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BRIEF REPORT

Effects of Virtual Walking Treatment on Spinal Cord Injury–Related Neuropathic Pain

Pilot Results and Trends Related to Location of Pain and at-level Neuronal Hypersensitivity

ABSTRACT

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Previous studies have shown that virtual walking to treat spinal cord injury–related neuropathic pain (SCI-NP) can be beneficial, although the type of SCI-NP that may benefit the most is unclear. This study's aims were to (1) determine the effect of location of SCI-NP on pain outcomes after virtual walking treatment and (2) examine the potential relationship between neuronal hyperexcitability, as measured by quantitative sensory testing, and pain reduction after virtual walking treatment. Participants were recruited from a larger ongoing trial examining the benefits of virtual walking in SCI-NP. Neuropathic pain was classified according to location of pain (at- or below-level). In addition, quantitative sensory testing was performed on a subset of individuals at a nonpainful area corresponding to the level of their injury before virtual walking treatment and was used to characterize treatment response. These pilot results suggest that when considered as a group, SCI-NP was responsive to treatment irrespective of the location of pain ($F_{1,44} = 4.82$, $P = 0.03$), with a trend for the greatest reduction occurring in at-level SCI-NP ($F_{1,44} = 3.18$, $P = 0.08$). These pilot results also potentially implicate cold, innocuous cool, and pressure hypersensitivity at the level of injury in attenuating the benefits of virtual walking to below-level pain, suggesting certain SCI-NP sensory profiles may be less responsive to virtual walking.

Key Words: Spinal Cord Injuries, Neuropathic Pain, Virtual Reality Therapy, Hyperesthesia

Many individuals with spinal cord injury (SCI) develop chronic, debilitating neuropathic pain that does not respond well to currently available treatments that mostly include pharmacologic regimens. However, studies have shown that visual illusory paradigms such as virtual walking, as a means of effective pain treatment, can be beneficial for patients who experience chronic SCI-related neuropathic pain (SCI-NP).[1] Understanding the benefits of visual illusory

paradigms is complicated by the fact that SCI-NP is a heterogeneous group of conditions with different, complex underlying mechanisms.

There are two subtypes of SCI-NP that have been classified relative to the level of injury.[2] According to the International Spinal Cord Injury Pain Classification system,[3] pain experienced at or within three dermatomes below the neurologic level of injury is considered at-level neuropathic pain, whereas pain that is present more than three dermatomes below the level of injury is categorized as below-level neuropathic pain. At-level SCI-NP and below-level SCI-NP are believed to reflect peripheral and central mechanisms of pain, respectively.[4] A clinical feature of central (below-level) pain is altered spinothalamic function, the degree of which can be measured by evoked sensitivity thresholds.[5] Interestingly, Finnerup and colleagues[6] found that the degree of hypersensitivity in the dermatomal segments corresponding to the level of injury is related to the severity of below-level (centrally mediated) SCI-NP. These researchers postulated that this was caused by neuronal hyperexcitability, possibly even at the supraspinal level, mediating this pain. Hyperexcitability of the somatosensory cortex has been found in rat models of SCI,[7] and this is particularly interesting in light of previous work by Wrigley et al.[8] Using functional magnetic resonance imaging, those researchers found functional reorganization in the sensorimotor cortex among those with SCI, with the greatest functional shifts to have occurred among those with below-level SCI-NP.

Given that below-level pain is believed to be centrally mediated with potential involvement of supraspinal mechanisms and moreover is characterized by hyperexcitability at the lesion level,[6] it is reasonable to assume that this type of pain would benefit most from virtual reality or visual illusory walking treatment. To date, however, little data exist to clarify this question. Villiger et al.[9] found that virtual movement, but not virtual walking per se, resulted in a decrease in central pain in most individuals with sensorimotor incomplete SCI. In a small pilot study of five persons with incomplete paraplegia,[10] virtual walking specifically was found to be effective for those with at-level pain, with one individual with below-level pain experiencing an increase in pain severity with treatment. Results from others indicate that while the greatest benefits were achieved with a combination of transcranial direct current stimulation and virtual walking,[1] virtual walking alone still produced significant reductions in SCI-NP severity. The participants in that study receiving virtual walking treatment only had mostly below-level SCI-NP, although the effect of location of pain was not specifically examined. One study[11] did find an immediate reduction in SCI-NP severity in sites below the level of injury, although the method of classifying location of pain was not described. Thus, it remains unclear as to what type of SCI-NP may be more responsive to visual illusory treatment paradigms.

The purpose of this pilot investigation was to investigate the effects of visual illusory walking—or virtual walking—on below-level pain when accounting for the degree of hyperexcitability at the level of injury. Furthermore, the effects of virtual walking on identified subtypes of SCI-NP, as measured by the location of the pain relative to the injury (centrally *vs.* peripherally mediated pain), were examined via preliminary analyses of data from an ongoing trial of virtual walking to treat SCI-NP. To this end, it was hypothesized that (1) below-level pain would respond more favorably to virtual walking treatment when compared with at-level pain and (2) greater at-level hypersensitivity would be associated with a greater reduction in below-level pain response after treatment.

METHODS

Participants

Preliminary data from 35 individuals with traumatic SCI participating in a larger, ongoing trial examining the effects of virtual walking on SCI-NP were examined for differences with respect to location of pain (at- or below-level pain). In addition, 15 participants were recruited from the study to undergo quantitative sensory testing (QST) before being exposed to the virtual walking paradigm. Of the 15 participants, 8 had been randomly assigned to receive the virtual walking treatment and therefore contributed data to examine the association between neuronal hypersensitivity and pain outcomes after virtual walking. For ethical reasons, participants who were taking medications to manage their SCI-NP were not asked to deviate from or discontinue their regimen on the day of testing. This study was approved by the institutional review board and informed written consent was obtained from all participants for all of the procedures.

Quantitative Sensory Testing

A similar QST methodology that has been used in an SCI population previously was used.[6,12] The QST approach used included five modalities as stimuli to measure somatic sensory abnormalities: brush allodynia (stimulation using a foam brush),

punctate hyperesthesia (stimulation with a von Frye filament), innocuous cool (stimulation using cool metal bar at room temperature), noxious cold (stimulation using a cold metal bar maintained at 0°C),[12,13] and pressure pain (stimulation using a pressure algometer). QST was performed at the dermatome(s) corresponding to the level of injury and was administered by examiner trained by a clinician specializing in chronic SCI-related pain. Injury level was classified as the most caudal segment of the spinal cord with normal functioning according to the International Standards for Neurological Classification of Spinal Cord Injury.[14] Beginning at the level of injury, participants were asked to identify the region at which sensation was diminished or no longer normal, and QST was performed at this site (within one to two dermatomes corresponding to the neurologic level of injury). Changes in painful or unpleasant sensations were reported on a 0 to 10 scale, with 0 = no evoked pain and 10 = worst imaginable evoked pain.

Visual Illusory Walking

In the ongoing, larger study examining the effects of an immersive, simulated walking experience, participants had been randomly assigned to receive illusory walking (treatment) or illusory wheeling (control). The walking stimuli consisted of a 20-min video of an actor, in first-person view, walking along a path. The control stimuli consisted of the same actor, in first-person view, propelling a manual wheelchair along the same path for the same length of time. The stimuli were presented on a three-dimensional monitor to participants without the examiner present in a quiet and dimly lit room. Before the presentation of the stimuli, participants were instructed to imagine that they themselves were performing the movements of the actor while watching. Examiner was blinded to condition until all testing had been completed.

Procedures

Pain was classified as neuropathic according to the classification scheme of Bryce and Ragnarsson.[15] Below-level pain was determined if the pain was located to be more than three dermatome segments below the level of injury. Below-level pain severity was measured via a 0 to 10 numeric rating scale, and a rating was obtained from each participant before and after exposure to one 20-min virtual walking treatment. For a subset of individuals, QST was performed on an area skin at the dermatome associated with the level of injury after pain classification but before presentation of visual illusory stimuli.

Analyses

Study 1

To investigate differential effects of virtual walking on below-level *vs.* at-level pain, a general linear mixed model was performed to account for any clustering effect because participants were allowed to "attribute" pain ratings to more than one location of pain if multiple pain sites (e.g., both at- and below-level) were present. Fixed effects included in the model were pain location, treatment condition, and, most pertinent to this study, the interaction between pain location and treatment condition.

Study 2

Given the pilot nature of examining associations between at-level neuronal hypersensitivity and changes in below-level pain after virtual walking, only descriptive correlations were calculated and scatterplots were also examined for linear trends. In cases where individuals experienced more than one site classified as below-level neuropathic pain, numeric rating scale pain ratings were averaged to produce one baseline and posttreatment rating. Change in pain was calculated by subtracting pretreatment ratings from posttreatment ratings for both studies 1 and 2.

RESULTS

Study 1

The demographics of the participants included in study 1 are depicted in Table 1. A total of 80 pain

TABLE 1 Demographic and injury characteristics of participants included in study 1

	Study 1
Age, mean (SD), years	47.5 (9.4)
Education, mean (SD), years	13.2 (2.8)
Injury duration, mean (SD), years	16.1 (10.4)
Sex, % (*n*)	
Male	77.1 (27)
Female	29.1 (8)
Race, % (*n*)	
African American	60.0 (21)
White	40.0 (14)
Injury level, % (*n*)	
Tetraplegia	48.6 (17)
Paraplegia	51.4 (18)
Injury severity[a], % (*n*)	
Complete	48.6 (17)
Incomplete	51.4 (18)

Study 1 involved participants for whom QST was conducted. Study 2 included participants whose pain outcomes were preliminarily analyzed based on pain location.

[a]Based on American Spinal Injury Association classification of injury; A = complete; B–D = incomplete.

TABLE 2 Mean baseline pain and change in pain following each condition, according to location of pain

	Baseline Pain, Mean (SD)	Change in Pain, Mean (SD)
Walk		
At-level	6.25 (3.14)	−1.58 (1.62)
Below-level	5.37 (2.27)	−0.78 (1.51)
Wheel		
At-level	5.42 (2.71)	−0.63 (1.49)
Below-level	5.32 (2.48)	0.14 (1.67)

sites were classified among the 35 participants. Of these, 24 were classified as at-level and 56 were classified as below-level. The mean changes in pain severity according to location of pain and treatment condition are shown in Table 2. The overall mixed model produced a nonsignificant test of interaction between treatment condition and location of pain ($F_{1,\ 44} = 0.15$, $P = 0.69$). Although there was a greater decrease in at-level pain from pre– to post–virtual waking pain ratings, this effect only trended toward significance ($F_{1,\ 44} = 3.18$, $P = 0.08$). A significantly larger decrease in pain was observed in the virtual walking condition compared with the virtual wheeling condition ($F_{1,\ 44} = 4.82$, $P = 0.03$), irrespective of location of pain, however.

Study 2

Demographics, injury characteristics, pain medication type, and the degree of change in below-level pain for the participants included in study 2 are shown in Table 3. Most of the individuals (7/8) did not experience any evoked pain from brush or punctate modalities of QST, and therefore, correlations were not performed. The correlations between evoked noxious cold, innocuous cool, and pressure pain and change in below-level pain from pre to post virtual walking are shown in Table 4. There were significant correlations among the QST modalities available for analysis. The strongest correlation was seen between the degree of innocuous cool and noxious cold sensitivity. Although none of the associations between at-level neuronal hypersensitivity and changes in below-level SCI-NP reached significance because of the small sample, the Pearson coefficients obtained were considered to be of moderate size.[16] The plotted data for the degree of innocuous cool, noxious cold, and pressure evoked pain suggest a possible trend for an inverse relationship: Higher at-level sensitivity as measured by QST was related to less favorable below-level SCI-NP outcomes after virtual walking treatment (see Fig. 1).

TABLE 4 Pearson correlations among QST measures and change in pain after visual illusory walking

	Δ Pain	Cool	Noxious Cold
Cool	0.60	–	
Noxious cold	0.47	0.98**	–
Pressure	0.55	0.89**	0.87**

*$P < 0.05$.
**$P < 0.01$.

DISCUSSION

Given the refractory nature of SCI-NP, there has been an increased effort in recent years to identify effective treatment alternatives to traditional pharmacologic agents. Previous studies have suggested that noninvasive walking stimulation paradigms can reduce SCI-NP[1,10,11] and may reverse maladaptive

TABLE 3 Demographics, injury characteristics, pain medication type, and change in below-level pain of participants who underwent QST for at-level hypersensitivity

Participant	Age	Gender	Race	Injury Level	AIS	Injury Cause	Daily Pain Medication Regimen	Δ Below-Level Pain[a]
1	45	M	AA	C7	A	MVC	Spasmolytic	−1.50
2	54	M	W	C6	B	MVC	Anticonvulsant	−1.50
3	49	M	AA	T4	A	GSW	Opioid	1.00
4	43	M	AA	C4	C	MVC	Opioid	−0.50
5	49	M	AA	T5	A	MVC	None	−3.50
6	53	F	AA	T10	A	MVC	Opioid, anticonvulsant, spasmolytic	0.00
7	49	F	W	T7	A	MVC	Opioid, anticonvulsant	0.50
8	38	M	AA	C4	B	MVC	Anticonvulsant	−2.00

AA indicates African American; W, white; AIS, American Spinal Injury Association Impairment Scale.
[a]Change in below-level pain as measured by an 11-point numeric rating scale for severity. Change scores were calculated by subtracting pre–virtual walking scores from post–virtual walking scores.

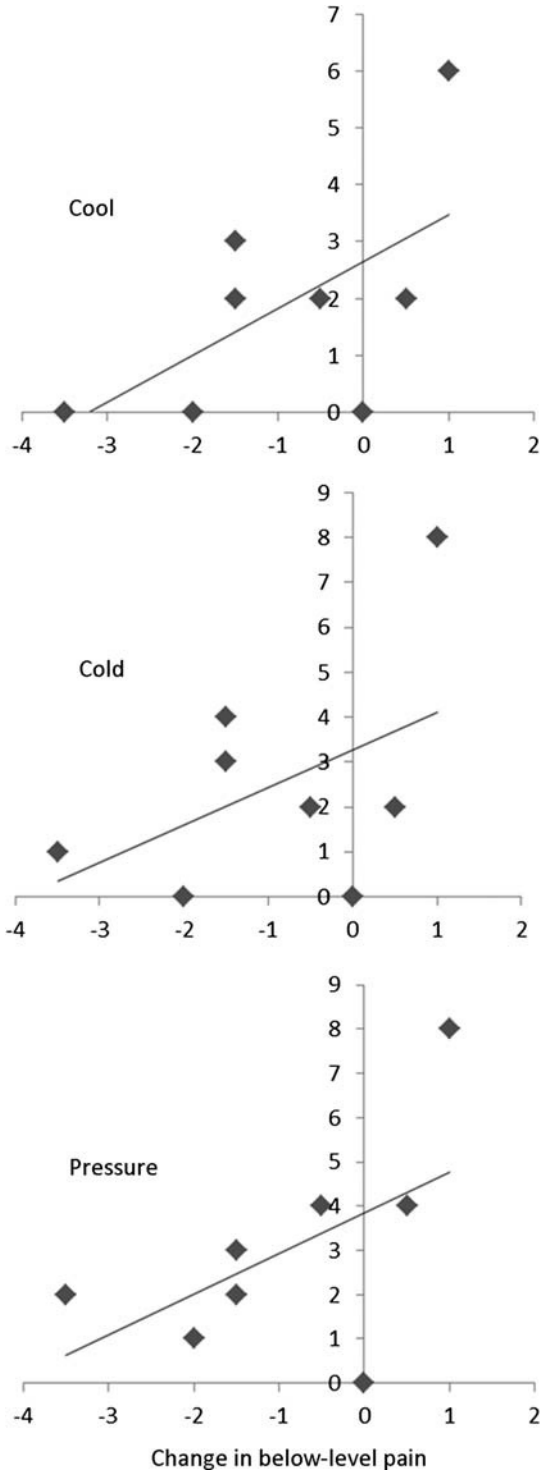

FIGURE 1 *Cool, noxious cold, and pressure sensitivity from QST (vertical axes) plotted against change in below-level neuropathic pain after virtual walking. Coefficient values for cool, noxious cold, and pressure sensitivity with change in pain are r = 0.60 (P = 0.12), r = 0.47 (P = 0.23), and r = 0.55 (P = 0.15), respectively.*

cortical reorganization–associated neuropathic pain as found in other rehabilitation populations.[17,18] However, the effect of such a treatment modality on subtype of SCI-NP is unclear and at times contradictory. For example, in a small pilot study, virtual walking was found to increase below-level pain in one subject,[10] whereas a larger, subsequent study found that all persons with SCI-NP experienced relief irrespective of location of neuropathic pain.[1] The latter study also attempted to clarify whether virtual walking was effective with certain characteristics of pain (e.g., continuous, paroxysmal, allodynia, and dysaesthesia), although it did not utilize methodology to better describe degree of afferent disconnection and subsequent hypersensitivity as can be done with QST.[6]

A complicating factor to interpretation of treatment outcomes in SCI-NP is the fact that this type of pain is likely not a unitary pathophysiologic phenomenon but likely a combination of different mechanisms resulting in a wide variety of sensory symptoms.[19,20] Sensory profiles in neuropathic pain, each with purported different mechanisms of onset and maintenance of pain, point to the need for personalized medicine approaches to account for differences in response to neuropathic pain treatment.[21] Similarly, this study's pilot results suggest that the type of SCI-NP symptom manifestation, as indicated by response to QST, may predict effectiveness of virtual walking treatment.

When modeling pain location by treatment condition (virtual walking *vs.* virtual wheeling) using the data collected to date, preliminary results suggest that, on average, SCI-NP was reduced by virtual walking treatment irrespective of location of pain. This is somewhat contrary to this study's original hypothesis that below-level pain would show the greatest benefit since this type of pain has been associated with supraspinal mechanisms[8,22] and virtual walking has been shown to activate certain cortical sensory regions.[23] However, mechanisms underlying pain at different locations may be a combination of pathophysiologies, in which a given at-level pain site may be more or less centrally mediated and therefore more or less susceptible to treatment effects.

Yet, the simple distinction by location of SCI-NP may not be sufficient, as even when accounting for location of pain, there is considerable variability in whether that pain is allodynic or hyperalgesic.[24] Only one participant in the present study experienced brush evoked pain or pinprick hyperalgesia at the level of injury, and those who experienced evoked pain on one modality (e.g., noxious cold) do not necessarily experience pain on another.[6] It is possible that with the small pilot, individuals with punctate or brush evoked hypersensitivity at the

level of injury were simply not captured. These pilot data also showed that the degree of evoked noxious cold, innocuous cool, and pressure pain at segmental level of injury were significantly and reliably correlated with one another, suggesting one possible SCI-NP "phenotype." It was hypothesized that those with an at-level hypersensitivity profile would experience a greater reduction in below-level pain after virtual walking because at-level hypersensitivity is indicative of centrally mediated below-level SCI-NP.[6,25] However, although nonsignificant because of this study's small pilot sample, trends in these data suggest the converse, in that those with more cold, cool, and pressure hypersensitivity tended to experience little to no benefit from virtual walking treatment. It is interesting that in a meta-analysis of experimentally induced and chronic persistent neuropathic pain of various etiologies, primary somatosensory activation occurred only in nonthermal evoked pain.[26] Because primary somatosensory cortex is activated during virtual walking,[23] this raises the question as to whether at-level innocuous cool and noxious cold hypersensitivities are associated with different functional cortical correlates that are perhaps not targeted by virtual walking treatment. Such a hypothetical relationship is only speculative given the nonsignificant but interesting trends in the data presented here but nevertheless warrants future research into how different neuropathic pain phenotypes are more or less responsive to novel treatments on the horizon.

It should be underscored that these results are pilot in nature; therefore, one cannot make reliable inferences about how location or different symptom profiles of SCI-NP differentially respond to virtual walking. Furthermore, results shed light only on immediate effects after only one session. Immediate analgesic effects of virtual walking on SCI-NP, at least in a non-first-person point of view modality, has been demonstrated previously, although the benefits do not seem to last after 2 wks.[11] Therefore, the long-term pain reduction of the virtual walking protocol generally and as related to phenotype of SCI-neuropathic pain remains unclear. Nevertheless, the results do implicate the need to incorporate QST or other methods to further characterize phenotypes of SCI-NP in future treatment trials that control for additional factors affecting outcomes (e.g., medications).

CONCLUSIONS

Although these data are preliminary and merely reveal potential trends, it seems that virtual walking may be of benefit, on average, for SCI-NP generally. While a better understanding is being gained of how virtual walking may target aspects associated with centrally mediated neuropathic pain,[23] benefits of this treatment may depend on the type of sensory manifestation that occurs in the context of below-level pain. This represents a potentially fruitful area of future research to not only identify those who may particularly benefit from this method of treatment but also to clarify understanding of the complexity of SCI-NP.

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