

Pain and somatic sensation are transiently normalized by illusory body ownership in a patient with spinal cord injury.

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Abstract

Purpose: Spinal cord injury (SCI), a profound impairment of sensorimotor functions, is often associated with pain related phenomena, including mechanical allodynia, a condition in which non-painful tactile sensation is perceived as pain. Pain and somatic sensation are undeniable markers of normal bodily awareness. However, the mechanism by which they are integrated into a coherent sense of the bodily self remains largely unclear. In this study, we investigated the effect of high-level multisensory manipulation on subjective experiences of pain, touch, and body-ownership.

Methods: We administered visuo-tactile stimulation based on the rubber hand illusion. In a longitudinal study, we compared the strength of the illusion in a male with SCI, who initially had lost somatosensation in all his fingers, but a few months later reported signs of tactile allodynia restricted to the left C6-dermatome.

Results: After the restoration of some somatosensation, even if it were painful, synchronous but not asynchronous visuo-tactile stimulation induced body illusion. Previously painful stimuli were temporarily perceived as less painful, and the patient further regained tactile sensations in adjacent numb areas.

Conclusions: The sensations of touch and pain are mutually influenced and inextricably linked to a coherent representation of one's own body. Multisensory manipulations affecting the perception and representation of the body might thus offer a powerful opportunity to mitigate nociceptive and somatic abnormalities.

Introduction

The experience of pain is intrinsically linked to the body, so that "disembodied pain does not make sense" (Haggard et al., 2013). Understanding the reciprocal interactions between pain and alterations of bodily awareness may therefore provide great insights into their underlying nature (Hänsel et al., 2011; Tsay et al., 2015).

Spinal cord injury (SCI), which causes extreme neurological impairment, alters or completely blocks afferent and efferent signaling (Lucci and Pazzaglia, 2015), increases abnormal somatic sensations (Lenggenhager et al., 2012), and entrains somatosensory cortex plasticity (Henderson et al., 2011). A reorganization of cortical representation might thus reflect peripheral body dysfunction (Bruehlmeier et al., 1998; Corbetta et al., 2002; Curt et al., 2002; Henderson et al., 2011). These changes are commonly accompanied by pain (Finnerup, 2013; Teixeira et al., 2013; van Gorp, 2015). Interestingly, however, in a previous case report, it was proposed that pain remains a fundamental resource to counteract a wholly disembodiment of the body (Cole, 2004).

Approximately 19% to 96% of the population with SCI has pain (Van Gorp et al., 2015). Touch-evoked pain is known as allodynia. Longitudinal studies indicate that allodynia is present in 78% of patients with SCI in the first few weeks, but is dramatically reduced afterward (Siddall et al., 1999). In 39% of patients with pain and cervical spinal cord injury, allodynia is reported after this period (Finnerup, et al., 2003). The mechanism that produces allodynia is explained by an increase in excitability in the dorsal horn via low-threshold inputs of the A δ - (Takazawa and MacDermott, 2010) and C-fibers (Liljencrantz et al., 2013).

Pain is intrinsically linked to touch. Convergent behavioral and neural evidence indicates an interaction between tactile and nociceptive processing (Mancini et al., 2014; Ploner and Schnitzler, 2004). Such interactions are partly spinal, but may also involve overlapping representations in the somatosensory cortices (Ploner et al., 2004; Tran et al., 2003). For example, acute pain not only decreases sensitivity to tactile stimuli on the affected limb (Apkarian et al., 1994; Bolanowski et al.,

2000), but also modulates tactile processing in human somatosensory cortices (Ploner et al., 2004; Rossi et al., 1998).

Here, we used tactile and visual stimulation based on the rubber hand illusion (RHI, Botvinick & Cohen 1998). Multisensory stimulation paradigms have been previously shown to successfully alter body representations (Tsakiris and Haggard, 2005), neuropathic pain (Villiger et al., 2013), and cortical plasticity (Flor, 2012). Furthermore, in SCI patients, synchronous visuo-tactile stroking has been shown to temporarily restore peripheral tactile sensation in numb fingers (Lenggenhager et al., 2013; Tidoni et al., 2014). We thus tested this paradigm in a patient with SCI who had complete loss of sensory afferent input from the limbs and subsequently regained painful sensation in response to tactile stimulation, in order to investigate the relationships between pain, touch, and alterations in the body representation.

Methods

Patient and study design

At the age of 38, a male patient (AD) had a traumatic lesion affecting the fourth cervical vertebra of his spinal cord after a motorcycle accident, with no associated brain injury. Neurological examination revealed complete paralysis of the legs and trunk, with some sparing of finger movements and a profound loss of sensory function below the level of injury. The patient was graded according to the American Spinal Injury Association Impairment Scale as grade A due to the absence of any sensory or motor function in the lowest sacral segments. He experienced central neuropathic pain and spasm-related pain below the level of injury and no area of allodynia at the time of his admission to the Santa Lucia rehabilitation center (see Table 1 for details). He was alert and well oriented, and thus assigned to actively participate in the hospital's rehabilitation treatment program. He accepted all treatment recommendations, including physical therapy, water therapy, occupational therapy, and tactile stimulation of his hands for the recovery of some functions after the injury. He had no history of neurological or psychiatric disease.

Eight months after injury, AD agreed to undergo his first RHI session as a participant of the study published in (Lenggenhager et al., 2013). During this session, AD did not report any tactile or painful sensation on any finger in any of the conditions. The same experimenter conducted two more sessions (one week apart) about 6 months after the first one. During the second session and the third session, he reported painful hypersensitivity to tactile stimulation in the left thumb, and to a lesser extent, in the index finger, with implications in daily life as well as during therapeutic sessions.

The patient provided written informed consent to participate in the study. The ethical review boards at the Fondazione Santa Lucia approved the study, and all procedures of the three sessions were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and the ethical guidelines of the International Association for the Study of Pain.

TIME SINCE INJURY (MONTHS)	DEMOGRAPHIC AND NEUROLOGICAL DATA				FUNCTIONAL DATA			TACTILE SENSATION					PAIN SENSATION VAS RATING				
	AGE	LESION	AIS GRADE	MOTOR SCORES	BARTHEL INDEX (0-100)	SCIM SELF-CARE (0-20)	SCIM MOBILITY (0-40)	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5
8 1 st SESSION	38	C4	A	12	0	0	10	0	0	0	0	0	0	0	0	0	0
14 2 nd -3 rd SESSION	39	C4	A	46	20	4	28	5	5	0	0	0	100	60	0	0	0

*** Table 1 ***

First experimental session: 8 months after SCI

Sensory examination

The patient’s reaction to tactile sensation was examined five times for each finger (Danziger et al., 1996). The patient was instructed to close his eyes and was gently touched with cotton wool perpendicular to the skin in the distal to proximal direction with a 3-cm stroke lasting 1 s. After each stimulation, he reported what he felt and where.

General RHI paradigm

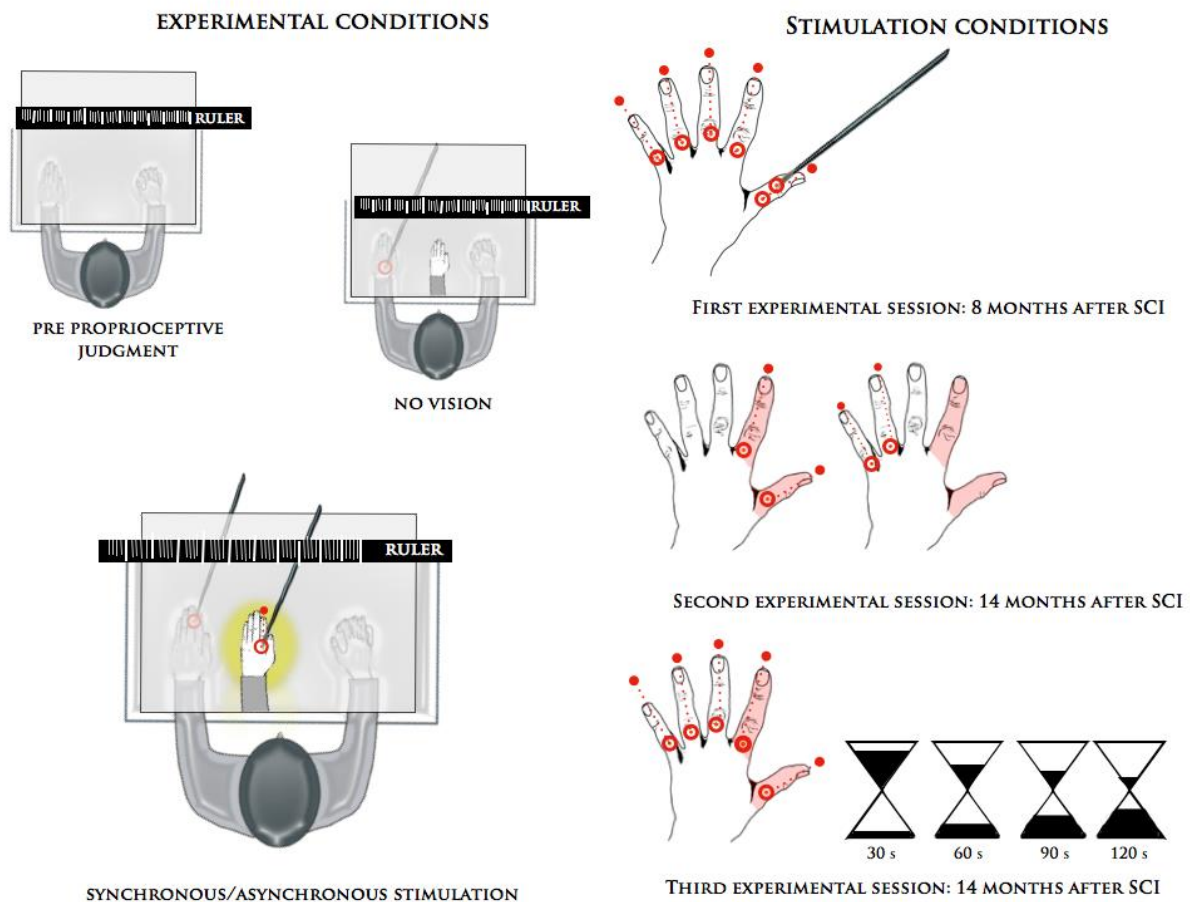
A classical RHI task was administered (Botvinick and Cohen, 1998). AD was seated in a wheelchair in front of a wooden box open on the sides and was instructed to fixate on a fake hand. AD’s actual left hand was placed inside the box, which was covered. A realistic-looking rubber left hand, positioned 13 cm away from AD’s arm and aligned with his midline, was visible to him.

Brush strokes were applied for 2 min in an irregular manner on all five fingers using two identical paintbrushes on both AD’s hidden hand and the visible rubber hand in two blocks: synchronous and asynchronous stroking.

In each session, before stroking and without the rubber hand or the patient’s own hand being visible, we measured the perceived initial position of AD's finger five times to get a measure of the constant error in proprioceptive judgment. AD was instructed to verbally indicate, in centimeters and millimeters, where the midpoint of his index finger was located using a ruler placed on top of

the box. The offset of the ruler was changed before each of the five trials, and the difference between the ruler offset and the answer of the patient indicated the perceived finger position. The exact same measure was used once after each RHI stroking condition with neither the rubber hand nor the patient's own hand being visible.

The difference between that measure and the constant error (the mean of the pretest baseline) indicated the proprioceptive drift as an implicit measure of the RHI. Immediately after, AD filled out an Italian version of the 9-item questionnaire consisting of 3 illusion-relevant (IR) and 6 illusion-control (IC) questions (Botvinick and Cohen, 1998). The level of agreement with each item was rated on a 7-point Likert scale ranging from -3 ("I totally disagree") to +3 ("I totally agree"). Scores on the 3 IR questions were used as the explicit measure of RHI. Fig. 1 shows the experimental set-up.



*** Fig. 1***

Second experimental session: 14 months after SCI

Sensory examination

We examined tactile sensation of the patient as in the first session. To assess the pain sensation reported on two fingers, AD was further asked to rate, on a 100-cm visual vertical analogue scale (VAS), the strength of the pain sensation in comparison to that of a reference painful stimulus applied on the face, where tactile sensations were normal. The reference stimulus was defined as the lowest pressure, applied using an algometer, that was considered painful. The VAS ranged from “no pain” (score of 0) to “most unpleasant” (score of 100).

General RHI paradigm with stroking only painful or non-painful areas

Previous evidence in healthy participants has shown that RHI might be induced by nociceptive-visual stimulation (Capelari et al., 2009). Since AD had regained painful sensations in two left fingers, we applied the synchronous and asynchronous visual-tactile stroking for 2 minutes on two specific skin regions. Specifically, stroking was applied either exclusively on the painful thumb and index finger (C6 dermatome: “Feel” condition), or exclusively on the non-sensitive ring and little finger (C8 dermatome, “No Feel” condition). In all conditions, proprioceptive drift and questionnaire measures were recorded.

Third experimental session: 14 months after SCI, one week after the second session

Extended RHI paradigm

We adapted the extended RHI paradigm used by (Lenggenhager et al., 2013), in which two patients showed illusion-specific increases of tactile sensation during the stroking time course. We thus applied stroking for 2 minutes under the following three conditions: 1) synchronous stroking, 2) asynchronous stroking, and 3) no vision: tactile stroking applied to the real hand while the patient observed the untouched rubber hand. As the classical RHI can induce analgesic effects in healthy participants (Hegedus et al., 2014), the patient was further asked to rate the sensation perceived. During the different stroking conditions, the patient thus rated how intense and unpleasant the tactile/pain sensation felt respectively on two vertical 100-mm visual analog scales (0 = absent/no unpleasantness; 100 = perfectly normal/most unpleasant) every 30 s for each finger. Accordingly, four measures of intensity and four of unpleasant sensation on each finger were taken during the 2 minutes. At the end of the stimulation, proprioceptive drift was measured and the questionnaire completed.

Results

First experimental session: 8 months after injury

Sensory examination

Eight months after injury, the patient did not report tactile or painful sensation on any finger and was unable to determine whether the stimulus was moving or not.

RHI in the absence of any somatosensation

The results are summarized in Fig. 2A. No difference was found between the average scores of the illusion relevant and control items (mean score of IR_{Q1-Q3} = 0; IC_{Q4-Q9} = 1). The location of the hand after the synchronous (12.7 cm) and asynchronous stroking (12.8 cm) was nearly identical and comparable to the pre-test baseline (mean \pm SD: 12.65 \pm 0.6).

Together, the results of first experimental session indicated that no RHI occurred in the complete absence of somatosensory perception.

Second experimental session: 14 months after injury

Sensory examination

Six months after the first session, the patient reported a clear sensation of pain after being touched on some fingers over the preceding 10 days.

Sensory examination of the left hand according to the international standards for neurological classification of spinal cord injury revealed areas of complete loss of sensory function in the left C8 dermatome (i.e., the middle, ring, and little fingers) and areas of perceived sensitivity in the left C6 dermatome (i.e., the thumb and index finger).

Upon lightly touching the skin of the thumb and index finger, AD reported a painful sensation in the thumb (VAS score = 100), and to a lesser extent, pain in the index finger (VAS score = 60) due to the tactile stimulation. The pain was described as a deep and burning sensation on the thumb and

as a more superficial sensation on the index finger. Similar stroking on the face was perceived as neutral or even pleasant. On the other fingers, AD did not report any touch or pain sensations.

RHI in pain sentient C6 and insentient C8 dermatomes

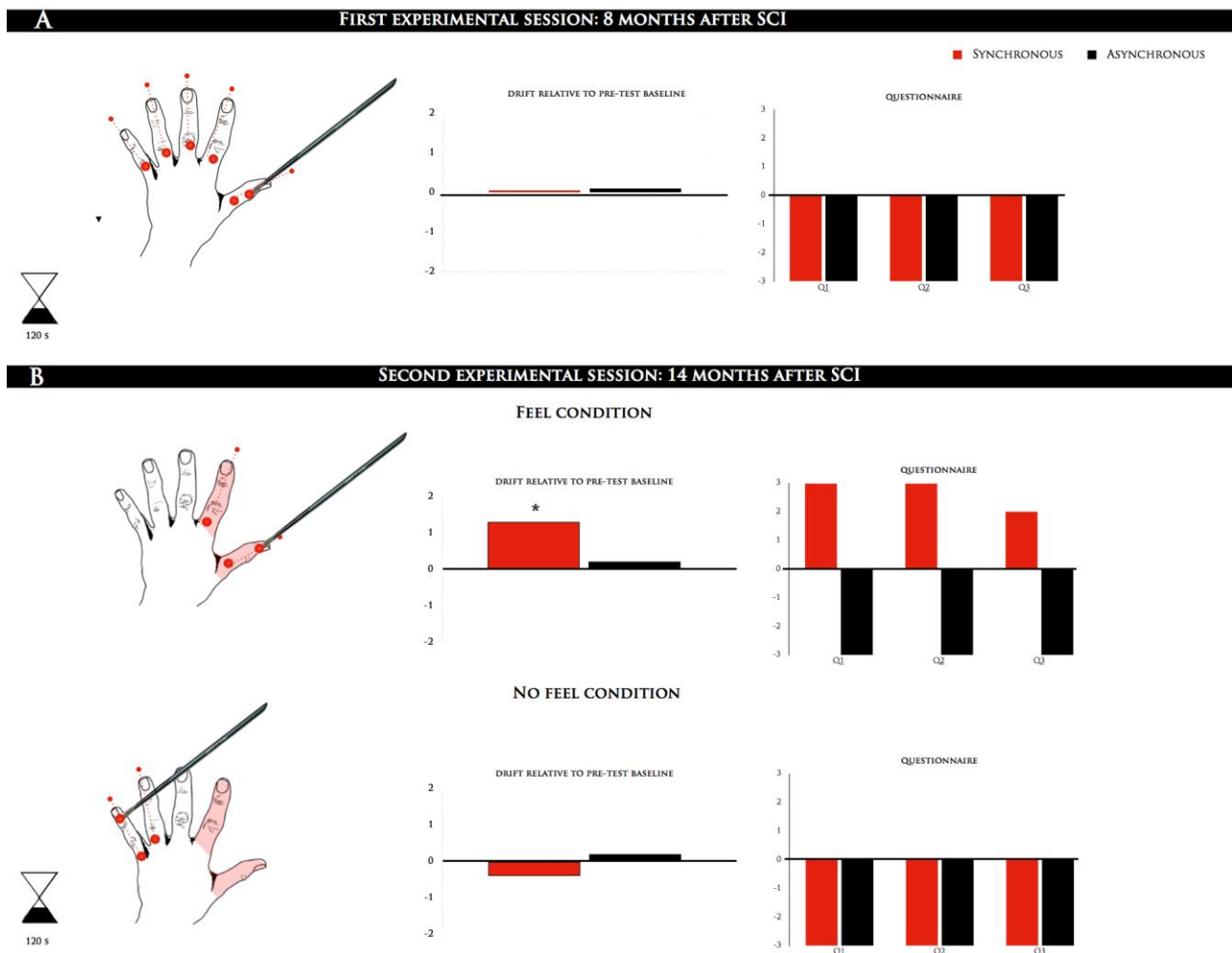
AD reported a distinct difference in the intensity of the RHI between sentient C6 and insentient C8 dermatomes. While he experienced no illusion during synchronous stroking of non-sentient C8 zones (No Feel condition), he experienced a strong RHI during synchronous stroking of the painful C6 zone (Feel condition). The results are summarized in Fig. 2B.

In the Feel condition, the patient demonstrated more illusory ownership and a referral of touch (as measured by the questionnaire) after synchronous than after asynchronous stroking (difference for the mean score of $IR_{Q1-Q3} = 5.66$). No difference was found for the illusion-control questions (mean score of $IC_{Q4-Q9} = 1$).

Furthermore, proprioceptive drift (see Fig. 1A) towards the fake hand was stronger after synchronous (1.3 cm) than after asynchronous (0.2 cm) stroking.

In a further control condition (No Feel), there was no illusion (difference between synchronous and asynchronous for mean score of $IR_{Q1-Q3} = 0$), and the proprioceptive drift was smaller and more negative after synchronous (-0.4 cm) than after asynchronous (0.2 cm) stroking.

In conclusion, the results of the second experimental session indicated that with the restoration of some sensation, even if painful, the rubber hand illusion could be evoked.



*** Fig. 2 ***

Third experimental session: 14 months after injury

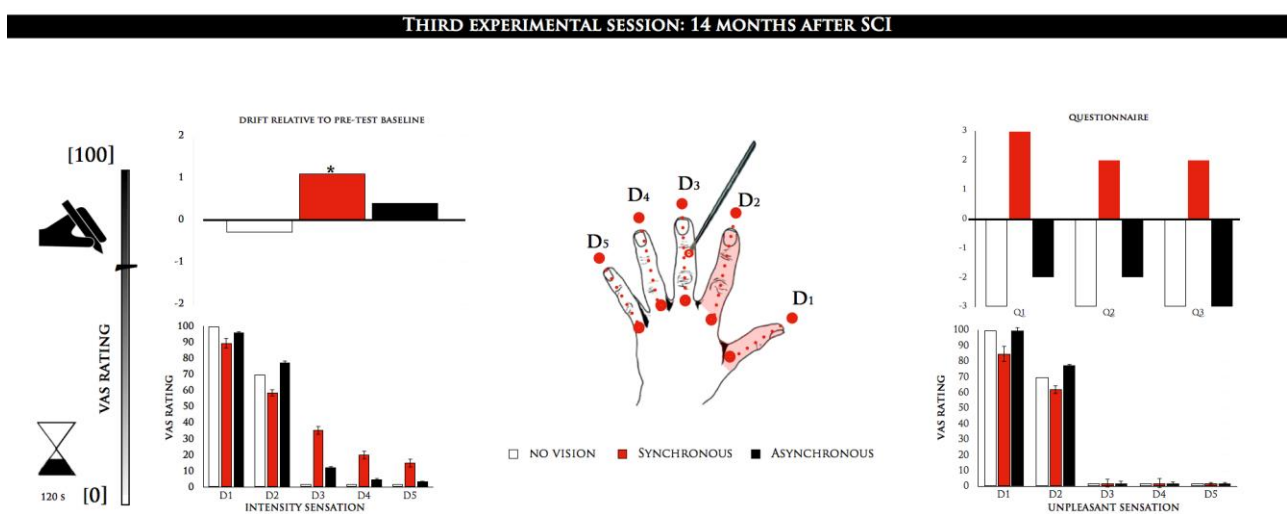
In third experimental session, two VAS were used every 30 s for each finger to measure perceived intensity and unpleasantness ratings for each of the three different stroking conditions. The mean VAS ratings are shown in Fig. 3.

During synchronous stroking, the perceived touch intensity increased for the insensitive fingers (i.e., D3-D5) (VAS: mean \pm SEM; middle: 35.75 ± 5.9 , ring: 20.25 ± 5.4 , little: 15.25 ± 5.5) On the sensitive fingers where the touch was felt as painful decreased both intensity (mean \pm SEM; thumb: 89.75 ± 7 , index: 58.75 ± 4.7 , Fig. 3) and unpleasantness (mean \pm SEM: thumb 85.25 ± 10.5 , index 62.5 ± 5.5 , Fig. 3) of sensation. Questionnaire data revealed an illusion (Syn-Asyn: $IR_{Q1-Q3} = 4.6$,

IC_{Q4-Q9} = 0; Syn-No vision: IR_{Q1-Q3} = 5.3, IC_{Q4-Q9} = 0) as well as a proprioceptive drift (Syn-Asyn = 0.6 cm, Syn-No vision = 1.3 cm).

During asynchronous stroking, AD did not report the illusion and the evoked sensation was very painful and unpleasant for the thumb and index finger (mean ± SEM; thumb; 96.25 ± 2.5, index: 77.5 ± 3). The touch intensity perceived (see supplementary figure) during asynchronous stroking was similar to the sensation typically evoked during sensory examination (see Table 1).

During the “no vision” control condition, the patient again did not report the illusion and similarly rated complete sensation on VAS (mean ± SEM: 100 ± 0) and strong unpleasantness (mean ± SEM: 100 ± 0) for the thumb, less intense (mean ± SEM: 70 ± 0) but unpleasant sensation (mean ± SEM: 70 ± 0) for the index finger, and no sensation for other fingers.



*** Fig. 3***

In conclusion, the results of third experimental session suggested that in skin regions where touch caused painful sensations, a synchronous RHI condition tended to reduce pain levels relative to control conditions, while the tactile sensation was increased in other skin regions. Rehabilitative

therapy may in principle contribute to normalized pain and somatic sensation. However, the normalization obtained was a specific effect of the synchronous condition and not of the asynchronous or no vision condition, indicating that was induced by body illusion.

Discussion

In this longitudinal study, we used a classic multisensory paradigm (RHI, Botvinick and Cohen 1998) to investigate the mutual role of pain and bodily awareness after sensorimotor interruption between the body and the brain. We reported the case of a man with SCI who lost all somatosensation in his hands, but regained some abnormal painful sensation in the form of allodynia confined to the left thumb and index finger a few months later. This case represented a unique opportunity to investigate subjective experiences such as tactile sensations or pain on exactly the same body part, in areas that were previously non-sentient.

Results from multiple RHI testing sessions revealed that: i) illusory ownership did not occur when applied to numb body parts; (ii) after the re-establishment of some sensation in the form of allodynia in two fingers, synchronous stimulation of the sentient dermatomes induced bodily illusions; iii) with continuing simultaneous multisensory stimulation exclusively after the synchronous stroking, the pain levels in the sentient body parts were reduced, with tactile sensation spreading to the non-sentient body parts. No such effects were found in the control conditions (asynchronous and visual) or after continuous stroking during clinical examination.

From a completely numb to painful state of the body

No illusion ownership or proprioceptive drift occurred in the complete absence of somatosensory perception; this, in itself, is not a trivial finding. Recent evidence suggested that it is more the conflict of the *asynchronous* stroking, rather than the sensory congruence during the synchronous stroking, that drives the rubber hand illusion (Rhode et al. 2011). However, a different question may be more informative. Can the vision of the RHI being touched override the tactile information to

induce illusory ownership and/or refer tactile sensations? Cole (2004) described a case of “phantom touch” in a patient with SCI, a vivid sense of touch felt in the lower limb, dependent on visual perception. This did not occur in our patient. He did not transfer seen touch from a visual to tactile mode when touched during therapy or in ecological contexts. Crucially, only when the patient regained sensory information from some fingers in the form of allodynia, could the illusory ownership and/or referred tactile sensations be induced by synchronous visuo-tactile stimulation as measured both by implicit and explicit measures. Previous results suggest that partial tactile (non-painful) sensations on the hand in SCI might be sufficient to induce RHI (Tidoni et al., 2014), and such illusion can even temporarily increase tactile sensations (Lenggenhager et al. 2012). The present results further extend these findings by showing that the RHI can suddenly be induced *within the same person* after the recovery of some somatosensation. Accordingly, it would be incorrect to categorize patients like AD as non-responders to the RHI based on the initial absence of illusion, which occurs in about 20% of healthy participants for reasons that remain unknown (Ehrsson et al., 2005).

Pain remaps tactile sensation in a disembodied body

Our patient reported pain sensations evoked by normally non-painful tactile stimuli (allodynia), in this case, the slow, gentle stroking of a paintbrush on the affected skin. The pain was significantly more intense on the thumb, while light touch on the index finger evoked somatic sensations, some of which were, however, painful. The prevailing pathophysiological explanation is that following nerve injury, pre-synaptic, post-synaptic, interneuron, and immune system changes (Basbaum, 1999) occur in a dysfunctional hypersensitive system in which the experiences evoked by distinct and separate painful and non-painful signals are lost (Iadarola et al., 1998; Koltzenburg et al., 1992; Torebjork et al., 1992). Because of altered connectivity between the periphery and somatosensory brain regions, patients with SCI frequently experience abnormal evoked pain sensations, disturbed cortical multisensory integration, and body image distortions (Boord et al., 2008; Henderson et al.,

2011; Jensen et al., 2013; Jurkiewicz et al., 2006; Jurkiewicz et al., 2007; Moore et al., 2000; Sabbah et al., 2002; Wrigley et al., 2009). Here, we induced the sense of body ownership via visuo-tactile stroking in the painful condition of allodynia. A previous study in healthy participants showed that the RHI can be induced using painful stimuli (Capelari et al., 2009), and patients with complex regional pain syndrome might perceive illusory ownership of a fake hand in place of their painful hand, despite their impairment in processing of static tactile stimuli (Reinersmann et al., 2013). Yet, our findings differed in that the patient could see that the stroking was innocuous, and the illusion was evoked despite this conflict between the visual (seen touch) and tactile (felt pain) modalities (White et al., 2010). Again, the conflict seems trivial, as such conflict is the hallmark of allodynia, but the seen touch was not applied on the patient's own hand but on a rubber hand to strengthen the true interaction of multisensory integration and pain processing to create a representation of the body.

Multimodal stimulation has been shown to re-shift physiological (Moseley et al., 2012) and homeostatic (Hegedus et al., 2014; Moseley et al., 2008a) activity patterns in favor of decreased sensory processing in the disowned hand or body (a sense of a lack of ownership of the intact, actual hand) resulting in increased pain thresholds (Hänsel et al. 2011) and decreased pain perception (Siedlecka et al. 2014). Additionally, the bidirectional flow of tactile discrimination and tactile stimulation (Moseley et al., 2008b) or the interplay between the pain experience and the vision of the body (Cole, 2004; Longo et al., 2012) might decrease limb pain, promoting multisensory analgesia. Here, we showed that illusory attribution of a rubber hand produced not only a temporarily induced analgesic effect but also a progressive and spreading normalization of tactile sensations (see also Lenggenhager et al., 2013).

We also believe that this might be further evidence that multisensory stimulation results in plastic normalization of mapping of contiguous peripheral representations that drive the topographic cortical representation of a numb body part (Pazzaglia and Molinari, 2015). Tactile sensations were experienced in a non-sentient area a few centimeters from the original painful segment, plausibly

indicating a remapping of tactile hand mechanism. Recently, studies in patients with tetraplegia (Lenggenhager et al., 2013; Tidoni et al., 2014) suggested that the experience of the RHI shifts onto an orderly somatotopic mapping from the periphery [hand/face (Tidoni et al., 2014) or D3/D1 finger (Lenggenhager et al., 2013)]. Our findings might potentially have important implications for therapeutic interventions, which aim to normalize sensory signals and related chronic and neuropathic pain by experimentally modulating the dynamic sensorimotor body representation and sense of self. For example, if a patient can feel a sensation on a painful area, but not on a contiguous area, stroking applied on the former might induce plastic changes in the cortex that spread to the contiguous territory.

The fact that pain does not block multi-sensory illusions, and there is a reciprocal interaction between touch and pain, might be promising findings for future therapeutic applications.

Limitation and conclusion

Although the effect demonstrated was transient and effective at only short neighboring locations, and although the evidence is restricted to a single case, we believe that these findings can pave the way for the development of sensation-related therapeutic interventions, especially based on virtual reality and prosthetics. Temporarily changing how the painful body is perceived may induce changes in cortical representation and increase analgesia. Importantly, we did not assess whether the patient had a more generalized modification of his pain and whether the effect was long-term, which should definitively be done in future studies. Another open question is to what degree our findings can be extended to other forms of pain (e.g. visceral, musculoskeletal, and neuropathic). Indeed, the RHI in our study was not induced by all nociceptive pathways, but only through a masked light touch, and some may be more likely than others to benefit from this approach. Still, this study is a first step towards understanding non-invasive multisensory pain therapy, which should be integrated with other therapies, based for example on motor (imagery and agency) intention or brain stimulation, as is successfully done in phantom limb pain (Lenggenhager et al.

2014).

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References

- Apkarian, A. V., Stea, R. A., & Bolanowski, S. J. (1994). Heat-induced pain diminishes vibrotactile perception: a touch gate. *Somatosensory & Motor Research*, 11, 259–267.
- Basbaum, A. I. (1999). Distinct neurochemical features of acute and persistent pain. *Proceedings of the National Academy of Sciences USA*, 96, 7739–7743.
- Bolanowski, S. J., Maxfield, L. M., Gescheider, G. A., & Apkarian, A. V. (2000). The effects of stimulus location on the gating of touch by heat- and cold-induced pain. *Somatosensory & Motor Research*, 17, 195–204.
- Boord, P., Siddall, P. J., Tran, Y., Herbert, D., Middleton, J., & Craig, A. (2008). Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. *Spinal Cord*, 46, 118–123.
- Botvinick, M., & Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature*, 391, 756.
- Bruehlmeier, M., Dietz, V., Leenders, K. L., Roelcke, U., Missimer, J., & Curt, A. (1998). How does the human brain deal with a spinal cord injury? *European Journal of Neuroscience*, 10, 3918–3922.
- Capelari, E. D., Uribe, C., & Brasil-Neto, J. P. (2009). Feeling pain in the rubber hand: integration of visual, proprioceptive, and painful stimuli. *Perception*, 38, 92–99.
- Cole, J. (2004). *Still lives*. Cambridge, MA: MIT press.

- Corbetta, M., Burton, H., Sinclair, R. J., Conturo, T. E., Akbudak, E., & McDonald, J. W. (2002). Functional reorganization and stability of somatosensory-motor cortical topography in a tetraplegic subject with late recovery. *Proceedings of the National Academy of Sciences USA*, 99, 17066–17071.
- Costantini, M., Bueti, D., Pazzaglia, M., & Aglioti, S. M. (2007). Temporal dynamics of visuo-tactile extinction within and between hemispaces. *Neuropsychology*, 21, 242-250.
- Curt, A., Alkadhi, H., Crelier, G. R., Boendermaker, S. H., Hepp-Reymond, M. C., & Kollias, S. S. (2002). Changes of non-affected upper limb cortical representation in paraplegic patients as assessed by fMRI. *Brain*, 125, 2567–2578.
- Danziger, N., Rémy, P., Pidoux, B., Dormont, D., Samson, Y., Fournier, E., Wall, P. D., & Willer, J.C. (1996). A clinical and neurophysiological study of a patient with an extensive transection of the spinal cord sparing only a part of one anterolateral quadrant. *Brain*, 119, 1835–1848.
- Ehrsson, H. H., Holmes, N. P., & Passingham, R. E. (2005). Touching a rubber hand: feeling of body ownership is associated with activity in multisensory brain areas. *Journal of Neuroscience*, 25, 10564–10573.
- Finnerup, N. B. (2013). Pain in patients with spinal cord injury. *Pain*, 154, S71–76.
- Finnerup, N. B., Johannesen, I. L., Fuglsang-Frederiksen, A., Bach, F. W., & Jensen, T. S. (2003). Sensory function in spinal cord injury patients with and without central pain. *Brain*, 126, 57–70.
- Flor, H. (2012). New developments in the understanding and management of persistent pain. *Current Opinion in Psychiatry*, 25, 109–113.
- Fuentes, C. T., Pazzaglia, M., Longo, M. R., Scivoletto, G., & Haggard, P. (2013). Body image distortions following spinal cord injury. *Journal of Neurology, Neurosurgery and Psychiatry*, 84, 201–207.

- Galli, G., & Pazzaglia, M. (2015). Commentary on: "The body social: an enactive approach to the self". A tool for merging bodily and social self in immobile individuals. *Frontiers in Psychology*, 6, 305.
- Haggard, P., Iannetti, G. D., & Longo, M. R. (2013). Spatial sensory organization and body representation in pain perception. *Current Biology*, 23, R164–176.
- Hänsel, A., Lenggenhager, B., von Känel, R., Curatolo, M., & Blanke, O. (2011) Seeing and identifying with a virtual body decreases pain perception. *European Journal of Pain*. 15, 874–879.
- Hegedus, G., Darnai, G., Szolcsanyi, T., Feldmann, A., Janszky, J., & Kallai, J. (2014). The rubber hand illusion increases heat pain threshold. *European Journal of Pain*, 18, 1173–1181.
- Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J., & Siddall, P. J. (2011). Functional reorganization of the brain in humans following spinal cord injury: evidence for underlying changes in cortical anatomy. *Journal of Neuroscience*, 31, 2630–2637.
- Iadarola, M. J., Berman, K. F., Zeffiro, T. A., Byas-Smith, M. G., Gracely, R. H., Max, M. B., & Bennett, G. J. (1998). Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain*, 121, 931–947.
- Jensen, M. P., Sherlin, L. H., Gertz, K. J., Braden, A. L., Kupper, A. E., Gianas, A., Howe, J. D., & Hakimian, S. (2013). Brain EEG activity correlates of chronic pain in persons with spinal cord injury: clinical implications. *Spinal Cord*, 51, 55–58.
- Jurkiewicz, M. T., Crawley, A. P., Verrier, M. C., Fehlings, M. G., & Mikulis, D. J. (2006). Somatosensory cortical atrophy after spinal cord injury: a voxel-based morphometry study. *Neurology*, 66, 762–764.
- Jurkiewicz, M. T., Mikulis, D. J., McIlroy, W. E., Fehlings, M. G., & Verrier, M. C. (2007). Sensorimotor cortical plasticity during recovery following spinal cord injury: a longitudinal fMRI study. *Neurorehabilitation and Neural Repair*, 21, 527–538.

- Koltzenburg, M., Lundberg, L. E., & Torebjork, H. E. (1992). Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain*, 51, 207–219.
- Lenggenhager, B., Pazzaglia, M., Scivoletto, G., Molinari, M., & Aglioti, S. M. (2012). The sense of the body in individuals with spinal cord injury. *PLoS One*, 7, e50757.
- Lenggenhager, B., Scivoletto, G., Molinari, M., & Pazzaglia, M. (2013). Restoring tactile awareness through the rubber hand illusion in cervical spinal cord injury. *Neurorehabilitation and Neural Repair*, 27, 704–708.
- Liljencrantz, J., Bjornsdotter, M., Morrison, I., Bergstrand, S., Ceko, M., Seminowicz, D. A., Cole, J., Bushnell, M. C., Olausson, H. (2013). Altered C-tactile processing in human dynamic tactile allodynia. *Pain*, 154, 227–234.
- Lenggenhager, B., Arnold, C. A., & Giummarra M. J. (2014). Phantom limbs: pain, embodiment, and scientific advances in integrative therapies. *Wiley Interdisciplinary Reviews: Cognitive Science* 5, 221–231. .
- Longo, M. R., Iannetti, G. D., Mancini, F., Driver, J., & Haggard, P. (2012). Linking pain and the body: neural correlates of visually induced analgesia. *Journal of Neuroscience*, 32, 2601–2607.
- Lucci, G., & Pazzaglia, M. (2015). Towards multiple interactions of inner and outer sensations in corporeal awareness. *Frontiers in Human Neuroscience*, 9, 163.
- Mancini, F., Nash, T., Iannetti, G. D., & Haggard, P. (2014). Pain relief by touch: A quantitative approach. *Pain*, 155, 635–642.
- Moore, C. I., Stern, C. E., Dunbar, C., Kostyk, S. K., Gehi, A., & Corkin, S. (2000). Referred phantom sensations and cortical reorganization after spinal cord injury in humans. *Proceedings of the National Academy of Sciences USA*, 97, 14703–14708.
- Moseley, G. L., Gallace, A., & Spence, C. (2012). Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. *Neuroscience & Biobehavioral Reviews*, 36, 34–46.

- Moseley, G. L., Olthof, N., Venema, A., Don, S., Wijers, M., Gallace, A., & Spence, C. (2008a). Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proceedings of the National Academy of Sciences USA*, 105, 13169–13173.
- Moseley, G. L., Zalucki, N. M., & Wiech, K. (2008b). Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. *Pain*, 137, 600–608.
- Pazzaglia, M., Galli, G., Scivoletto, G., & Molinari, M. (2013). A functionally relevant tool for the body following spinal cord injury. *PLoS One*, 8(3), e58312.
- Pazzaglia, M. & Molinari, M. (2015). The embodiment of assistive devices—from wheelchair to exoskeleton. *Physics of Life Reviews*. pii: S1571-0645(15)00211-0. doi: 10.1016/j.plrev.2015.11.006
- Ploner, M., Pollok, B., & Schnitzler, A. (2004). Pain facilitates tactile processing in human somatosensory cortices. *Journal of Neurophysiology*, 92, 1825–1829.
- Ploner, M., & Schnitzler, A. (2004). [Cortical representation of pain]. *Nervenarzt*, 75, 962-969.
- Reinersmann, A., Landwehrt, J., Krumova, E. K., Peterburs, J., Ocklenburg, S., Gunturkun, O., & Maier, C. (2013). The rubber hand illusion in complex regional pain syndrome: preserved ability to integrate a rubber hand indicates intact multisensory integration. *Pain*, 154, 1519–1527.
- Rohde, M., Di Luca, M., & Ernst, M. O. (2011) The rubber hand illusion: feeling of ownership and proprioceptive drift do not go hand in hand. *PLoS ONE* 6, e21659.
- Rossi, A., Decchi, B., Groccia, V., Della Volpe, R., & Spidalieri, R. (1998). Interactions between nociceptive and non-nociceptive afferent projections to cerebral cortex in humans. *Neuroscience Letters*, 248, 155–158.
- Sabbah, P., de, S. S., Leveque, C., Gay, S., Pfefer, F., Nioche, C., Sarrazin, J. L., Barouti, H., Tadie, M., & Cordoliani, Y. S. (2002). Sensorimotor cortical activity in patients with complete

- spinal cord injury: a functional magnetic resonance imaging study. *Journal of Neurotrauma*, 19, 53–60.
- Siddall, P. J., Taylor, D. A., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (1999). Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. *Pain*, 81, 187–197.
- Siedlecka M, Klimza A, Łukowska M, & Wierzchoń M. (2014). Rubber hand illusion reduces discomfort caused by cold stimulus. *PLoS One*, 9, e109909.
- Takazawa, T., & MacDermott, A. B. (2010). Synaptic pathways and inhibitory gates in the spinal cord dorsal horn. *Annals of the New York Academy of Science*, 1198: 153–158.
- Teixeira, M. J., Paiva, W. S., Assis, M. S., Fonoff, E. T., Bor-Seng-Shu, E., & Cecon, A. D. (2013). Neuropathic pain in patients with spinal cord injury: report of 213 patients. *Arquivos de Neuro-Psiquiatria*, 71, 600–603.
- Tidoni, E., Grisoni, L., Liuzza, M. T., & Aglioti, S. M. (2014). Rubber hand illusion highlights massive visual capture and sensorimotor face-hand remapping in a tetraplegic man. *Restorative Neurology and Neuroscience*, 32, 611–622.
- Torebjork, H. E., Lundberg, L. E., & LaMotte, R. H. (1992). Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *Journal of Physiology*, 448, 765–780.
- Tran, T. D., Hoshiyama, M., Inui, K., & Kakigi, R. (2003). Electrical-induced pain diminishes somatosensory evoked magnetic cortical fields. *Clinical Neurophysiology*, 114, 1704–1714.
- Tsakiris, M., & Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *Journal of Experimental Psychology: Human Perception and Performance*, 31, 80–91.
- Tsay, A., Allen, T. J., Proske, U., & Giummarra, M. J. (2015). Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. *Neuroscience Biobehavioral Reviews*, 52, 221–232.

- van Gorp, S., Kessels, A. G., Joosten, E. A., van Kleef, M., & Patijn, J. (2015). Pain prevalence and its determinants after spinal cord injury: a systematic review. *European Journal of Pain*, 19, 5-14.
- Villiger, M., Bohli, D., Kiper, D., Pyk, P., Spillmann, J., Meilick, B., Curt, A., Hepp-Reymond M. C., Hotz-Boendermaker S., Eng, K. (2013). Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. *Neurorehabilitation and Neural Repair*, 27, 675–683.
- White, R. C., Aimola Davies, A. M., Halleen, T. J., & Davies, M. (2010). Tactile expectations and the perception of self-touch: an investigation using the rubber hand paradigm. *Consciousness and Cognition*, 19, 505–519.
- Wrigley, P. J., Press, S. R., Gustin, S. M., Macefield, V. G., Gandevia, S. C., Cousins, M. J., Middleton, J. W., Henderson, L. A., & Siddall, P. J. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*, 141, 52–59.

Fig. Captions:

Table 1. Patient characteristics.

Clinical and demographic characteristics of patient (AD) at two different time points in the study. The spinal level of the lesion and the status of the injury, as determined by the American Impairment Scale (AIS) and motor scores, are indicated. The third version of the Spinal Cord Independence Measure (SCIM III; subscales: Self-care and Management and Mobility) and Barthel index were used to quantify functional ability. The level of tactile sensation was determined by gently moving cotton wool over the skin of the five fingers according to the correct perception reported (0 = absent sensation; 5 = sensation in all five types of static and dynamic stimulation). The level of pain sensation was assigned on VAS scale for each finger in comparison with a painful

sensation on the face. “D1” through “D5” refer to the five fingers from the thumb to the little finger, respectively.

Fig. 1. Schematic representations of the experimental procedure.

We administered a visual-tactile manipulation based on the rubber hand illusion while the participant was seated comfortably in his wheelchair as shown in the left panel.

In the pre-proprioceptive judgment, AD indicated the occluded left index finger position in the absence of stimulation. In the synchrony/asynchrony conditions, the stimulation was induced in the same way as in the original RHI when AD observed touches on a fake hand that were delivered simultaneously/not-simultaneously, respectively, to touches felt on his own hidden hand. In “no vision” control condition, AD observed the rubber hand and the stimulation was applied only on the real hand.

We administered different stimulation conditions based on regained sensations as shown in the right panel. In the first session, before regained sensations, we stimulated the entire non-sentient hand.

In the second session, after sensation was regained in two fingers (in red), we applied stimulation on the painful-only fingers and non-sentient-only areas. In the third session, we applied stimulation on the entire hand as a function of time (30-s intervals).

Fig. 2. Proprioceptive drift and responses to the illusion-related questionnaire for stroking the sensitive versus insensitive fingers.

- A. In the first session, before sensations were regained, we stimulated the entire non-sentient hand. Perceived finger position relative to the pretest baseline values and subjective ratings of illusion as assessed using an Italian version of questionnaire for synchronous and asynchronous stroking (red and black bars) are shown. No effects of the RHI stimulation were found.

B. In the second session, after sensation was regained in two fingers (red), we applied stimulation to the painful-only fingers (thumb and index finger) and the non-sentient-only areas (ring and little fingers). We demonstrated proprioceptive drift and responses to the illusion-related questionnaire when stroking the sensitive versus the insensitive fingers. The asterisks (*) indicate significant errors in the perceived position of the unseen hand compared to the five measures of pre-test judgment prior to stimulation ($p < .05$). The mislocalization of AD's unseen hand was closer to the viewed fake hand during the exclusive stimulation of the sentient dermatomes.

Fig. 3. Subjective ratings for intensity and unpleasantness of touch-related sensation.

Proprioceptive drift, and responses to the illusion-related questionnaire for synchronous and asynchronous stroking on the entire hand. The mean subjective Visual Analog Scale (VAS) ratings for intensity and unpleasant of the felt stroking for each finger during three conditions of stroking (no vision, synchronous, and asynchronous). "D1" through "D5" refer to the five fingers from the thumb to the little finger, respectively. The error bars indicate the standard error of the mean (SEM).

Supplementary Data

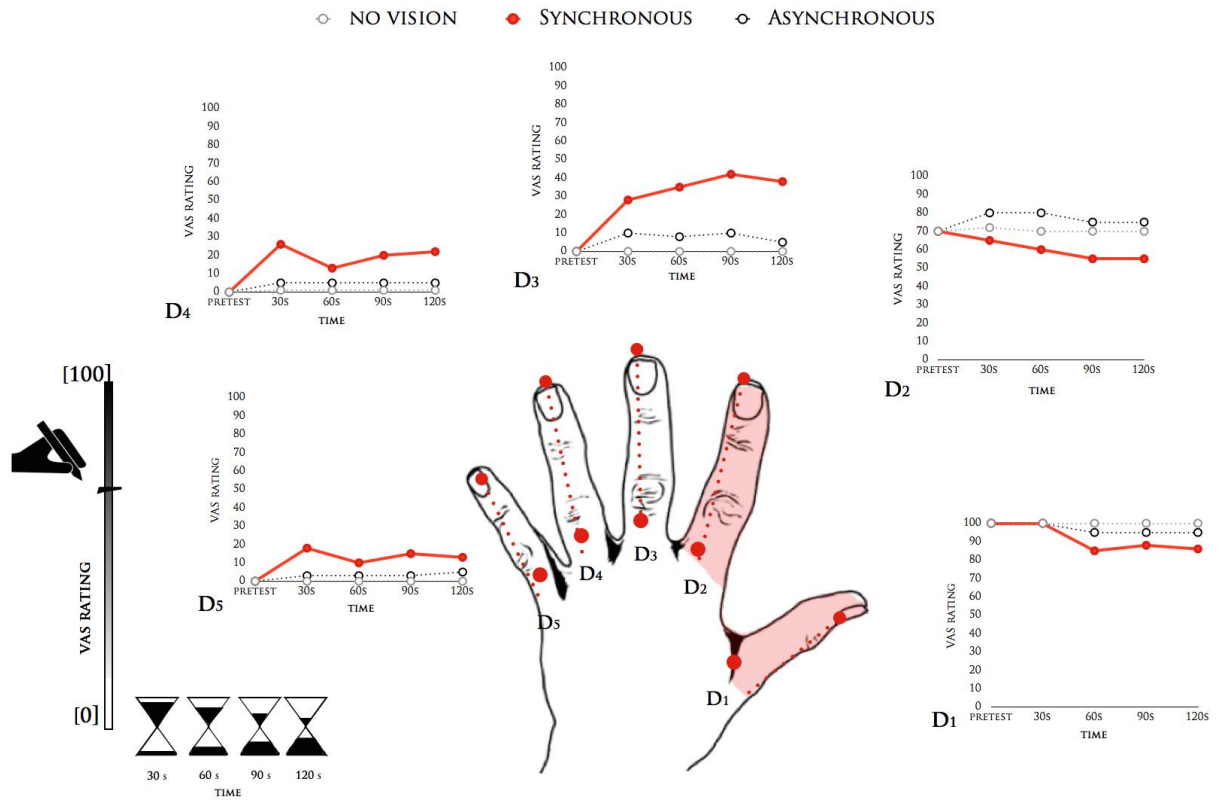


Fig. supplementary. Time course of subjective ratings for intensity of touch-related sensation.

At the end of each 30-second period, the patient was asked to rate on a continuous scale for each finger the intensity of the perceived stroking for each finger at 30 s, 60 s, 90 s, and 120 s during three conditions of stroking (no vision, synchronous, and asynchronous).