Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury

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Supplemental data at Neurology.org

ABSTRACT

Objective: To investigate changes in body ownership and chronic neuropathic pain in patients with spinal cord injury (SCI) using multisensory own body illusions and virtual reality (VR).

Methods: Twenty patients with SCI with paraplegia and 20 healthy control participants (HC) participated in 2 factorial, randomized, repeated-measures design studies. In the virtual leg illusion (VLI), we applied asynchronous or synchronous visuotactile stimulation to the participant's back (either immediately above the lesion level or at the shoulder) and to the virtual legs as seen on a VR head-mounted display. We tested the effect of the VLI on the sense of leg ownership (questionnaires) and on perceived neuropathic pain (visual analogue scale pain ratings). We compared illusory leg ownership with illusory global body ownership (induced in the full body illusion [FBI]), by applying asynchronous or synchronous visuotactile stimulation to the participant's back and the back of a virtual body as seen on a head-mounted display.

Results: Our data show that patients with SCI are less sensitive to multisensory stimulations inducing illusory leg ownership (as compared to HC) and that leg ownership decreased with time since SCI. In contrast, we found no differences between groups in global body ownership as tested in the FBI. VLI and FBI were both associated with mild analgesia that was only during the VLI specific for synchronous visuotactile stimulation and the lower back position.

Conclusions: The present findings show that VR exposure using multisensory stimulation differently affected leg vs body ownership, and is associated with mild analgesia with potential for SCI neurorehabilitation protocols. *Neurology®* **2017;89:1894–1903**

GLOSSARY

ABE = Anomalous Body Experience; **AIS** = American Spinal Cord Injury Association Impairment Scale; **ANOVA** = analysis of variance; **ASIA** = American Spinal Cord Injury Association; **CDS** = Cambridge Depersonalization Scale; **FBI** = full body illusion; **HC** = healthy controls; **HMD** = head-mounted display; **RHI** = rubber hand illusion; **SCI** = spinal cord injury; **VAS** = visual analogue scale; **VLI** = virtual leg illusion; **VR** = virtual reality.

Spinal cord damage can cause permanent loss of sensorimotor functions and persistent neuropathic pain,[1–4] leading to structural and functional changes in somatotopic regions of the CNS.[1,5] Recently, several studies showed that multisensory processing and the related sense of body ownership[6–8] are also impaired in patients with spinal cord injury (SCI),[9–11] suggesting that sensory impairments in SCI extend beyond unimodal deficits in the sensorimotor system. Although pain perception and leg and global body ownership can be experimentally manipulated through body illusions using multisensory stimulation,[12–21] previous SCI research only investigated ownership for the upper extremity.[9,11,22] Although virtual reality (VR) is becoming increasingly used in neurorehabilitation[23,24] (see appendix e-1 at Neurology.org), it has only rarely been integrated with multisensory stimulation, in particular for the legs and in SCI.

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We investigated leg and global body ownership in patients with SCI employing VR technology, using adapted virtual leg illusion (VLI)[12] and full body illusion (FBI),[13] respectively, and tested their potential analgesic effects. In the VLI, we simultaneously stroked virtual legs and the patient's nearest body site with preserved tactile perception (lower back), investigating whether such multisensory VR exposure induces leg ownership and illusory tactile leg percepts. Based on the findings on cortical reorganization after denervation,[1,17] we predicted that synchronous stimulation of the lower back would result in a stronger illusion and analgesia than stimulation of a more distant site (upper back). We further predicted finding differences between patients with SCI and healthy control participants (HCs) for leg ownership (VLI), but not for the global sense of body ownership (FBI), as tested separately with distinct multisensory stimulations.

METHODS

Participants. A total of 20 patients (2 female; 23–71 years, mean 47.3 ± 12.0 years) with SCI participated in the study. SCI was traumatic in 18 cases and nontraumatic in 2 cases. The time since injury varied between 3.5 months and 71 years (17.1 ± 18.1 years). According to the International Standards for Neurologic Classification of Spinal Cord Injury by the American Spinal Cord Injury Association (ASIA),[25] their lesions ranged from high thoracal (T2) to lumbar (L2); 15 participants had complete lesions (ASIA Impairment Scale [AIS] A), 3 sensory incomplete (AIS B), and 2 sensory and motor incomplete (AIS C) lesions. All participants with SCI had impaired tactile perception of the upper dorsal legs. None of the participants with SCI had a history of other neurologic or psychiatric disease. Eleven participants with SCI had chronic neuropathic pain at or below the SCI level (SCI-pain),[26] as defined by a prior clinical assessment. Demographic and clinical data of the SCI group are summarized in table e-1. Twenty healthy age-matched participants (2 female; 23–70 years, mean 43.0 ± 11.8 years; $p = 0.975$) were recruited as a control sample (HCs).

Standard protocol approvals, registrations, and patient consents. The local ethics committees approved the study protocol, which was conducted in accordance with the ethical standards of the Declaration of Helsinki. All participants were informed about the experimental procedure and gave their written informed consent prior to the study (for an example, see e-consent).

Experimental paradigms and design. ***Virtual leg illusion.*** We adapted the VLI protocol[12] to the present investigation of patients with SCI. Due to the impaired tactile perception in legs of the patients with SCI, we applied the visuotactile conflict between the seen virtual legs and the participant's back (tactile stimulation). The participants sat in a wheelchair and wore a head-mounted display (HMD; figure 1A). Fake legs were placed on another chair, mimicking a sitting posture. A camera was mounted above, corresponding to the participant's first-person viewpoint. The real-time video recording of virtual legs was fed to the HMD, appearing as superimposed over participants' physical legs, while the experimenter simultaneously stroked the participant's lateral back and the corresponding upper dorsal part of the ipsilateral virtual leg. Thus, the participants observed the virtual legs being touched simultaneously while they received touches on their back (figure 1A). Based on the findings on cortical reorganization after SCI (i.e., shift of neighboring cortical areas towards the denervated region[5]), we applied tactile stimulation to the lower back (immediately above SCI level) or to the upper back (distant, control site).

In a 2 × 2 repeated measures design, we manipulated the synchrony between the stroking of the virtual legs (synchronous, asynchronous) and the participant's back location (lower, upper back). In the synchronous condition, the stroking of the virtual legs was synchronized with the stroking of the participant's back. In the asynchronous condition, the visuotactile stimulation was delayed (approximately 1 second of delay). Each condition lasted for 60 seconds.

Full body illusion. We manipulated global body ownership through an adapted FBI protocol.[13] The participants sat in a wheelchair and wore an HMD. A camera, positioned 2 meters behind, filmed the participant's back, which the experimenter stroked. The real-time video was projected onto the HMD. The participants thus viewed their own body projected in front (virtual body) and were simultaneously stimulated on their back (figure 1B). This visuotactile stimulation (60 seconds) was synchronous or asynchronous (800 ms of the video delay).

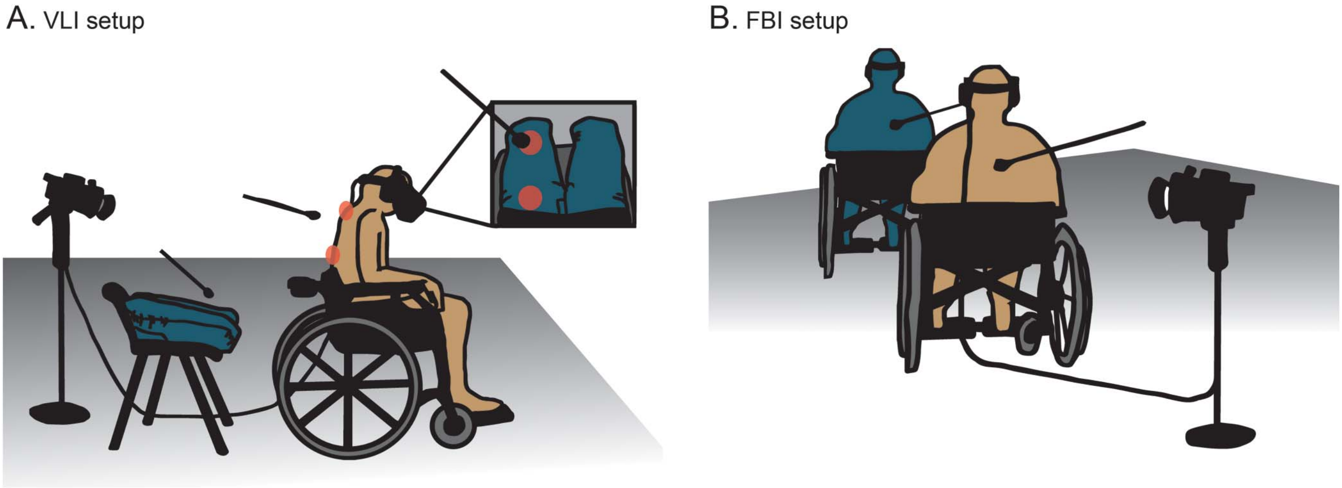
Assessments. The VLI was assessed with a 9-item questionnaire, adapted from body illusions studies,[13–15] with items referring to the experienced ownership for the virtual legs, illusory touch, and referred touch. The FBI was assessed with a 7-item questionnaire,[13] referring to the experienced ownership for the virtual body and illusory touch on the virtual body. Both questionnaires contained control items. All items are shown in table e-2. Participants rated the questionnaires on a 7-point Likert scale (−3, completely disagree; +3, completely agree). We assessed the intensity of actual neuropathic pain with a visual analogue scale (VAS) ranging from 0 (no pain) to 100 (worst pain imagined).[27] We assessed the presence of unusual body experiences with the Cambridge Depersonalization Scale (CDS).[28]

Procedure. We first conducted a short semi-structured interview with the SCI participants about their SCI, related pain, and bodily sensations, followed by the CDS administration. Before the experiment started, the experimenter carefully defined the level above which each patient had intact tactile perception on the back to ascertain the detectability of tactile stimulations. All patients with SCI with neuropathic pain rated the intensity of current pain on the VAS (baseline). The VLI and FBI protocol were then carried out in a counterbalanced order across participants. After each experimental condition, the participants rated the current neuropathic pain (only SCI-pain), the VLI, or FBI questionnaire (all participants). The order of the VLI conditions was randomized across patients, and the order of the FBI conditions counterbalanced.

Statistical analyses. The FBI and VLI illusion questionnaire ratings were first ipsatized using individual mean rating[29] (appendix e-1) and then averaged based on the measured component (tables e-2 and e-3). The VLI questionnaire scores were analyzed with a mixed analysis of variance (ANOVA), with synchrony (synchronous, asynchronous) and back location (lower back, upper back) as within-subjects factors and group (SCI, HC) as a between-subjects factor. The FBI questionnaire scores were analyzed with a mixed design ANOVA, with synchrony (synchronous, asynchronous) as a within-subjects factor and group (SCI, HC) as a between-subjects factor.

Linear and exponential curve estimations were performed for the relationship between the illusion ratings and the time since

Figure 1 Experimental setups



(A) In the virtual leg illusion (VLI) paradigm, the participant sits in a wheelchair and wears a head-mounted display (HMD) and headphones. The experimenter simultaneously strokes the lower or upper part of the participant's back and the corresponding part of the dummy leg. The camera films dummy legs from the distance and angle that corresponds to the participant's first-person viewpoint, and the real-time video recording is projected onto the HMD. Thus, the participant sees touch cues applied to the virtual legs while being touched on the back. (B) In the full body illusion (FBI) paradigm, the participant sits in a wheelchair and wears headphones and an HMD. A video camera, standing 2 meters behind, films the participant's back, while the experimenter is applying tactile stimulation to the participant's back with a wooden stick. The real-time (delayed for 800 ms in asynchronous condition) video is projected onto the HMD. The participant thus sees his or her own virtual body projected in front and being touched with the stick, while at the same time feels being touched on the back.

lesion or the SCI level; this was done for the synchronous–lower back and synchronous–upper back conditions in the VLI and the synchronous condition in the FBI. The questionnaire data were linearly transformed to non-zero positive values. To quantify the level of injury, we considered the SCI level as an integer ascribed to the ASIA-defined lesion level, ranging from 1 (lesion at T2) to 13 (lesion at L2).[10] If the lesion was defined between 2 neurologic levels, the score was calculated as the average of 2 integers (e.g., a T6/T7 lesion was scored with 5.5).

For the subgroup of patients with SCI with neuropathic pain (n = 11), the baseline pain rating was first subtracted from the postcondition pain ratings to obtain measures of pain modulation (pain change), which were then analyzed with repeated-measures ANOVA (VLI; 2 [synchrony] × 2 [back location] factorial design) and paired sample *t* test (FBI). The significance (α) level used was 0.05. One-tailed one-sample *t* tests were used to infer whether the pain change is significantly lower than zero (using Bonferroni method for multiple comparisons correction: FBI: $\alpha_{corr} = \alpha/2 = 0.025$; VLI: $\alpha_{corr} = \alpha/4 = 0.0125$).

In addition, we analyzed differences between SCI subgroups in their experience of VLI and FBI: between SCI with and without any preserved tactile sensation, between SCI with and without neuropathic pain, and between SCI with complete and incomplete SCI. We used mixed ANOVA with synchrony and back location (in VLI) as within-subjects and respective subgroups as between-subjects factors (appendix e-1).

We scored the CDS ratings according to Sierra and Berrios.[28] Based on a previous study showing increased occurrence of altered body perception in SCI,[9] we focused the analyses on the items in the Anomalous Body Experience (ABE) subscale,[30] using nonparametric Mann-Whitney *U*.

RESULTS **Virtual leg illusion.** We found significant main effects of synchrony, where synchronous visuotactile stimulation induced a stronger experience of illusory ownership for the virtual legs ($p = 0.037$), stronger sensations of illusory touch ($p = 0.008$), and stronger referred touch ($p < 0.001$), without significantly affecting the ratings of the control items ($p = 0.112$). We found a significant main effect of group on the ratings of illusory ownership ($p = 0.028$), showing that patients with SCI experienced weaker illusory leg ownership than HC, independently of the synchrony of stroking (interaction: $p = 0.263$). No such group differences were found in the ratings of illusory touch, referred touch, or control items (all $p \geq 0.153$). These findings suggest that SCI experienced weaker leg ownership, but equally strong illusory touch sensations as HC. We did not find any significant main effect of back location or interaction effects (all $p \geq 0.063$). We did not find any significant differences in the illusion or control ratings between the patients with SCI with and without preserved tactile leg sensations (all $p \geq 0.096$; table e-4), between the participants with SCI with and without neuropathic pain (all $p \geq 0.075$; table e-5), or between the participants with SCI with complete and incomplete lesions (all $p \geq 0.103$; table e-6).

A significant exponentially decaying relationship was found between duration of SCI and the magnitude of illusory leg ownership ($p = 0.016$) and between duration of SCI and the magnitude of illusory referred touch ($p = 0.036$). Importantly, both findings were only observed in the condition in which the lower back was stroked synchronously (other conditions: all $p \geq 0.081$). No significant correlations were found between the illusory ratings and the level

Table 1	Analysis of variance results for the questionnaire ratings in the virtual leg illusion (VLI)				
VLI ratings	Mean (SEM)	95% CI	$F_{1,36}$	p	η_p^2
Ownership					
Synchrony					
Synchronous	0.93 (0.20)	0.52, 1.34	4.69	0.037	0.115
Asynchronous	0.48 (0.21)	0.05, 0.92			
Back location					
Lower	0.75 (0.20)	0.35, 1.14	0.19	0.665	0.005
Upper	0.67 (0.21)	0.24, 1.09			
Group					
SCI	0.29 (0.26)	−0.23, 0.81	5.26	0.028	0.128
HC	0.67 (0.21)	0.60, 1.64			
Synchrony × back l			1.29	0.263	0.035
Synchrony × group			0.02	0.899	<0.001
Back l × group			0.02	0.885	0.001
Synchrony × back l × group			3.59	0.066	0.091
Illusory touch					
Synchrony					
Synchronous	0.40 (0.16)	0.08, 0.73	8.01	0.008	0.182
Asynchronous	−0.12 (0.14)	−0.40, 0.17			
Back location					
Lower	0.14 (0.16)	−0.18, 0.46	<0.01	0.974	<0.001
Upper	0.15 (0.15)	−0.16, 0.45			
Group					
SCI	0.10 (0.17)	−0.24, 0.44	0.13	0.721	0.004
HC	0.19 (0.17)	−0.16, 0.53			
Synchrony × back l			0.7	0.407	0.019
Synchrony × Group			0.1	0.749	0.003
Back l × group			1.35	0.253	0.036
Synchrony × back l × group			0.003	0.956	<0.001
Referred touch					
Synchrony					
Synchronous	1.27 (0.24)	0.78, 1.77	16.05	<0.001	0.308
Asynchronous	0.31 (0.18)	−0.06, 0.68			
Back location					
Lower	0.85 (0.21)	0.42, 1.28	0.36	0.552	0.01
Upper	0.73 (0.20)	0.33, 1.13			
Group					
SCI	0.70 (0.25)	0.18, 1.22	0.26	0.612	0.007
HC	0.88 (0.25)	0.37, 1.40			
Synchrony × back l			1.22	0.278	0.033
Synchrony × group			3.69	0.063	0.093
Back l × group			0.004	0.947	<0.001
Synchrony × back l × group			0.34	0.563	0.009
Control items					
Synchrony					
Synchronous	0.27 (0.10)	−0.47, −0.07	2.66	0.112	0.069

Continued

Table 1 Continued

VLI ratings	Mean (SEM)	95% CI	$F_{1,36}$	p	η_p^2
Asynchronous	−0.44 (0.09)	−0.63, −0.25			
Back location					
Lower	−0.33 (0.10)	−0.54, −0.13	0.21	0.647	0.006
Upper	−0.38 (0.09)	−0.56, −0.20			
Group					
SCI	−0.24, (0.12)	−0.47, −0.01	2.13	0.153	0.056
HC	−0.48 (0.12)	−0.71, −0.24			
Synchrony × back l			1.5	0.229	0.04
Synchrony × group			1.36	0.252	0.036
Back l × group			0.001	0.978	<0.001
Synchrony × back l × group			0.003	0.958	<0.001

Abbreviations: CI = confidence interval; HC = healthy controls; SCI = spinal cord injury.

of SCI (all $p \geq 0.125$). Statistical results are shown in table e-3.

We did not find any significant main effects of synchrony, back location, or interactions on the pain change ratings between the postillusion and the baseline ratings (all $p \geq 0.147$). However, when comparing the pain change against zero, we found a significant pain reduction when the lower back was stimulated synchronously with the virtual legs ($p = 0.04$), but not in any of the other conditions (all $p \geq 0.188$). However, this comparison did not survive correction for multiple comparisons: $\alpha_{corr} = 0.0125$. See table 1 for statistical reports and figure 2 for a graphic presentation of results.

Full body illusion. We found significant main effects of synchrony, where synchronous visuotactile stimulation induced stronger illusory body ownership ($p < 0.001$) and stronger illusory touch ($p < 0.001$) as compared to asynchronous stimulation, but it did not significantly modulate the ratings of control items ($p = 0.823$). In contrast to the VLI, we did not find significant main effects of group (all $p \geq 0.558$) or interaction effects (all $p \geq 0.146$) on any of the FBI questionnaire items. No differences in the illusion or control ratings were found between participants with SCI with and without preserved tactile leg sensations (all $p \geq 0.481$; table e-4), between participants with SCI with and without neuropathic pain (all $p \geq 0.332$; table e-5), or between participants with SCI with complete and incomplete lesions (all $p \geq 0.173$; table e-6). No significant correlations were found between ratings on body ownership and illusory touch with SCI duration or with SCI level (all $p \geq 0.052$; table e-3).

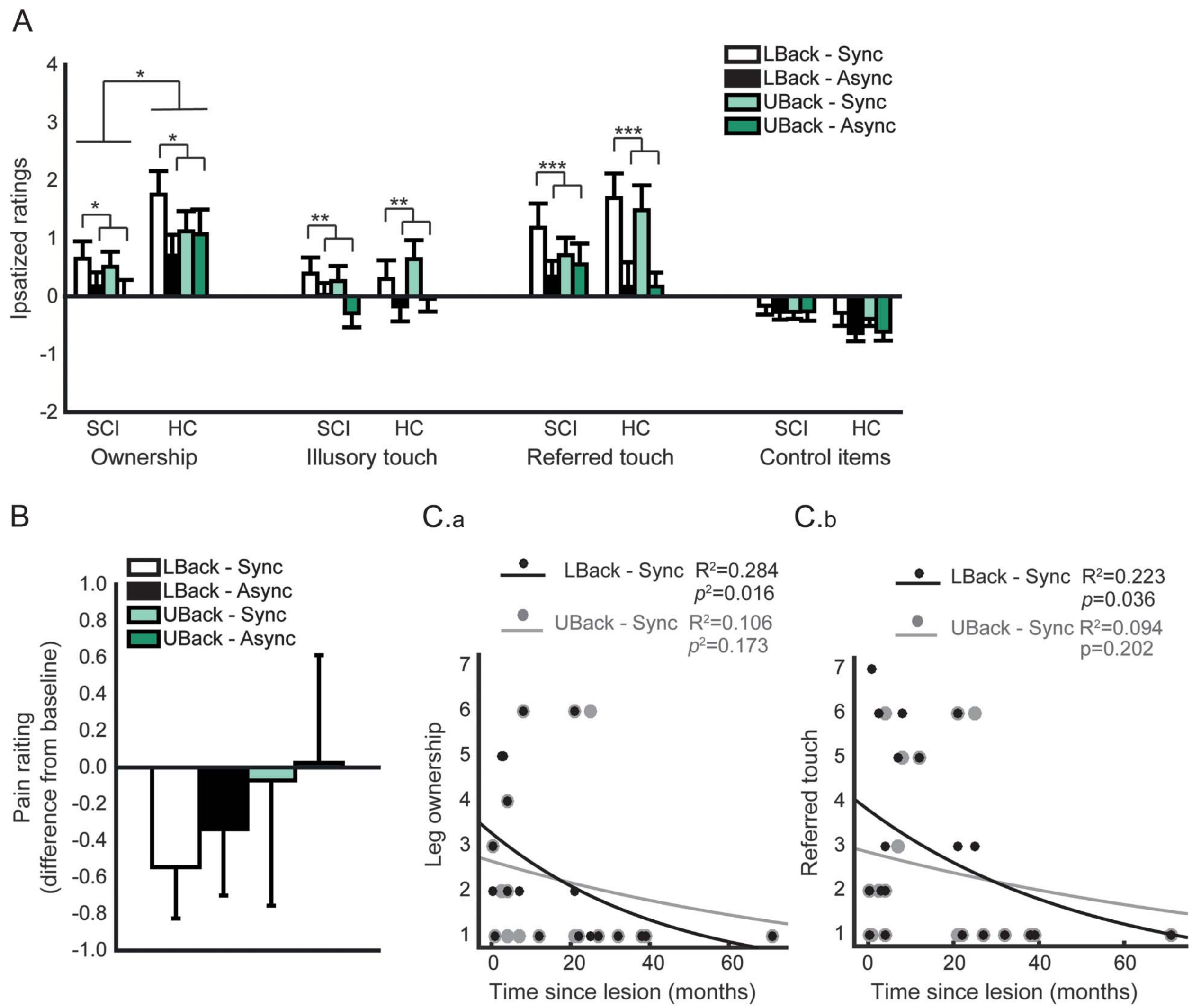
Concerning pain ratings, the synchrony of visuotactile stimulation did not modulate the pain change ($p = 0.920$). However, the FBI significantly reduced the pain compared to baseline measurements in both the synchronous ($p = 0.020$) and asynchronous ($p = 0.020$) visuotactile stimulation conditions (table 2 and figure 3).

Cambridge Depersonalization Scale. No significant differences between the participants with SCI and HC were found for the total CDS or ABE subscale scores (all $p \geq 0.260$). However, the participants with SCI rated significantly higher 2 individual items that are related to leg/body ownership: "Parts of my body feel as if they didn't belong to me" ($p = 0.028$) and "I have to touch myself to make sure that I have a body or a real existence" ($p = 0.009$) (see table e-7 for statistical results).

DISCUSSION We investigated SCI-related alterations of bodily self-consciousness through multisensory body illusion paradigms using VR. In particular, we tested whether the sensitivity to experimental manipulations of leg and body ownership is affected by SCI, and whether such multisensory stimulation has analgesic effects.

In the VLI paradigm, participants received tactile stimulation on their back while viewing, through an HMD, the virtual legs being touched. This manipulation, when temporally synchronous, is generally associated with stronger integration (as compared to asynchronous) of visual, proprioceptive, and tactile information[12]; here we show for the first time that it results in the illusory sensation that touching the virtual legs is causing the touch on the back (referred touch) and to a lesser extent in illusory touch on the legs in both SCI and HC groups. Important for understanding the effect of SCI on central leg representations, the SCI group showed a general reduction across conditions in proneness to experience virtual legs as one's own, indicating that individuals with paraplegia less readily integrate the available visual and tactile information to

Figure 2 Virtual leg illusion (VLI) results



(A) Mean ipsatized ratings of the VLI questionnaire items: significant main effects of synchrony were found for the ratings of ownership, illusory touch, and referred touch. Significant main effect of group was found for the ratings of ownership. (B) Mean differences in neuropathic pain between baseline and post-condition ratings in the VLI. (C) Exponential decaying relationship between the time since lesion and ratings of ownership (C.a) or referred touch (C.b) in The VLI: significant relationships between the illusion and time since lesion were found for synchronous stimulation of lower back, but not upper back. Async = asynchronous; HC = control group; L back = lower back; Sync = synchronous; SCI = spinal cord injury group; U back = upper back. SCI HC *$p < 0.05$, **$p < 0.010$, ***$p < 0.001$. Error bars show standard error of the mean.

experience illusory leg ownership. Moreover, time since injury negatively correlated with illusory leg ownership and referred touch, suggesting that with prolonged sensorimotor deficits, patients with SCI become even more resistant in their decreased sensitivity to the VLI. This may potentially be associated with alterations in central multisensory leg representations, and stronger reliance on off-line leg representations, as previously reported for upper limb amputees and the strength of the rubber hand illusion (RHI).[31]

We did not find any differences in the VLI between the lower and upper back stimulation conditions. Differences would have been compatible with SCI-induced changes in cortical reorganization in primary somatosensory cortex (S1), as shown for hand-face remapping effects in patients with tetraplegia during the RHI.[11] This negative finding thus indirectly suggests that other, multisensory leg representations (for example, in posterior parietal cortex[8]) and not S1 are involved in mediating the effects of the VLI, also supported by the negative correlation between the time since SCI and VLI ratings. Alternatively, the absence of the stimulation site effect could also be due to the relatively larger receptive fields on the back in S1 (as compared to hand or face), with both stimulations activating closely similar locations in S1 and in higher-tier areas.[32]

In contrast to these VLI findings, we found no differences between SCI and HC in the FBI, which in comparison to paradigms where the focus of the

Table 2 Analysis of variance results for the questionnaire items in the full body illusion (FBI) and pain change in the virtual leg illusion (VLI) and the FBI

FBI ratings	Mean (SEM)	95% CI	$F_{1,38}$	*p*	η_p^2
Ownership					
Synchrony					
Synchronous	2.53 (0.22)	2.09, 2.98	21.67	<0.001	0.363
Asynchronous	0.76 (0.32)	0.10, 1.41			
Group					
SCI	1.53 (0.28)	0.95, 2.10	0.35	0.558	0.009
HC	1.76 (0.28)	1.19, 2.33			
Synchrony × group			0.35	0.559	0.009
Illusory touch					
Synchrony					
Synchronous	2.93 (0.19)	2.55, 3.31	72.38	<0.001	0.656
Asynchronous	0.14 (0.26)	−0.39, 0.68			
Group					
SCI	1.59 (0.23)	1.13, 2.04	0.10	0.752	0.003
HC	1.49 (0.23)	1.03, 1.94			
Synchrony × group			1.22	0.276	0.276
Control items					
Synchrony					
Synchronous	−1.16 (0.14)	−1.46, −0.87	0.05	0.823	0.001
Asynchronous	−1.20 (0.12)	−1.45, −0.94			
Group					
SCI	−1.18 (0.16)	−1.51, −0.85	<0.00	0.972	<0.001
HC	−1.18 (0.16)	−1.51, −0.85			
Synchrony × group			2.21	0.146	0.055
VLI pain ratings	Mean (SEM)	95% CI	$F_{1,9}$	*p*	η_p^2
Synchrony					
Synchronous	−0.34 (0.47)	−1.41, 0.74	2.52	0.147	0.219
Asynchronous	−0.11 (0.46)	−1.16, 0.94			
Back location					
Lower	−0.42 (0.33)	−1.17, 0.33	1.04	0.335	0.103
Upper	−0.23 (0.63)	−1.45, 1.40			
Synchrony × back l			0.72	0.420	0.074
	Mean (SEM)	95% CI	*t*	*df*	*p*
Pain change vs zero comparison					
Lower back-synchronous	−0.54 (0.28)	−1.17, 0.08	−1.95	10	0.04
Lower back-asynchronous	−0.07 (0.68)	−1.62, 1.48	−0.10	10	0.461
Upper back-synchronous	−0.34 (0.36)	−1.14, 0.47	−0.97	9	0.188
	Mean (SEM)	95% CI	t_{10}	*p*	d
FBI pain ratings					
Synchrony					
Synchronous	−0.43 (0.18)	−0.84, −0.03	0.10	0.920	0.042
Asynchronous	−0.46 (0.19)	−0.88, −0.03			

Continued

Table 2 Continued					
FBI ratings	Mean (SEM)	95% CI	$F_{1,38}$	p	η_p^2
Pain change vs zero comparison					
Synchronous			−2.37	0.020	
Asynchronous			−2.37	0.020	

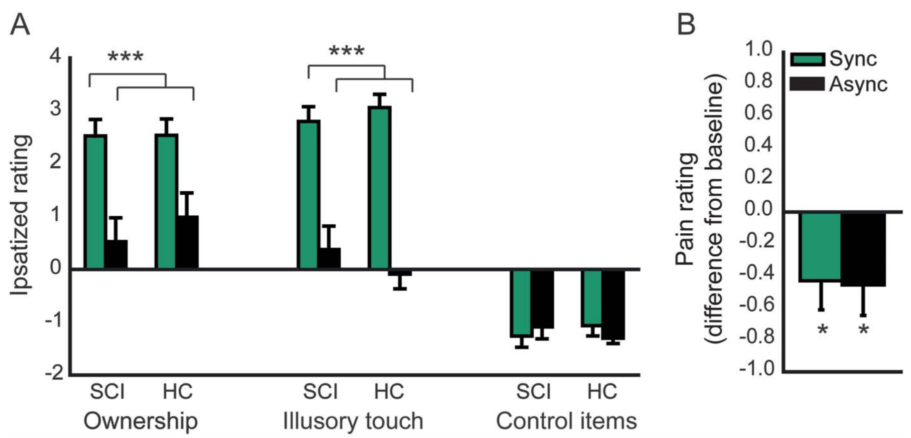
Abbreviations: CI = confidence interval; HC = healthy controls; SCI = spinal cord injury.

visuotactile stimulation is a body part (RHI[15] or VLI[12]) enables experimental manipulation of more global aspects of bodily self-consciousness, affecting ownership for the entire body.[13,33] In the current study we extended earlier findings[13,34] showing that synchronous (as compared to asynchronous) visuotactile stimulation induces stronger illusory ownership not just in HC but also in patients with SCI, suggesting that the chronic denervation of the lower trunk and legs in SCI does not alter the multisensory mechanisms important for global aspects of bodily self-consciousness.[13,34,35] We note that visuotactile stimulation in the FBI was applied at a body site with fully preserved sensory functionality (upper trunk, above the lesion level), which, however, was also the case during all conditions of the VLI, suggesting differential recruitment of multisensory bodily integration processes in patients with SCI in both VR illusion paradigms.

We also investigated whether the present multisensory VR paradigms modulate neuropathic pain. Despite the overall mild analgesic effects in the VLI, we observed that only synchronous visuotactile stimulation in the back condition (associated with the strongest experience of the VLI) resulted in a near significant reduction of neuropathic pain. This somatotopy-related analgesia (and VLI induction) suggests that this particular experimental manipulation might activate otherwise silent cortical regions representing the lower limbs, arguing for a potential central co-representation of pain and the multisensory VLI. We speculate that the stimulation may have transiently interfered with abnormally altered leg representations in SCI, arguably involved in the central origins of neuropathic pain[18,36] and previously explored using the RHI for alleviating neuropathic pain in upper limb amputees.[18] We found a condition-nonspecific mild analgesic effect of the FBI, which is potentially related to so-called visual analgesia (i.e., seeing one's own body already has analgesic effects in healthy participants)[21,37–39] or previously reported distraction effects of VR.[40] Future work is needed to investigate these differences.

Our results need to be interpreted with caution; the SCI sample with neuropathic pain was relatively small and clinically heterogeneous. Although excluding 2 patients with nontraumatic SCI from our analyses showed only slight deviations in our results (see appendix e-1), future studies should focus on larger cohorts of different SCI subgroups with uniform

Figure 3 Full body illusion (FBI) results



(A) Mean ipsatized ratings of the FBI questionnaire items: significant main effects of synchrony were found for the ratings of ownership and illusory touch, but not for control items. The differences between the groups were not significant. (B) Mean differences in neuropathic pain between baseline and postcondition ratings for synchronous and asynchronous condition in the FBI: significant main effect of synchrony was found for the ratings of ownership, illusory touch, and referred touch. Significant main effect of group was found for the ownership ratings. Async = asynchronous; HC = control group; SCI = spinal cord injury group; Sync = synchronous. * $p < 0.05$, *** $p < 0.001$. Error bars show standard error of the mean.

clinical presentations and etiology to replicate the present findings. These studies should preferably use prolonged and repeated stimulation and test different multisensory stimulation patterns including different body locations. These changes may boost the currently observed pain reduction and enable us to draw firmer conclusions about the paradigm's analgesic effects. Nevertheless, the present findings are relevant for the design of noninvasive SCI neurorehabilitation and pain management protocols, suggesting the importance of early interventions to strengthen multisensory body representation in the SCI population. Further work may also consider testing the current VR methodology and its analgesic effects in other acute and chronic pain conditions (see appendix e-1), such as complex regional pain syndrome, diabetic neuropathy, or multiple sclerosis.

Comment: Is virtual reality a useful adjunct to rehabilitation after spinal cord injury?

Spinal cord injury (SCI) has devastating effects on the CNS, leading to disruption of various neuromuscular, sensory, and autonomic pathways. However, the changes induced in the nervous system extend well beyond the tracts and neurons directly disrupted starting soon after the injury.[1] There is substantial neural plasticity that takes place throughout the CNS, including the cortex.[2] Trying to improve function and pain after a peripheral injury by intervening at the cortical level has been explored since the mid-1990s with classic mirror box therapy for phantom limb pain.[3]

Pozeg et al.[4] have assessed and tried to intervene in spinal cord injury patients' perception of body ownership and pain with a more complex approach, combining virtual visual and tactile input. Their paradigms are clear and the design is meticulous. They identified decreased leg ownership in the SCI group compared to healthy controls. Although the numbers were small and the patients were heterogeneous, the sense of ownership was lower the more remote the spinal cord injury. Data are not presented to compare patients with SCI with and without pain.

With virtual reality paradigms addressing both leg and body stimulation, illusions can produce modest improvements in neuropathic pain. Thus, this article offers a potentially useful way to address cortical representation in patients with spinal cord injury. It remains to be seen whether implementing these findings into a therapy will lead to decreased pain, improved function, or decreased likelihood to develop deafferentation pain.

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AUTHOR CONTRIBUTIONS

Dr. Pozeg: study concept and design, acquisition of data, analysis and interpretation of data, manuscript drafting, obtaining funding. Dr. Palluel: study concept and design, acquisition of data, manuscript drafting, obtaining funding. Dr. Ronchi: interpretation of data, study supervision, manuscript drafting. Dr. Solcà: acquisition and interpretation of data. Dr. Al-Khodairy: study concept and design, acquisition of data. Dr. Jordan: acquisition and interpretation of data. Dr. Kassouha: acquisition and interpretation of data. Dr. Blanke: study concept and design, interpretation of data, obtaining funding, study supervision, critical revision of manuscript for intellectual content.

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