiety-related cognitive distortions (Baldwin, Reuben, Newbury, & Danese, 2019; Paunovi, Lundh, & Ost, 2002; Samuelson, 2011). The impact of personal biases, cultural, linguistic and various other factors may also be considerable (Poels & Dewitte, 2006). Overall, there is a need for alternative, non-verbal, and less subjective methods of assessment, especially when testing among highly traumatized and vulnerable populations, such as ethnic or gender minorities and immigrants.

The insight- and cognition-related biases may be surpassed through measuring physiological processes governed by the autonomic nervous system. Electrodermal activity is an example of a discrete physiological sign that can be a measure of arousal below the conscious level, such as a gradual buildup of stress that cannot be otherwise captured by subjective measures (Leonard et al., 2018). Although psychophysiological measures are widely used in lab-based research, such as work on emotion regulation (Busch, Possel, & Valentine, 2017; Holzman & Bridgett, 2017; Ottaviani et al., 2016; Wallach, 2015; Watkins & Roberts, 2020; Zaehringer, Jennen-Steinmetz, Schmahl, Ende, & Paret, 2020), the utility and validity of their clinical use and in trials has not been synthetized and remains unclear (Savage et al., 2019).

In this systematic review, we describe psychophysiological measures used in a clinical setting as trauma intervention outcome measures. We integrate the knowledge about longitudinal changes in psychophysiological measures, their sensitivity to emotional change and concordance with psychometric scales, and indicators of response to trauma-based treatment.

2. Methods

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 Literature search

A search for studies on trauma-focused interventions was conducted in three databases: PubMed, Medline, and PsychInfo from inception to July, 2019. Hand-searches for supplemental grey literature was done on Google Scholar and through searching for citation relationships. Three levels of search terms were used; this included terminology for "post-traumatic stress disorder", "psychophysiological measures" and "treatment outcome". A full search strategy is presented in **Supplement 1.**

2.2 Eligibility criteria and study selection

Two blinded reviewers (MY and NM) selected the eligible abstracts and titles for further investigation. A third reviewer (OL) confirmed whether the selected articles met the eligibility criteria and rendered a decision on any discordance.

At the full-text review stage, the reviewers assessed all original articles for eligibility based on several criteria. Chosen studies reported psychophysiological measurement values at pre- and post-treatment. The selected populations included adults, veterans and patients with primary or comorbid PTSD, had elevated PTSD symptoms, or had experienced acute psychological trauma. The studies presented results on the intervention's effects on PTSD symptoms and on psychophysiological functioning. We included only studies with repeated psychophysiological markers from prospective and trauma-focused interventions. The chosen studies have comparable cases and controls and were published in English–language journals. We excluded studies with interventions directly reducing physiological dysregulation or were preventative training (including stress inoculation or resilience training), and nonrandomized quantitative assignments of treatment or retrospective or observational study designs.

For the definition of PTSD, we included, according to a recent meta-analysis (Campbell et al., 2019), any measure that assesses PTSD symptoms, including measures linked to The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for PTSD, measures linked to The International Classification of Diseases (ICD) criteria, or measures that pre-date the DSM but are well-established measures of PTSD. In cases of duplicate data (i.e., multiple studies included the same participant sample), the study that provided a larger dataset or was published first was used.

2.3 Data evaluation and synthesis

From each article, we extracted data on population characteristics, intervention types, both subjective and objective outcome measurements (see **Supplement 2 and 3)**, intervention's effect on psychophysiological measures, and measurement concordance between psychophysiological and psychometric measures. Results were grouped by theme of intervention (**Table 1 and 2)**. Trends in psychophysiological response were extracted and interpreted in terms of the clinical utility and limitations to the psychophysiological methodology taken by the studies. We analyzed the physiological data as raw values, reactivity, or reactions to stimulus cues specific to the study.

3. Results

3.1 Study Selection

Out of a total of 524 articles identified through the systematic search, 19 were included in this review. The PRISMA flow diagram of the study selection process is presented in **Fig. 1** (Moher et al., 2009). The description of study participants, interventions, and measures are presented in supplement 2. Although they met all inclusion criteria, one study was excluded due to missing raw data (Griffin, Nishith, Resick, & Yehuda, 1997), and another due to a lack of specified gold-standard instrument used to assess PTSD symptom levels (Brunet et al., 2014). Though they are psychophysiological measures governed by the autonomic nervous system, respiration (Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009), respiratory sinus arrhythmia (Sack, Lempa, & Lamprecht, 2007) and baroreflex sensitivity (Tegeler et al., 2017) were each only used once, they were not included in the analysis.

Effect sizes were infrequently reported by the studies; we instead relied on p-values when comparing the results of the interventions. We considered statistical significance at the $p<0.05$ level.

3.2 Sensitivity of psychophysiological measures to longitudinal change (Table 1)

Cardiac Markers: Heart Rate (HR) was the most useful marker of fear activation, and significant changes in HR reactivity to trauma cues were seen in 8/15 studies (Dunne, Kenardy, & Sterling, 2012; Hoge et al., 2012; Isserles et al., 2013; Loucks et al., 2019; Renfrey & Spates, 1994; Sack et al., 2007; Tucker et al., 2000; Wangelin & Tuerk, 2015). Reactivity, baseline, and recovery HR all improved as a result of treatment in 7/15 studies (Dunne et al., 2012; Isserles et al., 2013; Loucks et al., 2019; Renfrey & Spates, 1994; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco, Baker, & Sloan, 2016). At baseline, patients with PTSD usually presented lower Heart Rate Variability (HRV) than the range for healthy adults (Ramaswamy et al., 2015; Reyes, 2014; Zucker et al., 2009). As a result of treatment, 4/5 studies reported increased HRV (Ramaswamy et al., 2015; Reyes, 2014; Tegeler et al., 2017; Zucker et al., 2009), which correlated with reduced hyperarousal (Wahbeh, Goodrich, Goy, & Oken, 2016). High frequency HRV (HF-HRV) had more immediate sensitivity to intervention stimuli than low frequency HRV (LF-HRV) (Ramaswamy et al., 2015). However, LF spectrum showed maintained intervention effects by being significantly lowered at follow-up (Reyes, 2014). While Blood Pressure (BP) in PTSD patients was initially higher at baseline, BP consistently decreased following intervention in 3/4 studies (Dunne et al., 2012; Schubert et al., 2019; Tucker et al., 2000), reaching a normal range for healthy adults (Dunne et al., 2012; Rothbaum, Ruef, Litz, Han, & Hodges, 2003; Schubert et al., 2019; Tucker et al., 2000). Systolic blood pressure was more likely to improve than diastolic blood pressure (Rothbaum et al., 2003; Schubert et al., 2019; Tucker et al., 2000). This reflected how systolic blood pressure was more sensitive to phasic stress-responses than chronic (tonic) stress when presented with trauma scripts.

Electrodermal activity (EDA): Skin Conductance (SC) levels were notably decreased as a result of treatment in 6/8 studies (Hoge et al., 2012; Loucks et al., 2019; S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Van't Wout et al., 2017; Wangelin & Tuerk, 2015), and 3/8 showed statistically significant findings (Hoge et al., 2012; Van't Wout et al., 2017; Wangelin & Tuerk, 2015). These improvements in EDA were not always linear; SC changes were sometimes more profound at mid-treatment or at follow-up rather than at post treatment (S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Van't Wout et al., 2017; Wangelin & Tuerk, 2015).

Electromyography (EMG) startle response: Startle response was reduced in 2/4 studies (Carlson, Chemtob, Rusnak, Hedlund, & Muraoka, 1998; S. D. Norrholm et al., 2016). Some results proposed that startle response was more sensitive than SC and HR in indicating treatment outcome in the presence of enhancement (ie: D-Cycloserine) (S. D. Norrholm et al., 2016). Immediately following treatment, EMG outperformed other indicators of habituation effects (Carlson et al., 1998; S. D. Norrholm et al., 2016).

3.3 Concordance between treatment response and psychophysiological measures (Table 2)

Decreased HR: Although there were noticeable reductions in HR following most of the treatments, only 4/15 of the studies showed statistically significant correlations between HR and Clinician-Administered PTSD Scale at post-treatment (Isserles et al., 2013; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016). HR was used consistency as an outcome marker for exposure therapies.

Increased HRV: At post-treatment, an increase in HRV showed correlation with decreased PTSD symptoms in 4/5 studies (Ramaswamy et al., 2015; Reyes, 2014; Tegeler et al., 2017; Zucker et al., 2009) . Positive treatment response increased baseline and recovery HRV, and recovery HRV could indicate between group differences (Zucker et al., 2009); this was especially significant for biofeedback intervention. In one study (Ramaswamy et al., 2015), the direction of changes in HRV did not correspond to direction of change in PTSD severity.

Decreased EDA: While only 1/8 study found concordance between the intervention's effects on SC and on Clinician-Administered PTSD Scale (S. D. Norrholm et al., 2016), exposure interventions, in particular, had an impact on SC responses in 5/8 studies (Loucks et al., 2019; S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Van't Wout et al., 2017; Wangelin & Tuerk, 2015). SC was able to indicate specific components of virtual reality exposure that were the most arousing (S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Van't Wout et al., 2017), a property that gave SC utility in evaluating the intervention content of exposure therapies.

Decreased EMG: A decrease in the amplitude of startle responses was correlated with a decrease in PTSD symptom severity in 2/4 studies (Carlson et al., 1998; S. D. Norrholm et al., 2016). Similarly, baseline EMG accounted for a significant amount of variance in changes in psychometric values (S. D. Norrholm et al., 2016). Individuals with higher EMG startle responses at baseline were more likely to respond positively to eye movement desensitization and reprocessing treatment and exposure treatment.

Decreased BP: At the end of treatment, 1/4 studies demonstrated statistically significant concordance between decreased systolic blood pressure and improved PTSD symptoms (Tucker et al., 2000), in line with a pre-treatment correlation between. BP measured at the beginning of each following session reflected between-session intervention progress (Schubert et al., 2019), and when measured at baseline, systolic blood pressure correlated with PTSD symptoms (Tucker et al., 2000). Systolic and diastolic blood pressure outperformed HR as an indicator of improved PTSD symptoms following cognitive therapy (Schubert et al., 2019). Both BP raw values and reactivity decreased at post-treatment for cognitive therapy.

3.4 Frequency and trends in concordance

HR was the measure that showed concordance with gold-standard psychometrics most often (Isserles et al., 2013; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016). This was evaluated in terms of differences in mean arousal between exposure and neutral stimuli (Wangelin & Tuerk, 2015), reactivity to trauma cues (Isserles et al., 2013), differences in arousal (baseline to peak; peak to recovery) during one session (Tucker et al., 2000; Wisco et al., 2016), and differences in peak arousal between sessions (Wisco et al., 2016). The concordance between psychometric and psychophysiological measures was most frequently demonstrated in exposure interventions (Seth Davin Norrholm et al., 2016; Wangelin & Tuerk, 2015; Wisco et al., 2016), where changes in physiological measures between pre-treatment to post treatment and follow-up were correlated with the changes in Clinician-Administered PTSD Scale.

3.5 Prediction of treatment outcome

Studies indicated that patients with the largest HR reactivity during the first treatment session showed the strongest treatment response (Wisco et al., 2016). Greater pre- to post- intervention changes in SC predicted greater improvements in symptoms (Isserles et al., 2013; Loucks et al., 2019; S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Van't Wout et al., 2017; Wangelin & Tuerk, 2015). EMG also served as a predictor of PTSD severity; higher startle reactions prior to treatment predicted larger symptoms reduction (Carlson et al., 1998; S. D. Norrholm et al., 2016).

3.6 Changes in accuracy of psychophysiological measurement (Table 1 and 2)

The robustness of psychophysiological measures or its correlation with psychometrics did not depend on date of development of either the scale or the device. The scales used were Clinician-Administered PTSD Scale –I/-II and PTSD Checklist for DSM-V/Specific/Civilian version*,* which were all developed between 1990-1994 (Blake DD, 1990; F. W. Weathers et al., 2001; F. W. Weathers, Litz, B. T., Huska, J. A., & Keane, T. M., 1994). The statistically significant concordance between psychophysiological measures and psychometric measures could be detected with both newer and older instruments, as release dates for the publication of different interventions ranged from 2000-2016 (Isserles et al., 2013; S. D. Norrholm et al., 2016; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016; Zucker et al., 2009). However, the correlation between psychophysiological and psychometric measures seemed to depend on the method of measurement; the use of electrodes produced the most significant findings (Isserles et al., 2013; S. D. Norrholm et al., 2016; Tucker et al., 2000; Zucker et al., 2009). In comparison, other methods, including the use of sensor belts, wristwatches, or PPG (photoplethysmograph) did not correlate with self-reports, and or only correlated at certain assessment points or with select components of the measure (Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016; Zucker et al., 2009), even when those measures were taken by the same research team who had significant results using other assessment tools.

4. Discussion

To our knowledge, this is the first systematic review to integrate the knowledge on objective measures of trauma symptoms in longitudinal studies. The psychophysiological markers HR, HRV, EDA, BP, and EMG were used by several studies and performed well against the gold-standard instruments, Clinician-Administered PTSD Scale and PTSD Checklist. HR was the most commonly used, which, with reliable sensors, also predicted change and correlated well with gold-standard psychometric instruments.

Decreases in HR, HRV, SC, EMG, and BP showed statistically significant correlation with reduction of trauma symptoms in 6/20 studies (Isserles et al., 2013; Seth Davin Norrholm et al., 2016; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016; Zucker et al., 2009). These psychophysiological measures showed concordance with Clinician-Administered PTSD Scale (Isserles et al., 2013; Seth Davin Norrholm et al., 2016; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016) and PTSD-Checklist (Zucker et al., 2009). No psychophysiological marker corresponded with the Posttraumatic Diagnostic Scale at a significant level (Dunne et al., 2012; Sack et al., 2007).

4.1 Clinical Utility

Some wearable devices were shown to be sensitive in capturing psychophysiological measurements, suggesting that inexpensive and portable systems could be translated into clinical practice (Dunne et al., 2012; S. D. Norrholm et al., 2016; Wisco et al., 2016). They were used to readily examine patterns of emotional regulation by using physiological phenotypes. Psychophysiological measures could guide treatment progress (Dunne et al., 2012; Hoge et al., 2012; S. D. Norrholm et al., 2016; Schubert et al., 2019; Zucker et al., 2009), a property that can enable clinicians to extinguish previously conditioned fear responses and to know when to intervene when physiological responses may indicate missing or adverse treatment response (Rothbaum et al., 2003; Tucker et al., 2000; Van't Wout et al., 2017; Wangelin & Tuerk, 2015). However, confirming reliability of the sensors for medical use is essential before they are safe to be used to monitor treatment.

Certain trends in physiological reactions were seen when comparing the measures of different types of treatment. Successful interventions could normalize initially low HRV levels. EDA was a robust measure for exposure treatments due to its sensitivity to fear responses that could be induced by trauma stimuli. Similarly, SBP could detect phasic stress responses more readily than DBP. Decreased EMG reflected positive response to treatment because it could signify a habituation effect, which is a crucial component of trauma-focused therapies. Irrespective of treatment type, the used of skin electrodes, rather than other modes of psychophysiological sensing, seems essential for accurate measurement (Isserles et al., 2013; S. D. Norrholm et al., 2016; Tucker et al., 2000; Zucker et al., 2009).

At pre-treatment, patients with PTSD showed heightened physiological reactivity to trauma cues. This phenotypic reaction to trauma imagery was proposed as a potential objective predictor of PTSD symptomology. A higher degree of physiological arousal to trauma cues during pre-treatment or initial sessions was predictive of larger decreases, even at follow-up (S. D. Norrholm et al., 2016; Renfrey & Spates, 1994; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016). Similarly, regardless of baseline levels, people who showed larger reductions in physiological arousal following treatment showed greater reductions in PTSD symptom severity (Isserles et al., 2013; Van't Wout et al., 2017; Wangelin & Tuerk, 2015; Zucker et al., 2009). In particular, it was the immediate physiological responses at baseline, such as EMG, HR, and SC that accounted for a significant variance in the longitudinal changes in trauma measures (Isserles et al., 2013; S. D. Norrholm et al., 2016; Schubert et al., 2019; Wangelin & Tuerk, 2015; Zucker et al., 2009). Their ability to detect phasic stress responses that directly reflect the effect of the trauma-stimuli on emotional processing suggests a potential role for brief physiological assessment during trauma imagery as a clinically predictive tool in intervention protocols (S. D. Norrholm et al., 2016; Wangelin & Tuerk, 2015).

Tracking psychophysiological measures for biofeedback allows interventions to be adapted to optimize personalized content that have utility in extinguishing fear responses (Rothbaum et al., 2003; Wisco et al., 2016). Biofeedback information can be used to personalize trauma-scripts, allowing the intervention to profoundly impact the cognitive organization of the original traumatic incident(s) (Carlson et al., 1998). Discussions with therapists on biological alterations post-intervention have also led to the normalization of the patients' reactions, which may be a moderating factor in treatment efficacy (Carlson et al., 1998; Griffin et al., 1997; Loucks et al., 2019; Rothbaum et al., 2003). Baseline cue-activated physiological measures have been a salient indicator of emotional changes induced by therapy (S. D. Norrholm et al., 2016; Wangelin & Tuerk, 2015; Wisco et al., 2016).

Psychophysiological measurements also benefited the assessment of pharmacological treatments since they could guide real-time temporal tracking and detection of adverse psychopharmacological reactions (Ramaswamy et al., 2015; Rothbaum et al., 2003). Pharmacological agents, such as propranolol and D-cycloserine (DCS) are known to enhance extinction of fear responses (Hoge et al., 2012; S. D. Norrholm et al., 2016; Van't Wout et al., 2017). Since interventions that cause fear extinction may decrease psychophysiological responses (Davis, Ressler, Rothbaum, & Richardson, 2006; Vervliet, 2008), physiological evaluation may be crucial in assessing pharmacological treatment effects on PTSD. Selective serotonin reuptake inhibitors (SSRIs) were another class of pharmacological treatments used that have a hypothesized effect on the ANS. Some studies which used SSRIs to target physiological reactivity found evidence for its impacts through the longitudinal changes of psychophysiological measures (Tucker et al., 2000). This is supported by previous literature reporting that the ANS response to fear eliciting stimuli can modulate certain physiological responses, such as the startle reflex (S. D. Norrholm et al., 2016; Ramaswamy et al., 2015; Tucker et al., 2000).

Many studies that incorporate multi-modal assessment methods use cortisol levels as an outcome measure because the hypothalamic pituitary adrenal (HPA) axis, similar to the ANS, is a mediator of the stress response (Wahbeh et al., 2016). Although cortisol levels have been used to indicate normalized HPA axis functioning following successful treatment, in our reviewed studies, physiological markers made more accurate predictions of treatment outcome (S. D. Norrholm et al., 2016; Schubert et al., 2019; Wahbeh et al., 2016). The predictions from the ANS and HPA axis pathways were even seen to predict in opposite directions (S. D. Norrholm et al., 2016). These results favor a role for the ANS, but not the HPA axis in PTSD symptom improvement (S. D. Norrholm et al., 2016; Schubert et al., 2019). Moreover, these findings suggest that the ANS is the primary stress mediating pathway targeted by trauma-based interventions, and thus, should be considered above the HPA axis as measures in clinical intervention or trials.

4.2 Limitations to using psychophysiological outcome measures

The mechanical and functional limitations of physiological sensor devices are a notable limitation to accuracy of physiological data. Sensors that attach to the body using electrodes seem to be the most reliable way of capturing psychophysiological readings, whereas the measures taken from arm cuffs, chest belts, and photoplethysmography sensors seemed to yield less robust readings (Carlson et al., 1998; Jovanovic, Rauch, Rothbaum, & Rothbaum, 2017; Tucker et al., 2000; Zucker et al., 2009), which appears to be irrespective of when the instrument was developed. There was merit in using ambulatory devices, such as finger sensors during virtual reality exposure therapies, however, their shortcomings include the increased motion artifacts that create noisy data, and the trade-off between sampling frequency and the structural design (Jovanovic et al., 2017; Loucks et al., 2019; Tucker et al., 2000). Additionally, not all ambulatory devices for research or clinical use are well-validated against stationary physiological acquisition systems, creating the additional risk of ambulatory systems being less sensitive than stationary systems. In some studies, this rendered the instrument unable to register a pulse and necessitated the exclusion of certain study participants (Tucker et al., 2000; Zucker et al., 2009). Some studies had difficulties transforming raw values into interpretable psychophysiological recordings because currently, not all commercially available software is reliable at estimating physiological intervals, such as the waves of ECG (Ramaswamy et al., 2015).

When interpreting changes in psychophysiology, decreased arousal may potentially be the result of conditioning mechanisms (Carlson et al., 1998; Sack et al., 2007; Tucker et al., 2000; Wahbeh et al., 2016; Wangelin & Tuerk, 2015). Therefore, there is a chance that the treatment may not be actually improving PTSD symptoms when there is improved psychophysiological functioning (Ramaswamy et al., 2015). This response discordance can compromise the validity of psychophysiological markers. Other than intervention factors, unevaluated variables and biological differences may jeopardize the reliability of the physiological recordings. This included baseline aerobic (cardiac) fitness, anticipatory anxiety about the laboratory procedures, and substances that have an effect on the ANS, such as certain medication (S. D. Norrholm et al., 2016; Rothbaum et al., 2003; Tucker et al., 2000; Wallach, 2015; Wisco et al., 2016; Zucker et al., 2009).

Ensuring ideal testing conditions was crucial for the studies to ensure replicability. This included quiet treatment rooms and comfortable temperature settings, which is not always feasible or able to be standardized across clinical practices (Wisco et al., 2016; Zucker et al., 2009). Often in psychophysiological testing, a technician is needed ensure that sensors are properly attached and that participants are within safe levels of physiological arousal. However, it is not known what impact presence made on arousal levels in the studies (Carlson et al., 1998). Furthermore, most studies lacked a neutral stimulus condition in trials; this factor is essential to control for the stimulus effects, such as VR recordings, on physiology, and is necessary to confirm PTSD-related reactivity as a reliably measured construct across multiple clinical trials (Dunne et al., 2012; Isserles et al., 2013; Sack et al., 2007).

4.3 Future lines of work

Psychophysiological monitoring is yet to be validated for diagnostic use. To optimize the utility of biomarkers, multi-modal assessment methods should be considered. Specifically, this necessitates use of multiple psychophysiological markers, and in conjunction with subjective reports (S. D. Norrholm et al., 2016; Schubert et al., 2019; Wisco et al., 2016). Understanding and validating certain psychophysiological trends as phenotypic trauma reactions during specific treatments can help optimize future intervention strategies.

Further collaboration between device producers and researchers is needed to provide a standard of quality of ambulatory sensor devices appropriate to be worn during and between therapy sessions. Valid response cut-offs, multimodal assessments, and novel statistical methods should be taken into account. Work in artificial intelligence could advance personalized treatment through monitoring response during therapy and response prediction learning. Further development is necessary to allow for rapid automated data collection and psychophysiological data cleansing, and a user interphase that can guide clinicians in real-time when trauma treatments are being administered (Rothbaum et al., 2003; Tegeler et al., 2017; Wisco et al., 2016).

Many studies used narrative-based trauma cues (Carlson et al., 1998; Dunne et al., 2012; Hoge et al., 2012; Isserles et al., 2013; Renfrey & Spates, 1994; Sack et al., 2007; Tucker et al., 2000; Wangelin & Tuerk, 2015; Wisco et al., 2016; Zucker et al., 2009), however, ideally, the stimuli and psychophysiological reactions should be generalizable and function without the influence of linguistic or cultural factors (Wahbeh et al., 2016; Wisco et al., 2016; Zucker et al., 2009). Future development of trauma-based intervention protocols should consider the use of intervention content that has a cross-culturally validated effect on psychophysiological correlates of emotional regulation.

4.4 Study Limitations

We might not have identified all relevant literature through the database searches. To reduce risk, we conducted hand-searches and checked citation relationships. Additionally, we only considered studies published in English; this allowed us to have uniform psychometrics but may not reflect the global evidence. The sample sizes in the studies were relatively small, and the exact strength of correlations was commonly missing. The variability in the original reports' chosen interventions, use of the measures, devices, cleaning processes, and control for confounders further limited the comparability of measures. Finally, there are currently no gold-standard physiological measures or physiological sensing devices, standardized procedures, nor measurement cut-offs that can validate clinical use of the measures or their comparability to clinical interviews or psychometrics.

Because not all studies reported associations between physiological and psychometric measures, some outcome measures lacked validity since they have not been tested against gold-standard scales (Dunne et al., 2012; Hoge et al., 2012; Ramaswamy et al., 2015; Renfrey & Spates, 1994; Tegeler et al., 2017; Wahbeh et al., 2016). Moreover, a possible selection bias would not have biased our main findings about sensitivity to change and correlations between psychometrics and psychophysiological measures, but might have augmented the validity of some measures.

4.5 Conclusion

The results of the current study indicate that there are several physiological measures that show promising properties as outcome measures of PTSD treatment. Multimodal assessment methods combining psychometrics and psychophysiological responses provided the best estimate of successful treatment response, and sensors that attach to the skin provide the most reliable physiological recordings. Overall, psychophysiological methodology may be clinically useful as biofeedback, to verify clinical impressions and self-reports, to detect unconscious arousal, and to index specific reactions to target content and intensity of trauma-based therapy. Further research is needed to validate the cut-offs for healthy psychophysiological levels to be used in intervention trials as inclusion and exclusion criteria, or a measure of recovery.

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Conflicts of interest
The authors report no potential conflicts of interest.

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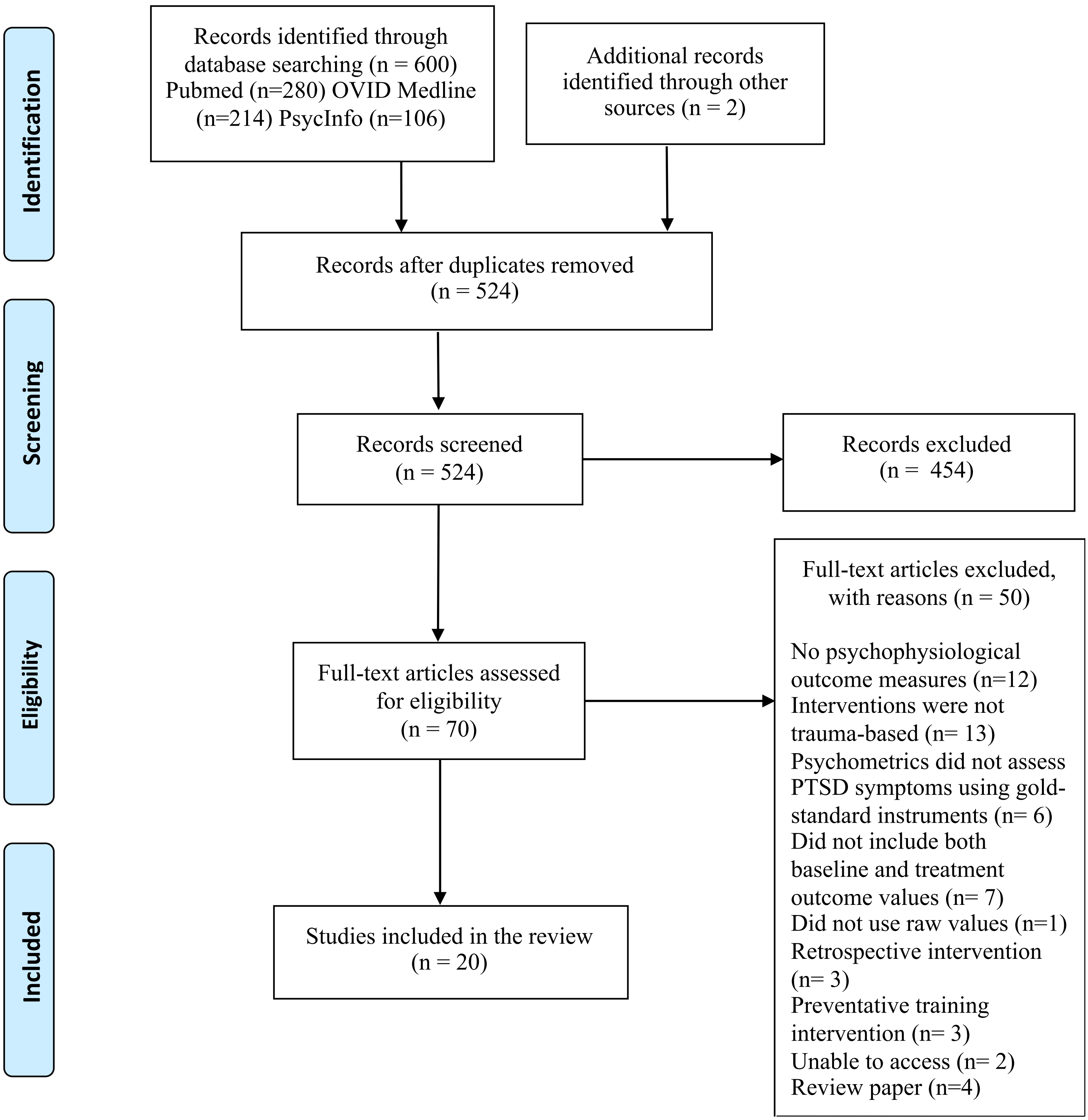
Figure 1. Flowchart of Search and Screening Process



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

Supplemental 1: Systematic Search Strategy

	PubMed	Ovid MEDLINE	PsycInfo
1	ptsd* [tiab]	ptsd.ti,ab.	ptsd.ti,ab.
2	"Stress Disorders, Post-Traumatic"[Mesh]	Stress Disorders, Post-Traumatic/	exp "Stress and Trauma Related Disorders"/
3	"post traumatic stress disorder"[Other Term]	post traumatic stress disorder*.ti,ab.	exp Posttraumatic Stress Disorder/
4	"Combat Disorders/diagnosis/psychology/therapy"[Mesh]	Combat Disorders/di, pp, px, th	exp Combat Experience/
5	"veterans/psychology"[MeSH Terms]	Veterans/px	exp Military Veterans/
6	"Psychophysiology"[Mesh]	Psychophysiology/	exp Psychophysiology/
7	"autonomic nervous system/physiopathology"[MeSH Terms]	Autonomic Nervous System/ph, pp	exp Autonomic Nervous System/
8	"sympathetic nervous system/physiopathology"[MeSH Terms]	Sympathetic Nervous System/ph, pp	exp Sympathetic Nervous System/
9	"Arousal/physiology"[MeSH Terms]	Arousal/ph	exp Physiological Arousal/
10	"Galvanic Skin Response/instrumentation/methods/physiology"[Mesh]	Galvanic Skin Response/is, mt, ph	exp Galvanic Skin Response/
11	Skin conductance* [tiab]	skin conductance*.ti,ab.	exp Skin Resistance/
12	"Heart Rate"[Mesh]	Heart Rate/	Exp Heart Rate/
13	"Heart rate variability"[Other Term]	Heart rate variability.ti,ab.	exp Heart Rate Variability/
14	"Blood pressure"[MeSH Terms]	Blood Pressure/	exp Blood Pressure/
15	"Electromyography"[Mesh]	Electromyography/	exp Electromyography/
16	"reflex, startle/physiology"[MeSH Terms]	Reflex, Startle/ph	exp Startle Reflex/
17	"eye movement measurements"[MeSH Terms]	Eye Movements/	exp Eye Movements/
18	"treatment outcome"[MeSH Terms]	Treatment Outcome/	exp Treatment Outcomes/
19	"outcome and process assessment, health care/methods"[MeSH Terms]	"Outcome and Process Assessment, Health Care"/mt	exp "Treatment Process and Outcome Measures"/
20	"therapy/psychology"[MeSH Terms]	Therapeutics/px	exp "Treatment Process and Outcome Measures"/
21	"biofeedback, psychology"[MeSH Terms]	Biofeedback, Psychology/	exp Biofeedback/
22	"cognitive behavioral therapy"[MeSH Terms]	Cognitive Behavioral Therapy/	exp Cognitive Behavior Therapy/
23	CBT [tiab]	CBT.ti,ab.	CBT.ti,ab.
24	"pharmacology/psychology/therapy"[MeSH Terms]	Drug Therapy/	exp Psychopharmacology/
25	"cycloserine/therapeutic use"[MeSH Terms]	Cycloserine/tu, th	Cycloserine.ti,ab.
26	"propranolol"[Mesh]	Propranolol/	exp Propranolol/
27	"eye movement desensitization reprocessing"[MeSH Terms]	Eye Movement Desensitization Reprocessing/	exp Eye Movement Desensitization Therapy/
28	EMDR* [tiab]	EMDR.ti,ab.	EMDR.ti,ab.
29	"implosive Therapy"[Mesh]	Implosive Therapy/	exp Implosive Therapy/
30	"exposure therapy"[Other Term]	Exposure therapy*.ti,ab.	exp Exposure Therapy/
31	"virtual reality exposure therapy"[MeSH Terms]	Virtual Reality Exposure Therapy/	exp Virtual Reality Exposure Therapy/
32	mindfulness / methods [MeSH]	Mindfulness/mt	exp Mindfulness-Based Interventions/
33	"transcranial magnetic stimulation"[MeSH Terms]	Transcranial Magnetic Stimulation/	exp Transcranial Magnetic Stimulation/
34	"psychotherapy"[MeSH Terms]	Psychotherapy/	exp Psychotherapy/
35	1 OR 2 OR 3 OR 4 OR 5		
36	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17		
37	18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34		
	35 AND 36 AND 37		

Supplemental 2: Description of the Participants in the Longitudinal Studies Comparing Trauma Patients from the Active Intervention to Controls

REFERENCE	INTERVENTION GROUP				INTERVENTION CONTROL GROUP		*CASES/ CONTROL (N)*
	Country	**Population**	**Inclusion criteria**	**Age, years (mean/range)**	**Population**	**Age, years (mean/ range)**	
CARLSON ET AL., 1998	USA	Combat veterans from Veterans Administration Medical Center clinics and community Veteran Centers	Clinical PTSD	52.7/41-70	Combat veterans from Veterans Administration Medical Center clinics and community Veteran Centers	45.4-46.9/41-70	23/12
DUNNE ET AL., 2012	Australia	Patients with WAD + MVC-related PTSD	WAD+SCID PTSD + PTSD symptoms related to MVC	32.5/20-49	Patients with WAD + MVC-related PTSD	32.5/20-49	13/13
HOGE ET AL., 2012	USA	Emergency department patients with acute (<12h) psychological trauma	DSM-IV PTSD A.1 and A.2 criteria	33.3/18-65	Emergency department patients with acute (<12h) psychological trauma	33.8/ 18-65	21/20
ISSERLES ET AL., 2013	Israel	PTSD patients	CAPS-II PTSD	NA/49.0	PTSD patients	NA/40.4-40.5	9/17
LOUCKS ET AL., 2019	USA	Veterans who experiences MST related trauma	CAPS-5, MINI, PCL-5 PTSD	46.0/32.0-72.0	N/A	N/A	15/0
NORRHOLM ET AL., 2016	USA	Combat veterans	DSM-IV PTSD	36.2/23-55	Combat veterans	34.7-37.5/23-55	13/37
RAMASWAMY ET AL., 2015	USA	Veterans with comorbid PTSD and Depression from a VA mental health clinic	MINI PTSD and MDD	28.0/19-55	N/A	N/A	11/0
RENFREY ET AL., 1994	USA	People who experienced trauma and currently have	DSM-III-R traumatic events+ PTSD	NA/18+	N/A	N/A	23/0

		intrusive symptoms.					
REYES, 2014	USA	Veterans at a transition residence for combat veterans	PCL-S	31.0/22. 0-50.0	N/A	N/A	27/0
ROTHBAUM ET AL., 2003	USA	A Vietnam veteran	PCL and Mississippi scale PTSD	52.0/NA	N/A	N/A	1/0
SACK ET AL., 2013	Germany	Outpatients from a specialized trauma clinic with type I trauma	DSM-IV PTSD	40.5/ 26-56	N/A	N/A	16/0
SCHUBERT ET AL., 2019	Germany	PTSD patients from a trauma outpatient clinic	CAPS score ≥ 45	36.7/18 +	N/A	N/A	25/0
TEGELER ET AL., 2017	USA	PTSD patients from a neurological clinic	DSM-IV-TR/PCL PTSD	47.0/NA	N/A	N/A	19/0
TUCKER ET AL., 2000	USA	PTSD patients	≥50 on CAPS	38.6/18-85	N/A	N/A	17/0
VAN'T WOUT-FRANK ET AL., 2019	USA	Veterans with warzone related PTSD	Clinical warzone-related PTSD	40.5/30-53	Veterans with warzone related PTSD	40.5/30-53	NA/NA
WAHBEH ET AL., 2016	USA	Combat veterans with PTSD	CAPS PTSD	53.3/NA	Combat veterans with PTSD	50.0-53.0	27/75
WANGELIN ET AL., 2015	USA	Combat veterans from a VA PTSD specialty clinic	CAPS PTSD	32.0/NA	N/A	N/A	35/0
WISCO ET AL., 2016	USA	Vehicle-accident related PTSD	CAPS score ≥ 40	39.5/18+	Vehicle-accident related PTSD	N/A	22/24
ZUCKER ET AL., 2009	USA	Participants with elevated PTSD symptoms from a residential treatment facility for substance use disorder	≥ 60 on the PTS-T scale of the DAPS	NA/18-60	Participants with elevated PTSD symptoms from a residential treatment facility for substance use disorder	NA/18-60	19/19

NA Not available*, PTSD* Post-traumatic stress disorder, *PTS-T* Posttraumatic Stress-Total, *DAPS* Detailed Assessment of Posttraumatic States, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *DSM-III-R* Diagnostic and Statistical Manual of Mental Disorders third edition, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders fourth edition, *CAPS* Clinician Administered PTSD Scale, *CAPS-5*, Clinician Administered PTSD Scale for DSM-5, *A.1 & A.2* Axis I and II, *WAD* Whiplash-associated disorders, *SCID* Structured Clinical Interview

Supplemental 3: Description of Intervention and Outcome Measurements

REFERENCE	INTERVENTION PROTOCOL						OUTCOME MEASURES			
	Intervention	Control	Assessment Periods	Assessment Points	Duration (weeks)	Follow-up (months)	Physiological Markers		PTSD Symptoms Scale	Other Measures Scale
							Measure (units)	Method of Evaluation		
CARLSON ET AL., 1998	EMDR	Biofeedback-Assisted Relaxation TAU Waitlist	PRE; POST; Within-session	N/A	6	3	HR (BPM)	PPG	CAPS-1	Mississippi Scale; STAI; IES; BDI
							SCL (µS)	SCL finger electrodes		
							EMG (µV)	EMG modules		
DUNNE ET AL., 2012	Trauma-Focused CBT	Waitlist	PRE; POST; Follow-up	N/A	10	6	HR (BPM)	ECG	SCID	PDS; PPT; CPT; HPT; IES-R, DASS, NDI; SF-36
							BP (mmHg)	Ambulatory BP device		
HOGE ET AL., 2012	Propranolol	PBO	Week 5 and 13	N/A	N/A	N/A	HR (BPM)	N/A	CAPS	Peritraumatic Emotional Distress Inventory, SCID
							SC (µS)			
ISSERLES ET AL., 2013	mPFC DTMS + Exposure	mPFC DTMS; Sham TMS+ Exposure	PRE; POST; Follow-up	N/A	4	2	HR (BPM)	Modular instrument system (Coulbourn instruments, PA, USA)	CAPS-II	PSS-SR; HDRS-24; BDI
							SC (µS)			
LOUCKS ET AL., 2019	VRET	N/A		N/A	6	3	HR (BPM)	Ag/AgCl electrodes and		

			PRE; POST; Follow-up				SCL (μS)	BIPOC MP150 system	CAPS-5; PCL-5	MINI; PHQ-9; CTQ-SF
							EMG (μV)			
NORRHOLM ET AL., 2016	VRET + D-cycloserine (DSC)	VRET+ alprazolam (ALP)	PRE; POST; Follow-up	N/A	6	6	HR (BPM)	ECG with Ag/AgCl torso and wrist electrodes	CAPS-1	PSS (1993), MINI, CTQ, DRRI, Cortisol reactivity
		PBO					SCL (μS)	Ag/AgCl finger electrodes		
							EMG (μV)	Ag/AgCl electrodes		
RAMASWAMY ET AL., 2015	Open-label trial of Escitalopram	N/A	PRE; POST	N/A	12	N/A	HRV (ln)	Bipoc MP150 system and ECG100C amplifier	CAPS-1	HAM-A; HAM-D; CGI
RENFREY ET AL., 1994	EMD (standard), EMD (automated tracking), EMD (visual fixation)	N/A	PRE; POST	N/A	2-6	1-3	HR (BPM)	Ear lobe pulse monitor	CAPS-1	IES, SUD
REYES, 2014	HRV Biofeedback	N/A	PRE; MID; POST	N/A	8	N/A	HRV (Hz)	emWave Desktop System	PCL-5	N/A
ROTHBAUM ET AL., 2003	VRET	N/A	PRE, 3 MID, POST, Follow-up	N/A	5	3; 6	HR (BPM)	Ag-AgCl electrodes with Beckman electrolyte on arm sites	CAPS-1	PCL; BDI; SUDS; SCID psychotic screen

							SC (µS)	Ag-AgCl electrodes with Unibase saline on hand sites		module; BSI; CES; Mississippi Scale; Boston Life Satisfaction Inventory.
							SBP and DBP (mm)	N/A		
SACK ET AL., 2013	EMDR	N/A	PRE; POST; Follow-up	N/A	N/A	6	HR (BPM)	ECG signals through Ag-AgCl chest electrodes	SCID–PTSD ratings	IES; PDS; SUD
							RSA [ln(ms)^2]			
SCHUBERT ET AL., 2019	Integrative Trauma-Focused CBT	N/A	PRE; MID	1800h;2030h; 1500h; 1630h	N/A	N/A	HR (BPM)	Hand wrist devices (Boso Medistar)	CAPS	Plasma adrenocorticotropin (ACTH), serum cortisol levels, RIQ, SVF-78
							BP (mmHg)			
TEGELER ET AL., 2017	High-resolutiion, relational, resonance-based, electroencephalic mirroring	N/A	PRE; POST	N/A	N/A	N/A	HR (BPM)	N/A	PCL-C	PCL-M, CES-D; BDI; Temporal lobe high frequency asymmetry (Hz)
							HF-HRV (SDNN)			
							BRS (mmHg)			
TUCKER ET AL., 2000	Open-label Fluvoxamine	N/A	PRE, POST	N/A	10	N/A	HR (BPM)	ECG	CAPS-1	HAM-D
							BP (mmHG)	Vital signs monitor		

VAN'T WOUT-FRANK ET AL., 2019	VRET+ tDCS	VRET+ sham tDCS	PRE; POST; Follow-up	N/A	2	1	SCR (µS)	N/A	PCL-5	NA
WAHBEH ET AL., 2016	Mindful Meditation	Sitting quietly; Slow breathing; Mindful meditation + Slow breathing	PRE; POST	N/A	6	N/A	HR (BPM)	ECG with Kubios HRV	PCL	PSS (1988); IT; BDI-II; GPSE; PSQI; MQ; ANT; PANAS; CEQ; GIC; Frontal cortex activity cognitive task
							HRV (SDNN)			
WANGELIN ET AL., 2015	Prolonged Exposure Therapy	N/A	PRE; Session 4; POST	N/A	N/A	N/A	HR (BPM)	Fingertip blood-volume pulse sensor	CAPS	PCL-Military
							SC (µS)	Fingertip SCL sensors		
WISCO ET AL., 2016	Written Exposure Therapy	Waitlist	Weekly	IFA; BSC; WSC	5	N/A	HR (BPM)	Ambulatory wristwatch HR monitor	CAPS	Emotion Self-Assessment Manikin
ZUCKER ET AL., 2009	RSA Biofeedback	Progressive muscle relaxation	PRE; POST	BASE, RELAX, REC	4	N/A	HRV (SDNN)	ECG wrist sensors	PTST & PCL-C	ISI ; BDI-II

		Respiration (breaths per minute)	Respiration sensors monitoring belt	

N/A Not available, *PTSD* Post-Traumatic Stress Disorder, *PBO* Placebo, *PRE* Pre-treatment, *POST* Post-treatment, *EXP* Experimental/active group, *CON* control/sham group, *SC(R)/SC(L)* Skin Conductance (Response/Level), *HR/HRV* Heart Rate/Heart Rate Variability, *HF-HRV* High Frequency Heart Rate Variability, *LF-HRV* Low Frequency Heart Rate Variability, *SBP/DBP* Systolic/Diastolic blood pressure, *BRS* Baroreflex Sensitivity, *EMG* Electromyography (startle response), *RSA* Respiratory Sinus Arrhythmia, *SDNN* Standard derivation of all normal-to-normal RR intervals, *BPM* Beats per minute, *μV* Microvolts, *μS* Microsiemens, *mm/mmHg* Millimeters of Mercury, *Hz* hertz, *ECG* Electrocardiogram, *PCL(-C)* PTSD Checklist(- Civilian Version), *CAPS(-5)* Clinican-Administered PTSD Scale (for DSM-5), *PDS* Posttraumatic Diagnostic Scale, *PSS-SR* PTSD Symptom Scale - Self-Report Version, *PSS (1993)* PTSD Symptom Scale, *IES* Impact of Event Scale, *SUDS* Subjective Units of Distress Scale, *VRET* Virtual Reality Exposure Therapy, *mPFC (D)TMS* Medial prefrontal cortex (Deep) transcranial magnetic stimulation, *PMR* Progressive muscle relaxation, *EMD(R)* Eye movement desensitization (and reprocessing), *(TF-) CBT* (Trauma Focused-) Cognitive Behavioral Therapy, *DSC* D-cycloserine, *IFA* Initial Fear Activation, *BSC* Between-Session Change, *WSC* Within-Session Change, *BASE* Baseline session, *RELAX* Relax session, *REC* Recovery session, *MINI* Mini International Neuropsychiatric Interview, *BDI* Beck's Depression Inventory, *CTQ(-SF)* Childhood Trauma Questionnaire (-Short Form), *DRRI* Deployment Risk and Resilience Inventory, *STAI* State-Trait Anxiety Inventory, *P/H/CPT* Pressure/Heat/Cold pain threshold, *SF-36* Short Form-36 Health Survey, *RIQ* Response to Intrusions Questionnaire, *SVF-78* The Stress Coping Style Questionnaire-78, *CES-D* Center for Epidemiologic Studies Depression Scale, *CGI* Clinical Global Impression, *BSI* Brief Symptom Inventory, *CES* Combat Exposure Scale, *BHS* Beck Hopelessness Scale, *HDRS-34* Hamilton Depression Rating Scale 24 items, *PHQ-9* Patient Health Questionnaire, *GPSE* General Self-Efficacy Scale, *PSQI* The Pittsburgh Sleep Quality Index, *MQ* Five-Factor Mindfulness Questionnaire, *PSS (1988)* Perceived Stress Scale, *PANAS* Positive and Negative Affect Schedule, *CEQ* Credibility/Expectancy Questionnaire, *GIC* Global Impression of Change, *IT* Intrusive Thoughts Scale

Table 1: Longitudinal Changes in Psychophysiological Measures

Intervention type	Physiological measurement context	Physiological measure (units)	REFERENCE	Assessment Points	Within-group changes					Between-group differences
					Values			Significance		
					PRE	POST	Follow-up	POST	Follow-up	Significance
Cognitive	Reactivity to trauma cues (post stimulus minus pre stimulus)	HR (BPM)	DUNNE ET AL., 2012		5.29	3.82	3.15	**p=0.005**	**p<0.001**	**p=0.01**
		SBP (mmHg)			4.54	2.23	2.54	**p=0.01**	**p=0.002**	p>0.05
		DBP (mmHg)			5.92	4.00	3.62	**p=0.004**	**p<0.001**	**p=0.01**
	Raw values	HR (BPM)	SCHUBERT ET AL., 2019		N/A	N/A	N/A	p≤0.1	N/A	N/A
		SBP (mmHg)			N/A	N/A	N/A	**p≤0.05**	N/A	N/A
		DBP (mmHg)			N/A	N/A	N/A	**p≤0.05**	N/A	N/A
Exposure	Response to trauma cue	HR(BPM)	LOUCKS ET AL., 2019		73.4	66.1	N/A	**p=.001**	N/A	N/A
		SC (µS)			4.8	1.9	N/A	p=.109	N/A	N/A
		EMG (µV)			5.9	1.1	N/A	p=.206	N/A	N/A
	Recordings while viewing the standard VR recordings	HR (BPM)	NORRHOLM ET AL., 2016		N/A	N/A	N/A	p>0.05	N/A	p>0.05
		SCL (µS)			N/A	N/A	N/A	**p=0.01**	N/A	p>0.05
		EMG (µV)			N/A	N/A	N/A	**p=0.01**	N/A	**p<0.05**
	Raw values	HR (BPM)	ROTHBAUM ET AL., 2003		74.09	58.3	N/A	N/A	N/A	N/A
		SC (µS)			6.53	7.92	N/A	N/A	N/A	N/A
		SBP (mm)			137.0	133.0	N/A	N/A	N/A	N/A
		DBP (mm)			84.0	82.0	N/A	N/A	N/A	N/A

	Raw values	SC (μV)	VAN'T WOUT-FRANK ET AL., 2019		N/A	N/A	N/A	**p=0.03**	N/A	N/A
	Differences in means between neutral and trauma conditions	HR (BPM)	WANGELIN ET AL., 2015		5.1	-0.4	N/A	**p=0.002**	N/A	N/A
		SC (μV)			2.6	0.6	N/A	**p=0.008**	N/A	N/A
	Peak HR analyzed as between session change (BSC), within session change (WSC), and initial fear activation (IFA)	HR (BPM)	WISCO ET AL., 2016	BSC	N/A	N/A	N/A	p=0.85	N/A	N/A
				WSC	N/A	N/A	N/A	**p<0.001**	N/A	N/A
				IFA	N/A	N/A	N/A	**p=0.04**	N/A	N/A
Biofeedback	Cardiac Coherence (HRV): Peak Power/ (Total power- Peak power)	LF- HRV (Hz)	REYES, 2014		0.25	0.28	0.83	p > .05	**p<0.05**	N/A
	Arousal at baseline to neutral recording (BASE), during paced breathing intervention (RELAX), and to neutral recording during recovery (REC)	HRV (SDNN)	ZUCKER ET AL., 2009	BASE	0.037	0.054	N/A	**p=0.03**	N/A	p=0.048
				RELAX	0.058	0.060	N/A	p>0.05	N/A	p=0.41
				REC	0.046	0.060	N/A	**p<0.02**	N/A	p=0.56
		Respiration (Breaths per minute)		BASE	15.01	12.37	N/A	p=0.57	N/A	**p=0.014**
				RELAX	7.78	7.19	N/A	p>0.05	N/A	p=0.094
				REC	11.96	11.26	N/A	p>0.05	N/A	**p=0.006**
Mindfulness	Raw Values	HRV (SDNN)	WAHBEH ET AL., 2016		3.7	2.8	N/A	p = 0.73	N/A	p>0.05
		HR (BPM)			72.5	72.7	N/A	p = 0.92	N/A	p>0.05
EMDR	Proportion of the mean of	HR (BPM)	CARLSON ET AL., 1998		0.99	0.95	0.94	p=0.06	p=0.64	p>0.05
		SCL (μS)			0.99	1.07	1.08	p=0.76	p=0.81	p>0.05

	corresponding trials (responses to traumatic scrips)	EMG (µV)		1.57	1.19	1.27	**p<0.001**	p=0.41	p>0.05
	Negative heart rate reactivity scores	HR (BPM)	RENFREY ET AL., 1994	9.48	0.82	N/A	**p<0.0001**	N/A	N/A
	Reactivity to trauma script	RSA ([ln(ms)²)	SACK ET AL., 2007	4.5	5.5	5.5	**p=0.040**	**p=0.027**	N/A
		HR (BPM)		86.6	78.9	79.6	p=0.11	p=0.051	N/A
Pharmacological	Responses to trauma scripts	SC (µS)	HOGE ET AL., 2012	N/A	N/A	N/A	N/A	N/A	**p=0.009**
		HR (BPM)		N/A	N/A	N/A	N/A	N/A	p=0.19
		EMG (µV)		N/A	N/A	N/A	N/A	N/A	p=0.68
	Raw values	HF-HRV (ln)	RAMASWAMY ET AL., 2015	6.31±1.16	5.48±0.67	N/A	**p<0.05**	N/A	N/A
		LF-HRV (ln)		6.53±1.11	6.05±0.86	N/A	p>0.1	N/A	N/A
	Change in scores (Peak test value – PRE test value)	HR (bpm)	TUCKER ET AL., 2000	8.6	2.4	N/A	**p=0.003**	N/A	p>0.05
		SBP (mmHg)		13.9	5.3	N/A	**p=0.004**	N/A	p>0.05
		DBP (mmHg)		6.1	2.4	N/A	**p=0.02**	N/A	p>0.05
TMS	Response to trauma recall	HR (BPM)	ISSERLES ET AL., 2012	N/A	N/A	N/A	**p =0.042**	N/A	N/A
		SC (µS)		N/A	N/A	N/A	N/A	N/A	N/A
	Raw values	HR (BPM)	TEGELER ET AL., 2017	63.3	65.3	N/A	p>0.2	N/A	N/A
		HF-HRV (SDNN)		46.2	53.4	N/A	**p=0.026**	N/A	N/A
		BRS sequence up (ms/mmHg)		13.2	17.3	N/A	**p=0.009**	N/A	N/A

Bold values mark statistical significance, *N/A* Not available, *PRE* Pre-treatment, *POST* Post-treatment, *SC(R)/SC(L)* Skin Conductance (Response/Level), *HR/HRV* Heart Rate/Heart Rate Variability, *HF-HRV* High Frequency Heart Rate Variability, *LF-HRV* Low Frequency Heart Rate Variability, *SBP/DBP* Systolic/Diastolic blood pressure, *BRS* Baroreflex Sensitivity, *EMG* Electromyography (startle response), *RSA*

Respiratory Sinus Arrhythmia, *SDNN* Standard derivation of all normal-to-normal RR intervals, *BPM* Beats per minute, *µV* Microvolts, *µS* Microsiemens, *mm/mmHg* Millimeters of Mercury, *Hz* hertz, *TMS* transcranial magnetic stimulation, *EMDR* Eye movement desensitization, *IFA* Initial Fear Activation, *BSC* Between-Session Change, *WSC* Within-Session Change, *BASE* Baseline session, *RELAX* Relax session, *REC* Recovery session

Table 2: Measurement Concordance Between Symptom Scales And Physiological Measures Used In Longitudinal Studies Reporting Both Values

Intervention type	Reference	PTSD Symptom Scale	PTSD symptoms score			Physiological measures used	Assessment points	Concordance between Symptoms scale and Physiological measures			
			PRE	POST	Follow-up			POST		Follow-up	
								r	p-value	r	p-value
Cognitive	SCHUBERT ET AL., 2019	CAPS	72.06	53.94	N/A	HR (BPM)		N/A	N/A	N/A	N/A
						BP (mmHg)		N/A	N/A	N/A	N/A
Exposure	LOUCKS ET AL., 2019	CAPS-5	41.5	28.9	27.9	HR(BPM)		N/A	N/A	N/A	N/A
						SC (µS)		N/A	N/A	N/A	N/A
		PCL-5	48.3	26.8	35.0	EMG (µV)		N/A	N/A	N/A	N/A
	NORRHOLM ET AL., 2016	CAPS	N/A	N/A	N/A	HR (BPM)		N/A	p>0.05	N/A	p=0.06
						SC (µs)		N/A	p>0.05	N/A	**p<0.05**
						EMG (µV)		N/A	**p<0.05**	N/A	**p=0.001**
	ROTHBAUM ET AL., 2003	CAPS	40	49	30	HR (BPM)		N/A	N/A	N/A	N/A
						SC (µS)		N/A	N/A	N/A	N/A
						SBP (mm)		N/A	N/A	N/A	N/A
						DBP (mm)		N/A	N/A	N/A	N/A

	VAN'T WOUT-FRANK ET AL., 2019	PCL-5	41.83	32.5	29.0	SCR (µS)		N/A	N/A	N/A	N/A
	WISCO ET AL., 2016	CAPS	63	19	N/A	HR(BPM)	BSC	N/A	p=0.83	N/A	N/A
							WSC	N/A	p=0.63	N/A	N/A
							IFA	N/A	**p=0.02**	N/A	N/A
	WANGELIN ET AL., 2015	CAPS	66.3	24.9	N/A	HR (BPM)		N/A	**p=0.008**	N/A	N/A
						SC (µS)		N/A	N/A	N/A	N/A
Biofeedback	REYES, 2014	PCL-S	63.3	56.0	50.1	LF- HRV (Hz)		N/A	N/A	N/A	N/A
	ZUCKER ET AL., 2009	PCL-C	52.59	38.53	N/A	HRV (SDNN)		N/A	**p=0.019**	N/A	N/A
						Respiration (breaths per minute)		N/A	p>0.05	N/A	N/A
Mindfulness	WAHBEH ET AL., 2016	PCL	56.3	50.7	N/A	HR (BPM)		N/A	N/A	N/A	N/A
						HRV (SDNN)		N/A	N/A	N/A	N/A
EMDR	CARLSON ET AL., 1998	CAPS-I	2.4	N/A	0.8	SC (µS)		N/A	N/A	N/A	N/A
						HR (BPM)		N/A	N/A	N/A	N/A
						EMG (µV)		N/A	N/A	N/A	N/A
	SACK ET AL., 2007	PDS	1.75	1.00	0.95	HR (BPM)		N/A	p>0.05	N/A	p>0.05
						RSA [ln(ms)²		N/A	p>0.05	N/A	p>0.05
Pharmacological	TUCKER ET AL., 2000	CAPS	83.8	23.2	N/A	HR (BPM)		N/A	**p=0.003**	N/A	N/A
						SBP (mmHg)		N/A	**p<0.001**	N/A	N/A
						DBP (mmHg)		N/A	N/A	N/A	N/A

TMS	ISSERLES ET AL., 2012	CAPS	88.0	61.0	N/A	HR (BPM)	r=0.69	**p=0.039**	N/A	N/A
						SC (µs)	N/A	N/A	N/A	N/A

* Data was not available for 5 studies otherwise fulfilling the inclusion criteria [1-5]

Bold values mark statistical significance, *N/A* Not available, *PRE* Pre-treatment, *POST* Post-treatment, *CAPS(-I)* Clinician-Administered PTSD Scale, *CAPS -5* Clinician-Administered PTSD Scale for DSM-5, *PCL(-5/-S/-C)* PTSD Checklist (for DSM-V/Specific/Civilian version), *SC(R)/SC(L)* Skin Conductance (Response/Level), *HR/HRV* Heart Rate/Heart Rate Variability, *HF-HRV* High Frequency Heart Rate Variability, *LF-HRV* Low Frequency Heart Rate Variability, *SBP/DBP* Systolic/Diastolic blood pressure, *BRS* Baroreflex Sensitivity, *EMG* Electromyography (startle response), *RSA* Respiratory Sinus Arrhythmia, *SDNN* Standard derivation of all normal-to-normal RR intervals, *BPM* Beats per minute, *µV* Microvolts, *µS* Microsiemens, *mm/mmHg* Millimeters of Mercury, *Hz* hertz, *TMS* transcranial magnetic stimulation, *EMDR* Eye movement desensitization, *IFA* Initial Fear Activation, *BSC* Between-Session Change, *WSC* Within-Session Change, *BASE* Baseline session, *RELAX* Relax session, *REC* Recovery session

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6.3.2 Appendix 2: Validation of a Culturally Adapted VR Treatment for Trauma

Methods

Rationale:

Currently, increasing the cultural safety of psychotherapy among the Inuit of Quebec is needed, especially therapy that can be conducted safely in remote communities. We will test the feasibility and efficacy of a culturally adapted VR-assisted Cognitive Behavioral Treatment (VR-CBT) focused on emotion regulation skills. We also use biofeedback as a method of monitoring and tracking progress during the trials.

Research aims:

1. To determine the feasibility, cultural safety and acceptability of a VR-CBT intervention among Inuit from Nunavik.
2. To confirm that a VR-CBT intervention improves emotion regulation (ER) and to confirm sustained treatment gains.
3. To determine effect of treatment on psychiatric symptoms: PTSD, substance use, anxiety, mood and disability.
4. To assess the utility of psychophysiological measures as outcome variables of VR-CBT.

Research question(s):

1. What factors predict and effect the feasibility, culturally safety and acceptability of VR-CBT treatment? (Aim 1)
2. What aspects of ER change and how much? (Aim 2)
3. What is the change in psychiatric symptoms during the intervention and in the long term? (Aim 3)
4. How sustainable are the changes? (Aim 2 &3)

5. Do psychophysiological changes during therapy associate with psychiatric outcomes? (Aim 4)

Study Design:

An open-label randomized controlled trial of a culturally adapted, VR-assisted CBT using emotion-regulation building paradigms. This study is aimed at comparing an Inuit group receiving the VR-CBT intervention and another control group of Inuit who will only use the VR headset and guided relaxation as a self-management strategy. Each participant in the active intervention group will undergo a total of 10 sessions.

Participants:

Inclusion criteria:

Trauma History

(1) The patients are first screened for having a self-reported trauma. (2) They must also show a positive response to minimum 3 questions on PC-PTSD-5 scale through a phone screening. During the first appointment, the score of (3) PCL-5> 33 is needed to further confirm current symptoms due to trauma.

Indigenous Identifying

The participants have to be (4) self-identifying as Inuit originally from Nunavik, living in Montreal (5) and be 14–60 years old

Safety

(6) Having the ability to tolerate a virtual reality helmet (7) alcometer measure <0.5% (8) Being able to comprehend his or her role in the study as well as the risks and possessing a level of English or French that allows one to make informed consent and understanding instructions during the study (9) have an existing contact to local health care or community center (contact person).

Exclusion criteria

Safety and Accuracy of Measures

(1) Being mentally unstable as defined by referring personnel or a checklist (current suicidality, fluctuating mood, need for hospitalization) (2) currently abusing (over the last 2 weeks) alcohol or drugs, an AUDIT>8 cut-off for heavy use or DAST>3 (3) changes to psychoactive medications in the past 4 weeks; history of psychosis or schizophrenia (4) active suicidal risk (suicidal or homicidal ideation with intent or plan) (5) medical history of heart conditions or epilepsy (6) alcohol, caffeine and stimulants, and cannabis within 24 hr before the session (7) nicotine consumption within 15 min of the session and (8) inability to provide consent.

Sample Size:

Due to the predicted recruitment limitations of this vulnerable and small population in Montreal, we aim to recruit a total of 40 participants. Inuit participants (*N*=20) who meet the inclusion criteria will be recruited to undergo the VR-CBT intervention. There will be one control group (*N*=20), also comprised of Inuit community members.

Setting:

The participants will be recruited from local centers in Montreal (e.g. Friendship Montreal, Irrivik), using social media, through word-of-mouth and flyers. The testing will take place locally at the Douglas Mental Health Institute.

Intervention:

VR-CBT

The VR-CBT intervention will be developed by the Cyberpsychology Lab at the University Quebec in Outaouais and will be standardized across participants using a treatment manual. During weekly sessions, participants will follow a hierarchical treatment plan. This intervention is aimed at improving stress related symptoms and relaxation techniques and will be goal-oriented in nature. The therapist may adjust the duration of each goal on an individual basis.

Measures:

Primary Outcome:

PTSD symptoms will be assessed through the CAPS-5, a 30-item structured interview that has been previously validated (high internal consistency on the CAPS-5 full scale [α=.88] with subscales α ranging from [.55-.77]) and commonly used in trauma intervention studies that involve psychophysiological metrics, as indicated by a systematic review conducted by our group (Weathers et al., 2018; Yang, Mady, Linnaranta, 2020). The full clinical interview lasts for approximately 45-60 minutes and will be assessed prior to the treatment, at the end of the treatment and at follow-up. An Inuit translator will be available in the room during the interview. A recent review comparing VR exposure therapy interventions (versus placebo or waitlist) for PTSD, where the majority of the studies utilized the CAPS as a measure, found a medium effect size for VRET (g=0.59; Carl et al., 2019). Therefore, we can predict a decrease in symptom scores in our participants by the end of the intervention.

Secondary Outcomes:

A) Trauma and related symptoms continued:

The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) comprised of 6-items, will be used as a screening tool, at weekly sessions, at the end of treatment and at follow-up (Prins et al., 2016). This scale is self-administered and demonstrates excellent diagnostic accuracy (area under the curve wax .94) and excellent test retest reliability (r=.83). **The PTSD checklist for DSM-5 (PCL-5)** will be used as a severity measure for PTSD symptoms as part of screening, at the end of treatment and at follow-up (Weathers, et al., 2013). The PCL-5 is a 20-item validated questionnaire to assess PTSD symptoms based on the DSM-5 over the previous month and has previously used in studies to asses trauma symptoms at various time points.

B) More information on anxiety and trauma will be collected using the **Generalized Anxiety Disorder 7 (GAD-7)**, **Childhood Trauma Questionnaire (CTQ)** and the **Visual Analogue Scale (VAS).** The GAD-7 consists of 7-items and assesses symptoms of anxiety in the previous two weeks (Spitzer, Kroenke, Williams, & Löwe, 2006). It has previously shown reliability for screening and monitoring purposes and will be used at baseline, end of treatment and follow-up. The short form of the CTQ, a validated measure of abuse experienced in childhood and teenage years, will be used at baseline (consisting of 28-items; Bernstein et al., 2003). The Visual Analogue Scale (VAS; Monk, 1989) is a 3-item visual self-report, measure aiming to assess participants' subjective emotional responses experienced during testing. This will be measured at baseline, before each CBT-VR, at the end of all treatment sessions, and at follow-up. All of these scales will be translated to Inuktitut.

C) **Emotion Regulation:** Please see supplementary tables (p. 64-67) for more information on emotion regulation scales and how they relate to psychophysiological measures. The ER assessment will be selected with the help of the Inuit advisory committee.

D) **Substance Abuse:** For screening, after treatment and follow-up, we will use the Development of the alcohol use disorders identification test (AUDIT), a gold-standard 10-item measure that assesses alcohol consumption and drinking behaviors (Saunders et al., 1993). The Abuse Screening Test (DAST) is a 10-item validated self-report scale, and will be used to screen for assessing drug use over the previous 12 months (Skinner, 1982). The Severity of Dependence Scale (SDS) for Cannabis, consisting of 5-items, will be used at baseline, after treatment and at follow-up as well (Martin, Copeland, Gates, & Gilmour, 2006).

E) **Mood scale**: the Kessler Psychological Distress Scale (K6; Anderson, 2015) is a self-administered, 6-item assessment that was selected by the advisory committee to be used in this trial. It will be used before each therapy session and it has been translated to Inuktitut.

F) **Psychosocial wellbeing**: **the Sheehan Disability Scale** is a 3-item assessment assesses various components of wellbeing such as symptoms over the last week which may relate to family, work and interpersonal dynamics (Sheehan, 1983). It has shown good specificity (83%) and moderate sensitivity (69%) in previous work (Leon, Olfson, Portera, Farber & Sheehan, 1997).

G) **Satisfaction with Therapy:** A one item VAS and open field item will be used at every assessment to determine how satisfied participants are with the VR-CBT therapy.

Psychophysiological measures

We will collect psychophysiological data will be collected to monitor physiological reactions prior, during and between sessions. Data on raw values, reactivity and change over time will be obtained. This will be collected through a wearable finger sensor from Thought Technology (TPS). It collects the following psychophysiological data (except BP which will be measured independently):

1. **Cardiac Activity:** Heart Rate (HR): Beats Per Minute (BPM); Heart Rate Variability (HRV)
2. **Finger Temperature:** degrees Celsius
3. **Skin Conductance/Electrodermal Activity (SC/EDA):** μSiemens
4. **Blood pressure (SBP/DBP):** millimetre of mercury (mmHg)

Procedure

The frequency of questionnaire administration is outlined in Table 1. Psychophysiological assessments are completed after the interviews at pre- and post-treatment, and at 3-month follow-up visits.

Table 1. Measurements Outlined

	Instrument	Items	Translated To Inuktitut	Screening Baseline	Weekly at Session	End of Treatment*	3 Month Follow-up
Trauma/PTSD	CAPS-5	30	✓**	✓	-	✓	✓
Trauma/PTSD	PC-PTSD-5	5	✓	✓	✓	✓	✓
Trauma/PTSD	PCL-5	20	✓	✓	-	✓	✓
Anxiety	GAD-7	7	✓	✓	-	✓	✓
Anxiety	CTQ	28	✓	✓	-	-	-
Anxiety	VAS	3	✓	✓	✓	✓	✓
Emotion Regulation	To be Chosen		✓	✓	-	✓	✓
Satisfaction with Therapy	VAS + open field	1	✓	✓	✓	✓	✓
Alcohol Use	AUDIT	10	✓	✓	-	✓	✓
Drug Use	DAST	10	✓	✓	-	✓	✓
Cannabis Use	SDS	5	✓	✓	-	✓	✓
Mood	K6	6	✓	-	✓	-	-
Psychosocial	Sheehan DS	3	✓	✓	-	✓	✓

Note. * At the completion of all 10 sessions. ** Translator will be present at the structured interview.

Data Analysis:

The effect of the VR-CBT treatment will be assessed through mixed linear models. Between-group comparisons will be conducted across several time points. Latent analysis will be used to analyze change over time between various variables such as mood and trauma symptoms.

Remote Monitoring and Intervention Platform:

The National Research Council (NRC) developed a platform for this project called bConnected. The purpose of this interface is to have a web portal through which therapists and patients may use as an access point. This interface includes a supporting back-end server and will gather sensor information (psychophysiological measures) during the sessions. Therefore, bConnected is responsible for management of the data obtained from the wearable TPS sensor and all patient physiological data.

Physiological Information Management:

The TPS wearable sensors used in this project are developed from Thought Technology (Montreal) and are commercially available. This sensor is wearable on the finger and able to connect wirelessly, where a storage and analysis software is able to provide real time data on the physiological variables of interest. All psychophysiological data collected through the sensor will be transferred through a Bluetooth wireless connection. This information is then uploaded to the bConnected interface of the NRC-MUHC back-end server through a secured internet connection. The data is then uploaded to the back-end server at MUHC for visualization, storage, and analysis.

Financial Compensation:

Participants will receive financial compensation at each session, including the screening. Those who complete the VR-CBT therapy will receive additional compensation.

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Protocol Supplementary Tables

Scale	Versions	Translated to French	Adapted	Definition	Model	Subscales	Psychophysiological correlates
Emotion Regulation Questionnaire [1]	ERQ-10/1]	Yes[2]	Yes, in Europe, Asia, the Caribbean, and in Persian/Arabic.	ER as strategies	Process Model[3]	Cognitive reappraisal	Finger temperature[4]
	ERQ-9[5]					Expressive suppression	Mean arterial pressure[4] Heart rate[4] Respiration amplitude[4] Electromyography (corrugator) [4]
Difficulties in Emotion Regulation Scale[6]	DERS-36[6]	Yes[7]	Yes, in Europe, Asia, and in Persian/Arabic.	ER as ability	Gratz's 4 dimensions of ER [6]	Nonacceptance	Vagally mediated heart rate variability[8]
	DERS-18[9]					Goal-directed behaviour	Heart rate[10]
	DERS-16[11]					Impulse control	Electrodermal activity[10]
	DERS-SF(18) [12]					Emotional Awareness	
	M-DERS(29) [13, 14]					Access to strategies	

						Emotional clarity	
Cognitive Emotion Regulation Questionnaire [15]	CERQ-36[15]	Yes	Yes, in several European countries.	ER as strategies	Process Model l[3]	Self-blame	Heart rate[4, 16, 17]
	CERQ-Short (18) [18]					Acceptance	Diastolic blood pressure[16, 17]
						Rumination	Systolic blood pressure[16] [17]
						Positive refocusing	Cortisol[17]
						Refocusing on planning	Heart rate variability[17, 19]
						Positive reappraisal,	Electromyography (corrugator) [4]
						Putting into perspective	
						Catastrophizing	
						Other blame	

Table 1: Several validated measures of Emotion Regulation that are translated into French. ER: emotion regulation; ERQ: Emotion Regulation Questionnaire, DERS: Difficulties in Emotion Regulation Scale; CERQ: Cognitive Emotion Regulation Questionnaire

Emotion regulation Construct							
Response modulation (cognitive suppression) [4]	**Cognitive change (cognitive reappraisal)** [4]	**Attention deployment (rumination)** [17, 19]	**Goal behaviours and impulse control[8]**	**Awareness, understanding, acceptance**[10]	**Adaptive ER[4, 10]**	**Maladaptive ER[4, 16, 17]**	**Several constructs[20, 21]**
Finger temperature*	Heart rate*	Heart rate*	Vagally mediated heart rate variability+	Heart rate*	Heart rate*	Heart rate*	Heart rate variability
Mean arterial pressure*	Electromyography (corrugator)**	Diastolic blood pressure**		Electrodermal activity**	Electrodermal activity^	Diastolic blood pressure**	Resting cardiac vagal control
Respiration amplitude+		Systolic blood pressure*			Electromyography (corrugator)**	Systolic blood pressure*	
		Cortisol*				Cortisol*	
		Heart rate variability*				Heart rate variability*	
						Finger temperature*	
						Mean arterial pressure*	
						Respiration amplitude^	

Table 2: Summary of review and meta-analysis evidence supporting measurement of each emotion regulation (ER) construct with listed psychophysiological measure. *small to medium effect size; ** medium to large effect size; +other

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6.3.3 Appendix 3: Qualitative Interviews

Interview guide for the individual interview—Study 1

A) Content:

Could you understand the instructions of the application?

Did you have any problems in understanding the instructions of the application? What kind of problems?

Did you have any difficulties with the language?

Which language would be the most relevant for this program/video?

Were some parts easier to understand than others? (If so: which were easier and why; which more difficult and why?)

Did you have any difficulty paying attention to the different aspects of the program? (If so: why?)

What kind of material did you prefer (visual, sounds, music, landscape)?

Were any elements more interesting than other ones? (If so: why?)

Were any aspects more relevant than other ones? (If so: why; and, why were other aspects less relevant?)

B) General point view:

What did you like about the application/video?

What didn't you like about the application/video?

Were there aspects you found to be particularly helpful?

Were there aspects you found to be inappropriate?

Did you experience any help from the application/video?

Did it help you feel better, have less pain or anxiety and/or better manage your pain/anxiety?

C) Presentation Format:

What are your impressions of the visual appearance of the application/video?

Did you find any aspect of the design of the application/video particularly engaging? (If so: which?)

Did you find any aspect of the design of the application/video particularly frustrating? (If so: which?)

Are the images relevant and meaningful?

Would there be other more meaningful, impacting images that would help you more?

Are the sounds relevant and meaningful?

Would there be other more relevant, impacting sounds that would help you more?

Would there be other more meaningful, impacting characters and scenes that would help you in the healing process?

Are there images or thoughts that help you be less anxious or have less pain?

D) Suggestions for Improvement:

Is there some important information that you think we should add to the application/video?

What could we improve to increase your motivation and interest to use this kind of application?

Do you think this kind of application may help others with health/wellbeing problems?

Have you any other comments or suggestions for improvement regarding the content of the application/video?

E) Ethical considerations:

Does this application/video seem safe and secure?

Does the content of the video respect your culture and beliefs?

Is the content of the video related to your background and environment?

Were you concerned by your privacy rights or confidentiality?

Do you have any additional ethical concerns?

What do you think about the accompaniment/guide you had?

Did the coaching and guidance you had seemed adequate, relevant, safe?

What suggestions do you have to improve the coaching and the guide of the person who would be with you during the sessions?

Interview guide for the focus group - Study 1

Focus group number :	Date :
Participants :	

General overview:

What did you like about the application/video?

What didn't you like about the application/video?

Were there aspects you found to be particularly helpful?

Were there aspects you found to be unsuitable?

Content:

Did you have any problems in understanding the instructions of the application? What kind of problems?

Did you have any difficulties with the language?

What kind of material did you prefer (visual, sounds, music, landscape)?

Were any elements more interesting than other ones? (If so: why?)

D) Presentation Format:

Did you find any aspect of the design of the application/video particularly engaging? (If so: which?)

Did you find any aspect of the design of the application/video particularly frustrating? (If so: which?)

Are the images relevant and meaningful?

Are the sounds relevant and meaningful?

Would there be other more meaningful, impacting characters and scenes that would help you in the healing process?

Suggestions for Improvement:

Is there some important information that you think we should add to the application/video?

What could we improve to increase your motivation and interest to use this kind of applications?

Do you think this kind of application may help others with health/wellbeing problems?

Have you any other comments or suggestions for improvement regarding the content of the application/video ?

Ethical considerations:

Does this application/video seem safe and secure?

Is the content of the application consistent with you and your background/culture/environment?

Do you have any additional ethical concerns?

What do you think about the accompaniment/guide you had?

What suggestions do you have to improve the coaching and the guide of the person who would be with you during the sessions?

6.3.4 Appendix 4: Psychophysiological Measures Study Psychometrics

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Psychophysiological measures - a validation study
Page 1 of 7

Sq En A

ID:	____________
Initials:	____________
Date:	____________
Visit:	____________

VISUAL ANALOGUE SUBJECTIVE AFFECT SCALES (1/6)

Purpose: This scale includes questions about how you are feeling.
Time: Please indicate how you are feeling currently.
Instructions: Please place click on the line shown below to indicate how you feel right now for each item.

How are you currently feeling	0, Not at all anxious — 1, Very Anxious *(Place a mark on the scale above)*
How calm or excited are you currently feeling?	0, Very calm — 1, Very excited *(Place a mark on the scale above)*
How pleasant or unpleasant do you currently feel?	0, Very pleasant — 1, Very unpleasant *(Place a mark on the scale above)*

GENERALIZED ANXIETY DISORDER 7-ITEM (GAD-7) SCALE(2/6)

Purpose: This scale includes questions about the symptoms of anxiety.
Time: In the past 2 weeks, including today.
Instructions: For each item, please indicate how well it describes your feelings during the past two weeks.

	Not at all sure	Several days	Over half the days	Nearly every day
1, Feeling nervous, anxious, or on edge	○	○	○	○
2, Not being able to stop or control worrying	○	○	○	○
3, Worrying too much about different things	○	○	○	○
4, Trouble relaxing	○	○	○	○

5, Being so restless that it's hard to sit still	○	○	○	○
6, Becoming easily annoyed or irritable	○	○	○	○
7, Feeling afraid as if something awful might happen	○	○	○	○

Patient Health Questionnaire (3/6)

Purpose: The following questions are related to your general health.
Time: Over the last 2 weeks, including today.
Instructions: Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1, Little interest or pleasure in doing things	○	○	○	○
2, Feeling down, depressed, or hopeless	○	○	○	○
3, Trouble falling or staying asleep, or sleeping too much	○	○	○	○
4, Feeling tired or having little energy	○	○	○	○
5, Poor appetite or overeating	○	○	○	○
6, Feeling bad about yourself	○	○	○	○
7, Trouble concentrating on things, such as reading the newspaper or watching television	○	○	○	○
8, Moving or speaking so slowly that other people could have noticed? Or the opposite	○	○	○	○
9, Thoughts that you would be better off dead or of hurting yourself in some way	○	○	○	○

	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	○	○	○	○

PCL-5 (4/6)

Purpose:The following questions are about problems that people sometimes have in response to a very stressful experience.
Time: Over the last month, including today.
Instructions: Please select the option for each item, based on your experiences over the last month. In the past month, how much were you bothered by:

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1, Repeated, disturbing, and unwanted memories of the stressful experience?	O	O	O	O	O
2, Repeated, disturbing dreams of the stressful experience?	O	O	O	O	O
3, Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	O	O	O	O	O
4, Feeling very upset when something reminded you of the stressful experience?	O	O	O	O	O
5, Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	O	O	O	O	O
6, Avoiding memories, thoughts, or feelings related to the stressful experience?	O	O	O	O	O
7, Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	O	O	O	O	O
8, Trouble remembering important parts of the stressfulexperience?	O	O	O	O	O
9, Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	O	O	O	O	O
10, Blaming yourself or someone else for the stressful experience or what happened after it?	O	O	O	O	O
11, Having strong negative feelings such as fear, horror, anger, guilt, or shame?	O	O	O	O	O

12, Loss of interest in activities that you used to enjoy?	○	○	○	○	○
13, Feeling distant or cut off from other people?	○	○	○	○	○
14, Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	○	○	○	○	○
15, Irritable behavior, angry outbursts, or acting aggressively?	○	○	○	○	○
16, Taking too many risks or doing things that could cause you harm?	○	○	○	○	○
17, Being "superalert" or watchful or on guard?	○	○	○	○	○
18, Feeling jumpy or easily startled?	○	○	○	○	○
19, Having difficulty concentrating?	○	○	○	○	○
20, Trouble falling or staying asleep?	○	○	○	○	○

CTQ (5/6)

Purpose: These questions ask about some of your experiences growing up as a child and a teenager.
Time: childhood, teenage years
Instructions: When I was growing up, . . .

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	Never true	Rarely true	Sometimes true	Often true	Very often true
1, I didn't have enough to eat.	O	O	O	O	O
2, I knew that there was someone to take care of me and protect me	O	O	O	O	O
3, People in my family called me things like "stupid", "lazy", or "ugly".	O	O	O	O	O
4, My parents were too drunk or high to take care of the family.	O	O	O	O	O
5, There was someone in my family who helped me feel important or special.	O	O	O	O	O
6, I had to wear dirty clothes.	O	O	O	O	O
7, I felt loved.	O	O	O	O	O
8, I thought that my parents wished I had never been born.	O	O	O	O	O
9, I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	O	O	O	O	O
10, There was nothing I wanted to change about my family.	O	O	O	O	O
11, People in my family hit me so hard that it left me with bruises or marks.	O	O	O	O	O
12, I was punished with a belt, a board, a cord (or some other hard object).	O	O	O	O	O
13, People in my family looked out for each other.	O	O	O	O	O
14, People in my family said hurtful or insulting things to me.	O	O	O	O	O
15, I believe that I was physically abused.	O	O	O	O	O

VISUAL ANALOGUE SUBJECTIVE AFFECT SCALES (6/6)

Purpose: This scale includes questions about how you are feeling.
Time: Please indicate how you are feeling currently.
Instructions: Please place click on the line shown below to indicate how you feel right now for each item.

How are you currently feeling

0, Not at all anxious — 1, Very Anxious

(Place a mark on the scale above)

How calm or excited are you currently feeling?

0, Very calm — 1, Very excited

(Place a mark on the scale above)

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How pleasant or unpleasant do you currently feel?	0, Very pleasant ... 1, Very unpleasant *(Place a mark on the scale above)*

You have now completed the survey. Thank you for your responses. All your answers will be kept confidential.

6.3.5 Appendix 5: Preliminary Qualitative Raw Data

Some protective factors for Inuit. Some evidence on feasibility and acceptance of VR for Inuit*

Participants who commented	**General ideas of factors that have an impact on well-being**	**Opinions on the virtual reality video**
Inuit Advisory Committee for GEM (4 members)	COLORS: -blue, " feel blue" (rather negative) -green is nature (rather positive) -orange is growth (rather positive) -pink because of the seal lover (rather positive) -purple (rather positive)	
	NATURE, LAND: -water, view of the sea, wide open spaces: healing elements -respecting land and animals -country foods: beluga, raw meat containing blood, fish, seal meat	
	SEASONS: - (…) happier during the winter time because you can go visit family because all the lakes are frozen so you can go anywhere (…)a lot more of people come together during the winter (…) greater sense of community in the winter	
	SOCIAL RELATIONSHIPS: -feeling of being included and part of a group/community/social network -"welcome people, fostering spirits", social harmony -to feel welcome where one is -company of family is important in healing processes	
	HOME: -feeling at home is important	
	TRADITIONAL ACTIVITIES: -artwork (eg, necklaces) -drummers, throat singers -observation, mentoring	
	SOUNDS: -throat singing -drums -"Inuit support you with silence (…) by being with you quietly, not with words"	

Conversations with 5 Inuit		ACCEPTANCE AND UTILITY: - a VR mobile app is an excellent and interesting idea, especially for Inuit youth - no doubt about the pertinence of the project -a relaxing video is a good option because it constitutes a gentle introduction to a health treatment using this technology -begin with something gentle/soft in order to not provoke different and strong reactions (probably produced by having multiple stimuli)
		SOUNDS: -throat singing -drums - Elder who tells stories (storyteller)
Health professionals and Staff (9 no Inuit)		EASE OF USE: -"just to learning to know on what to do, you are not relaxing you are learning" -"user friendly, just use your vision, no loosing time in learning" -the Oculus Go is easier -make it as simplest as possible: not many windows, only use 1 handle, not too many elements; it is difficult for Inuit patients to be present and to focus
		FEASIBILITY AND UTILITY: - a mobile app is a great idea, especially for young people in Nunavik - no doubt about the pertinence of the project
		BODY POSITION: - (..) should be in sitting down, you are guided to be relaxing but you cannot when standing - physically able to relax, laying down would be better - the sitting one brings directly to the breathing and relaxing
		COLORS: -light and color, it is calm and plain first - light and darkness are soothing - the snow daytime and dark
		NATURE, LAND: -it should be northern landscapes
		SOUNDS: -"the voice was perfect, she speaks very slowly" - to have the choice for music -throat singing

**Preliminary results of the project on VR led by Dr Outi Linnaranta and coordinated by Liliana Gomez Cardona. We thank the collaboration of members of the Inuit community in Montreal and staff of the Ullivik center for their participation*