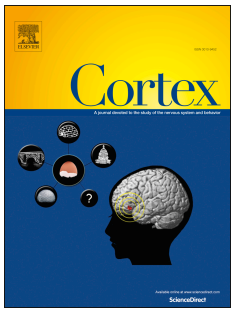

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Phantom touch: how to unmask sensory unawareness after stroke

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ABSTRACT

Comprehending the nature of tactile disorders following brain damage is crucial to understand how the brain constructs sensory awareness. Stroke patients may be unaware of being touched on the affected hand if, simultaneously, they are touched on the unaffected hand (i.e. tactile extinction). More rarely, they feel touches on the two hands, when they are solely touched on the unaffected hand (i.e. synchiria). Using a novel assessment tool, we investigated whether in stroke patients with apparent intact tactile awareness on standard evaluation, tactile extinction might be possibly masked by phantom (synchiric) sensations (i.e. elicited by ipsilesional stimulation) arising exclusively during Double Simultaneous Stimulation (DSS). Patients with right (n=17) and left (n=8) hemisphere lesions and age-matched healthy controls (n=13) were tested with the Tactile Quadrant Stimulation test, consisting in delivering unilateral or bilateral touches to one of four quadrants, identified on the participants' hands. In DSS trials, stimuli were applied to asymmetric quadrants. Participants reported the side(s) and then pointed to the site(s) of stimulation. We found that, with the exception of one patient who showed tactile extinction, about 50% of patients with overall intact tactile perception on classical evaluation, although reporting two stimuli in DSS, failed in pointing to the correct contralesional stimulated site. They reported the felt sensation in positions that corresponded to the ipsilesional stimulated sites. Thus apparent detections of contralesional touches in DSS were accounted for by 'phantom' sensations of ipsilesional stimulation that masked unawareness of contralesional touches when classic assessment was applied. Preliminary lesion analyses indicate that the symptom was associated with damage to structures often affected in tactile extinction. These findings, while unveiling important underestimation of the patients' neurological condition, provide a framework for investigating bihemispheric contributions to altered tactile perception following stroke.

Highlights:

- Using a novel assessment tool we unmask sensory unawareness in patients after stroke

- Phantom sensations of touches applied to the unaffected hand masked extinction

- The new tactile tool unveils underestimation of the patients' neurological condition

- These findings have implications for models of bilateral representations of touch

1. Introduction

Understanding the nature of disrupted sensory awareness after brain damage is crucial to comprehend how the brain processes tactile information. Tactile perception in patients after stroke is clinically assessed by delivering unilateral or bilateral (Double Simultaneous Stimulation, DSS) touches to symmetrical points on the back of the patients' hand(s) and by asking them to report the side(s) of stimulation (Bisiach, 1999). This classical procedure allows to assess failure to report contralesional single stimulation, as in primary somatosensory deficit and in neglect (Ricci et al., 2016), and failure to detect contralesional stimuli under DSS trials, as in extinction (Bisiach, 1999). It also allows to reveal the presence of positive, dyschiric symptoms, such as bilateral sensations during single ipsilesional stimulation, as in synchiria (Medina & Coslett, 2016; Medina & Rapp, 2008) or mislocation of contralesional stimuli to symmetrical points of ipsilesional body, as in allochiria (Kawamura, Hirayama, Shinohara, Watanabe, & Sugishita, 1987; Obersteiner, 1881; Young & Benson, 1992). However, the standard procedure, in which patients are required to simply report the side(s) of stimulation and stimuli are applied to symmetrical points, cannot assess whether the sensation reported on the contralesional side during DSS is due to normal sensory processing or whether the contralesional sensation is actually extinguished but extinction is masked by 'phantom' sensations elicited by the ipsilesional stimulation.

Indirect evidence of the possibility that apparent contralesional detections, during DSS, are accounted for by bilateral sensations after ipsilesional stimulation - i.e. synchiric sensations - comes from a stroke patient described by Medina and Rapp (2008) who showed tactile synchiria, extinction, and mislocalization following extensive left-hemisphere lesion. During a brief assessment in which bilateral stimuli were applied to different locations of the patient's hands, the patient reported contralesional sensations to homologous locations of

ipsilesional stimulation. However, this patient manifested classical synchiria, for which tactile phantoms were primarily observed during single ipsilateral stimulation.

To investigate whether in stroke patients without classical synchiria on standard evaluation, synchiric errors might emerge under DSS trials, we designed a novel assessment protocol, the Tactile Quadrants Stimulation (TQS) task. On this task, bilateral stimuli were applied to non-symmetrical quadrants and patients reported the side(s) and then pointed to the site(s) of stimulation. This simple test allowed us to assess whether, during DSS, successful detection of contralesional stimuli is always accompanied by their correct localization as it would be expected if the response reflects underlying normal sensory processing or whether the behavioral response is the result of synchiric effects.

2. Materials and methods

In this section we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

Patients were consecutively recruited from the Stroke Unit of the Department of Neuroscience, at the University of Turin. From 03/2015 to 10/2016 patients with an acute stroke were screened for eligibility to participate in the study.

Inclusion criteria were 1) first-ever acute right or left-hemisphere ischemic or haemorrhagic stroke. Exclusion criteria were severe aphasia, cognitive impairment as evaluated by the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), hemianesthesia and severe hemiparesis (Bisiach, Pattini, Rusconi, Ricci, & Bernardini, 1997). Hemianesthesia was

evaluated using a confrontation test in which patients were asked to detect unilateral or bilateral touches, administered by the examiner's using her finger(s), in the left/right dorsum of the patients' hand(s) (Bisiach, Cappa, & Vallar, 1983). Ten single and 10 double, symmetrical, and simultaneous tactile stimuli were applied following a fixed random order. The scores were assigned as follow: 0= eight or more double stimuli and all single stimuli were perceived (normal performance); 1= less than eight double stimuli, but more than seven single stimuli were perceived (i.e. tactile extinction); 2=four to seven single stimuli were perceived out of 10 (mild somatosensory deficits/hemianesthesia); 3=less than four single stimuli were perceived out of 10 (severe somatosensory deficits/hemianesthesia).

On this test, one RHL patient (#5) showed a score of 1 while all other patients scored 0. Thus, the only patient showing tactile extinction was included in the sample while patients showing a score >2 were excluded from the study. All of them were able to stand up, move and sit down at the table, where they were tested.

Seventeen patients with right-hemisphere lesions (RHL), eight patients with left-hemisphere lesions (LHL) and thirteen age-matched healthy Controls (C) participated in the study. The three groups did not differ for mean age (RHL: Mean= 64.3 years, SD= 15.9 years; LHL: Mean= 62.5 years, SD= 9.7 years; C: Mean= 66.6 years, SD= 16.6 years) or educational level (RHL: Mean= 9.2 years, SD= 3.6; LHL= 9.8 years, SD= 5.4; C= 10.38 years, SD= 3.1) as assessed using the non-parametric Kruskal–Wallis test. Participants gave informed consent for participation in the study, and experimental procedures were approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki. Patients' demographic and clinical data are reported in Table 1. The onset of the stroke was haemorrhagic in 4 patients and ischemic in 21 patients. Participants were all right-handed, with the exception of one RHL patient (#5) who was left-handed. For both groups of patients the mean duration of illness was 4.16 (±2.08) days (see Table 1).

Visuospatial neglect was assessed using the letter H cancellation task (Diller & Weinberg, 1977) and the line bisection task (Ricci, Calhoun, Chatterjee, 2000). Specifically, patients were asked to bisect five 180-mm long and 1-mm thick black horizontal lines (Bisiach, Ricci, Lai, De Tanti, & Inzaghi, 1999; Ricci, Pia, & Gindri, 2004). Patients' performance on the Diller cancellation task was evaluated by considering left-side and right-side omissions and by calculating the difference between contralesional and ipsilesional omissions. For the line bisection task, the deviation of the subjective midpoint from the true center of the lines was the dependent variable. Errors to the right or to the left of the line's midpoint were measured to the nearest millimeter. Rightward errors were preceded by + and leftward errors by –. The presence of neglect was defined on the basis of either (or both) of the following criteria (Bisiach et al., 1999): 1) mean bisection error towards the ipsilesional side exceeding 10 mm, 2) contralesional side minus ipsilesional side omissions on the cancellation task being = or > of 5. Individual lesion analyses were performed in RHL patients and in 5 LHL patients (scans of patients #2, #3, and #5 were not available). For these patients' clinical files reported occipital lesion (patient #2), parietal lesion (patient #3), and occipito-parietal lesion (patient #5). Lesion locations were identified through MRI or CT brain scans and coded by anatomic region using published procedures (Maier, Schröder, Forkert, Martinetz, & Handels, 2015).

Table 1 about here

No part of the study procedures or analyses was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

2.2. Behavioral tasks

2.2.1. Classical tactile extinction task.

A canonical extinction protocol was used to assess the presence of contralesional tactile extinction in RHL and LHL patients. As typically done, unilateral left, right or bilateral stimuli were delivered on the back of the patients' hand(s). Tactile stimuli were light touches, applied by the experimenter using the tip of the right and/or left index fingers. The patients were asked to report whether they were touched on the left, right or both hands. Patients performed the task with their eyes closed. Stimuli were delivered in two blocks of 24 trials, 8 trials for each condition (left, right, both), for a total of 48 trials. Bilateral stimuli were applied to symmetrical locations. Tactile stimuli were administered following two of three possible pseudo-random orders with the constraints that bilateral stimuli were always preceded by unilateral right (for half of the trials) or left stimulus (for the other half of the unilateral trials). The lists of stimuli were balanced across participants. The three lists of stimuli are reported in Supplementary Methods S1. All LHL patients were able to use a verbal response to report the side(s) of stimulation.

2.2.2. Tactile Quadrants Stimulation (TQS) task.

Four quadrants were identified by two perpendicular 'virtual' lines (the lines were not drawn on the patient's hand), centered on the back of each hand. Light touches were delivered by the experimenter using the tip of the index fingers to one of the four quadrants on the left, right or both patients' hand(s). Bilateral stimuli were applied to non-symmetrical quadrants (Fig. 1A). Stimuli were delivered following two sets of 24 trials, 8 trials for each condition (left, right, both), for a total of 48 trials (i.e. 16 trials for each condition). For each set, during unilateral stimulation trials, each quadrant was stimulated twice. Also for DSS trials, each quadrant was stimulated twice according to two different combinations: stimuli administered on the two hands were always on the opposite side of the horizontal virtual line. There were eight possible combinations for bilateral stimuli. Stimuli were administered

following two of three possible pseudo-random orders. The lists of stimuli were balanced across participants. The three lists of stimuli are reported in Supplementary Methods S2. Patients, blindfolded, were asked to *verbally* report the side(s) of stimulation and then to *point* to the location(s) where they felt the tactile sensation(s), using the opposite hand. Patients were asked to point first to the contralesional stimulated site (with the intact hand) and then to the ipsilesional stimulated site (with the affected hand). TQS task was also administered to healthy participants, using the same procedure and stimuli as described above with the exception that they were not instructed on which hand to use first. All of them used the dominant hand first. RHL patients #10-#17 and LHL patients #5-#8 underwent the whole TQS task also with eyes open.

2.2.2.1. Data Analyses

Individual patients' performances were analyzed using a modified t-test for individual scores versus the C control sample (Crawford's test) or a binomial two-tailed test, when necessary. Between and within-group analyses were performed using the Mann-Whitney U test and Wilcoxon test, respectively (with Bonferroni correction when necessary).

2.3. Lesion mapping and analysis

Patients' lesion locations were identified through MRI or CT scans and mapped onto the 1 mm3 MNI 152 standard space (SPM2 Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) by means of the software MRIcro (Rorden & Brett, 2000). As first, an experimenter ignoring all the features of the study, rotated the MNI template on horizontal, coronal and sagittal planes according to the patient's scan given scan angle. Then, she manually mapped the lesion onto each correspondent template slice and

another skilled rater double-checked for the tracing accuracy (no cases of disagreement happened). Thirdly, the obtained maps were back rotated into the standard space. Quantitative estimates of grey and white matter regions involvement were obtained by superimposing the Anatomical Labelling map template AAL and the JHU-white matter template.

Statistics were performed entering continuous measures in a voxel-based lesion-symptom mapping (VLSM) analysis. Indeed, by avoiding a-priori categorizations and subsequent lesion subtraction approach, this technique is the most appropriate in order to examine the association between lesion sites and continuous behavior. The number of synchiric errors during DSS as well as lesion reconstructions in the RHL group only (the number of LHL patients was too small) were entered into a nonparametric permuted Brunner-Munzel rank-order test with permutation derived correction ($p < .05$) for each brain voxel ($p < .05$) as implemented in the NPM included in MRIcron (Medina, Kimberg, Chatterjee, & Coslett, 2010).

The conditions of our ethics approval do not permit public archiving of anonymized CT/MRI scans. Readers seeking access to the data should contact the corresponding author RR at the Department of Psychology, University of Turin. Access can be granted only to named individuals in accordance with ethical procedures governing the reuse of sensitive clinical data.

3. Results

3.1. Behavioral Results

3.1.1. Visuospatial neglect

Only RHL patient #10 and LHL patient #2 showed visuospatial neglect on cancellation (see Table 1).

3.1.2. Classical tactile extinction task

On classic evaluation, only RHL patient #5 manifested tactile extinction in 8 out of 16 bilateral trials (50%). All other patients were 100% correct in detecting contralesional (and ipsilesional) stimuli under single and DSS conditions, i.e. they did not show any tactile neglect, extinction, synchiria or allochiria.

3.1.3. Tactile Quadrants Stimulation (TQS) task

Detection Task: Patients' performance on the detection task of TQS protocol - i.e. patients had to verbally report the side(s) of stimulation - replicated findings observed on the classical extinction task: only RHL patient #5 manifested tactile extinction in 8 out of 16 bilateral trials (50%), while all other patients were 100% correct in detecting contralesional (and ipsilesional) stimuli under single and DSS conditions.

Localization Task: On the localization task of TQS protocol patients were asked to point to the stimulated site(s) and during DSS to first point to the contralesional side. Despite these instructions, many patients, at the beginning of the task, tended to first point to the ipsilesional side. In these patients the instructions were repeated by the examiner until, after few trials, they correctly followed them. None of the patients spontaneously reported not to know where the stimulus was located.

Individual patients' performance is reported in Table 2. Ten (#1, 4, 5, 7-10, 13-15) out of 17 RHL patients (58.8%) showed, during DSS trials, a significant number of errors due to

localization of contralesional stimuli at homologous locations of ipsilesional stimulation, i.e. they did not point to the quadrant stimulated on the contralesional hand but they pointed to the quadrant corresponding to the one stimulated on the ipsilesional hand (see example in Fig. 1A). Since this type of error resembled 'synchiria' (i.e. bilateral sensations induced by single stimulation) but it exclusively occurred during DSS trials, we called it 'synchiric extinction'. Anecdotally, when occasionally asked, patients reported that 'synchiric sensations' were qualitatively similar to real touches, but less intense. Patients #7, #8, and #15 also showed contralesional 'mislocalization' errors during DSS, i.e. they pointed to a location that was not touched in either hands. In other words, they pointed to one of the two quadrants that were not touched in either contralesional (i.e. correct response) or ipsilesional (i.e. synchiric extinction) hands. Patient #7 and #8 also showed mislocalization errors during single stimulation (i.e. they pointed to one of the three quadrants that were not touched in the contralesional hand). In these two patients proprioceptive deficits, that are common following stroke, might have underlain mislocalization error under single stimulation trials.

Four (#2, #3, #7, #8) out of 8 LHL patients (50%) showed synchiric extinction. Two of them also manifested contralesional (#7) or ipsilesional (#2) mislocalization errors during bilateral stimulation. One patient (#4) only showed contralesional mislocalization errors. Synchiric extinction did not differ (Chi-squared test) between RHL and LHL groups. Performance was 100% correct with eyes open, in the sub-group of patients.

Table 2 about here

Fig. 1B depicts groups' performances for DSS trials. Between-groups analyses showed that RHL produced more (p=0.001; d=1.287) synchiric extinction (Mean= 3.47, SD= 3.63) and more (p=0.005; d=0.9) mislocalization (Mean= 2.18, SD= 2.09) than C (synchiric extinction: Mean= 0.15 SD= 0.36; mislocalization: Mean= 0.69 SD= 1.07) on the left hand.

Within-group analyses showed that RHL produced more synchiric extinction (p=0.004; d=0.9) for the left (Mean= 3.47 SD= 3.63) than for the right hand (Mean= 0.47 SD= 0.61). C produced more mislocalization (Mean= 1.77 SD= 1.25) than synchiric extinction (Mean= 0.15 SD= 0.36) for the right hand (p=0.007; d=1.5).

Importantly, as shown in Fig. 1B, both groups of patients were quite accurate in localizing touch on the ipsilesional hand (with the exception of RHL patient #7, who showed ipsilesional mislocalization in both DSS and single stimulation conditions and RHL patient #14 and LHL patient #2 who showed ipsilesional mislocalization under DSS), providing a within subject control for potential confounds such as non-visually guided reaching errors.

Figure 1 about here

Performance on the TQS task excludes the presence of motor neglect and body neglect in these groups of patients. Indeed, patients were able to correctly reach their contralesional hand when blindfolded (excluding the presence of body neglect) and to correctly use their contralesional hand to point ipsilesionally (excluding motor neglect).

All behavioral data can be found at the URL https://data.mendeley.com/datasets/9sy9fbkwg4/draft?a=2c547ec4-0c73-4b6d-aea4-6b6afe3e49a2.

3.2. Lesion analyses

In the RHL group, the lesional pattern involved the middle/inferior regions of the frontal lobe, the superior/middle regions of the temporal lobe, the insular regions, the putamen, the internal/external capsule, the thalamus, the corona radiata, the superior fronto-occipital fasciculus and the superior longitudinal fasciculus. The LHL group displayed a

lesional pattern mainly involving the inferior regions of the frontal lobe, the superior regions of the temporal lobe, the insular regions, the posterior-superior regions of the parietal lobe, the putamen, the external capsule, the corona radiata, the superior fronto-occipital fasciculus and the superior longitudinal fasciculus (Fig. 2A).

VLSM analysis (Brunner-Munzel rank-order test) showed that synchiric extinction correlated with lesions of internal capsule, putamen and caudate nucleus (Fig. 2B).

Figure 2 about here

4. Discussion

The novel TQS test, applied to acute right and left hemisphere stroke patients who showed - with the exception of one extinction patient - intact tactile perception on classical evaluation, revealed altered tactile awareness on DSS in about 50% of patients. When bilateral stimuli were applied to asymmetrical positions, patients erroneously located the contralesional stimulus on the symmetrical location of the ipsilesional one. These synchiric sensations selectively arose during DSS masking sensory unawareness of contralesional touches when classic protocol of tactile perception was applied. Since tactile extinction was hidden by synchiric sensations, we called the phenomenon ‘synchiric extinction’.

Excluding the possibility that synchiric extinction can be ascribed to primary sensory deficits or neglect, because they dissociate from the disorder, we may advance the following hypothesis to explain this particular form of extinction. Synchiric extinction might reflect neuroplastic mechanisms, triggered by the brain lesion, that unmask pathological bilateral touch representation following unilateral stimulation (Hansson & Brismar, 1999; Noachtar, Lüders, Dinner, & Klem, 1997; Tamè et al., 2012; Tamè, Braun, Holmes, Farnè, & Pavani, 2016). Hyperactivation of the healthy hemisphere (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Grefkes et al., 2008; Johansen-Berg et al., 2002; Kinsbourne, 1977; Salatino et

al., 2014) might abnormally activate, via inter-hemispheric transfer (Bagattini, Mele, Brignani, & Savazzi, 2015; Eickhoff, Grefkes, Fink, & Zilles, 2008; Fabri et al., 2001; Iwamura, 2000; Iwamura, Iriki, & Tanaka, 1994; Raffaella Ricci et al., 2012; Salatino, Poncini, George, & Ricci, 2014; van der Knaap & van der Ham, 2011), homologous representations of the healthy side in the damaged hemisphere thus producing phantom sensations.

However, why abnormal activation of ipsilateral representation would arise exclusively during DSS trials? We propose that the relative weight of homotopic representations, in the damaged hemisphere, might be enhanced by stimulation of the affected hand, as it occurs in the phenomenon of stochastic resonance (SR), whereby adding noise to sub-threshold stimuli improves their detection (Collins, Imhoff, & Grigg, 1996; Perez, Cohn, Medina, & Donoso, 2007; Perez, Donoso, & Medina, 2010). In the SR phenomenon, detection of sub-threshold stimuli is especially enhanced when the noise is applied simultaneously ('coincidence-enhanced stochastic resonance') but is disrupted when the noise is huge.

Synchiric sensations during DSS might not only mask tactile extinction, but also provide a hint on putative mechanisms underlying extinction per se. Classical theories of tactile extinction assume inter-hemispheric competition between ipsilesional and contralesional stimuli, whereby the ipsilesional stimulus, processed by the healthy hemisphere, 'wins the race' and reaches awareness (de Haan, Karnath, & Driver, 2012; Kamtchum-Tatuene et al., 2017). The present findings seem to suggest that inter-hemispheric competition might instead occur between the *homotopic representation* of the signal reaching the healthy hemisphere and the *weaker/damaged representation* of the signal reaching the lesioned hemisphere. The ipsilesional stimulus would 'win the race' via hyperactivation of its homologous/homotopic representation. Abnormal activation of homotopic representations might (as in synchiric extinction) or might not (as in classical extinction) reach supra-

threshold values, depending upon the relative weight of ipsilesional and contralesional touch representations. In line with this interpretation, preliminary findings of patients' lesions analysis suggest a correlation between synchiric extinction and structures often damaged in classical tactile extinction (Chechlacz et al., 2013; de Haan, Karnath, & Driver, 2012; Kamtchum-Tatuene et al., 2017; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994). This account can also explain classical synchiria (Medina & Coslett, 2016; Medina & Rapp, 2008), whereby intact side representations would always reach supra-threshold activation, and anti-extinction (White & Aimola Davies, 2013), whereby improved contralesional detection during DSS might be explained by synchiric phantoms.

If synchiric extinction is the expression of brain reorganization processes revealing altered bilateral integration of sensory representation, it might be relevant to explore its presence in other somesthetic senses and sensory modalities. Earlier evidence in extinction patients performing tactile (Vaishnavi, Calhoun, Southwood, & Chatterjee, 2000) and visual (Ricci, Genero, Colombatti, Zampieri, & Chatterjee, 2005) tasks seem to indicate that the phenomenon may likely arise in other sensory modalities and cognitive domains.

Alternatively, the observed behavior might be explained by mislocalization of correctly detected contralesional stimuli towards the homologue quadrant where stimulation occurred on the ipsilesional hand. In other words, the stimulated ipsilesional quadrant might serve as a perceptual 'anchor' or 'attractor', possibly explaining the systematic displacement of touch perception. While this account fits well with the behavior of patients manifesting both *contralesional mislocalization and synchiric extinction* during DSS (RHL # 7, 8, 15 and LHL # 7, i.e.16% of all patients), it hardly explains the behavior of patients exclusively showing *contralesional synchiric extinction* (RHL # 1, 4, 5, 9, 10, 13 and LHL # 3, 8, 32% of all patients) or contralesional synchiric extinction associated *with ipsilesional mislocalization* (RHL patient #14 and LHL patient# 2). Moreover, although several patients at the beginning

of the experimental session tended to point first to the ipsilesional hand, patients were promptly reminded to point first to the contralesional hand. Thus, patients performed the TQS task pointing to the contralesional hand first. This excludes the possibility that they were guessing based on the position of the ipsilesional stimulus, after having pointed to it. Another possible interpretation is that the observed findings depend upon differences between the standard extinction task and the TQS task (introduction of asymmetric touches in quadrants and addition of pointing movements). However, it is unlikely that more demanding task/instruction would have led to such a specific directional bias. It would have rather led to generalized decreased performance, such as, for example, mislocalization errors (together with 'synchiric extinction') in about all patients. Instead, 40% of the patients did not show any decreased performance (i.e. 10 out of 25 patients continue to perform well on TQS, as they did in the standard assessment), 28% of them (7/25: 4/25 of RHL and LHL patients showed *contralesional* mislocalization and synchiric extinction, RHL patient #14 and LHL patient# 2 showed *contralesional* synchiric extinction and *ipsilesional* mislocalization, LHL patient #4 showed contralesional mislocalization) manifested 'synchiric extinction' and/or mislocalization in contralesional and/or ipsilesional hand (and in these patients lower performance might be explained by the use of a more demanding task), but 32% of patients (8 out of 25) exclusively showed 'synchiric extinction'. In few first pilot patients (here not reported) we administered symmetric trials on the TQS and patients performed correctly on this condition (i.e. they said to be touched bilaterally and pointed to the correct stimulated sites), while showing synchiric extinction in the asymmetric trials. Since in the symmetric trials it was not possible to disentangle contralesional stimulus location from the sensation elicited by the ipsilesional stimulation and in order to make the task less fatiguing, we decided to administer only asymmetric trials. However, in future studies the introduction of a condition with symmetric touches and pointing movements will be relevant to definitely

exclude the possibility that results attributed to the asymmetric touches are an artefact of the instruction changes (i.e. pointing). Finally, the observed phenomenon might be explained by memory deficits in the encoding and/or recalling the site of stimulation (Thompson, 1992), although this explanation does not account for the observed directional bias. One limitation of the current study is the small sample size of the two groups of patients. However, statistical analyses showed large to very large effect size values, suggesting that, from a clinical point of view, the TQS can be considered a reliable protocol for assessing synchiric extinction in patients after stroke. Future investigations, in larger groups of patients, are necessary to disambiguate the above interpretations.

These findings provide evidence that disorders of apparently intact tactile awareness can be revealed by applying a simple tactile tool. Importantly, they shed new light on bihemispheric contributions to altered tactile perception following stroke, setting a framework for future investigations of postlesional plasticity (Edelman & Gally, 2001) underlying disrupted sensory awareness and possible functional recovery. Finally, they are relevant for recent models of bilateral representations of touch in the healthy brain (Tamè et al., 2016, 2012).

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Competing interests

The authors declare no conflict of interest.

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Figure and Table Legends

Table 1. Demographic and Clinical data of RHL and LHL patients.

Abbreviations: Sex: M =Male, F= Female. Education (years of formal education). Etiology: H= Hemorrhage, I= Ischemia. Length of illness (days): number of days between the onset of the disease and the assessment. MMSE= Mini Mental State Examination (patients' scores were corrected for age and education). N/A= Not Available. Scans of patients #2, #3, and #5 were not available. For these patients' in Table is reported the lesion recorded in the clinical files. Bisection errors (and relative standard deviation) are in millimeters: rightward errors are preceded by + and leftward errors by –. Diller= number of omitted targets in the left (L) and in the right (R) side of the page, respectively. On this task, patients were stopped after 5 minutes from the beginning of the trial.

Table 2. Experimental data on the TQS task for RHL and LHL patients.

Legend: Numbers of errors (N) and percentages of errors (%) with respect to the total number of trials for condition (i.e. 16) and statistical values are reported for RHL (A) and LHL (B) patients. For Double Simultaneous Stimulation (DSS) conditions, individual analyses were performed using a modified t-test for individual scores versus a control sample (Crawford's two tailed t-test). ***= $p<0.001$, **= $p<0.01$, *= $p<0.05$. On Single Stimulation trials (SS) the control group performed 100% correct (mean error=0 SD=0) while some of the patients show mislocalization errors. Thus mislocalization errors in this condition could not be analyzed using the Crawford's t-test. To analyze whether patients' mislocalization on Single Stimulation condition were not different from chance level a binomial two-tailed test with Bonferroni correction was performed. The § near to the number of mislocalization errors in the SS condition indicates a performance that do not differ from chance level.

Figure 1. Tactile Quadrant Stimulation (TQS) task and groups' performance.

A. Upper panel: Example of Double Simultaneous Stimulation (DSS) trial on the TQS task. Four quadrants were identified by two perpendicular 'virtual' lines (the lines were not drawn on the patient's hand), centered on the back of each hand. Light touches were delivered by the experimenter to non-symmetrical quadrants. Lower panel: example of correct response, synchiric extinction and mislocalization errors in patients with right hemisphere lesion. During DSS trials, patients with synchiric extinction consistently report contralesional tactile sensation in the quadrant homologous to the quadrant stimulated in the ipsilesional hand.

B. Groups' performances on the TQS task. The graph depicts means (and standard deviations) of synchiric extinction and mislocalization errors during Double Simultaneous Stimulation trials for each group (RHL= Right Hemisphere Lesion, LHL= Left Hemisphere Lesion, C= Controls) and hand (Left and Right). Significant differences between conditions are shown (* $p \leq 0.01$; ** $p \leq 0.001$).

Figure 2. Patients' lesion analyses

A. Overlays of regional lesion plots of the two groups of patients. In the upper panel are displayed data of Right Hemisphere Lesion patients (RHL), in the lower panel, data of Left Hemisphere Lesion patients (LHL) (available scans). The frequency is represented trough a color scale ranging from black to red. MNI coordinates of each transverse section are reported.

B. Results of the voxel-based lesion-symptom mapping (VLSM) analyses in RHL patients. All voxels which survived to the Brunner-Munzel rank order test are displayed. The color scale represents Z-scores.

Table 1. Demographic and Clinical Data of Right Hemisphere Lesion (RHL) and Left Hemisphere Lesion (LHL) patients.

RHL patients									
Patient	Sex	Age	Education (years)	Etiology	Length of illness (days)	MMSE	Bisection	Diller	Lesion
1	F	78	8	I	7	30	+6.3 (2.2)	0-0	Rolandic operculum, Heschl gyrus, superior temporal gyrus
2	M	74	8	I	1	30.2	+1.6 (5.8)	22-26	Hippocampus, parahippocampal gyrus, calcarine fissure, lingual gyrus, fusiform gyrus, middle and inferior occipital gyri, inferior temporal gyrus
3	M	77	5	I	1	31	-1.6 (2.5)	0-0	Parietal periventricular white matter,
4	M	81	5	I	9	28.9	-0.7 (2.1)	0-0	frontoparietal periventricular white matter
5	F	42	13	I	5	22	-0.2 (2.1)	0-0	Rolandic operculum, inferior parietal gyrus, supramarginal gyrus, angular gyrus, Heschl gyrus, superior and middle temporal gyri
6	F	68	8	I	4	30.5	-1.8 (2.6)	0-4	Frontal periventricular white matter, putamen

7	F	56	13	I	3	28	N/A	N/A	Superior temporal pole
8	F	54	8	I	2	29	-2.2 (2.0)	0-0	Inferior parietal lobe, supramarginal gyrus, angular gyrus, Heschl gyrus
9	M	59	8	H	6	29.7	+5.4 (3.0)	1-1	Caudate nucleus, thalamus
10	M	52	13	I	5	28	+3.3 (4.3)	6-0	Insula, caudate nucleus, putamen, pallidum
11	F	22	11	I	3	30.2	-2.4 (2.1)	0-1	putamen
12	M	74	8	H	2	26.6	+1.7 (7.7)	0-0	Inferior,middle and superior occipital gyri
13	M	65	17	I	3	28	-1.6 (1.5)	0-0	Frontotemporoparietal periventricular white matter
14	M	77	5	I	5	29.03	-1.2 (3.3)	0-0	Precentral gyrus, cuneus, superior occipital gyrus, inferior and middle temporal gyri

15	M	80	5	I	2	28.03	+1.7 (4.0)	0-0	Anterior cingulum
16	M	76	8	I	3	27	4.2 (3.2)	0-0	Hyppocampus, parahyppocampal gyrus, calcarine fissure, lingual gyrus, inferior occipital gyrus, fusiform gyrus, middle and inferior temporal pole
17	M	58	13	I	4	28.9	-2.7 (1.3)	0-0	Rolandic operculum, insula, frontoparietal periventricular white matter

Table 1 Continued

LHL patients

Patient	Sex	Age	Education (years)	Etiology	Length of illness (days)	MMSE	Bisection	Diller (omissions L-R)	Lesion
1	M	60	17	I	7	25.3	+5.3 (2)	0-0	Caudate, putamen, pallidum, thalamus
2	M	68	2	I	3	26.0	-7.6 (5.6)	0-11	*Occipital
3	F	79	5	I	5	30.0	-4.4 (4.3)	0-0	*Parietal
4	M	65	13	H	4	28.5	-6.1 (3.4)	0-0	Temporo-occipital periventricualr white matter
5	M	62	8	I	3	30.0	-3.7 (1.5)	0-0	*Parieto-occipital
6	F	44	17	I	4	28.2	+2.8 (1.5)	0-0	Hyppocampus, parayppocampal gyrus, calcarine fissure, lingual gyrus, fusiform gyrus
7	F	60	8	H	8	29.0	-4.4 (2.7)	0-0	Inferior frontal gyrus (triangular part), insula, caudate, putamen, pallidum, Heschl gyrus
8	M	62	8	I	5	29.5	N/A	N/A	Insula, putamen

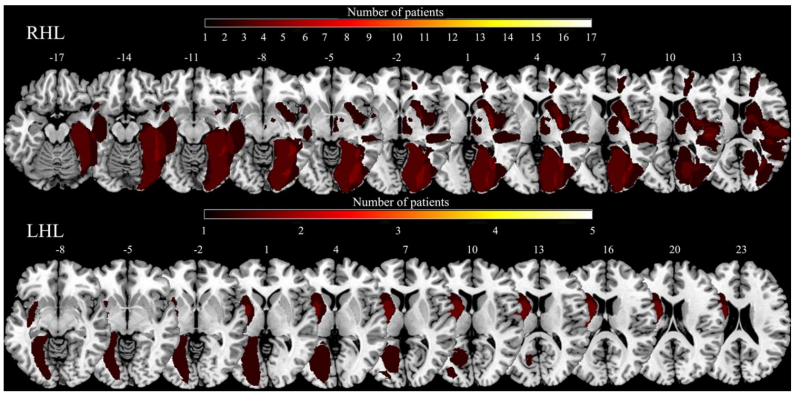
Table 2 Experimental data for Right hemisphere Lesion (RHL) patients and Left hemisphere Lesion (LHL) patients

RHL												
	Left hand/ CONTRALESIONAL HAND						Right hand/ IPSILESIONAL HAND					
	Synchiric Errors			Mislocalization Errors			Synchiric Errors			Mislocalization Errors		
	SS	DSS		SS	DSS		SS	DSS		SS	DSS	
	N	N	%	N	N	%	N	N	%	N	N	%
1	0	14***	88%	0	1	6%	0	0	0%	0	0	0%
2	0	0	0%	1	2	13%	0	0	0%	0	0	0%
3	0	0	0%	0	1	6%	0	0	0%	0	1	6%
4	0	3***	19%	1	2	13%	0	2**	13%	0	1	6%
5	0	6***	38%	4	2	13%	0	0	0%	0	0	0%
6	0	1	6%	2	1	6%	0	0	0%	0	2	13%
7	0	5***	31%	7§	8***	50%	0	0	0%	6§	5*	31%
8	0	5***	31%	6§	6***	38%	0	1	6%	1	2	13%
9	0	7***	44%	0	2	13%	0	1	6%	0	1	6%
10	0	7***	44%	1	2	13%	0	1	6%	0	1	6%
11	0	1	6%	0	0	0%	0	1	6%	0	2	13%
12	0	0	0%	0	1	6%	0	0	0%	0	0	0%
13	0	3***	19%	1	2	13%	0	1	6%	2	1	6%
14	0	2**	13%	0	1	6%	0	0	0%	0	7**	44%
15	0	5***	31%	0	5***	31 %	0	0	0%	0	2	13%
16	0	0	0%	0	1	6%	0	1	6%	0	2	13%
17	0	0	0%	0	0	0%	0	0	0%	0	0	0%

Table 2 Continued

LHL												
	Left hand/ IPSILESIONAL HAND						Right hand/ CONTRALESIONAL HAND					
	Synchiric Errors			Mislocalization Errors			Synchiric Errors			Mislocalization Errors		
	SS	DSS		SS	DSS		SS	DSS		SS	DSS	
	N	N	%	N	N	%	N	N	%	N	N	%
1	0	0	0%	0	0	0%	0	0	0%	0	0	0%
2	0	1	6%	5	5***	31%	0	5***	31%	4	1	6%
3	0	0	0%	0	0	0%	0	2**	13%	0	1	6%
4	0	0	0%	0	0	0%	0	1	6%	0	5*	31%
5	0	0	0%	0	2	13%	0	0	0%	0	0	0%
6	0	0	0%	0	1	6%	0	0	0%	0	0	0%
7	0	0	0%	2	2	13%	0	4***	25%	4	5*	31%
8	0	1	6%	0	1	6%	0	7***	44%	0	2	13%

A


Number of patients
RHL
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
-17 -14 -11 -8 -5 -2 1 4 7 10 13
Number of patients
LHL
1 2 3 4 5
-8 -5 -2 1 4 7 10 13 16 20 23

B

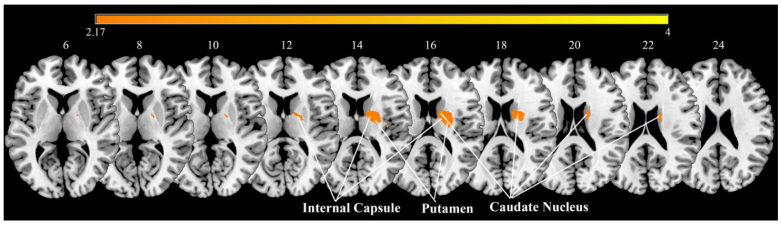
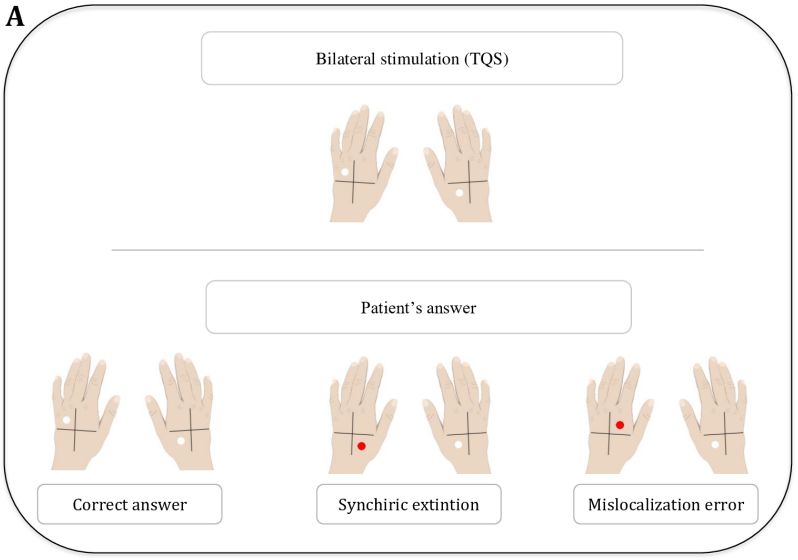

2.17
4
6 8 10 12 14 16 18 20 22 24
Internal Capsule
Putamen
Caudate Nucleus

Figure 2


A
Bilateral stimulation (TQS)
Patient's answer
Correct answer
Synchiric extintion
Mislocalization error

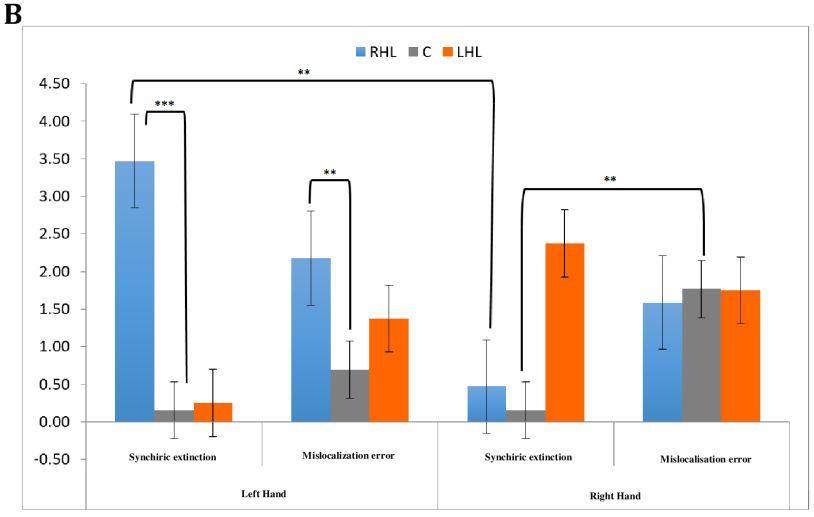

B
RHL
C
LHL
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
**
***
**
**
Synchiric extinction
Mislocalization error
Synchiric extinction
Mislocalisation error
Left Hand
Right Hand

Figure 1

Authors Contribution

CORTEX-D-19-00067

Phantom touch: how to unmask sensory unawareness after stroke

Raffaella Ricci, Adriana Salatino, Michela Caldano, Paola Perozzo, Paolo Cerrato, Maria Pyasik, Lorenzo Pia, Anna Berti.

Raffaella Ricci: Conceptualization, Methodology, Formal analysis, Investigation, Supervision, Writing – original draft, Funding acquisition.

Adriana Salatino: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft.

Michela Caldano: Data curation, Project administration, Formal analysis, Writing – review & editing.

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