UNIVERSITA' DEGLI STUDI DI MILANO-BICOCCA

Dottorato di Ricerca in Psicologia Sperimentale, Linguistica e

Neuroscienze Cognitive.

Ciclo XXIII

PRODUCTIVE SYMPTOMS IN RIGHT BRAIN DAMAGED PATIENTS.

BEHAVIOURAL AND ANATOMICAL OBSERVATIONS.

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Anno Accademico 2010-2011

Ai miei genitori,

per avermi cresciuta così testarda.

A Roberto,

perché ami sempre scoprire.

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Abstract

This thesis describes behavioural observations and anatomical investigations concerning productive symptoms observable in right brain damaged patients with spatial neglect. A "productive" symptom is defined here as a behavioural manifestation that, contrary to what observed when performance is lacking or its failure is acknowledged by patients, is characterized by the active generation of acts or verbal reports reflecting a distorted mental representation of reality.

A first classification of productive symptoms in neglect patients pertains the spatial frame of their manifestation, extrapersonal or personal. Following this classification, I examine these manifestations in separate sections of the thesis. Section 1 is dedicated to the peri/extrapersonal space, while, in Section 2, I focus on symptoms manifesting in the own bodily space.

In chapter 2, I concentrate on <u>graphic perseveration</u> in cancellation tasks, the main productive symptom observable for the extrapersonal space in neglect patients. Together with omission of left-sided targets, a variety of irrelevant marks over already cancelled targets on the ipsilesional side can be observed. It is not clear whether these perseverative behaviours are functionally and anatomically connected, nor whether they correlate with the severity of spatial neglect. We retrospectively identified two well-distinct forms of perseveration on cancellation tasks ("additional marks" and "inkblot") in 33 neglect patients, and we investigated their relationship with neglect severity and their anatomical correlates. We show, on both a behavioural and anatomical level, that different kinds of perseverative behaviours are differently related with neglect.

From chapter 3 onwards I concentrate on productive manifestations in personal space. One main such productive symptom is <u>somatoparaphrenia</u>, the delusional belief whereby a patient feels that a paralyzed limb does not belong to his body; the symptom is typically associated with unilateral neglect and most frequently with anosognosia for hemiplegia. In chapter 3, I describe the anatomical pattern associated with somatoparaphrenia in a wide sample of patients, and I propose that somatoparaphrenia occurs providing that a distributed cortical lesion pattern is present together

with a subcortical lesion load that prevents most sensory input from being processed in neocortical structures.

 In chapter 4, I also show how somatoparaphrenia, that, so far, has been often considered simply the most severe and delusional manifestation along a continuum of body disorders also including anosognosia for hemiplegia, can be also observed in isolation from this symptom. I report anatomical observations on a small group of pure somatoparaphrenic patients and discuss the implications of this uncommon symptomatological dissociation.

The experiments mentioned so far were based on classical anatomoclinical correlation inference. The study of productive/positive symptoms, however, would ideally need functional methods as well, in order to capture the neural correlates of the "active" component implied by the symptoms under investigation.

I present an initial attempt along these lines. I considered the delusional behaviour of patients with anosognosia for hemiplegia (AHP): this has been often classified as a "negative" symptom as patients crucially "lack" the awareness of the motor deficit. However, beyond this defective aspect, AHP is usually characterized by an active delusional component that manifests in the patients' firm assertion of having performed a movement with the paralyzed limb, in spite of any *clear evidence* that no movement has actually occurred. In this case, one has to postulate the presence of a residual, and maybe misinterpreted, motor brain activity to account for this delusional component. Here I illustrate, for the first time, the missing direct imaging evidence that the illusory movement of the left plegic hand is associated with brain activation of intact cortical motor regions implicated in motor control and intention (see chapter 5). It is suggested that motor delusions observed in AHP depend on a combination of well placed lesions and the presence of some motor intentionality represented by residual activity within the spared motor cortices.

The diversity of the phenomena considered in this thesis makes it difficult to generalize anatomical considerations about productive manifestations associated with spatial neglect; yet, it is worth of notice the fact that all these disorders can be also conceptualized as self-monitoring disorders

particularly related to motor/sensory control aspects in which the opercular part of the inferior frontal gyrus seems to play an important role. Indeed, we found it constantly involved in all the productive disorders considered, irrespective of whether defective monitoring was about the left plegic limb or the right intact one.

In addition, we find it promising the adoption of functional methods to gather a more complete description of the neural underpinnings of symptoms of great complexity like the productive ones.

Prologue

Stroke and related cognitive symptoms.

In the worldwide population aged between 65-84 years, stroke prevalence is reported as 6,5 %; a similar rate has also been found for the Italian population. Stroke's incidence progressively increases with aging, with a rate of 0,1-0,3 x 1000 for year in subjects younger than 45 years, and 12-20 x 1000 for year in subjects aged between 75 and 84 years [1]. Nowadays, progresses in surgery and intensive care medicine have allowed a reduction of mortality in the acute phase of disease in stroke patients, leading however to higher rates of post-stroke complications that deeply impact on the patients' care, management and quality of life. Stroke is indeed the first cause of disability in the elderly. Cognitive functions impairments represent one of the most common and severe complications in stroke patients in the acute phase of disease, and, if not appropriately detected and rehabilitated, also in chronic phases, worsening the quality of the patients' functional recovery.

Defective awareness symptoms following right-hemispheric strokes.

The lack of awareness for cognitive and neurological symptoms is a very disabling condition that severely entangles their rehabilitation. The deficit of awareness often manifests as delusional verbal reports of the patients, as it happens for example in anosognosic subjects. This kind of defects has been more often reported as a consequence of stroke involving the right cerebral hemisphere, rather than the left. Even if some studies pointed out the possibility of an underestimation of these disorders in left brain damaged patients, given the higher prevalence of global aphasia that prevents their verbal manifestation, such evidence clearly supports the important role played by the right hemisphere in different aspects of spatial awareness, including the own bodily space.

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1 See "Ictus cerebrale: Linee guida italiane di prevenzione e trattamento". Volume completo. SPREAD 6.a Edizione – 2010. Stesura di gennaio 2010.

More debated is the intra-hemispheric localization of the neural networks crucial for different aspects of self and spatial awareness.

Right brain damage may result in "defective awareness" symptoms that may manifest in different contralesional spatial frames (personal space, peripersonal and extrapersonal space), such as, for example, the "defective awareness of targets in the neglected sector of space" (spatial neglect); "defective awareness of the contralesional side of the body" (personal neglect); "defective awareness or denial of contralesional neurological deficits" (anosognosia); "defective programming of movements of the ipsilesional limbs toward targets in the neglected sector of space" (motor neglect) etc. (see Vallar, 1998; 2001). Even if the number of behavioural dissociations among these disorders described in the literature has increased in recent years, many of these symptoms have not found a definite anatomical counterpart.

Beyond the spatial frame of manifestation, these symptoms can be usually also distinguished in negative (or defective) or positive (or productive) manifestations (see Vallar, 1998). "Productive pathological manifestations" (Vallar, 1998) are characterized by the "presence of specific behaviours that cannot be accounted for simply in terms of defective orientation of attention or representational scotomas" as for defective symptoms (which are characterized by the absence of specific behavioural responses). Rather they imply a misrepresentation of space. This distorted mental representation of reality is reflected by the active generation of acts or verbal reports manifested by these patients.

Structure of this thesis.

In this thesis, I focus on the main productive symptoms, characterized by a defective self-monitoring, which are usually observable in the personal and peripersonal space in patients with left

spatial neglect, aiming at investigating their anatomical substrates and contributing to the clarification of their cognitive and neurofunctional mechanisms.

In Chapter 1, I introduce the definition of "productive" symptom and provide a short overview of the status of art regarding the main positive defects that may manifest in the context of spatial neglect: somatoparaphrenia, anosognosia for hemiplegia and, as for the extrapersonal space, perseveration in cancellation tasks. I also explain why including anosognosia for hemiplegia among productive, rather than negative (see Vallar, 1998, 2001), symptoms.

The following chapters focus more specifically on each of these symptoms, in separate sections, starting from the extrapersonal space to the personal space of the own body.

Starting from classical anatomo-clinical correlation studies, in Chapter 2, I present an investigation of the anatomical bases of the main productive symptom that manifests outside the personal space, in the peripersonal space of the sheets of cognitive tests used to diagnose spatial neglect: namely, graphic perseveration in cancellation tasks.

Neglect patients' performance during cancellation tasks is not only characterized by left sided target omissions, but also, in many cases, by the production of various kinds of extra marks (e.g. additional marks over already cancelled targets, inkblots, flying marks, irrelevant drawings) in the ipsilesional space. In chapter 2, after a comprehensive review of the types of perseveration described in the literature under different labels, I present data collected from cancellation tests of 33 neglect patients, in which I noticed a sizeable frequency of perseveration of two well distinct types: (1) 'additional marks' perseveration where subjects marked a target line with two or more well separated marks; (2) 'inkblot' perseveration, where patients produced inkblots, much wider than the single stroke line requested by the task, in which no clear distinction between separate marks could be identified.

As it is not clear whether these perseverative behaviours are functionally and anatomically connected nor whether they correlate with the severity of spatial neglect, in this study I used a

combined qualitative analysis on these different kinds of perseverations and their differential correlation with neglect severity, plus, an anatomo-clinical correlation approach, in the attempt to identify discrete anatomical correlates for the different kinds of perseveration.

From chapter 3 onwards, I focalized on productive symptoms manifesting in the personal space. One main such productive symptom is somatoparaphrenia, the delusional belief whereby a patient feels that a paralyzed limb does not belong to his body. In close collaboration with the Stroke Unit of Niguarda Cà Granda Hospital of Milan and the Cognitive Neuropsychology Centre directed by Prof. Gabriella Bottini, I had the opportunity to collect clinical and anatomical data (partially retrospectively) from a relatively wide sample of somatoparaphrenic patients (n=11), given the well-known rarity of this symptoms. This lesion-mapping study showed that somatoparaphrenia occurs providing that a distributed cortical lesion pattern is present together with a subcortical lesion load that prevents most sensory input from being processed in neocortical structures. These results are discussed in light of the recent advance in the field of the neuropsychology of body-ownership in healthy subjects and neurological patients.

Somatoparaphrenia has always been described as a disorder tightly linked to anosognosia for hemiplegia, with somatoparaphrenic delusions being considered simply as a more severe manifestation of the same defect, also related to the damage of the same crucial cortical region (namely the right posterior insula). Only a few scanty and not clear descriptions of somatoparaphrenia in absence of anosognosia can be found in the literature. Since I had the opportunity to observe some of these cases, in chapter 4, I extensively describe the clinical and anatomical data of these rare pure somatoparaphrenic patients and I show that the sparing of right premotor regions may bring about somatoparaphrenia even in absence of anosognosia, providing evidence that body-ownership and motor awareness cognitive processes are independent and separately damageable.

The experiments mentioned so far were based on classical anatomoclinical correlation inference. The study of productive/positive symptoms, however, would ideally need functional methods as well, in order to capture the neural correlates of the "active" component implied by the symptoms under investigation.

In the last chapter, I present an initial attempt along these lines. I considered the delusional behaviour of patients with anosognosia for hemiplegia (AHP). In Chapter 5, I briefly introduce the large body of theories that, so far, have been suggested trying to explain the cognitive mechanisms underlying anosognosia for hemiplegia. In particular, I introduce the debate regarding the role of the intention to move in leading to anosognosic motor delusions, the active and productive aspect of AHP. I then describe recent findings of a small sample of anosognosic patients, who were able to undergo a functional magnetic resonance experiment during a simple motor task. In this study, I aimed at investigating if any residual neural activity was still present in these patients in spared cortical regions known to be involved in motor intention and planning (e.g. the supplementary motor area and premotor regions), during the illusory movement of the plegic hand. Increasing behavioural evidence supports the presence of some residual motor intentionality in anosognosic patients, but we still lack its direct neurofunctional evidence. In this study I aimed at providing antomofunctional evidence that may help the clarification of the cognitive mechanisms underlying this disorders and I succeeded in demonstrating, for the first time, that, in anosognosic patients, the illusory movement of the left plegic hand is associated with brain activation of intact cortical motor regions implicated in motor control and intention. Thus, I finally suggest that motor delusions observed in AHP seem to depend on a combination of well placed lesions and the presence of some motor intentionality represented by residual activity within the spared motor cortices.

Despite the apparent diversity of the considered phenomena, due to their diverse manifestations (verbal or motor acts, personal or extrapersonal space, right or left side of the space), it is however worth of hemphasis the recurrent finding of a damage of the opercular part of the right inferior frontal gyrus in neglect-related perseveration, anosognosia for hemiplegia and somatoparaphrenia,

which supports a link between these apparently different manifestations. Ventral premotor cortices, especially of the right hemisphere, have frequently been related to several aspects of complex actions processing and performance of complex motor acts with higher degree of sensorimotor control (for a detailed discussion about the role of this brain region see Binkofski and Buccino, 2006). These observations support, from an anatomical viewpoint, that the symptoms discussed in this thesis may be conceptualized as forms of defective monitoring of sensory-motor aspects of the self.

Forword

While I take full responsibility for the empirical observations, analyses and interpretations described below, the experiments described in this Thesis are the result of my close collaboration with several other investigators, including Gabriella Bottini, Eraldo Paulesu, Martina Gandola and Alessio Toraldo. The use of *"we"* in this manuscript refers to this research group to which goes my heartfelt thank you!

1. Chapter 1. Productive Symptoms in right brain damage. An Introduction. [2]

Productive - or positive - symptoms in right brain damaged patients are behavioural manifestations that, contrary to what observed when performance is lacking or its failure is acknowledged by patients, are characterized by the active generation of acts or verbal reports reflecting a distorted mental representation of reality.

Here we introduce productive manifestations usually associated with unilateral spatial neglect, in separate sections depending on the spatial frame of their manifestation, personal or extrapersonal.

1. Productive symptoms in the personal space.

1.1 Anosognosia for hemiplegia.

Anosognosia for hemiplegia (AHP) is the lack of awareness for contralesional motor deficits following brain damage (Babinski, 1914). If questioned, anosognosic patients firmly deny their difficulties in performing actions with affected limbs and, in severe cases, they claim they're moving even despite the evidence. Although AHP was usually considered a negative behaviour as patients "miss" the awareness of a deficit (Vallar, 2008), we believe that this disorder has an important productive component which consists in the delusional belief and assertion of having moved the plegic hand.

Many theories have been proposed trying to explain the cognitive mechanisms underpinning this symptom (see Vallar et al., 2003, for a review). Recently, anosognosia has been contextualized inside motor control models (Frith et al., 2000) and the debate is now focused on the role of

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[2] This chapter is based on our work "Productive symptoms in right brain damage". By Bottini G. et al, Curr Opin Neurol. 2009 Dec; 22(6):589-93. Review. Reused under licence provided by Wolters Kluwer Health.

intention to move (Berti et al., 2007; Desmurget and Sirigu, 2009; Fotopoulou et al., 2008; Haggard, 2005). Heilman and colleagues provided evidence supporting that anosognosic patients lack motor intention and do not even trigger planning mechanisms nor generate movement expectancies (Gold et al., 1994a; Heilman, 1991; Heilman et al., 1998). The main lack of this theory resides in not explaining the more productive aspect of AHP, the delusional belief of having moved. Furthermore recent evidence argued in favour of preserved motor planning (Berti et al., 2007; Fotopoulou et al., 2008; Jenkinson et al., 2009a). The feed-forward model proposed by Frith et al. in 2000 (Frith et al., 2000), included a further level of motor analysis, the comparison between desired and predicted states of motor system. This level would be preserved in anosognosia, hence the delusion of having moved. Denial of motor deficit would be caused by a failure in detecting mismatches between predicted positions and actual movements due to absent or neglected sensory feedbacks, while moving illusions would be created by the matching between intended and predicted representations. AHP patients would be biased by their motor intentions. Current experiments are now providing evidence for these hypotheses. In 2007, Berti and colleagues (Berti et al., 2007) registered left proximal muscle EMG activation in one anosognosic patient despite left paralysis, suggesting an intact motor planning. However, the first direct evidence of this ability preservation in a group study was provided by Jenkinson and collaborators (Jenkinson et al., 2009a) that investigated motor representations by comparing hemiplegic patients with and without AHP in a motor imagery task (grip selection task). Results showed that AHP patients still retained- though distorted- the ability to generate motor representations involving their hemiplegic limb.

A recent experiment (Fotopoulou et al., 2008) covered a further step investigating the role of motor planning in awareness, by examining if the ability to visually detect presence or absence of movement varied according to whether the action was internally or externally generated. While non anosognosic subjects weren't influenced by condition changing, anosognosic patients ignored their motionless arm more often in the first condition (when they did intend to move) than in the second one (when they hadn't planned any movement nor generated predictions). This result first

demonstrated that the false movement belief derives from an overcoming of motor intentions on actual state of motor system.

Accounts of AHP suggesting a failure to discriminate between internally predicted and external actual movement were supported by evidence of a reality monitoring deficit (the process by which subjects distinguish internal and external information) in anosognosic patients (Jenkinson et al., 2009b). In Jenkinson's experiment patients were asked to perform, imagine or observe actions and were subsequently asked to recognize a movement as self or other performed. AHP patients failed this test suggesting that anosognosia may be linked to reality monitoring failures.

Insights concerning the role of motor intention and planning in AHP are also incoming from lesional data. A crucial role of brain regions localized outside the parietal cortex , premotor cortex (Berti et al., 2005) and insula (Karnath et al., 2005), was suggested. Berti and colleagues found a correlation between AHP and right premotor cortex damage, suggesting that conscious "monitoring can be implemented in the same neural network responsible for the process that has to be controlled" (Berti et al., 2005). The idea of a modular structure of awareness is supported by recent evidence of distinct brain networks responsible for monitoring different functions (Spinazzola et al., 2008). Indeed, while AHP is associated with lesion of motor planning regions (Berti et al., 2005),anosognosia for hemianestesia is associated with lesions of sensory related areas (insula, temporal lobe and subcortical structures) (Spinazzola et al., 2008). This preliminary observation, although notable, is to be better explored in more systematic studies with larger samples and statistical anatomical comparison between different groups of patients.

Interestingly for the current debate on motor intention in AHP, in the study of Berti and collaborators (2005), the supplementary motor cortex (SMA) was spared in anosognosic patients allowing "the construction of conscious intention of action". The crucial role of premotor and SMA cortices in motor awareness suggested by results of Berti and colleagues is also supported by electrophysiological and neuroimaging studies in healthy subjects (Lau et al., 2004a). Nevertheless, a recent electrophysiological experiment in patients undergoing neurosurgery questioned the role of

SMA in generating motor intentions (Desmurget et al., 2009), showing that stimulating inferior parietal cortex with electrodes generated experiences of "urge" to move (Desmurget et al., 2009; Lau et al., 2004a).This suggests that parietal cortex, not just frontal areas, may be involved in experiencing conscious action intention (Desmurget and Sirigu, 2009). Two brain regions would contribute to distinct aspects of conscious movement intention: SMA as a conscious correlate of motor commands preparing and parietal cortex as a correlate of sensory prediction of the consequences of commands (Desmurget and Sirigu, 2009; Haggard, 2009).

In contrast with Berti and colleagues' results, Karnath and co-workers (Karnath et al., 2005) found an association between AHP and damage of right posterior insula, an important centre of multisensory integration. More recently these authors replicated this result studying the lesions' distribution of anosognosic patients with different kinds of disownership deficits (Baier and Karnath, 2008) concluding for a tight link between these defects and AHP. Nevertheless, the relationship between these phenomena is to be further investigated since Baier's study misses a crucial comparison between patients perfectly matched for all characteristics but delusions, that could allow the identification of specific anatomical substrates for somatoparaphrenia.

In conclusion, the definition of brain networks involved in awareness of sensory and motor functions and ownership is a still an open debate, and further anatomo-clinical and fMRI studies are needed to better define this issue.

1.2 Somatoparaphrenia

Somatoparaphrenia (SP), as defined originally by Gerstmann (Gerstmann, 1942), is characterized by "illusions or distortions concerning the perception of, and confabulations or delusions referring to the affected limbs or side" (Gerstmann, 1942). Patients perceive limbs as belonging to other persons (for instance strangers, doctors or relatives) (Assal, 1983; Bottini et al., 2002). These beliefs do not depend on a generalized delirium or to psychiatric disorders. The specificity of SP may be questionable and the debate on whether SP is part of a *continuum* of body schema disorders or an isolated disownership symptom is far from being settled (Baier and Karnath, 2008). Since

Gerstmann's seminal paper, in fact, many different definitions have been proposed for SP, some including asomatoagnosia and other kinds of delusions about body parts, at times complicated by an aversive aggressive reaction against the paralyzed limb (Loetscher et al., 2006; Pearce, 2007), a symptom called misoplegia since Critchley original description (Critchley, 1974). This problem of classification may also depend on the fact that SP usually presents in close association with other symptoms that cluster in the spatial neglect syndrome (Baier and Karnath, 2008; Bisiach et al., 1991; Vallar and Ronchi, 2009), as much as it can be reversed by left cold caloric vestibular stimulation as for spatial neglect (Bisiach et al., 1991).

SP is most often associated with right rather than left brain damage (Vallar and Ronchi, 2009): as SP is mainly investigated through interviews, its presence may be difficult to diagnose in left brain damaged patients with severe aphasia. On the other hand, its appearance in left brain damaged patients (Miura et al., 1996; Vallar and Ronchi, 2009) may be due to a reversed hemispheric specialization, as in the case described by Miura et al. (1996) where SP coexisted with AHP and spatial neglect for the right half of space, with a minimal language disorder.

Anatomical studies are contributing information that may add specificity to SP.

Early studies, based on single case reports, were clearly not conclusive as SP was described in association with lesions of the parietal lobe (Bottini et al., 2002; Gerstmann, 1942), fronto-temporal (Bisiach and Geminiani, 1991b), supramarginal gyrus (Feinberg et al., 1990), basal ganglia (Bottini et al., 2002) and of the thalamus (Daprati et al., 2000b).

Recent findings, based on more rigorous anatomical comparisons between groups of patients, indicate the insula and the right temporo-parietal junction as crucial lesion sites (Baier and Karnath, 2008; Tsakiris et al., 2007). It remains to be seen whether isolated lesions of these brain regions are sufficient to bring about SP or whether the co-existence of a more diffuse damage is a necessary pre-requisite. In addition, the patients enrolled for the more recent group anatomical studies showed a number of productive behaviours not always coherent with strict definition of SP.

The search for dissociations of symptoms is also informative. For example, SP has been recently

dissociated from anosognosia for hemiplegia, while early studies suggested that AHP and SP always coexist (Baier and Karnath, 2008; Tsakiris et al., 2008).

Different theories have been proposed to explain the sense of non-belonging of body parts, the main feature of SP.

Although SP is tightly associated with different sensory deficits, these impairments are not sufficient to generate the misownership (Vallar and Ronchi, 2009). It has been demonstrated, for example, that while the change of position of the paralyzed limb of neglect patients may induce a dramatic, transient recovery of tactile deficit, no such effect can be seen for the coexistent somatoparaphrenia (Moro et al., 2004). Furthermore the repeatedly failed attempts to demonstrate to patients, through visual input, that the limb belongs to them, reinforce the speculation that the disorder requires the distortion of a higher-level representation (Vallar and Ronchi, 2009).

Interestingly, seemingly hemianaesthesic patients may deny to be touched when touches are said to be given to their left hand; on the other hand, they may "feel touches in someone's else hand" (Bottini et al., 2002), providing that the examiner pretends to deliver them to the person to which the patient misattributes ownership. Again, this is more evidence for SP as a higher-order deficit not necessarily associated with a complete disorder of elementary somatosensory functions.

While a clear explanation of SP is still lacking, this fascinating symptom continues to offer ways of testing the structure of body schema and the sense of ownership and spatial cognition in general.

2. Productive symptoms in the extra-personal space: graphic perseveration.

Graphic perseveration (GP) in cancellation and drawing tasks is a common productive phenomenon often described in right brain damaged patients. Patients usually ''overscore lines already drawn'' (Gainotti and Tiacci, 1970), a behaviour called "simple" perseveration (Rusconi et al., 2002a), or "add irrelevant writing or drawing not requested by the investigator on the right half of the sheet''

(Gainotti and Tiacci, 1971), an attitude called "complex" perseveration (Rusconi et al., 2002a) (Bottini and Toraldo, 2003; Ronchi et al., 2009; Toraldo et al., 2005; Vallar et al., 2006).

The tight association with hemispatial neglect reported by many authors (Rusconi et al., 2002a) is still to be fully explained. Pathological mechanisms of perseveration are still debated and several interpretations have been proposed (Pia et al., 2009; Ronchi et al., 2009; Vallar et al., 2006). These disorders might be independent but clinically associated because of the co-occurrence of frontal and parietal damage in neglect triggering GP as a result of a "motor control dysinibition" (Denny-Brown, 1958; Rusconi et al., 2002b; Vallar et al., 2006). However, evidence exists suggesting a single-factor mechanism: the implicit processing of controlesional neglected targets (Bottini and Toraldo, 2003; Manly et al., 2002; Toraldo et al., 2005). Functional analyses of the behavioural patterns (e.g. the modulation of ipsilesional perseveration by neglected targets (Bottini and Toraldo, 2003) support two possible explanations: it has been proposed that perseveration is a consequence of a directional hypokinesia that makes patients stuck on ipsilesional stimuli because of a "reluctance" to move leftwards. It has also been proposed that, at least in some cases, perseveration on right-sided targets during cancellation tasks may be the consequence of an alloaesthesic perception of the left-sided visual stimuli, as if they also were on the right side of the display (Bottini and Toraldo, 2003; Toraldo et al., 2005).

Recently, Pia and collaborators tested these hypotheses systematically studying the influence of left located stimuli on ipsilesional perseveration (Pia et al., 2009). Supporting that different mechanisms could be involved in neglect and perseverative behaviour, authors found that left targets didn't influence perseveration on the right side; furthermore they found a correlation between GP and right basal ganglia lesions, and not with neglect. Further supports derive from Nys et al (Nys et al., 2008) and Khurshid et al (Khurshid et al., 2009) studies investigating the effect of prism adaptation (Nys et al., 2008) and monocular patching (Khurshid et al., 2009) on neglect and perseveration severity. Prisms and patching both ameliorated only neglect while GP increased or remained unvaried. As suggested by Kim and co-workers (Kim et al., 2009) alternative forms of perseveration may exist

differently related to neglect. Patients can make uninterrupted multiple strokes on each target (consecutive motor perseveration: CMP) or return to previously cancelled targets and remark them (return perseveration: RMP). These forms of production were differently altered by using background movements as a treatment for neglect showing a tight link between visuospatial deficit and RMP only, while CMP seemed to be related to a disengagement disorder (Kim et al., 2009).

Anatomical correlates of perseveration are not clearly defined yet. Many studies reported an involvement of right anterior frontal areas and basal ganglia (Na et al., 1999; Nys et al., 2008; Pia et al., 2009; Rusconi et al., 2002a). However, recent evidence showing different forms of this behaviour let us suppose that perseveration is not a unitary phenomenon and that different perseverative manifestations could be associated to distinct anatomical lesional substrates.

Conclusions

Productive behaviours associated with right brain damage and frequently seen together with spatial neglect have diverse manifestations and may be underpinned by different mechanisms.

In what follows we will provide evidence for specific anatomical correlates much as cognitive investigations for specific mechanisms; we will try to test explicitly some of the theories proposed to further explain these complex phenomena and understand to what extent they can be disentagled from spatial neglect.

SECTION 1

EXTRAPERSONAL SPACE

2. Chapter 2. How many forms of perseveration? Evidence from cancellation tasks in right brain damaged patients.

Abstract

Neglect patients' performance during cancellation tasks is characterized by left sided omissions and, in some cases, by the production of extra marks of various kinds (e.g. additional marks over already cancelled targets, inkblots, flying marks, irrelevant drawings) in the ipsilesional space. It is not clear whether these *perseverative behaviours* are functionally and anatomically connected nor whether they correlate with the severity of spatial neglect. Here we report a retrospective study on 33 right brain damaged patients with spatial neglect in whom we found a sizeable frequency of perseveration of the two following kinds: (1) 'additional marks' perseveration where subjects marked a target line with two or more well separated marks (2) 'inkblot' perseveration, where patients produced inkblots, much wider than the single stroke line requested by the task, in which no clear distinction between separate marks could be identified. We found that 'additional marks' perseveration correlated with severity of spatial neglect in cancellation tasks, while 'inkblot' perseveration did not, with difference between the two correlation coefficients being significant. The functional independence between these two kinds of perseveration was further supported by the analysis of the anatomical brain damage patterns: 'additional marks' perseveration was associated with prevalent damage of the right ventral premotor cortex, of the rolandic operculum, of the right middle and superior temporal gyri, while 'inkblot type' perseveration was associated with lesions of the right prefrontal cortex and basal ganglia. The former anatomical pattern supports the view of a functional relationship between 'additional marks' perseveration and spatial neglect. Conversely, the 'inkblot' type, because of its independence of spatial neglect and its specific anatomical correlates, may be reconciled with a dys-executive disorder of motor control as other forms of *frontal* perseverations.

1.Introduction: the multifarious phenomenology of perseveration in cancellation tasks.

Perseveration has been historically defined as 'any continuation or recurrence of experience or activity without the appropriate stimulus' (Sandson and Albert, 1984). This pathological behaviour can manifest in different cognitive domains, e.g. visual, motor, sensory, or verbal perseveration (Allison and Hurwitz, 1967; Critchley, 1964; Kinsbourne and Warrington, 1963; Yamadori, 1981) and can be observed in a number of neurological or psychiatric disorders (Cohen and Dehaene, 1998; Luria, 1965). A unitary classification of perseveration is difficult, unless a very general definition is adopted like in the case of the taxonomies by Liepmann (Liepmann, 1905), Luria (1965) or Sandson and Albert (1984, 1987).

In this study, we will focus on those forms of motor perseveration elicited by the cancellation tasks typically used to explore and diagnose spatial neglect in right brain-damaged (RBD) patients (from now on, the word *perseveration* - in *italics* - will refer to these particular forms). Consider, for example, the popular cancellation task devised by Albert (Albert, 1973). During the task, patients are presented with a paper-sheet with 40 pre-drawn lines. The patient holds a pen in his/her non-paralyzed hand and he/she is instructed to cross out each line with a single pen stroke, starting from the centre of the sheet. It is worth mentioning here that on such a task, normal subjects of similar age/education as that of the patients cross each target out with a single pen-stroke, without adding redundant or irrelevant graphic productions (see also the Section 'Methods' later in this manuscript).

Different forms of *perseveration* have been described and various taxonomies have been proposed. This point deserves some clarification, as the terminology generated by the various classifications is somewhat confusing. One important distinction is between: (i) classifications based on the retrospective examination of the end product of the patients' performance on the paper sheet, like for example in Na et al. (Na et al., 1999) or in Rusconi et al. (Rusconi et al., 2002a) and, indeed,

like in the present paper; (ii) classifications that take into account the dynamics of the patients' performance (see Figure 1).

We start from the former class. The first such taxonomy was proposed by Na et al. (1999) who discriminated between two types of perseverative patterns: 'Type I' *perseveration*, when patients draw more than one mark on the same target, and 'Type II' *perseveration*, when subjects first draw new extra target-lines and then cross them out. A similar classification, but with a different terminology, was introduced by Rusconi et al. (2002). They labelled 'simple' *perseverations* those cancellation marks exceeding one single mark upon a target and those produced nearby a target (the latter have been called 'flying marks' by (Toraldo et al., 2005). Furthermore Rusconi et al. (2002) labelled as 'complex' the perseverative behaviour that Na et al. (1999) called 'Type II', together with the behaviour of adding irrelevant − not requested − graphic productions on the sheet (e.g. the patient's signature or the goose depicted in Figure 1, taken from Bottini et al., 2002). Irrelevant drawings were classified as perseverative behaviours by Rusconi at al. (2002), namely, as 'drawing activities, which continued steadfastly after the termination of the task'. The degree of complexity of the graphic productions by the patients was used as an index of *severity* of *perseveration* by Vallar et al. (Vallar and Ronchi, 2006), to be compared to the severity of spatial neglect in a correlation analysis.

Finally, and most importantly, a sizeable proportion of cancellation marks look like 'inkblots' (Toraldo et al., 2005); these are arguably the end product of back-and-forth movements of the pen-tip across the target, made without breaking of the pen-to-paper contact. Toraldo et al. (2005) proposed that this form could be reminiscent of the 'continuous' type of perseveration described by Sandson and Albert (1984, 1987) with different materials in patients with frontal lesions. Similar graphic productions had already been reported in previous works; yet, no explicit distinction had been made with other kinds of simple *perseverations*: see, for example, the performance of patient 48 in Na et al. (1999, Figure 1A, p. 1571) or the performance of patient 4 in Rusconi et al. (2002, Figure 4B, p. 599). A richer classification of perseverative behaviours may be achieved by

analysing the movements made by the patients while cancelling the targets (dynamic component of the behaviour). Kim et al. (Kim et al., 2009) recently video-recorded the patients while they were performing a cancellation task and distinguished between two different kinds of 'additional marks' perseverative behaviours: in one case a patient 'repeatedly marked through a target with consecutive but spatially distant strokes before moving to the next target' (consecutive motor *perseveration*, CMP); in another case a patient 'moved from a cancelled target to another target and then returned to cancel a previously cancelled target again' (return motor *perseveration*, RMP; p. 122). As this observation was based on three patients only (two of whom showed a significant prevalence of one behaviour over the other), it remains unknown to what extent the two behaviours contribute to the 'additional marks' end product classified in the previous literature as 'Type-I *perseveration'* (Na et al., 1999) or 'simple *perseveration'* (Rusconi et al., 2002).

Since the present study is retrospective, we could not tell between CMP and RMP; hence, to avoid confusion, we will use the term 'additional marks', meaning that a given target have been crossed out with more than a single mark.

To summarize, from the description of the admittedly obscure terminology used to classify *perseverations*, and from Figure 1, it should be clear that there is no single taxonomy covering the entire spectrum of perseveration types, and that much more clarity would be needed when specifying which method (retrospective vs on-line) has been used to classify *perseverations*. It should also be apparent that a further distinction between two types of simple perseverations, what we call 'additional marks' and 'inkblot' *perseverations*, is necessary.

A 'revisiting' behavior has also been observed in right brain damage patients with neglect in visual search and cancellation tests in which no visible trace was left over the detected targets (Husain et al., 2001). The authors were able to attribute such re-visits to a spatial working memory deficit, exactly because there was no way other than memory to recall what targets had already been explored. Clearly, re-visiting in such experimental conditions cannot be easily conceived as a form of perseveration.
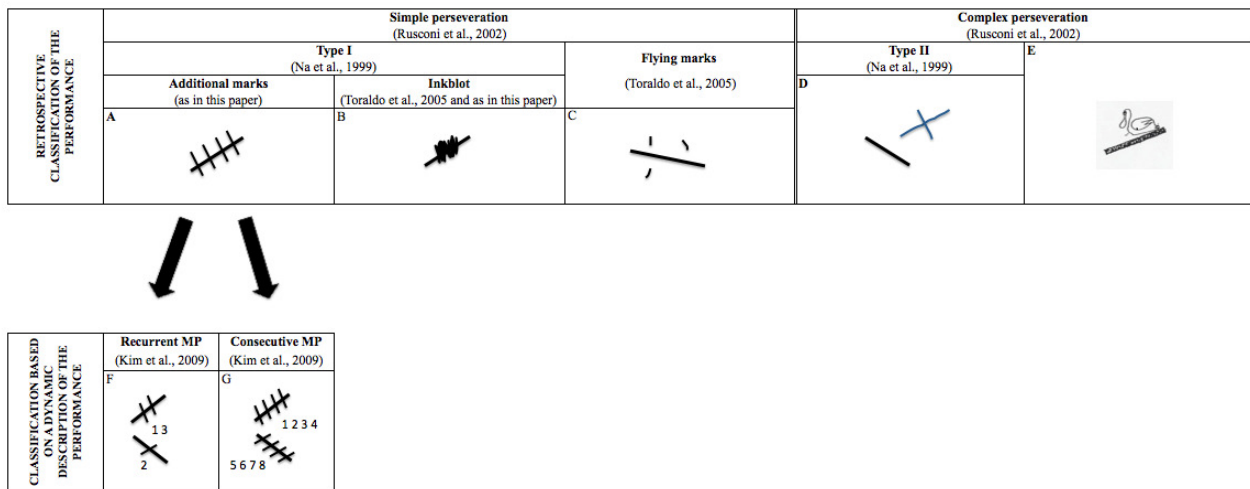
Figure 1. Classifications of perseveration. The figure illustrates the multifarious terminology used in the literature to describe perseverative behaviors observed in clinical tasks.

Perseveration in cancellation tasks is very frequently associated with right hemisphere lesions (Sandson and Albert, 1987) involving up to 30% of right brain damaged patients (Na et al., 1999); however, the probability of showing *perseveration* is massively influenced by the presence of spatial neglect: in the series reported by Rusconi et al. (2002) the symptom was observed in about 88% of the RBD patients with neglect, while it appeared in only 12% of patients without neglect.

It is interesting to note that *perseveration* occurs on what should be considered to be the *good side* for neglect patients following the metaphor proposed by Halligan et al. (Halligan et al., 1992), i.e. a region of space which should be 'normally' explored and processed.

Pathological mechanisms underlying perseveration in cancellation tasks are still debated and different interpretations have been proposed (Pia et al., 2009; Ronchi et al., 2009; Vallar and Ronchi, 2006).

The tight association between perseveration and neglect reported by many authors (Na et al., 1999; Rusconi et al., 2002) is one of the main issues. These two disorders might be functionally independent and their frequent clinical association might merely depend on the anatomical contiguity of functionally heterogeneous brain structures. The usually large lesions of

cerebrovascular patients would tend to damage both of them at the same time, thus producing the statistical association (Bottini and Toraldo, 2003). One possibility is that neglect – the omission of contralateral targets – depends on parietal structures, and graphic *perseveration* depends on frontal structures, being the result of 'motor control disinhibition' (Denny-Brown, 1958; Rusconi et al., 2002a; Vallar and Ronchi, 2006). The frequent association of frontal and parietal lesions would produce the clinical association between neglect and graphic perseveration. A different functional hypothesis is based on the evidence that, in some cases, perseveration is modulated by the presence/absence of left-sided targets. The idea is that in such cases perseveration might be due to the implicit processing of contralesional neglected targets, either because they are misperceived as located on the right side or because of a failure in the programming leftward movements (Bottini and Toraldo, 2003; Manly et al., 2002; Toraldo et al., 2005). However, recently Pia et al. (2009) studied a series of eight patients and were unable to detect an effect of neglected information on *perseveration*. In addition, the mechanism postulated by Bottini and Toraldo (2003) and Toraldo et al. (2005) cannot explain complex perseverations either, suggesting that this hypothesis cannot be elected as a complete account of the spectrum of *perseverations*.

Further support to the idea that a variety of mechanisms may underlie *perseveration* in neglect derives from studies that investigated the effect of prism adaptation (Nys et al., 2008) and monocular patching (Khurshid et al., 2009). Both techniques ameliorated only neglect, while perseveration increased or remained unchanged. Moreover the two forms of perseveration described by Kim et al. (2009: i.e. RMP an CMP; see Figure 1) were differently modulated by using shifts[3] of the background as a treatment for neglect, showing a tight link between the latter deficit and RMP only, while CMP seemed to be related to a disorder of disengaging attention from ipsilesional targets (Kim et al., 2009).

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[3] A line cancellation task was superimposed on a background of blue and white vertical stripes, which could move leftwards, rightwards, or be stationary.

To our knowledge, the anatomical correlates of different forms of *perseveration* remain to be defined.

While a right frontal and subcortical (basal ganglia) involvement is the anatomical correlate most commonly invoked for *perseveration* (Na et al., 1999; Nys et al., 2006; Pia et al., 2009; Rusconi et al., 2002), this anatomo-clinical association was proposed without taking into account the different types of *perseveration*, nor were these anatomical correlations based on more recent voxel-by-voxel statistical methods for lesion mapping.

However, the observation of different forms of *perseveration* in cancellation tasks legitimates the hypothesis that they might be due to different mechanisms and hence associated with discrete lesional correlates. In the present paper we followed this line of reasoning: thus we performed a retrospective study on a sample of 33 patients in which we identified a substantial proportion of simple *perseverations* of two aforementioned kinds, the *'additional marks'* and the *'inkblots'*. The prevalence of both kinds of perseveration and their different correlation with the severity of spatial neglect set the rationale for testing the hypothesis of the existence of discrete anatomical patterns. We reasoned that the detection of a reliable anatomical dissociation here would reinforce the hypothesis that different mechanisms operate in the generation of the two kinds of *perseveration*.

2.Materials and methods

2.1 Patients

We retrospectively selected 33 cases from a continuous series of patients who had been admitted at the Neurological Ward of the Niguarda Ca' Granda Hospital in Milano. Selection criteria were: (i) evidence of a single, vascular lesion confined to the right hemisphere, as assessed by inspection of CT scans; (ii) no history or evidence of previous cerebrovascular disease, dementia or psychiatric disorders; (iii) evidence of neglect on at least one cancellation task (see Section "Visual Neglect" below).

The patients' mean age was 68.8 (range: 39-86, SD: 10); their mean education was 6.8 (range: 0-14, SD: 3.6). Patients' demographic and clinical data are summarized in Table 1. All patients gave their informed consent to be tested, which has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964) and approved by the Local Ethical Committee of the Niguarda Ca' Granda Hospital in Milano.

All patients underwent a standard evaluation that included a neurological examination, a neuropsychological assessment, and the Mini Mental State Examination, which was used to assess global cognitive functioning (MMSE; Folstein et al., 1975) [4]. Handedness was assessed by means of the Edinburgh Handedness Inventory (EHI; Oldfield, 1971).

2.2 Neurological Examination

A standardized clinical examination for motor, sensory, and visual field deficits was administered to all patients according to the procedure proposed by Bisiach et al. (1986).

2.3 Neuropsychological assessment

2.3.1 Visual neglect

We used two tests of neglect for selecting patients: (i) a modified version of the *Albert line cancellation task* (Albert, 1973) and a (ii) a modified version of the *Diller letter cancellation task* (Diller and Weinberg, 1977). In the modified Albert test forty black lines (25 mm long and 2 mm thick) were dispersed on an A4 (297 x 210 mm) sheet of paper. The array consisted of six columns with six lines each, three on the left and three on the right side of an A4 sheet, and one central column with four lines. Thus there were 18 lines on each half of the sheet. Patients were requested to cross out all the lines on the sheet using only one mark per target. This test was also used to

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[4] The average MMSE global score adjusted for age and education was 24.1±3.5. Since the presence of neglect may affect the patients' performance in some MMSE subtests (e.g. sentence reading, attention/concentration, and figure copy), hence lowering the overall score for reasons different from generalized mental deterioration, we also included patients who presented a marginally low MMSE score, but were correctly oriented in space and time, and showed a level of comprehension sufficient to understand the rather very simple instructions of cancellation tasks.

assess the presence and type of *perseverative* responses.

In the modified Diller test the patients' task was to explore an A4 sheet printed with six rows of 52 letters each. The 312 letters were capital 3-mm-tall Times New Roman characters. Of these, 106 were H letters, and had to be cancelled out (targets), leaving out the other 206 (distractors). The targets were symmetrically distributed around the array midline (53 on each side). The Albert test was administered first; then, if the patient's clinical conditions allowed the examiner to do so, the more demanding Diller test was also administered.

All patients performed the Albert test; only 25/33 patients could also perform the Diller test.

The criteria for the diagnosis of spatial neglect were derived from the performance of a control group of healthy subjects on the same tasks. In the control group (n = 25; mean age: 60.09, SD: 6.93; range 45-74), the maximum difference between the number of left-sided and right-sided omissions was 1 for both tests. Hence patients with a left-right difference in omissions of at least 2, and in at least one of the tests, were classified as suffering from spatial neglect and thus included in the study (n = 33). Twenty-seven out of the 33 patients showed spatial neglect already at the Albert test. The remaining six patients all showed neglect on the Diller task, and had a minimum left-right difference of 7 omissions. In any event, a more accurate measurement of neglect severity was later obtained by computing the 'centres of gravity' of cancellation performances (see paragraph 2.4.1). A full description of the performance of each patient is given in Table 1.

Patients	Age	Education (years)	Onset - Assesment (days)	Neurological deficits			AHP	PN	Neglect severity		Perseveration Index		
				M	SS	V			Albert test	Diller test	AM	B	FM
P1	71	13	5	1	1	1	0	0	2.75	46.04	1.00	0.00	0.00
P2	77	3	10	0	0	0	n.a.	n.a.	2.60	n.e.	1.40	0.86	0.00
P3	75	8	10	3	3	3	3	3	3.00	48.97	1.83	0.00	0.50
P4	83	6	18	3	1	2	0	0	0.62	36.59	1.61	0.84	0.00
P5	69	5	13	3	1	1	0	0	0.00	21.99	1.03	0.00	0.00
P6	65	5	3	3	2	3	0	0	2.06	35.91	1.12	0.05	0.00
P7	68	5	20	3	0	3	0	0	-0.05	19.98	1.00	0.14	0.03
P8	86	5	0	2	0	0	0	0	0.03	37.36	1.43	0.05	0.29
P9	65	5	7	3	3	3	3	0	3.00	49.61	3.17	0.00	2.67
P10	82	13	1	3	3	3	3	3	2.67	n.e.	2.00	0.00	0.50
P11	75	5	36	3	1	1	0	0	2.00	30.50	1.00	1.00	0.00
P12	71	3	0	3	3	1	3	0	2.60	n.e.	2.00	0.10	2.00
P13	59	9	22	3	1	1	2	1	0.46	n.e.	1.20	0.73	0.00
P14	61	8	2	3	3	1	2	1	0.05	38.12	1.12	0.00	0.00
P15	67	8	2	3	3	3	0	0	2.55	45.78	1.91	0.00	0.00
P16	48	3	3	2	1	3	0	0	0.34	30.40	1.08	0.00	0.00
P17	62	5	1	3	3	0	0	0	0.02	14.97	1.00	0.00	0.03
P18	39	6	10	3	3	1	0	0	1.06	36.19	1.27	0.82	0.00
P19	62	14	11	3	3	1	0	0	0.23	18.11	1.00	0.00	0.06
P20	75	8	7	3	0	1	0	0	0.55	n.e.	1.42	0.03	0.31
P21	71	7	16	3	1	1	0	0	1.18	35.38	1.50	0.00	0.00
P22	71	3	3	2	3	3	0	0	0.00	4.68	1.00	0.00	0.00
P23	73	10	5	3	3	1	0	0	1.07	24.18	1.04	0.00	0.00
P24	78	3	8	3	3	3	0	0	1.75	47.22	2.76	0.04	0.12
P25	65	5	8	3	0	0	0	0	0.22	28.34	1.07	0.00	0.00
P26	82	0	5	3	3	0	3	0	2.00	n.e.	1.06	0.00	0.06
P27	82	5	4	2	3	3	3	0	1.62	38.35	2.00	0.17	0.00
P28	72	12	6	3	3	3	3	1	2.75	n.e.	1.13	0.00	0.13
P29	63	13	35	3	3	3	2	0	3.00	49.36	1.33	0.38	0.50
P30	72	13	11	3	0	0	0	0	2.50	21.52	1.17	0.00	0.00
P31	56	5	28	3	3	3	3	3	2.60	50.00	1.20	0.17	0.20
P32	65	8	7	0	0	0	0	0	0.00	3.46	1.00	0.00	0.00
P33	62	5	22	2	3	3	0	0	0.47	n.e.	1.41	0.02	0.14

Table 1. **Demographic and clinical data of the 33 right brain damaged patients.**
Legend: M: motor deficits; SS: somatosensory deficits; V: visual half-field deficits; AHP: anosognosia for hemiplegia; PN: personal neglect; AM: additional marks index; B: inkblot perseveration index; FM: flying marks index; n.e.: = test not performed because of sight defects; n.a.: not assessed.

2.3.2 Assessment of anosognosia for hemiplegia

Anosognosia for contralesional motor deficit was assessed by means of the four-points scale of Bisiach (1986).

2.3.3 Assessment of personal neglect

Personal neglect was assessed by asking the patients to touch their left hemiplegic hand with the right one. Each patient's performance was then given a score from 0 to 3 (Bisiach et al., 1986).

2.4 Quantitative evaluation of spatial neglect and perseveration

2.4.1. Indexes of neglect severity

To quantify neglect severity, one of the investigators (AT) developed a scoring method which considers the average position of the detected targets across the array (*centre of gravity*). Given the symmetrical distribution of targets in the array, a left-right balanced performance corresponds to a centre of gravity located at the array centre; neglect of left-sided targets produces a shift of the centre of gravity to the right, whose size is proportional to neglect severity. The procedures for estimating the centre of gravity were the following.

Albert test: each detected target was given a score reflecting its horizontal position across the sheet, ranging from -3, extreme left column, to +3, extreme right column (see Figure 2 for an example). The average score out of all detected targets was the estimate of the centre of gravity, i.e. our index of neglect severity. This ranged from -3, extreme right neglect, to 0, no neglect, to +3, extreme left neglect.
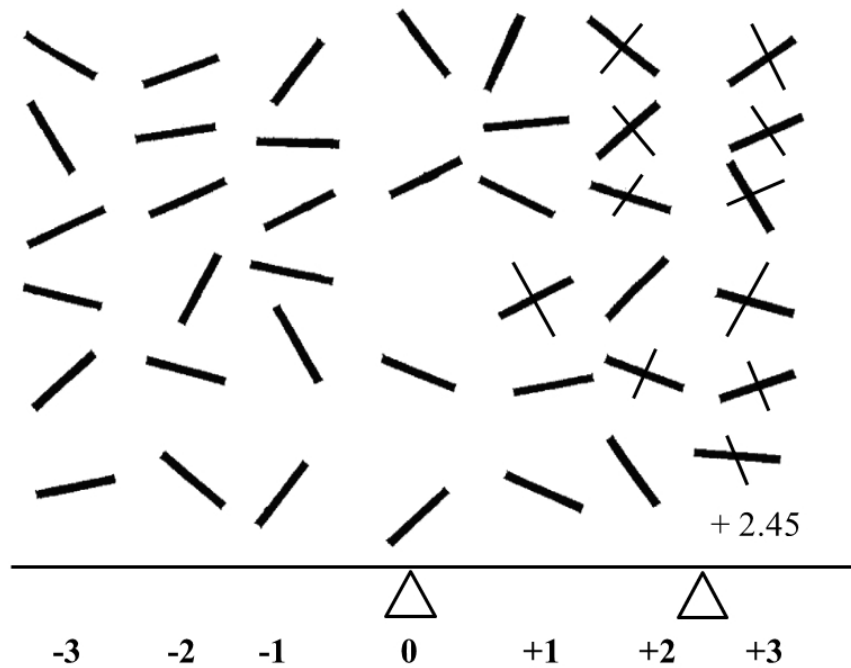
Figure 2. Schematic representation of the procedure used to calculate the *centre of gravity* of the detected targets in the modified version of the Albert test, also called 'neglect severity index' in the manuscript. In this particular case, the positions of the 11 detected targets were: +1, +2, +2, +2, +2, +3, +3, +3, +3, +3, +3; the average position was +2.45, witnessing a marked neglect (the maximum score is +3).

Diller test: to measure neglect severity on the Diller task, we used the same logic. Thus the position of each target (letter H) was measured in mm with respect to the centre of the display, and the average position of cancelled targets was computed. This centre of gravity was then normalized into a percentage score, with 0% indicating the display centre, -50% the leftmost letters' positions and +50% the rightmost letters' positions, with 100% being the overall horizontal extent of the display. Hence +50% indicates extreme left neglect, -50% extreme right neglect, 0% no neglect.

Both neglect severity indices are reported in Table 1.

2.4.2 Types of perseveration

On the basis of the patients' behaviour on the modified Albert test, we retrospectively identified well distinct types of perseveration:

(i) *'Additional marks' perseveration*, when patients crossed a target line with more than one distinct mark [5] (Figure 1A).

(ii) *'Inkblot' perseveration*, when patients produced cancellation marks that are so crowded as to be indistinguishable from an inkblot – these have most likely been produced with a continuous gesture, without breaking the pen-to-paper contact (Figure 1B) as described by Toraldo et al. (2005).

(iii) *'Flying' marks*, when patients produce cancellation marks which do not touch any target, and thus lie in an empty region of the sheet (Figure 1C; see for an example performance of the patient EZ in Toraldo et al., 2005; p.229).

We also observed other types of perseveration, previously described in literature. Two patients drew extra targets and then crossed them out (Type II perseveration in Na et al., 1999; 'complex' perseveration in Rusconi et al., 2002; 'score 3' in the scale proposed by Vallar et al., 2006). Furthermore, three patients in our sample produced, together with other forms of perseveration, complex drawings (such as, for example, drawings of animals, their own signature or other irrelevant writings close to the targets or in empty regions of the sheet). As this kind of behaviour was observed in a limited number of patients, we did not consider these productions for further analyses.

2.4.3 *Indices of perseveration*

To quantify the degree of perseveration we used three indices, which were mutually independent from the mathematical viewpoint: the 'additional marks' perseveration index (AM index), the 'inkblot' perseveration index (B index) and the 'flying' mark index (FM index):

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[5] Since we did not video-record the patients' performance, this category potentially includes the types of perseveration classified as *return* or *consecutive* perseveration by Kim et al. (2009).

(i) ***'Additional marks' perseveration index (AM index)***. To compute the AM index, we divided the number of marks produced on the targets by the overall number of cancelled targets.

(ii) ***'Inkblot' perseveration index (B index)***. The B index was defined as the proportion of 'inkblots' out of the overall number of cancellation marks produced on targets. Thus for instance if 10 out of 40 marks produced on targets were inkblots, B equalled 0.25.

(iii) ***'Flying' marks index (FM index)***. We defined as 'flying' (FM) a mark drawn on the sheet which does not overlap any target by any degree. We then divided the number of 'flying' marks by the number of detected targets, in order to obtain a measure of the density of 'flying' marks in the empty area explored by the patient. As only a minority of patients presented with this particular form of perseveration, these data were used only in the analysis of correlations between different forms of perseveration and neglect severity.

2.5 Lesion mapping

Brain lesions were identified by computerized tomography (CT) and mapped, using a computerized method, in the stereotactic space of the Montreal Neurological Institute as defined by the templates released with SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). For each patient, we carefully selected the CT scan (normally, from a series of 2-3 scans) which best showed the lesion. Usually this was the one collected in a sub-acute phase.

Brain lesions were mapped using a standard MRI volume (voxels of 1 mm^3) that conformed to that stereotactic space. Images' manipulations were performed with the free software MRIcro (Rorden and Brett, 2000; www.mricro.com). The mapping procedure included the following steps:

1. *Adaptation of the MRI template to the patient's CT scan*. The standard MNI template was rotated on coronal, sagittal and horizontal planes to conform to the patients CT acquisition angle using, typical landmarks as the ventricles, the frontal and temporal lobes and the cerebellum.

2. *Lesion mapping*. A skilled rater (MG), using anatomical landmarks, manually mapped the lesion onto each correspondent template slice. A second skilled rater (EP) double-checked for the accuracy of the tracings for each patient. In cases of disagreement, an intersection lesion map was used.

3. *Lesion re-orientation*. The lesion maps, stored as binary images, were then rotated back into the standard space using the inverse of the transformation parameters used on the stage of template adaptation to the patient brain scan.

4. *Statistical analysis*. We used the Brunner-Munzel test implemented in the NPM program distributed with the MRIcron package (Rorden et al., 2007). By using this test, the presence/absence of damage in a given voxel is used as a classifying criterion that separates subjects as having or not-having the lesion, while the behaviour is the dependent variable scrutinized for significance by the non-parametric test: accordingly, in each voxel, the statistical maps visualizes the significance of a behavioural difference between two groups of subjects identified on the ground of having or not-having a lesion. The anatomical distribution of the statistical results was assessed using the Automated Anatomical Labelling map (template AAL; Tzourio-Mazoyer et al., 2002) which classifies the anatomical distribution of digital brain images in stereotactic space.

5. *Identification of white matter involvement*. Identification of the regional distribution of the white matter damage was made thanks to the JHU-white matter labels template (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007) distributed with the software MRIcron (www.mricron.com). This template, while allowing the identification of some important fasciculi and their subdivisions, does not provide a full classification of the white matter of the cerebral hemispheres. For lesions of white matter regions not classified by the atlas, we referred to the classical lobar subdivision of the cerebral hemispheres.

3. Results

Ninety-one % of the patients presented with at least one type of perseveration (AM, BLOT or flying marks perseveration).

3.1. Correlation between types of perseveration and neglect severity

Using the non-parametric Spearman's rank correlation test (see Table 2), we found a positive correlation between 'additional marks' *perseveration* and neglect severity at both the Albert and the Diller test. Conversely, no significant correlation was found between 'additional marks' and 'inkblot' *perseveration* and between 'inkblot' *perseveration* and neglect severity indexes. We also found a positive correlation between the AM index and the density of 'flying' marks; 'flying' marks also correlated with neglect severity indexes. 'Flying' marks perseveration did not provide enough statistical power for the subsequent anatomoclinical correlation analysis. Only 'additional marks' behaviour, which was observed more frequently, was included in that analysis, bearing in mind its high correlation with the 'flying' marks index.

		Albert neglect severity	Diller neglect severity	'Additional marks'	'Inkblots'
Diller neglect severity	*Rho*	.767**			
	Two-tailed p	<.001			
	N	25			
'Additional marks'	*Rho*	.506**	.739**		
	Two-tailed p	.003	<.001		
	N	33	25		
'Inkblots'	*Rho*	.093	.320	.229	
	Two-tailed p	.605	.119	.200	
	N	33	25	33	
'Flying marks'	*Rho*	.391*	.441*	.437**	.000
	Two-tailed p	.025	.027	.011	1.000
	N	33	25	33	33

Table 2. Non-parametric Spearman's rank correlation test within the set of behavioural variables.

We carried out a Monte Carlo simulation study to learn whether the correlation between Neglect Severity at the Albert test and 'additional marks' was significantly higher than the correlation between Neglect Severity at the Albert test and 'inkblot' perseveration. To do so, we generated 10,000 samples from bivariate distributions having the same Neglect Severity, 'additional marks' and 'inkblots' values as the real sample, under the null hypothesis that both Rho correlation coefficients were identical and equalled the average Rho found experimentally (the correlation coefficients were controlled by manipulating the level of noise in the random extraction of AM and 'inkblots' values). The observed difference between the two Rho coefficients, $(.506 - .093) = .413$, was significantly higher than the differences obtained from the simulation, with one-tailed p = .023. We repeated the procedure using the Diller Centre of Gravity as a measure of Neglect Severity, and again obtained that the Rho difference, $(.739 - .32) = .419$, was significantly higher than expected under null hypothesis (one-tailed p = .009).

3.2. Lesion analysis

We failed to find significant correlations between total volume of brain damage and different types of perseveration (AM index: Rho: .183; one-tailed p value= .307; B index: Rho: .267; one-tailed p value= .133).

However, discrete anatomical patterns were found for the two different classes of *perseveration*. 'Additional marks' *perseveration* was associated with lesions of the right rolandic operculum, the precentral and postcentral gyri, the inferior frontal gyrus (opercular part), the insula, the superior and middle temporal gyri (also including the Heschl gyrus; Table 3; Figure 3) and the white matter. The topographical analysis of the white matter damage, performed by using the JHU template, indicated the involvement of the superior longitudinal fasciculus (SLF).
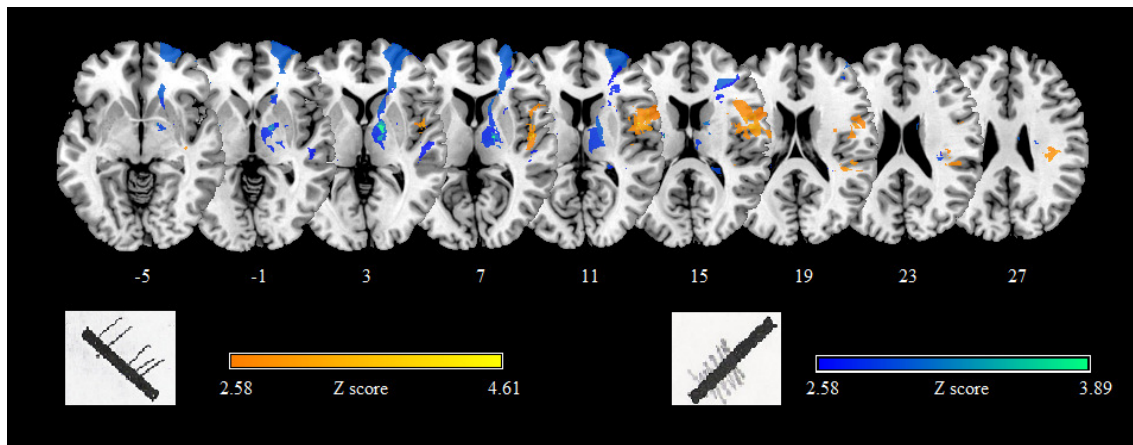
Figure 3. Brain regions significantly associated with different types of perseveration in patients with neglect. Voxels that survived to the statistical threshold of p <.005 uncorrected for multiple comparisons are shown. The colour scale illustrates the corresponding Z score values. MNI z coordinates of each transverse section are reported.

Brain region	Voxel count at BM test	Z-score	MNI coordinates		
	P < .005		X	Y	Z
Precentral gyrus	225	3.0	53	0	20
Inferior frontal gyrus (opercular part)	1343	3.1	60	17	7
Rolandic operculum	2927	4.6	48	2	10
Insula	269	4.1	48	-7	7
Postcentral gyrus	151	3.1	60	-1	18
Heschl gyrus	275	4.1	47	-10	7
Superior temporal gyrus (STG)	501	3.5	51	-1	4
Middle temporal gyrus (MTG)	106	2.8	46	0	-16
Other not cortical areas	903	3.9	41	-22	26

Table 3. Results for the VLSM analysis: additional marks perseveration. The table reports brain regions significantly associated with the additional marks perseveration index, the total number of voxels significant at the statistical threshold of p<.005 uncorrected, and the maximum Z-score. The MNI coordinates of the most significant voxels are also reported. Other not cortical areas: subcortical white matter regions not included in the AAL template.

Conversely, 'inkblot' perseveration was associated with lesions of the superior and middle frontal gyrus, orbitofrontal cortex, basal ganglia, thalamus and superior temporal gyrus (Figure 3; Table 4).

The topographical analysis of the damage in the white matter indicated the involvement of the internal capsule (anterior and posterior limb) and of the anterior corona radiata.

Brain region		Voxel count at BM test	Z-score	MNI coordinates		
		p < .005		x	y	z
Superior frontal gyrus		1701	3.0	23	54	-2
Middle frontal gyrus		1851	3.0	28	52	-1
Orbitofrontal cortex	Superior	1553	3.0	13	67	-17
	Middle	371	3.0	22	63	-17
	Medial	237	3.0	11	52	-14
Basal ganglia	Caudate	630	3.4	14	6	13
	Putamen	182	3.1	27	0	-3
	Pallidum	320	3.9	17	-1	3
Thalamus		2151	3.9	17	-9	4
Superior temporal gyrus		636	3.5	70	-9	11
Other not cortical areas		4047	3.9	18	-6	3

Table 4. Results for the VLSM analysis: 'inkblot' perseveration. Table reports brain regions significantly associated with the 'inkblot' perseveration index, the total number of voxels significant at the statistical threshold of p < .005 uncorrected, and the maximum Z-score. The MNI coordinates of the most significant voxels are also reported. Other not cortical areas: subcortical white matter regions not included in the AAL template.

4. Discussion

The aim of this study was to investigate the relationships between different perseverative manifestations and the deficit of contralesional exploration observed in neglect patients in cancellation tasks, at both the behavioural and the anatomical level. This is precisely the level of inference that we propose here, aware as we are that spatial neglect is a multifarious syndrome

characterized by a variety of dissociable behaviours depending, for example, on the spatial frame of reference (personal, peripersonal and extrapersonal), and the specific task under consideration (for a review, see for example (Parton et al., 2004; Vallar, 2001).

As far as *perseveration* in cancellation tasks is concerned, the main debate is whether or not *perseveration* and contralesional omission could be accounted for by a single factor mechanism (i.e., is *perseveration* a mere by-product of spatial neglect?). Our study confirms a high incidence of perseverative responses in patients with extrapersonal neglect, as reported in previous studies (Na et al., 1999; Nys et al., 2006; Rusconi et al., 2002). In our sample, 91% of neglect patients presented with at least one type of perseveration on the Albert cancellation task (see Table 1). This is a very high rate, especially if one considers the low frequency of perseveration errors observed in right brain damaged patients without neglect reported in previous studies (Nys et al., 2006; Ronchi et al., 2009; Rusconi et al., 2002).

We also observed a strong correlation between the severity of neglect in cancellation tasks and the '*additional marks' perseveration*, as found in some previous studies (e.g. Bottini and Toraldo, 2003; Manly et al., 2002). A similar correlation was found between neglect severity and the density of 'flying' marks, i.e. marks produced in the empty space between targets.

In contrast with our results, other studies (Pia et al., 2009; Ronchi et al., 2009; Vallar et al., 2006) showed no relationship between omissions in cancellation tasks and the intensity of perseveration. This discrepancy may derive from a variety of methodological factors such as, for example, the technique used to quantify perseveration (density of perseverations versus number of perseverations; for further discussion, see Toraldo et al., 2005), the type of targets (lines, circles, letters or stars), the density of targets and the presence of distractors. Moreover, the failure to find a significant correlation between omissions and perseveration errors in previous studies might be related to low statistical power due to small patient sample sizes.

More crucially, our data revealed that only certain kinds of perseveration correlate with neglect severity: in our study, a significant correlation was found with '*additional mark' perseveration* but

not with '*inkblot' perseveration*. Even though occasionally seen, '*flying' marks perseveration* also correlated with neglect severity. Our results are therefore in keeping with the proposal previously made by Kim et al. (2009) in an attempt of explaining divergent data in the literature.

Is it possible to provide a functional interpretation of the mechanisms underpinning the different kinds of perseveration?

The more frequent type of perseveration observed in neglect patients, the 'additional marks' type, may be interpreted as the consequence of a two-factor mechanism, whereby a 'frontal' deficit interacts with the spatial bias typical of neglect (Rusconi et al., 2002; Vallar et al., 2006) or alternatively by the more parsimonious hypothesis of a single pathological mechanism related to neglect: patients would perseverate as a consequence of an *allochiric perceptual transposition* of left sided stimuli or because of a *directional hypokinesia* (Bottini and Toraldo, 2003; Toraldo et al., 2005).

Different strategies can be followed to address this issue. For example, Bottini and co-workers (Bottini and Toraldo, 2003; Toraldo et al., 2005) documented a modulatory effect by the number of left sided stimuli on perseveration on the right side of space and searched for correlations between neglect severity and perseveration.

Here we used a combined qualitative analysis on different kinds of perseverations and their differential correlation with neglect severity; in addition, we used an anatomo-clinical correlation approach, in an attempt to identify discrete anatomical correlates for the different kinds of perseveration.

The results of this effort were clear-cut. The '*additional marks*' perseveration, which strongly correlated with neglect severity in cancellation tasks, was associated with damage to cortical and subcortical brain regions known to be involved in neglect, such as the superior temporal gyrus (Karnath et al., 2001; Karnath et al., 2004), the rolandic operculum (Karnath et al., 2011), the premotor cortex and the opercular part of the inferior frontal gyrus (see for a review Figure 1, p. 28 in (Husain and Rorden, 2003), and the white matter fibres of the superior longitudinal fasciculus

(Bartolomeo et al., 2007; Doricchi et al., 2008). This anatomical pattern notably spares prefrontal cortex and/or the subcortical structures connected to it, making it more unlikely that 'additional marks' perseveration, at least in its pure manifestation, requires an additional prefrontal dysfunction to emerge.

On the contrary, the frequency of *'inkblot' perseveration*, uncorrelated with the severity of spatial neglect, was associated with a prefrontal and subcortical lesion pattern including the thalamus and the basal ganglia, suggesting the contribution of a specific, higher-order dysfunction of motor control. This form of perseveration appears to be independent of neglect and may be caused by a deficit in inhibiting an initiated motor response. This behaviour is similar to what has been labelled in many different ways in the literature - *efferent motor perseveration* (Luria, 1965), *clonic perseveration* (Liepmann, 1905) or *continuous perseveration* (Sandson and Albert, 1987) - and has been associated with frontal or/and basal ganglia lesions (Luria, 1965; Sandson and Albert, 1987). An association between this kind of perseveration and a frontal lesion extending to the basal ganglia has been described, for example, in the seminal paper by Luria (1965) where he suggested that this kind of perseveration is due to a deficit in the inhibition of an initiated efferent motor activity: the resulting performance is illustrated, for example, in his Case 1 (Luria, 1965; Figure 1; Plate 1, performance 2).

Furthermore, the prefrontal cortex, with a right hemisphere lateralization (Casey et al., 1997; Garavan et al., 1999; Rieger et al., 2003), and the basal ganglia are involved in response inhibition as demonstrated by lesional, electrophysiological and neuroimaging studies in humans, and by data emerging from animal studies. A role of basal ganglia in the inhibition of ongoing responses also emerges from the study of patients with Parkinson disease, e.g. (Cooper et al., 1994).

To summarize, our data strongly suggest the existence of (at least) two dysfunctional mechanisms producing perseveration in neglect. One mechanism, linked to a first set of areas (rolandic operculum, superior temporal cortex, premotor cortex), produces 'additional marks' perseveration, which in turn is statistically correlated with neglect severity. A second mechanism, anatomically

determined by a lesion of the prefrontal cortex and basal ganglia, produces 'inkblot' perseveration, which is *not* statistically related to neglect severity. The straightforward inference is that the latter mechanism does not entail anything spatial in nature, but rather, relates to aspects of motor control. An ideal candidate is a mechanism of action monitoring (Luria, 1965), whose disruption leads to inability to stop an initiated motor response – hence the inkblots. The other mechanism, producing additional cancellation marks, is related to the intensity of the lateral spatial bias, measured using cancellation tasks. Hence possible candidates are neglect-related phenomena, like the inability to disengage attention from the right side (Posner et al., 1984), visual allochiria or directional hypokinesia (Toraldo et al., 2005).

The proposed distinction between two systems/dysfunctions can explain the discrepancies across studies concerning, for instance, the relationship between perseveration and neglect severities (Bottini and Toraldo, 2003; Na et al., 1999; Pia et al., 2009; Ronchi et al., 2009; Rusconi et al., 2002; Toraldo et al., 2005), the effect of the presence of left sided targets on the severity of perseveration (Bottini and Toraldo, 2003; Manly et al., 2002; Pia et al., 2009; Toraldo et al., 2005) and the effect of physiological manipulations (Khurshid et al., 2009; Nys et al., 2008; Vallar et al., 2006).

Our interpretation can also account for the performance of patients with mixed behaviour (more than an 'inkblot' perseveration on the same target). In these cases, a combination of factors would contribute to the performance: while cancellation of the same target with multiple marks might be induced by neglect-related phenomena (failure to disengage attention; directional hypokinesia; see (Posner et al., 1984; Toraldo et al., 2005) an additional frontal-basal ganglia involvement might prevent the patient from interrupting the production of each cancellation mark, thus leading to the generation of inkblots.

Our interpretation is also compatible with cases in which omissions are observed without perseveration and cases in which perseverations are observed without omissions (Na et al., 1999; Rusconi et al., 2002). In the first situation, one can hypothesize forms of 'perceptual neglect' (see

(Bisiach et al., 1990a; Toraldo et al., 2004), uncomplicated by allochiria or hypokinesia. Conversely, perseverative responses observed in patients without neglect would be explained by assuming isolated damage to the pre-frontal-basal ganglia system; in functional terms, these patients would suffer from defective monitoring of complex motor behaviours, leading to perseveration.

One final remark is to be made here. Lesion to the frontal-basal ganglia system has been assumed to disrupt the ability to stop an initiated motor response – hence the production of 'inkblot' perseverations. However, this lesion is likely to produce a range of monitoring deficits, among which, possibly, the inability to inhibit a *new* motor act – like that of re-marking an already cancelled target. Thus, we do not exclude that the frontal-basal ganglia system also contributes to additional mark perseveration, although such behaviour is unlikely to be the dominant one. In any event, the prediction of this scenario is that, among patients *without* neglect and with frontal-basal ganglia lesions, patients should be found who show additional mark perseveration, albeit such patients should be less frequent than patients with 'inkblot' perseveration. This conjecture requires further anatomical and behavioural studies.

SECTION 2

PERSONAL SPACE

3. Chapter 3. An anatomical account of somatoparaphrenia. (⁶).

Abstract

Somatoparaphrenia is a delusional belief whereby a patient feels that a paralyzed limb does not belong to his body; the symptom is typically associated with unilateral neglect and most frequently with anosognosia for hemiplegia. This association of symptoms makes anatomical inference based on single case studies not sufficiently specific. On the other hand, the only three anatomical group studies on somatoparaphrenia are contradictory: the right posterior insula, the supramarginal gyrus and the posterior corona radiata, or the right medial or orbito-frontal regions were all proposed as specific lesional correlates. We compared 11 patients with and 11 without somatoparaphrenia matched for the presence and severity of other associated symptoms (neglect, motor deficits and anosognosia). To take into account the frequent association of SP and neglect and hemiplegia, patients with and without somatoparaphrenia were also compared with a group of fifteen right brain damage patients without neglect and hemiplegia. We found a lesion pattern involving a fronto-temporo-parietal network typically associated with spatial neglect, hemiplegia and anosognosia. Somatoparaphrenic patients showed an additional lesion pattern primarily involving white matter and subcortical grey structures (thalamus, basal ganglia and amygdala). Further cortical damage was present in the middle and inferior frontal gyrus, postcentral gyrus and hippocampus.

We propose that somatoparaphrenia occurs providing that a distributed cortical lesion pattern is present together with a subcortical lesion load that prevents most sensory input from being processed in neocortical structures; involvement of deep cortical and subcortical grey structures of the temporal lobe may contribute to reduce the sense of familiarity experienced by somatoparaphrenic patients for their paralyzed limb.

1.Introduction

Somatoparaphrenia (SP), mostly associated with right brain damage and spatial neglect [7], is characterized by delusions concerning the contralesional paralyzed body parts, including feelings of non-belonging and the tendency to attribute parts of the own body to someone else (Gerstmann, 1942) [8]. SP has attracted the curiosity of many students of spatial neglect, body representation and conscious processes. The tight link between SP and unilateral neglect, and its joint remission following left cold caloric vestibular stimulation (Bisiach and Geminiani, 1991a; Rode et al., 1992), motivated the unitary interpretation proposed by Bisiach and co-workers whereby all these phenomena are explained as a consequence of a global spatial misrepresentation (dyschiria; (Bisiach and Berti, 1987; Bisiach and Berti, 1995; Zingerle, 1913). On the other hand, Halligan et al. (Halligan et al., 1995)(1995), in line with Gazzaniga's interpretation (Gazzaniga, 1989; Gazzaniga, 1995) of split-brain patients behaviour, suggested that SP may also arise from an inter-hemispheric disconnection, much as Geschwind proposed for anosognosia for hemiplegia (AHP; (Geschwind, 1965a): the left hemisphere, an interpreter or narrator in charge for providing verbal descriptions about the state of left paralyzed limbs, deprived of somatosensory evidence about them, would try to make sense of conflicting information such as the sight of a proximal limb without any feeling for it. However, this interpretation leaves open the question on the nature of the distorted information received by the interpreter and the mechanisms whereby an inter-hemispheric disconnection may lead either to AHP or to SP or to both. Furthermore, this interpretation cannot explain why SP patients, when asked about the ownership of their left limb, do not simply say they do not recognize it, rather they claim that it belongs to someone else. This productive component of the SP symptomatology (see (Bottini et al., 2009) for a discussion of productive/positive symptoms

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[7] There are only few cases of SP without motor (Anton, 1893; Cereda et al., 2002) and proprioceptive impairments (Nightingale, 1982; Starkstein et al., 1990); on the other hand dissociations from sensory and visual deficits and anosognosia for hemiplegia (AHP) are relatively more frequent (see references cited by Vallar and Ronchi, 2009).

[8] Gerstmann grouped under the label "somatoparaphrenia" a variety of "positive psychopathologic phenomena" also including illusions, distortions or confabulations concerning the affected body parts (Gerstmann, 1942).

in neuropsychology) makes it unlikely a simple lack of afferent information as the causal and sufficient mechanism for the delusion, rather one may hypothesize that the delusion may involve a complex mechanism that impairs the ability to integrate a corrupted or globally missing sensory-motor information in a coherent and emotionally congruent body representation. May these hypotheses find support from anatomical investigations as in other domains of neuropsychology? This remains to be established. Indeed, while spatial neglect as a syndrome (Bartolomeo et al., 2007; Doricchi et al., 2008; Doricchi and Tomaiuolo, 2003; Karnath et al., 2001; Karnath et al., 2004; Mort et al., 2003; Vallar and Perani, 1986), or in some of its specific manifestations (Committeri et al., 2007; Karnath et al., 2003; Sapir et al., 2007; Vallar et al., 1994; Verdon et al., 2010) including AHP (Berti et al., 2005; Fotopoulou et al., 2008; Karnath et al., 2005), has been studied systematically at the anatomical level, the anatomical correlates of SP are still not well defined. The data mainly derive from single case reports generally showing an extensive fronto-temporo-parietal lesion (see review in (Vallar and Ronchi, 2009). However, there are also cases on record with a more focal cortical or subcortical damage (e.g., a lesion confined to right basal ganglia, thalamus and subcortical white matter; (Bisiach and Geminiani, 1991a; Halligan et al., 1993; Healton et al., 1982). The few lesion-mapping group studies on SP available at present provide contrasting results (Baier and Karnath, 2008; Feinberg et al., 1990; Feinberg et al., 2010). These inconsistencies may depend on a number of methodological variables such as, for example, the different inclusion criteria and lesional mapping techniques across studies. Feinberg et al. (1990) found an involvement of the supramarginal gyrus (SMG), the posterior corona radiate (Feinberg et al., 1990) and in a more recent study, of the right medial and orbito-frontal areas (Feinberg et al., 2010). In particular, in this last study the authors suggested the existence of a discrete anatomical pattern for different degrees and types of asomatognosia and somatoparaphrenia: while the lesion of the medial frontal cortex would be crucial for the development of asomatognosia in general, orbito-frontal lesions were associated to somatoparaphrenia (defined by the authors as a subtype of asomatognosia associated with a

delusional misidentification and confabulation). Conversely, Baier and Karnath (2008) correlated the "disturbed sensation of limb ownership" (DSO) with a lesion in the right posterior insula. Nevertheless, in these studies the presence of AHP has not been formally assessed (Feinberg et al., 2010) or the control group was not matched for the presence of this crucial variable (Baier and Karnath, 2008). In fact, in the study of Baier and Karnath (2008) the comparison between patients with AHP plus DSO and patients without AHP and with DSO, didn't allow to isolate the anatomical substrate of DSO independently from anosognosia. In order to study the anatomical correlates of somatoparaphrenia, we believe that a more crucial comparison would be that with the closest clinical condition namely patients matched for presence and severity of unilateral neglect, hemiplegia and anosognosia without somatoparaphrenia. Here, we readdress the issue of the anatomical correlates of SP: we adopted strict inclusion criteria and we recruited only patients with a "delusional belief concerning the sense of ownership of contralesional body parts" (Bottini et al., 2002; p. 249); on the other hand, we excluded other forms of body delusions, such as for example kinaesthetic hallucinations and supernumerary phantom limb. Furthermore, to make our anatomical inference as strict as possible, the lesion distribution of SP patients was compared with the one of patients fully matched for neurological and neuropsychological deficits with the exception of the presence of SP.

2. Materials and methods

2.1. Subjects

From a series of right brain damaged patients admitted to the Stroke Unit Department of Niguarda Ca' Granda Hospital from 1997 to 2009[9] ,we retrospectively selected a group of eleven patients who had shown a disorder of the ownership of contralesional paretic limb due to an acute cerebral ischaemic or haemorrhagic lesion (mean age: 70 +/- 8 years, range 56-82; mean education: 7 +/- 4 years, range 2-16; days from onset: 9 +/- 7, cases P1-P11, Table 1). All patients with SP presented

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[9] We excluded patients with a history or evidence of previous cerebrovascular disease, dementia or psychiatric disorders.

complete left hemiplegia and extrapersonal neglect. From the same series of brain injured patients, we selected a control group including eleven patients with stroke (mean age: 67 +/- 14 years, range 36-82; mean education: 6 +/- 4 years, range 0-13; days from onset: 6 +/- 5) without SP (cases P12 - P22, Table 1), matched for the presence of extrapersonal neglect and severity of the motor deficit and for the presence/absence and severity of AHP. The two groups were also comparable for the presence of sensory deficit and visual field defects. The Mini Mental State examination (MMSE; (Folstein et al., 1975) scores of the two groups were also balanced (SP+: mean 21.7; SD: 5.3; SP-: mean 23.2; SD: 4.3; unpaired t-test (20): .7; p= .46].

For our anatomical analyses, a group of 15 right brain damaged patients without neglect nor sensory-motor or visual deficit with a documented computerized tomography (CT) lesion (mean age: 64 +/- 11 years, range 43-81; mean educational: 9 +/- 3 years, range 5-13) was also included.

This was used as a control group for the twenty-two afore mentioned neglect patients in order to identify the common lesional pattern associated with the occurrence of neglect and hemiplegia. All patients gave their informed consent to participate in the study, which has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964) and approved by the Local Ethical Committee of the Niguarda Ca' Granda Hospital of Milano.

Groups	Patients	Aetiology	SP	Standard neurological examination			AHP	PN	N
				Motor deficits	Sensory deficits	Visual field deficits			
Patients with SP	P1	I	+	3	3	3	3	3	+
	P2	I	+	3	3	3	3	1	+
	P3	I	+	3	3	3	3	3	+
	P4	I	+	3	1	3	1	1	+
	P5	I	+	3	3	3	2	2	+
	P6	I	+	3	3	3	3	2	+
	P7	E	+	3	3	0	3	1	+
	P8	E	+	3	3	3	3	3	+
	P9	E	+	3	3	3	1	2	+
	P10	E	+	3	3	1	0	2	+
	P11	E	+	3	3	3	2	2	+
Patients without SP	P12	I	-	3	3	3	3	3	+
	P13	I	-	3	3	1	3	0	+
	P14	I	-	3	3	2	3	0	+
	P15	I	-	3	3	2	1	1	+
	P16	I	-	3	3	3	2	3	+
	P17	I	-	3	3	3	3	0	+
	P18	E	-	3	3	0	3	0	+
	P19	E	-	3	3	3	3	0	+
	P20	E	-	3	3	3	1	1	+
	P21	E	-	3	3	0	0	0	+
	P22	E	-	3	3	1	2	1	+

Table 1: Neurological and neuropsychological deficits of patients with and without SP. N= extrapersonal neglect; PN= personal neglect; SP= somatoparaphrenia; E= haemorrhagic aetiology; I= ischaemic aetiology; AHP=anosognosia for hemiplegia; + presence of the deficit;; - absence of the deficit. 0= absence of the deficit; 3= maximum deficit. For further details see the main text.

2.2. Neurological assessment

Patients were assessed for (i) global cognitive functioning (MMSE; Folstein et al., 1975), (ii) hand-dominance (Oldfield, 1971), (iii) presence and severity of neurological deficits, (iv) of extrapersonal and personal neglect, (v) of awareness of the deficits (anosognosia), (vi) of false beliefs concerning the contralesional body parts. Neurological deficits were assessed by means of a standardized evaluation (Bisiach et al., 1986) and given a score from 0 (no deficit) to 3 (severe deficit). All patients with SP (cases P1-P11, Table 1) and without SP (cases P12-P22, Table 1) showed a severe contralesional hemiplegia (score 3/3). Patients' scores for tactile and visual modalities are shown in Table 1.

2.3. Neuropsychological assessment

2.3.1. Extrapersonal neglect

Extrapersonal neglect was assessed with the following tests: (i) Albert line cancellation test (Albert, 1973): a two or more targets omissions difference between left and right was used as an indication of the presence of spatial neglect (N+). (ii) Diller H cancellation test (Diller and Weinberg, 1977): patients were diagnosed as N+ in case of four or more Hs omissions difference between left and right sided stimuli. A pathological performance in at least one of the above tests was considered as a sign of neglect (see Table 1).

2.3.2. Personal neglect

Personal neglect was assessed by asking the patients to touch their left hemiplegic hand with the right hand. Patients' performance was scored from 0 to 3 as follows (Bisiach et al., 1986):

 0. The patient promptly reaches for the target.

1. The target is reached with hesitation and search.

2. The search is interrupted before the target is reached.

3. No movement towards the target is performed.

2.3.3. Anosognosia

Anosognosia for the motor deficit was assessed by means of a four-points scale (Bisiach et al., 1986):

0. Complete awareness of the deficit. The disorder is spontaneously reported or mentioned by the patient in reply to general questions about his complaints.

1. The disorder is reported only following specific questions about the strength and the ability to move of the contralesional affected limb.

2. The disorder is acknowledged only after its demonstration through the neurological examination.

3. Severe anosognosia. No acknowledgement of the disorder can be obtained even with demonstration.

2.3.4. Somatoparaphrenia

SP was investigated by means of an interview progressively tackling the delusional disorder. The experimenter brought the patient's left arm in the mid-sagittal plane and asked her/him: "Whose armis this?" In the event that the patientmisattributed his/her hand to someone else, we also asked: "Why a hand belonging to someone else is laying here?"; "Where is your hand?" In addition we also noted whether the symptom was persistent in spite of the attempts of the examiner to "explicitly" demonstrate to the patient that his/her hand was physically connected to his/her body. Patients were included in the somatoparaphrenic group if they firmly denied that the arm belonged to them and/or attributed it to someone else. All patients in our sample presented an elaborated and repeated confabulatory delusional content. They constantly attributed the left hemiplegic arm/hand to someone else (a doctor, a relative etc.), with the exception of the case P4 who was unable to identify a precise person as the owner of the hand. Even if she did not attribute the arm to someone else the denial of ownership was persisting and refractory to correction (see P4 verbalizations in Appendix). To maximize the chance of detecting a specific anatomical pattern for SP, by design ,we chose to select SP+ cases with a clear-cut ownership disorder rather than cases with milder symptoms such as, for example, feeling of alieness towards the contralesional limb (Bisiach and Geminiani, 1991b). Patients in the SP- group were able to promptly recognize the affected limb as their own with no hesitation and did not present any occasional feelings of non-belonging or strange sensations (such as for example alienation or sensation of fading away) about the limb. The verbalizations of patients with SP are reported in the Appendix.

2.4. Lesion mapping

Brain lesions were identified by CT and mapped, using a computerized method, in the stereotactic space of the MNI as defined by the templates released with SPM2 (Statistical Parametric Mapping,

Wellcome Department of Imaging Neuroscience, London, UK). The brain lesions were mapped using a standard MRI volume (voxels of 1 mm3) that conformed to that stereotactic space. Image manipulations were performed with the free software MRIcro (Rorden and Brett, 2000); www.mricro.com).

The mapping procedure included the following steps:

1. Adaptation of the MRI template to the patient's CT scan. The standard Montreal Neurological Institute (MNI) template was rotated on coronal, sagittal and horizontal planes to conform to the patients CT acquisition angle using, typical landmarks as the ventricles, the frontal and temporal lobes and the cerebellum.

2. Lesion mapping. A skilled rater, using anatomical landmarks, manually mapped the lesion onto each correspondent template slice. A second skilled rater double-checked for the accuracy of the tracings for each patient. In cases of disagreement (this happened for two patients), an intersection lesion map was used.

3. Lesion re-orientation. The lesion maps, stored as binary images, were then rotated back into the standard space using the inverse of the transformation parameters used on the stage of template adaptation to the patient brain scan.

2.5. Statistical analyses of the lesion patterns.

In the statistical analyses described below, the anatomical distribution of the statistical results was assessed using the Automated Anatomical Labelling map (template AAL; (Tzourio-Mazoyer et al., 2002) which classifies the anatomical distribution of digital images in stereotactic space.

2.5.1. Identification of the "anatomical prerequisite" to the manifestation of somatoparaphrenia.

Since SP is not an isolated symptom but it is almost invariably associated with neglect and motor disorders, we assumed that these symptoms and their anatomical bases may represent a prerequisite to the manifestation of somatoparaphrenia. Accordingly, before investigating the specific lesional

pattern associated with SP, we also explored the anatomical regions related to neglect and hemiplegia. This was achieved by a between group voxel-by-voxel statistical analysis: we compared 11 SP+ and 11 SP- (in total 22) subjects with a set of 15 control RBD patients not showing neglect and hemiplegia or somatosensory deficits. The statistical analysis was done using the Liebermeister test as implemented in the Nonparametric Mapping tool (NPM) included in the MRIcron software (Rorden et al., 2007).

2.5.2. Comparison of SP+ and SP- lesion patterns

This comparison was also based on the Liebermeister test as implemented in the NPM included in MRIcron (Rorden et al., 2007).

2.5.3. Identification of white and grey matter involvement

We also defined the specific involvement of white/grey matter and the border of the two regions, inside each of the brain regions significantly associated with SP. To this end, we used the a-priori classification images provided by SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) that identify the probability for each voxel to be considered as part of the white matter and grey matter compartments. To classify the distribution of the statistical maps derived from the above comparisons, these a-priori images were used as masks of grey matter (61% or greater probability of being grey matter), of white matter (61% or greater probability of being white matter) and of the border between the twos (intersection mask). In particular, the region at the border between grey and white matter (intersection mask) was identified as having a chance between 40 and 60% of belonging to one of the two tissues. From these masks, we isolated the basal ganglia and thalamic spaces so that the lesion load of these areas was evaluated separately, rather than being assigned to either grey or white matter.

Identification of the regional distribution of the white matter damage was also made thanks to the JHU-white matter labels template (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007) distributed with the software MRIcron (www. mricron.com). This template, while permitting the

identification of some important fasciculi and their subdivisions, does not provide a full classification of the white matter of the cerebral hemispheres. For lesions of white matter regions not classified by the atlas, we refer to the classical lobar subdivision of the cerebral hemispheres.

2.5.4. Controlling for stroke aetiology

Five SP+ patients and their SP- controls presented with a prevailingly striato-capsular and thalamic haemorrhagic damage (cases P7-P11 and P18-P22, Table 1). This kind of lesion, while associated with a profound dysfunction of the overlying cortices (Perani et al., 1987) that is missed by structural imaging, tends to cluster subcortically, introducing a potential bias towards "subcortical findings" for any lesion mapping group study. To check that our analyses were not influenced by this potential confound, we compared the lesion distribution of the six SP+ patients with an ischaemic lesion (P1-P6, Table 1) with their SP- matched controls (P12-P17, Table 1) using the subtractive method included in the software MRIcron. Patients with haemorrhagic aetiology were excluded from this analysis.

3. Results

The behavioural pattern of the three patients' groups is summarized in Table 1. It is worth recalling that the SP+ and SP- groups were fully matched for all symptoms (e.g., anosognosia), but somatoparaphrenia.

3.1. Identification of the "anatomical prerequisite" to the manifestation of somatoparaphrenia

.
The voxel-by-voxel Liebermeister test on the SP+ & SP- patients versus the fifteen RBD control subjects without neglect, shows the involvement of the postcentral and inferior frontal gyri (opercular and triangular parts), the rolandic operculum, the insula, the putamen, the superior temporal gyrus and Heschl's gyrus (Fig. 1, Table 2). The 48% of this lesion map involved grey

matter, while damage of white matter and the greyewhite matter junction represented the 24% and 21% respectively. The lesion load in the lenticular nucleus (the putamen) represented a final 7% of the lesion load in the statistical map. The topographical analysis of the damage in the white matter indicated the involvement of the superior and posterior corona radiata, the external capsule and the superior longitudinal fasciculus (SLF).

3.2. Anatomy of somatoparaphrenia: group comparison between SP+ and SP- patients.

We did not find a significantly larger 'total lesion volume' (total number of damaged voxels) in patients with SP compared with patients without somatoparaphrenic delusions (p = .28, Mann Whitney U test).

On the other hand, the voxel-by-voxel statistical analysis revealed an association between SP and the damage of subcortical white matter of the right hemisphere (including the internal capsule, the corona radiata, the SLF and superior fronto-occipital fasciculus, the body of corpus callosum and the white matter located in the depth of the temporal pole and the hippocampus), basal ganglia (caudate nucleus, globus pallidus and putamen) and thalamus. The lesion included the ventrolateral nucleus (VL), the ventral posterior lateral nucleus (VPL), the ventral anterior nucleus (VA) and the lateral posterior nucleus (LP) of the thalamus. In addition to these subcortical lesions, we also found an involvement of the middle (dorsal prefrontal cortex, BA 46) and inferior (opercular part, BA 44) frontal gyri and of the postcentral gyrus. A damage of the right hippocampus and amygdala was also significantly associated with the presence of SP (Figs. 2 and 3, Table 3).

The analysis of whether the SP+ pattern involved primarily grey rather than white matter demonstrated that the vast majority of the statistical map involved white matter (69% of the statistical map volume) or the junction between white and grey matter (8%): only the 6% of the statistical map involved grey matter. In addition, the proportion of the statistical map in the basal

ganglia and thalamus was 17%. This pattern is in sharp contrast with what observed for the statistical map of "spatial neglect" described above.

3.3. Effect of stroke aetiology

The results of the subtractive analysis, performed with the exclusion of patients with haemorrhagic stroke, are basically consistent with the anatomical pattern emerged in the anatomical analysis without using any aetiological classification. The centre of overlap was defined as those voxels in the subtracted lesion overlap that were damaged 100% more often in the SP+ group than in the group of patients without SP (red regions in Fig. 4). These voxels were localized in the white matter (SLF and internal capsule) and basal ganglia (caudate nucleus, globus pallidus and putamen).

Figures and tables of the results.
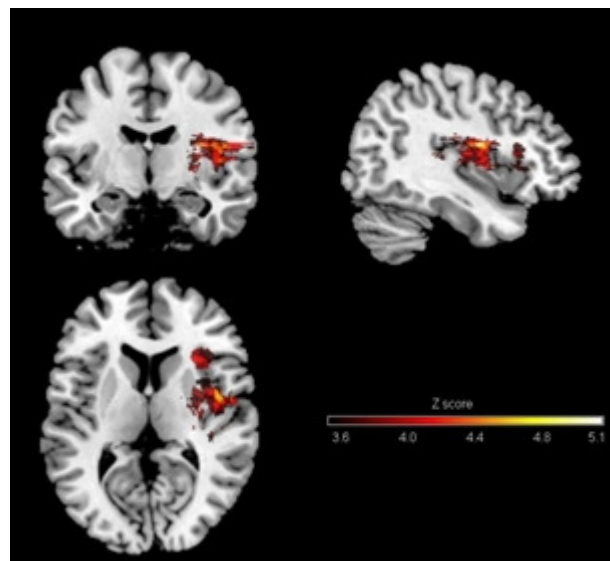
Fig. 1.The figure shows the brain regions significantly associated with neglect and motor deficits (N+M+ vs N-M+).Voxels that survived to the statistical threshold of p<.01, false discovery rate (FDR) corrected for multiple comparison, are shown. The colour scale illustrates the corresponding Z values.

Brain regions		Voxel count at Liebermeister test	MNI coordinates			Z-score	Grey/White matter %		
		p < .01	X	Y	z		White matter	Intersection	Grey matter
Inferior frontal gyrus	Opercular part	1195	36	17	10	4.11	6.78	38.24	54.98
	Triangular part	406	37	21	11	3.87	57.39	30.54	12.07
Rolandic operculum		3212	43	-2	15	5.15	11.02	35.15	53.83
Insula		3389	39	-1	17	5.15	11.30	18.32	70.38
Postcentral gyrus		172	60	-10	18	4.11	.00	.00	100.00
Putamen		794	32	-13	4	4.45	---	---	---
Temporal lobe	Heschl gyrus	460	51	-4	7	4.36	.22	.43	99.35
	STG	115	41	-27	9	4.04	13.92	31.30	54.78
White matter		2224	40	-1	18	4.61	---	---	---

Table 2. Brain regions significantly associated with neglect and hemiplegia.

The table shows the brain region associated with neglect and motor deficits (Liebermeister test N+M+ vs N-M-, number of voxels significant at the statistical threshold of FDR p < .01 and MNI coordinates of the most significant voxel).
The percentage of white matter, of grey matter, of the border between the two (intersection), included in each anatomical region are shown.
STG: superior temporal gyrus; **FDR:** false discovery rate.
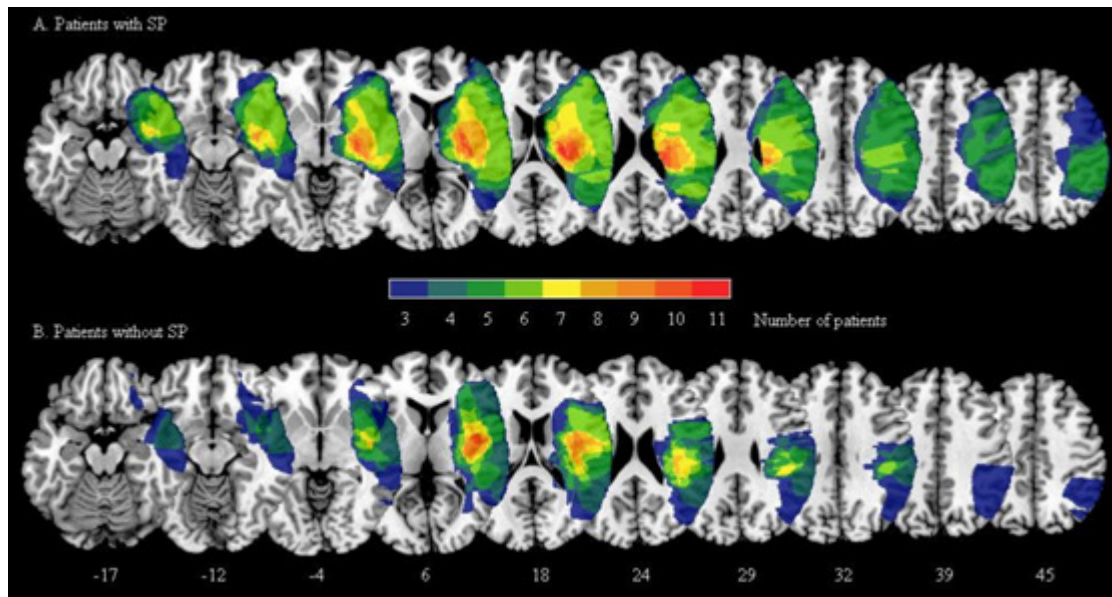
Fig. 2. Overlay lesion plots of the (A) 11 SPD patients and (B) 11 SPL patients. The regional frequency of brain lesions in each area is expressed according to the colour scale ranging from black (lesion present in 3 patients) to white (lesion present in 11 patients). MNI z coordinates of each transverse section are reported.
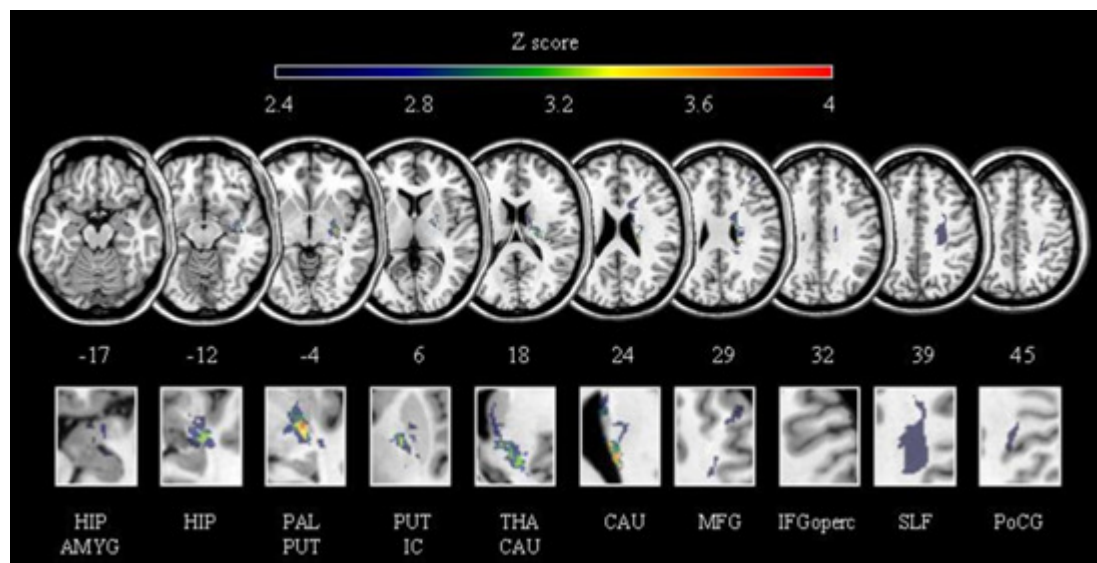
Fig. 3 . Anatomical comparison between patients with SP (n = 11) and patients without SP (n = 11).

The figure shows brain region more frequently damaged in patients with SPD as identified using the Liebermeister test, implemented in the NPM tool included in the MRIcron software package. Voxels that survived to the statistical threshold of p < .01 uncorrected are shown. The colour scale illustrates the corresponding Z values. MNI z coordinates of each transverse section are reported.

HIP: hippocampus; AMYG: amygdala; PUT: putamen; PAL: pallidum; CAU: caudate nucleus; THA: thalamus; MFG: middle frontal gyrus; PoCG: postcentral gyrus; SLF: superior longitudinal fasciculus; IFGoperc: inferior frontal gyrus, opercular part; IC: internal capsule.

Brain region		Voxel count at Liebermeister test	MNI coordinates			Z-score	Grey/White matter %		
		p < .01	x	Y	Z		White matter	Intersection	Grey matter
Middle frontal gyrus		172	30	28	25	2.84	9.30	66.86	23.84
Inferior frontal gyrus (opercular part)		42	63	18	28	2.46	0.00	100.00	0.00
Limbic system	Hippocampus	223	39	-13	-12	3.59	39.46	11.66	48.88
	Amygdala	47	32	0	-17	2.60	.00	100.00	.00
Postcentral gyrus		136	60	2	37	2.46	88.97	2.21	8.82
Basal ganglia	Caudate nucleus	455	19	-20	24	3.87	-----	-----	-----
	Putamen	323	30	-12	-4	3.41	-----	-----	-----
	Pallidum	345	29	-11	-5	3.41	-----	-----	-----
Thalamus		296	17	-11	18	3.41	-----	-----	-----
White matter		6441	22	-26	24	3.99	-----	-----	-----

Table 3. Brain lesion analysis: patients with SP (n = 11) versus patients without SP (n =11).

Table reports the brain regions significantly associated with SPþ at the Liebermeister test, the total number of voxels significant at the statistical threshold of p < .01 uncorrected and the percentage of white matter, of grey matter, of the border between the two (intersection), included in each anatomical region. The MNI coordinates of the most significant voxel are also reported.
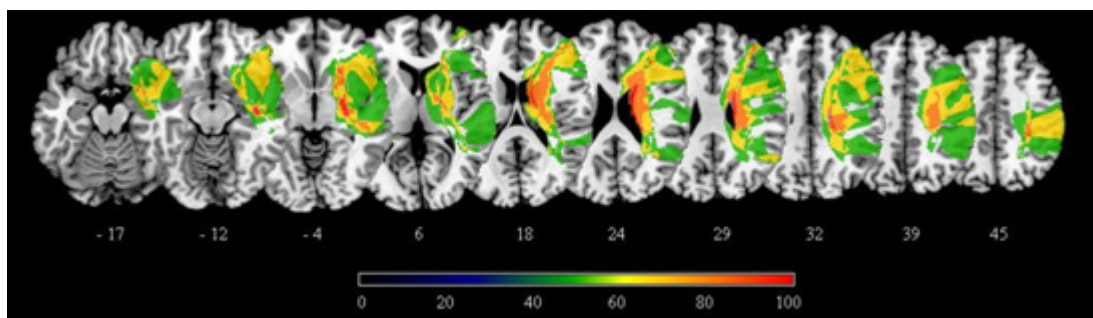
Fig. 4. Subtraction lesion plots of patients with SP and patients without SP with ischaemic stroke. The percentage of overlapping lesions of the SP+ group after subtraction of the SP- group is illustrated by different colours, coding increasing frequencies from dark blue (difference =17%) to red (difference = 100%). Only brain regions that were damaged the 50% or more frequently in patients with SP than in patients without SP are showed. No regions were injured the 50% or more frequently in patients without SP than in patients with SP.

4. Discussion

Somatoparaphrenia is so tightly associated with spatial neglect, hemiplegia and anosognosia that one might have wondered on whether a specific anatomical pattern could ever be found when comparing SP patients with those sharing the same symptoms but SP. Indeed, given the transient nature of this disorder, one may have also predicted that the appearance of SP could simply reflect a more diffuse functional depression of right hemispheric networks involved in body and space representation. However, as shown by our results, structural imaging was sufficient to provide anatomical evidence that additional brain damage, compared with that of spatial neglect, hemiplegia and anosognosia, is needed for SP to emerge. The additional damage needs to be focally placed as SP+ and SP- patients did not merely differ in terms of global lesion loading. In what follows we will argue that a vast predominantly subcortical damage, in addition to a distributed cortical damage typical of spatial neglect [10], is a key anatomical feature of SP. We will suggest that this anatomical pattern may justify the symptoms of SP because of a profound de-afferentation from somatosensory and visual right hemispheric information to a left-hemispheric narrator. We will also suggest that the narrator, in charge of making sense of conflicting or missing sensory evidencemay also suffer of a lack of sense of familiarity for his own left limbs because of a lesion to the hippocampal-amygdaloid complex or to the fibre bundles projecting there. This additional damage may make emotionally more vivid the sense of non-belonging for the paralyzed limbs.

4.1. The anatomy of somatoparaphrenia before somatoparaphrenia

Intrinsic to subtractive anatomoclinical correlation designs is the tendency to report a small set of brain areas resulting from an anatomical statistical "subtraction" as the crucial set of regions whose damage should bring about a specific and complex disorder. However, such presentation of the data may lead the unsophisticated reader to believe that a small focal lesion, outside primary cortices,

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[10] Cortical damage could be anatomical as in ischaemic lesions or functional-anatomical, as a distant consequence of subcortical haemorrhagic lesions.

might be sufficient to cause complex and perhaps enduring symptoms and to make such inference as an anatomical definitive assignment at a population level. This, we believe, is seldom the case. Here, we entertained the more realistic approach of first exploring the brain damage associated with neglect and hemiplegia, using a hierarchical approach. Since in our sample all patients with SP also presented with neglect and hemiplegia, we assume that this frequent behavioural association should have an anatomical counterpart. The comparison of SP+ and SP- patients versus brain damaged patients without neglect and hemiplegia allows us to propose that the damage, or a profound functional disruption, of a distributed right hemispheric neural network is the prerequisite for the eventual manifestation of SP, may an additional and well placed damage occur. The network includes a fronto-temporal and rolandic operculum circuit together with basal ganglia and the corona radiata and the SLF. This network broadly corresponds to the anatomical lesion pattern of spatial neglect as described in previous studies: in particular, our results most resemble to those reported by Karnath et al. (2001, 2004) or to those described by Vallar and Perani (1986) in figures 1 and 2, for the patients with lesions not restrained to a particular sub-territory of the middle cerebral artery. In those studies, the patients were in the acute phase. In addition, our data also support the recent notion for an important contribution of white matter lesion in the SLF as suggested by Doricchi et al. (Doricchi et al., 2008) and Bartolomeo et al. (Bartolomeo et al., 2007). We also note that our results differ from those of some other studies: for example, Vallar and Perani (1986; see their figure 5) attached great importance to a right SMG damage, while the parietal damage identified in our data was primarily in the rolandic operculum: however, behind Vallar and Perani (1986) finding there was an a-priori subdivision of the patients sample in pre- versus retro-rolandic cases and cases with antero-posterior lesions: the SMG emerged as a prominent correlate only for severe cases with a retro-rolandic lesion. These and other methodological differences may explain slightly different outcomes in this area (for discussion, see also (Rorden et al., 2007). The proposal for the existence of an anatomical prerequisite [11] for the emergence of SP requires a further

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[11] With the wording anatomical prerequisite we indicate a lesion pattern needed but not sufficient to bring about SP, a

clarification: because of the systematic association of SP and spatial neglect and hemiplegia, this should broadly correspond to the anatomical counterpart of these symptoms within a distributed fronto-temporo-parietal network. Much as SP appears mostly in the acute state after stroke, we imply that this might be associated with a direct anatomical and/or with more indirect-functional disruption, with the implication that one should not necessarily expect in a given patient the complete anatomical damage of the network, while a profound functional damage would be probably always needed (see also the discussion below on haemorrhagic patients).

4.2. Anatomy of somatoparaphrenia

4.2.1. Subcortical and limbic damage

Our results are also very clear in indicating that a vast additional prominent subcortical damage of the white matter in the right hemisphere (including the posterior limb of the internal capsule, the corona radiata and the SLF) and of subcortical grey nuclei (thalamus and basal ganglia) is crucial in causing SP. These regions represent the core of our findings in terms of number of voxels significantly associated with SP.

Indeed, the proportion of the greyewhite matter damage for SP was the reverse -in favour of white matter damage- of the one observed in the comparison between neglect patients (SPþ & SP_) versus non-neglect patients. This finding reinforces previous single cases reports of SP associated with subcortical damage (Healton et al., 1982; Bisiach and Geminiani, 1991; Halligan et al., 1993; Bottini et al., 2002). Moreover, Feinberg et al. (1990) compared two groups of patients with and without delusions and suggested a correlation between verbal asomatognosia and a lesion of the posterior corona radiata in the depth of the SMG. Of course, it is not possible to formulate a precise description of the functional impact that this widespread damage might have in SP. However, observation of such a prominent subcortical anatomical pattern, legitimates the following considerations. It is well known that the thalamus and the basal ganglia are linked with high-order

disorder systematically associated with spatial neglect.

cortical brain regions involved in motor functions, spatial cognition and body representation through their connections with the primary motor (MI), the premotor (PMC) and the supplementary motor (SMA) cortices (Romanelli et al., 2005), as well as with brain areas located in the posterior parietal and in the superior temporal cortices (Yeterian and Pandya, 1998). According to our analyses, the thalamic nuclei involved in SP were the ventrolateral nucleus (VL), the ventral posterior lateral nucleus (VPL), the ventral anterior nucleus (VA) and the lateral posterior nucleus (LP), all connected with somatosensory (SI and SII) regions and motor areas such as M1, PMC and the SMA, cortices involved in motor execution, preparation and intention to move.

We hypothesize that a lesion to these subcortical grey nuclei or a damage to the white matter tract linking these structures with cortical sensory-motor and associative areas, could have an important role in the occurrence of the feeling of disownership, as it may lead to a deficit in the construction of a coherent body representation including the affected limb. Such damage most likely causes a disconnection from the cortex, which is broadly damaged itself, that may prevent the processing and the integration of diverse afferent information arising from the affected body part (bottom-up processes) with higher-order and pre-existing body representations normally computed in higher-order cortices (top-down processes). In the absence of such convergent information, the patient's internal body representation would not be updated to incorporate the paretic limb that would be considered as non-existing or non-belonging to the rest of the body (Tsakiris et al., 2008; Tsakiris et al., 2006).

Our account differs from the one previously offered in a study addressing the anatomical correlates of "disturbed sensation of body ownership" (DSO) [12]. Baier and Karnath (2008) attributed great importance toa lesionin the insula. However, in that study the control group was not matched with the experimental group for the presence of AHP, and the presence of disownership was not the only variable isolated by the group comparison, making this anatomical inference not as conclusive. The

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[12] The label DSO is used by Baier and Karnath (2008) as a unifying definition of both somatoparaphrenia and asomatognosia.

contribution of a insular damage in provoking AHP and/or disorders of ownership remains to be fully established: clearly called into play by a number of studies, as a single correlate from group anatomical comparisons (Karnath et al., 2005; Baier and Karnath, 2008), or in the context of a more distributed lesion patterns (Berti et al., 2005; Fotopoulou et al., 2010; Vocat et al., 2010), an isolated insular damage is unlikely a sufficient cause to induce AHP and SP. In a study on isolated insular strokes, a transient disturbed sense of ownership was present in only one of two cases with an isolated right posterior insular infarct (Cereda et al., 2002). This evidence, per se, militates in favour of our position of considering the "specific" lesion pattern of SP (see Table 3) as an addition the anatomo clinical correlates of spatial neglect (see Table 2).

Finally, the right hippocampus and its white matter and the amygdala were also involved in SP. For the hippocampus it has been suggested a pivotal role in maintaining a stored "memory for the spatial location of body parts" (Carpenter et al., 1995); in addition, Carpenter et al. (1995) found that patients with right unilateral temporal lobe epilepsy failed in recalling the motor deficit occurred during right intracarotid sodium amytal injection. Furthermore damage to the amygdala may worsen any right hemispheric residual processing of sensory information related to the paralyzed limb, depriving the contents of such processing of emotional connotations [13].

4.2.2. Neocortical damage

This was proportionally a minor component in the anatomical pattern specifically associated with SP. Yet we note that the cortical pattern involved frontal areas, like BA 44, well known for subserving multisensory integration in which visual, tactile and proprioceptive information converges to create a coherent representation of a body part with the body schema. Activation of cortical multisensory areas, such as bilateral ventral premotor cortex, has been found in

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[13] An alternative explanation for the hippocampus involvement could be an unbalanced presence of memory deficits in the two groups of patients. If that were the case, the involvement of this region could be related to an episodic memory dysfunction rather than to a body schema disorder. The analysis of the only memory test available for episodic memory, the immediate and delayed recall of three words from the MMSE, showed no difference between SPþ and SP_ patients (p values of ManneWhitney U tests >.3). Nevertheless, this is a preliminary observation that requires to be confirmed with a more complete evaluation of memory performance, particularly as the minimal test of episodic memory from the MMSE is exclusively based on language.

neuroimaging studies using the rubber hand illusion paradigm, while subjects were feeling the illusion that an artificial limb was a part of their own body (Ehrsson et al., 2005; Ehrsson et al., 2004; Tsakiris et al., 2007). Inside the frontal lobe, we also found a significant association between SP and a lesion of the dorsal prefrontal cortex (BA 46). It has been suggested that a malfunction of the dorsolateral prefrontal cortex, including BA 46, could play a role in many types of delusional beliefs, because of an impairment in a "belief evaluation system" (Coltheart et al., 2011). The association between frontal lesion and asomatognosia and somatoparaphrenia has been recently suggested by Feinberg et al. (2010), who, nevertheless, did not separate out anosognosia from somatoparaphrenia in their analyses.

4.2.3. Haemorrhagic patients and the role of diaschisis in the temporal dynamics of SP.

In this paper, we also reported a series of 5 patients with SP and haemorrhagic lesions involving subcortical structures. Prima facie, this observation may invite to dismiss the importance of the contribution of a cortical damage in somatoparaphrenia. However, any subcortical (haemorrhagic) lesion implies a damage affecting bidirectionally connecting fibre bundles (and their neuronal populations) travelling from the cortex to subcortical grey structures and back; the haemorrhagic lesions may cause damage of subcortical grey structures as well, as it happened in our five cases; these patterns are usually accompanied by a profound functional depressionof the overlying corticalmantle, as demonstrated by Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) studies (Baron, 1985; Perani et al., 1987; Vallar et al., 1988) particularly in the acute phase of stroke. Hence, although we do not have SPECT or PET measurements of rCBF of these patients, we assume a similarity between the ischaemic cortical damage, and the subcortical one, at least during the acute and sub-acute phases of the stroke, the time of testing in our study. Indeed, in previous studies on aphasia and neglect due to subcortical lesions, recovery from "cortical" cognitive signs (e.g., spatial neglect or aphasia) was associated with the functional recovery of cortical perfusion (Vallar et al., 1988). A functional recomposition of the activity of undamaged brain networks is also a viable hypothesis for the explanation of the

remissionfromSP even in caseswiththe involvement of the cortex. This should be tested using functional imaging techniques such as resting state PET or fMRI, or, indeed, a combination of the twotechniques in longitudinal studies. Too little is known about the behavioural dynamics of SP and the related symptoms to make further hypotheses on this subject (for further discussion, see the Section Outstanding issues).

4.3. Reflections on the nature of somatoparaphrenia.

We conclude our discussion with a number of considerations that are partly based on our data and that partly represent our educated reflections on somatoparaphrenia and its phenomenology. We also outline a series alternative hypotheses whose testing needs further empirical work. Hopefully these may inspire the reader to designs pecific experiments on this subject. Delusions of somatoparaphrenia typically become manifest during the clinical examination thanks to the verbal descriptions/ complaints made by the patients. Only in some cases they may emerge spontaneously, for example, when misoplegia is also present, in the context of aggressive behaviours towards the paralyzed limb. This is why somatoparaphrenia is to be considered a "productive or positive symptom", that is, a behavioural manifestation that, contrary to what observed when performance is lacking, is characterized by the active generation of acts or verbal reports reflecting a distorted mental representation of reality (Bottini et al., 2009) [14]. Of course, the productive nature of the symptoms of somatoparaphrenia represents a major conceptual challenge for any anatomical interpretation that might have the ambition of going beyond the mere description of the most-likely lesion site associated with the syndrome [15]. In fact, a discussion of the functional implications of

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[14] Feinberg et al. (1990, 2010) introduced a distinction between somatoparaphrenia, as described in our paper (a refractory and persisting delusion about left limb ownership), and a milder form of disorder of disownership sensation called asomatognosia. To maximize the chance of detecting a specific anatomical pattern for SP, by design, we chose to select cases with a more clear-cut ownership disorder or controls with a complete lack even of milder symptoms such as those labelled as asomatognosia.

[15] A more complete description of somatoparaphrenia in functional terms would necessarily require functional imaging experiments not only on somatoparaphrenic patients but also on normal controls during task tackling the sense of ownership for their body parts.

the pattern of structural damage is necessarily somewhat speculative here: yet, it may permit to formulate testable hypotheses on mechanisms underlying the manifestations of somatoparaphrenia. According to our data, somatoparaphrenia is associated with an extensive cortical and subcortical anatomical and/or functional damage [16] of a right fronto-tempo-parietal network subserving body and space representation. It is worth of further emphasis the fact that, due to the extensive subcortical damage, whatever might be spared of the right cortical mantle in a given patient, this is most likely largely disconnected from sensory input eventually reaching the thalamus, which is itself damaged. With most of cortical somatosensory and motoric representations being damaged, and most of peripheral sensory information being unavailable, or "unused" (Bottini et al., 2002; Moro et al., 2004), the contralesional half of the body may loose its status within the body map; this would occur despite the remaining possibility of the visual observation of the contralesional limb via the intact left-hemispheric structures - indeed, visual inspection of the paralyzed hand may contribute to make somatoparaphrenia more evident or even to reveal it (Bisiach and Berti, 1995) - and in spite of the possibility that some residual somatosensory information is, in fact, somehow available as recently demonstrated by Bottini et al. (2002) and by Moro et al. (2004). The SP phenomena, we propose, might be aggravated by the damage of the medial temporal lobe structures including the amygdala, reducing the sense of familiarity for a body part seen but not perceived as one's own[17],and, in the more severe cases, inducing a sense of disgust for the paralyzed limbs. This highly impoverished functional mapping of the contralesional side of the body is what the left-hemispheric narrator has to deal with when questioned by the examiner about the ownership of the left arm and while being exposed to the sight of a limb that has lost citizenship in the territory of body representation. No prior knowledge about the existence of a body segment, as stored in the

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[16] For the purely subcortical cases like the haemorrhagic ones, we assume a diffuse cortical dysfunction, as demonstrated by PET or SPECT studies in similar cases.

[17] A similar interpretation has been proposed for Capgras' syndrome (Ellis and Lewis, 2001; Frith, 2004).

cortex [18], nor sensory information from the periphery would be accessible by the left hemisphere. Thus, the left hemisphere will eventually say what he knows, namely that there is "a" limb rather than a limb belonging to his body.

However, what strikes the imagination of those involved in the study of SP, is the following: the patient, when visually exploring the paralyzed arm and when interrogated about whose limb is that one, generally prefers to give extreme explanations, alluding, for example, to the presence of an alien limb in his proximity instead of reasonably assuming personal ownership of the limb (in the end, most humans have two arms nearby their trunk.); as surprising, patients neither do wave a white flag and admit of not knowing whose arm it that one.

An "active" mental representation might be needed for this behaviour together with a left-hemispheric bias of "positively" making sense of the available information, no matter how imprecise. One may hypothesize that patients may experience a vivid left-hemispheric representation of a "halved body" that may induce to consider as intolerable the concept of having a second set of left-sided limbs, given the "prior knowledge" essentially based on one hemisphere, and the limited incoming sensory information available. Alternatively, patients may rely on a vague and distorted somatic representation of where their left arm might possibly be, somewhere certainly not matching the information gathered from visual inspection and degraded somatosensory information. This mechanism, that reminds of the dyschiria interpretation of Bisiach (1995), may also explain, at least in part, somatoparaphrenia.

These distorted representations may inform the left-sided narrator while dealing with the examiner's requests about the ownership of the paralyzed limb.

4.4. Outstanding issues

The transient nature of the delusion and its association with other temporary deficits (such as for example neglect and AHP) warrants further discussion. SP is a rare symptom usually described in

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[18] With the terminology "prior knowledge" we imply the results of the activity of specific cortical areas in which somatosensory and motor maps and schemes should be stored.

acute stroke patients. Delusions may disappear after few days and only in rare cases they persist later on (see review in Vallar and Ronchi, 2009). Our study, much as previous investigations on the anatomical bases of SP (Baier and Karnath, 2008; Feinberg et al., 2010), was focused on the evaluation of SP in the initial phase after the stroke, when the delusion appears and its manifestation may be more vivid and elaborated. This has the obvious advantage of permitting the study of a relatively large sample of patients for a neuropsychological syndrome that is quite rare. Unfortunately, in our records there was no sufficient data to permit a systematic evaluation of the time course of the somatoparaphrenic delusion. Yet, it is clear that a systematic study of the time course of SP and its related symptoms, together with the relevant anatomical correlates, may contribute to clarify a number of outstanding issues (for a recent longitudinal study on the anatomy of neglect, see (Karnath et al., 2011). First, what is the exact time course of somatoparaphrenia in relation to the time course of other sensory, motor or cognitive symptoms related to spatial neglect and AHP? What is the role of residual elementary somatosensory information described in some SP patients? Is the remission of somatoparaphrenia associated with an explicit recognition of the ownership of the paralyzed limb, or is it then associated with the admission of a lack of information about the matter, for cases with severe sensory disconnection and hemiplegia? Is there a particular lesion pattern associated with a greater likelihood of a persistent deficit? What are the physiological correlates of the remission of the disorder? All these are questions that one needs to answer to gain a deeper understanding of somatoparaphrenia and that are left for future experiments.

Appendix

Relevant abstracts of the verbalizations of patients with somatoparaphrenia (P1-P11, Table 1)

P1

"This hand is cold and sweaty, it's not mine". "It's plump. It's the hand of my niece Arianna". "She left it here because she doesn't care about that". "I found it there and took it with me, now it stays here as it was mine, it keeps me company, please leave it here with me". "It's the hand of S.B. (an Italian political leader), it was on his desk and he left it there, he didn't need it and gave it to me".

P2

"I can't understand why I'm here. I' don't know. Whose hand is this? Yours. why are you asking me these things? Don't ask me riddles." "It's the hand of a guy.it's very hairy.my hand is beyond the river Piave". "You're still telling me riddles about this hand. it's the hand of a boxer". "It's the hand of this stupid man near me". "My left hand went to Iraq to defend S.H., it has been two years since it went there".

P3

"No, it's not my hand.it is yours". "It occupies a lot of space in this bed, it's so uncomfortable". "It is an artificial limb. Not mine. it is of the nurse. it is very intrusive, I've no more space in this bed!" "Yes, please take it away. I don't care about its destiny as it is not mine".

P4

"The problem is that this hand is not mine. I've already told it to the other doctor". "How am I supposed to know whose hand is this? It's not mine". "My hand is not like this, this is different, it's too short. I don't know who left it here". "It's of someone that passed by, but I don't know who he was exactly". "The problem is this hand that cannot move is not mine".

P5

"It's warm.it's my niece's hand". "My hand is there. Maybe it has gone on holiday because it was too tired, it always works a lot, poor little." "There was another woman here with me. yes in the same bed. it should be her hand.maybe there were no more beds and they put her here with me". "No, it's not mine because it's too heavy".

P6

"Yes, it's your hand. Whose other should it be?" "It's a left hand. I suppose that it should be your left hand". "Anyway, I'm sure that it could not be mine because my hand is on my

stomach. Can't you see?"

P7

"It's not my hand. It's a female hand". "It's the hand of that young nurse named Jasmine". "It's very strange.terrible.If I have her hand, she should have been wounded and she should have lost it". "The nurses are joking, someone took my arm away.I couldn't see because I was eating, and then they replaced it with this one. It's a puppet".

P8

"It's my niece's hand". "She is so kind, she left it here to keep me company." "My niece is so sweet. she's always making me some massages. but she's also very absent minded. look here, she was rushing home and forgot her hand here!"

P9

"Mine or yours?. it's a female hand. it could be of the nurse but it wears my pyjamas. it's strange." "It really doesn't look like mine. My hand is more thin and dry". "I don't know. I feel nothing. obviously it's not mine. it's yours. if you want it, I'll give it to you as my gift, since I have no need for it. It doesn't work. Maybe you'll be able to get it working". "I woke up last night and called the nurse because there was this hand here and I thought that Nadia forgot it. I wanted to give it back to her. She cannot work without it. Poor Nadia".

P10

Examiner: the experimenter brings the patient left hand in front of her face and asks: "Whose arm is this?". "It's your hand. Sure, whose hand is it supposed to be?". Examiner: where is your left hand?. "My hand is on my stomach and it cannot move" (the patient's hand is not on her stomach but it was brought by the experimenter in the mid-sagittal plane of the patient). It could be yours, I don't care, take it away if you need it". "No it's not mine, I've already told you, are you joking? Why should it be mine?" "My hand is different, not so heavy.then maybe it's the hand of the doctor who examined me before. Give it back to him".

P11

"It's your hand". "No I'm not sure, it's not a female hand". "It's the hand of that handsome guy, the other doctor". "No no, it's not my hand, this is so little.my hand is big as a shovel". "It's the hand of your colleague, the guy that was here with you, my hand is on the bed".

Abbreviations: AHP, anosognosia for hemiplegia; BA, Brodmann area; SP, somatoparaphrenia; SP+, patients with somatoparaphrenia; SP-, patients without somatoparaphrenia; RBD, right brain damage.

4. Chapter 4. What is mine? Behavioral and anatomical dissociations between somatoparaphrenia and anosognosia for hemiplegia.

Abstract

We describe the clinical manifestations and the lesion patterns of five patients with somatoparaphrenia, the denial of ownership for a paralyzed limb, who showed the rare dissociation from anosognosia for hemiplegia. Similar cases have been only occasionally cited in the literature with scanty descriptions of their symptoms and no detailed anatomical assessment. All patients had extrapersonal and at least mild personal neglect. The lesions pattern was mainly subcortical, with a significant involvement of the right thalamus, the basal ganglia and the internal capsule. A formal comparison between the anatomical pattern previously associated with anosognosia in a study performed in 2005 by Berti and colleagues, and the lesion distribution of each patient clearly shows that our pure somatoparaphrenic patients had a sparing of most of the regions associated with anosognosia for hemiplegia. The behavioral dissociation between SP and anosognosia for hemiplegia, together with this new anatomical evidence, suggests that motor awareness is not sufficient to build up a sense of ownership and therefore these two cognitive abilities are at least in part functionally independent and qualitatively different.

1. Introduction

Somatoparaphrenia (Gerstmann, 1942) is a delusional belief whereby a patient feels that a paralyzed limb, usually the upper left one, does not belong to his body; the symptom is typically associated with unilateral spatial neglect[19] and most frequently with anosognosia for hemiplegia (see for a review (Vallar and Ronchi, 2009). A possible difference between somatoparaphrenia and

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[19] Interestingly, SP is systematically associated with extra-personal neglect (the inability to explore/represent extra-personal space) rather than with personal neglect (defined here as the inability to reach out the paralyzed limb while keeping the eyes shut) (see Table 1, in Vallar and Ronchi, 2009). While the dissociation with personal neglect is a well documented one, there is only one case with a focal right insular damage (Cereda et al., 2002) in which SP may had been present without any sign of spatial neglect: the techniques used to assess neglect by Cereda and colleagues (2002) however, were not specified leaving a vast margin of uncertainty on whether neglect was completely absent in that patient.

selective anosognosia for hemiplegia (AHP) was already pointed out by Gerstmann in 1942 (Gerstmann, 1942). Soon after, Critchley stressed that it is not always obvious how to distinguish between these two symptoms, frequently proposed as different forms or degrees of severity of the same defect (Critchley, 1974; Gerstmann, 1942), SP being a more severe manifestation of a body representation disorder. Indeed, while many patients with AHP do not have SP, only very few dissociations between SP and AHP have been reported in the literature (Daprati et al., 2000a; Halligan et al., 1993; Halligan et al., 1995; Ives and Nielsen, 1937; Lhermitte and Tchehrazi, 1937; Schilder, 1935a). A recent study investigating the clinical features and the anatomical correlates of AHP and "disturbed sensation of limb ownership" (DSO) pointed out that additional abnormal attitudes towards the affected limb (including SP) are almost invariably (92% of cases) associated with AHP (Baier and Karnath, 2008). The authors suggested the existence of a continuum of symptoms of altered body awareness, and that self-attribution of actions and the sense of limb ownership may be "the front and the reverse side of one coin", both associated, at the neural level, with the same structure: the right posterior insula (Baier and Karnath, 2008).

Evidence for a double dissociation of these two deficits has come from a study based on the WADA test: it has been found that 68% out of 62 subjects showed both anosognosia for the left arm's weakness and asomatognosia[20], while only the 11% were only anosognosic (Meador et al., 2000). Interestingly, 10% of the patients presented with an isolated asomatognosia, as when asked about their left plegic limb they manifested feelings of non belonging for it and attributed their limb to someone else.

Vallar and Ronchi (2009) have recently reviewed the neurological and neuropsychological features of 56 brain damaged somatoparaphrenic patients described in the literature. For 44 cases detailed information concerning motor deficit and awareness for it was available. Among these, only 7 patients, among which 4 recent cases, showed SP apparently dissociated from AHP (Daprati et al.,

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[20] The term *asomatognosia* is used to define, in comparison with somatoparaphrenia, milder forms of body ownership disorders ranging from simple feelings of an arm missing or fading away to a feeling of non-belonging without elaborated delusional contents (Baier and Karnath, 2008; Feinberg et al., 2010; Feinberg et al., 1990).

2000a; Halligan et al., 1993; Halligan et al., 1995; Ives and Nielsen, 1937; Lhermitte and Tchehrazi, 1937; Schilder, 1935a); all of them had a right sided hemispheric lesion, mainly in temporo-parietal regions or in the subcortical structures (see Table 1). All of them suffered from a dense hemiplegia or hemiparesis, from a gross deficit in somatosensory sensation and proprioception, and a mild or severe deficit of visual field. In all cases in which the testing was reported, there was visuo-spatial neglect and personal neglect. With few exceptions, AHP was tested by means of an informal interview. Although patients are described as to have been aware of their motor deficit, nevertheless, from the description, it looks as if the level of awareness was frequently fluctuant. As the authors of these reports were not specifically interested in the identification of double dissociations between these disorders, description of AHP and SP is not always clear or detailed (Ives and Nielsen, 1937; Lhermitte and Tchehrazi, 1937; Schilder, 1935a). For example it is not completely clear whether the reported sensations of disownership could be classified as somatoparaphrenia (defined as an elaborated, bizarre, repeated and refractory to correction delusion of disownership for a paralyzed limb, see (Feinberg et al., 2010), or the comparatively less profound form of body schema disorder asomatognosia, more likely to appear in isolation from other disorders of body awareness (Meador et al., 2000).

To summarize, while there are indications that SP and AHP may be dissociable, the available evidence is based on cases with incomplete descriptions either of the SP symptoms or of the level of AHP. Yet, a detailed analysis of such dissociations may give some insights on the cognitive processes underpinning the sense of ownership and motor awareness, two key components of self-awareness, the relationships of which are a current matter of debate in cognitive sciences and philosophy. In addition, a detailed description of the anatomical correlates of dissociated cases may also prove useful particularly if such anatomical patterns were supportive of a double dissociation between SP and AHP.

To explore these issues, we retrospectively examined the records of a sample of 75 right brain damaged patients who had an extensive neuropsychological assessment for personal and

extrapersonal neglect and associated symptoms. We found five cases showing disownership delusions without anosognosia for their left hemiplegia. These cases are the object of a detailed description here.

		AUTHOR AND YEAR			
CLINICAL FEATURES		**Halligan et al.,1993**	**Halligan et al.,1995**	**Daprati et al., 2000**	**Moro et al., 2004**
Neurological Deficits	**Motor**	+++	++	++	+++
	Sense of touch	+++	+++	+++	+++
	Visual Field	+++	+++	+	+
	Proprioception	+++	++	+++	+++
Neuropsychological deficits	**Neglect**	+	+	+	+
	Anosognosia	- (fluctuating)	-	-	-
	Personal Neglect	-	+	-	+
Features of delirium	**Object of delirious**	left arm and leg	left foot	left hand	left hand
	Whose hand?	n.r.	Cow	Son	another patient
	Type of delirious	Disownership	Attribution	Attribution	Attribution
Lesion Side	**Right**	X	X	X	X
	Left				
Brain regions involved in the lesion	**Frontal Lobe**				X
	Temporal Lobe		X	X	X
	Parietal Lobe		X	X	X
	Thalamus			X	
	Basal Ganglia	X			

Table 1. Cases of dissociation between SP and AHP reported in the recent literature.
Neurological, neuropsychological and anatomical characteristics of non-anosognosic patients with somatoparaphrenic delusions reported in the literature quoted in the Pub Med database (see also Vallar and Ronchi, 2009).
– No deficit; + mild deficit; +++ severe deficit. n.r. Not reported in the original paper.

"Disownership": simple feeling of non-belonging in which , contrary to "attribution", the patient does not recognize a limb as his/her own one, but does not explicitly identify the believed owner of the deluded body part.

2. Case reports.

We evaluated (partially retrospectively) the prevalence of AHP and SP and of the co-occurrence of both these symptoms in a population of right brain damaged patients with neglect, admitted to the Stroke Unit of Niguarda Ca' Granda Hospital of Milan from 2000 to 2009, for whom it was asked a specific neuropsychological evaluation at the Cognitive Neuropsychology Centre of the same hospital. All patients were formally assessed for neurological and neuropsychological deficits, after giving their informed consent to be tested, in accordance with the ethical standards laid down in the Declaration of Helsinki (1964), as soon as their clinical conditions allowed a cognitive examination (1-5 days after the stroke) and before leaving the stroke unit (6-35 days).

Twenty four out of 75 patients with extrapersonal and/or peripersonal neglect presented with AHP for left hemiplegia and 12 showed SP. Among these, 5 showed SP dissociated from AHP [21].

2.1 Neurological Evaluation

The standardized examination for motor, sensory and visual field deficits has been administered according to the procedure proposed by Bisiach et al. (1986). Proprioception has been investigated with the examiner placing the patient's plegic arm in 5 different positions (arm pointing towards, arm pointing up/down, arm pointing to the right/left) and asking him to place his own right limb in the same position with his eyes closed.

2.2 Neuropsychological Evaluation

The index of global cognitive functioning has been measured through the Mini Mental State Examination (MMSE) (Folstein et al., 1975), taking into account that the presence of neglect could prevent patients from correctly perform some of the subtests. The presence of spatial extra-personal neglect has been investigated by means of the Albert Line-cancellation (Albert, 1973), the Letter-cancellation tasks (Diller et al., 1980; Diller and Weinberg, 1977) and the Line-bisection task. A pathological performance on at least one of these tests indicated the presence of neglect. The

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[21] Two of these patients (CT and GB) have been also included in a previous work focussed on the anatomical patterns underlying SP where no distinction was made between pure cases and cases with AHP (Gandola et al., 2011).

following additional tests have also been performed: drawing from memory, copy drawing, clock drawing test and sentences reading task.

Personal neglect was assessed by asking the patient to reach, with his eyes closed, his/her left hand according with the procedure proposed by Bisiach and colleagues (1986).

2.3 Anosognosia for hemiplegia and somatoparaphrenia
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In order to investigate the presence and the severity of AHP and SP, patients were tested with different semi-structured interviews. Awareness for contralesional motor deficits has been explored by means of the four-points scale by Bisiach and colleagues (1986). The patient scored from 0 (in case of full awareness of the deficit) to 3 in case of severe anosognosia (1986). Patients tested after 2005 have been also asked to evaluate their current ability of execution of a set of bimanual tasks by using the diagnostic test of unawareness of bilateral motor task abilities in anosognosia for hemiplegia as proposed by Nimmo-Smith and collaborators (Nimmo-Smith et al., 2005) (patients assessed before the publication of this test had been similarly interviewed on the accuracy of their performance of unimanual and bimanual actions). According to the scale, a score of five or more has to be considered as an overestimation of one's own abilities. We reported the mean value of the patients' subjective evaluation of motor capabilities of performing the different proposed actions for the patients with pure SP.

Somatoparaphrenia was investigated by interviewing patients about the selective delusion confined to the contralesional limb including the following questions: "What is this? Whose hand is this? Where is your hand? Why is a foreign hand here?".Patients were considered as somatoparaphrenic in case they firmly denied that the arm belonged to them and/or attributed it to someone else providing elaborated, bizarre, persistent and refractory-to-correction explanations of their delusion (Feinberg et al., 2010). Any other milder forms of body ownership disorders such as feelings of arm missing or fading away, were classified as asomatognosic symptoms as proposed by Feinberg and colleagues (Feinberg et al., 1990; Feinberg et al., 2010) but have not been considered in our study as our focus of interest was the association between AHP and clear-cut SP.

Results of neurological and neuropsychological evaluation of all pure SP patients are shown in Table 2.

2.4 Lesions Mapping

Cerebral lesions of pure SP patients have been mapped using the MRIcro software application (www.mricro.com) on each corresponding slice of a standard M.R.I. template (a T1-weighted template M.R.I. scan from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm view) appropriately rotated to conform with the patient's C.T. scan acquisition angle (see the detailed mapping procedure in Gandola et al. (2011). The percentage of damaged voxels inside each brain regions of interest of the A.A.L. template of MRIcro has also been calculated.

Given the small sample size of this series of pure SP patients, it was impossible to perform any statistical comparison with any control group of patients.

To provide an indication of the distribution of the brain lesions, we report a lesion plot overlay made by superimposition of the regions of interest (ROIs) of each patient's lesion map and isolated from it the set of brain regions that were constantly damaged in all of them pure SP patients.

The presence of SP in isolation from AHP would suggest at least a certain degree of anatomical independence of the two symptoms with the sparing in pure SP of certain brain structures previously associated with AHP.

To test this possibility, we assessed the degree of anatomical congruency of the brain lesions associated with these cases of selective SP, with the results of a previous study from our group in which the anatomical patterns of AHP were investigated (Berti et al., 2005). To this end, the ROI of the region commonly involved in all five patients and the single ROIs of each patient lesions were superimposed on the statistical map results of Berti and colleagues (2005): as the data were complying to the same stereotactic space, for each SP patient, it was possible to assess congruencies and dissociations in comparison with the AHP lesion pattern. The same was done with the set of brain regions that resulted to be constantly involved in all of the pure SP patients.

Demographic, neurological and neuropsychological features.	Patients with somatoparaphrenia				
	CT	GB	MA	AS	CP
Age	60	69	71	84	70
Sex	F	F	M	F	M
MMSE	22,27	28	22	22	27
Extrapersonal Neglect	+	+	+	+	+
Personal neglect	1	2	2	2	3
Anosognosia for hemiplegia*	1	1	0	0	0
Anosognosia for hemiplegia §	0	0,5	0,5	0,5	0
Motor deficit	3	3	3	3	3
Deficit of the sense of touch	1	3	3	1	3
Visual field deficit	3	3	1	3	3
Proprioception deficit	Deficit	Deficit	Deficit	Deficit	Deficit
Lesion site	right thalamus/BG	right frontal, temporal, insular, parietal regions	Right thalamus/BG	right temporo-occipital regions, thalamus / BG , internal capsule	right thalamus, BG and internal capsule

Table 2. Features of the patients.

Neurological, neuropsychological and anatomical characteristics of CT, GB, MA, AS and CP. *: Bisiach's scale. §: Nimmo- Smith test (mean score) ; + = Presence of the symptom. 0-1-2-3 = Scores at the Bisiach's Scale; 0= no deficit; 3=severe deficit; for AHP: score 1 simply indicates that the patient is not aware of the occurrence of a stroke but knows about his/her paralysis. MMSE = Mini Mental State Examination; scores are reported corrected for age and level of education. BG= Basal Ganglia.

3. Case report

3.1 Case Report 1

Patient CT was a 60 years old right-handed woman who worked as a school caretaker (educational

level: 5 years) admitted to our Stroke Unit because of an ischemic stroke in the vascular territory of

the middle cerebral artery, as assessed with C.T. scan. The first neurological examination (5 days after the stroke) revealed left complete haemianestesia and a severe motor deficit of the left sided body with loss of proprioception and extinction to double visual stimulation. CT had a severe extrapersonal neglect (that lowered her total score at the MMSE slightly under the common cut-off for normality), and a mild personal neglect. Also, she showed neglect dyslexia and perseveration in cancellation tasks (see Table 2). The patient was not aware of having suffered from a stroke but was fully aware not to be able to move her left arm and not to perceive touches on her left hand. However, she continuously complained of a "foreign, strange and short hand" in her bed, which had been left there by someone she did not know. CT also referred that she had already complained with other doctors about that extraneous and "immobile, as dead" hand lying there, that someone has attached to her own body.

Before patient CT left the hospital (10 days after the onset), we could briefly re-assess her and registered an unvaried neurological examination with the same disownership sensations.

3.2 Case Report 2.

GB was a 69 years old right-handed woman who suffered a hemorrhagic subcortical stroke involving the right thalamus, hippocampus, basal ganglia (caudate, putamen, pallidum) and the deep white matter as documented by a C.T. scan. We assessed her 3 days after the stroke, when she presented with a dense hemiplegia of the left arm and leg, hemianopia, a severe hemianestesia and a complete loss of proprioception. GB was correctly oriented in space and time, the MMSE score fully in the range of normality. Her neuropsychological evaluation was also adequate for linguistic functions and memory. However, she had extrapersonal neglect, moderate neglect dyslexia on a sentences reading task and suffered from a moderate personal neglect. GB appeared unaware of her hemianopia, while being fully aware of her motor impairment: when asked to actually execute actions with the left arm, she suddenly detected her failures with no hesitations. She was also completely aware of her somatosensory loss that seemed to trigger somatoparaphrenic delusions.

Indeed, GB often began to deny the ownership of her left hand as, she said, she could not "feel touches" in it. Sometimes the patient stated that the paralyzed limb was that of her niece Nadia, of a nurse or of a patient previously admitted to the hospital in the same bed. GB often woke up in the night calling the nurses, scared for the presence of a foreign hand on her stomach.

On the second evaluation, 8 days after the stroke, GB neurological deficits were not improved. Again, her awareness for motor impairment was complete, she always detected her failures when actual execution of actions was required and she was able to ascribe them to their real cause. The firm sense of non-belonging of the left hand with attributions to other people remained unvaried.

3.3 Case report 3.

MA was a 71 year old man (education level: 16 years) who suffered a hemorrhagic subcortical stroke involving the right thalamus, the hippocampus, the basal ganglia (putamen, pallidum and caudate nucleus) and the deep white matter, as assessed with a C.T. scan.

The neurological evaluation (5 days after the stroke) revealed a severe hemiplegia of the left arm and leg, hemianesthesia and loss of proprioception and extinction to double visual stimulation. The score at the MMSE was slightly under the criterion for normality only because of the deficit in copying and reading for the presence of extrapersonal neglect. MA also showed a moderate personal neglect.

The patient was fully aware of his hemiplegia and spontaneously complained and asked information about it. Instead, he was anosognosic for his hemianesthesia. Interestingly, when asked about the ownership of the left plegic hand, he often ascribed it to the examiner maintaining that his "real" left hand should have been placed on his stomach and was not the hand shown by the examiner.

At the follow-up (7 days after the stroke) no changes were present in somatoparaphrenic symptoms, while eleven days after stroke the delusions had disappeared.

3.4 Case report 4

AS was an 84 years old woman (education level: 11 years) who suffered a stroke in the right brain hemisphere involving temporo-occipital regions , the thalamus , the basal ganglia and the white matter fibers of the internal capsule. We had the opportunity to test this patient 3 weeks after the stroke, but we had detailed clinical data available also for the acute phase. In the acute phase of the disease, AS had a severe hemiplegia of the left arm and leg, hemianestesia and haemianopia. A severe hemineglect was present in all the performed tests. Her detailed case history described the presence of delusion about the ownership of the paretic limb, while there were no records of AHP. When we evaluated AS three weeks later, her total global cognitive functioning index (MMSE) was slightly below normality mainly because of the presence of a severe neglect that invalidated tasks based on visuospatial exploration. AS also showed a severe personal neglect. At the neurological examination only the tactile defect had improved and now she only showed extinction to double stimulation. She was fully aware of the left hemiplegia and of her visual field deficit. As her case history described disownership delusions in the acute phase, AS was then interviewed about the sense of limb ownership. Again, these delusions emerged and the patients immediately denied the ownership of the left arm at the question "whose hand is this?". She also maintained that the arm shown by the examiner couldn't be her own one because it was too fat, puffy and disobedient to her commands. She didn't know where her real arm was, she was fully convinced that someone had hidden it and asked to find it and replace that foreign hand with her own one.

A further follow-up (5 weeks after the stroke) revealed no neurological ameliorations, AHP was still absent and somatoparaphrenic delusion had been replaced by a milder form body ownership unawareness. The patient correctly attributed the plegic arm to herself but declared to still have some doubts.

3.5 Case report 5.

CP was a 70 years old man admitted to the stroke unit following a stroke mainly involving the right thalamic region and subcortical white matter. At the first neurological and neuropsychological

assessment performed the day after the onset, CP was densely hemiplegic and also showed severe hemianestesia , haemianophia, and deficit of proprioception. He also had a severe personal neglect and extra-personal visuospatial neglect in all the proposed tasks. His MMSE was in the range of normality as reported in Table 2. When questioned about his problems, CP spontaneously complained about his hemiplegia and his inability of feeling touches in the left arm and of finding its position. As the examiner placed the paretic hand in front of CP's eyes, he suddenly affirmed that it was the doctor's hand or of a friend of his. He was completely sure of this misattribution and when the examiner placed his own left hand near to the patient's one, he was totally unable to decide which one of them belonged to his body, also maintaining that both of them belonged to the doctor. When presented with three hands (his own one and the experimenter's right and left hands), he persisted in attributing them to the experimenter in spite of the obvious nonsense of three arms in the same human body. The days after, CP always remained fully aware of his neurological deficits, somatoparaphrenic delusions fluctuated throughout the day but persisted until six days after the stroke.

4. Anatomical observations.

The lesion plot over revealed the structures most commonly damaged in these patients (regions commonly damaged in 100% of patients): right thalamus, basal ganglia (putamen and globus pallidum), white matter of the posterior limb of the internal capsule (see Fig. 2). This pattern is consistent with what was described in the study of Gandola et al. (2011) and by Zeller et al. (2011). However, the same pattern is considerably different from the one reported for AHP (Berti et al., 2005) (see Fig. 2).
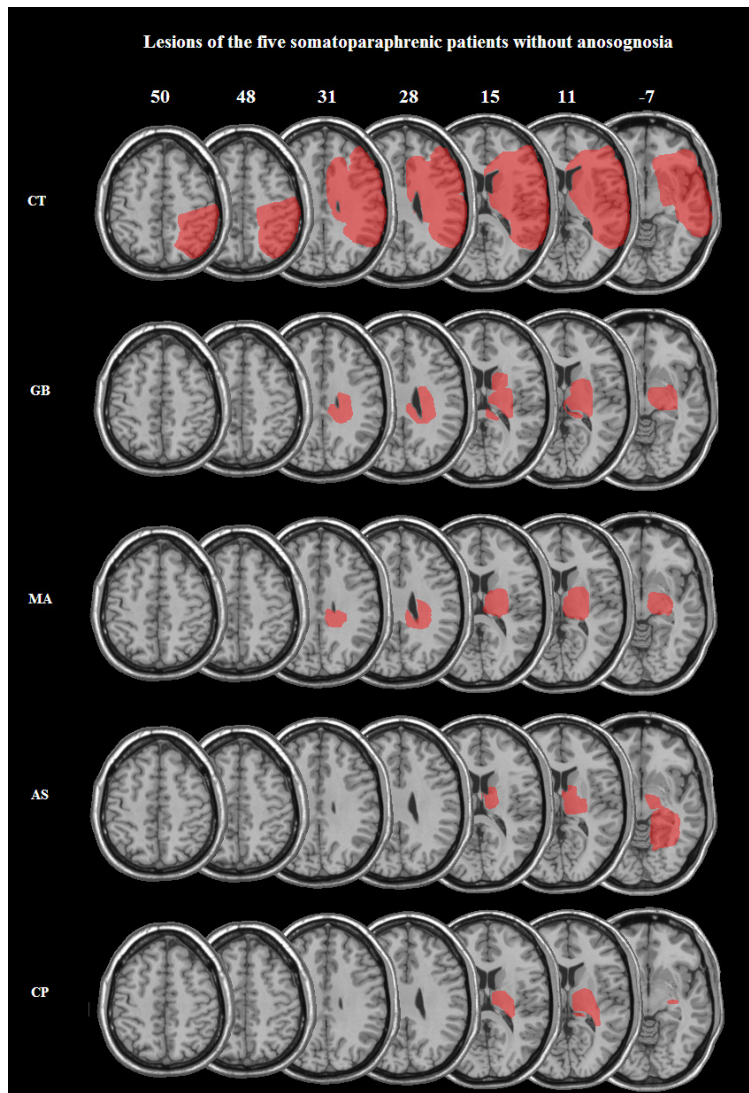
Fig. 1: C.T. scans of the five patients with somatoparaphrenia without anosognosia for hemiplegia.
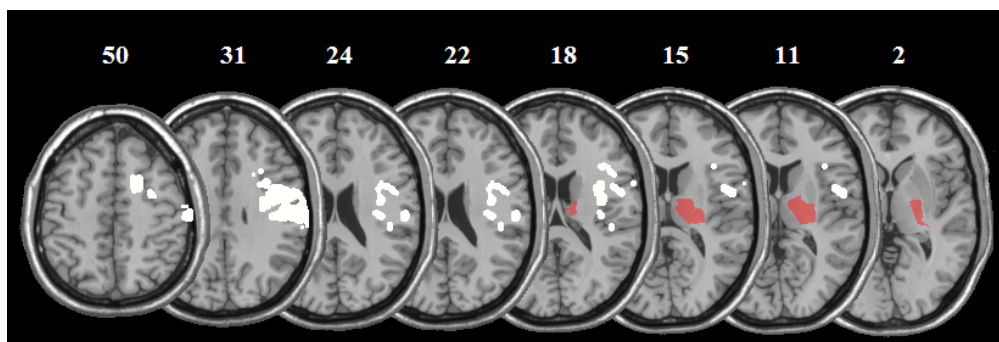
Fig. 2: The figures shows, in red, the center of overlap of the lesions of pure SP patients (the center is defined as regions commonly damaged in 100% of patients) and, in white, regions most commonly associated with AHP (Berti et al., 2005).

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The comparison of each single lesion of our patients with the statistical map results of Berti and

collaborators (2005) revealed that 4 out 5 patients had no lesion overlap with regions associated to

AHP in that work (2005). Only the lesion of patient CT overlapped, in part, with the cerebral structures previously associated with anosognosia: her lesion involved a large fronto-temporo-parietal cortical network and subcortical grey nuclei as well. However, her damage was clearly more ventral than the one described for AHP, with a remarkable sparing of dorsal motor and premotor regions, and dorso-lateral prefrontal cortex; the voxel count inside each of these regions showed the sparing of the 93% of voxels in the dorsal premotor cortex (BA 6), the 62 % in BA 44, the 78 % in the precentral gyrus (BA 4) including the hand-motor area, the 68 % in the postcental gyrus, and the 93% of area BA 46. Interestingly, the right insula, a brain region that has been related to anosognosia by others (Karnath et al., 2005), was extensively damaged (98 % of voxels) and yet patient CT did not manifest signs of unawareness for hemiplegia (see Fig.3) while having a clear-cut somatoparaphrenia.
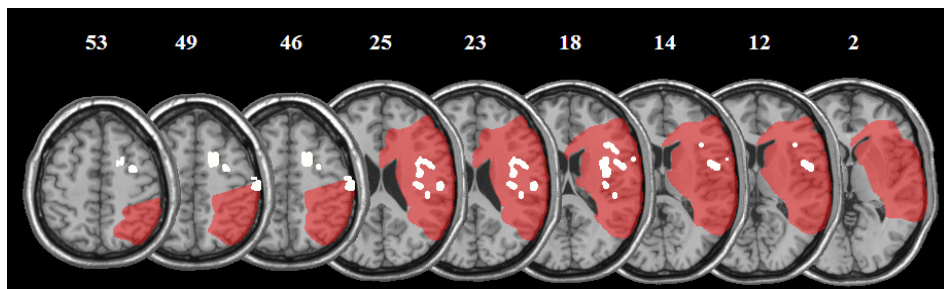
Fig. 3: In red, the lesion of CT, the patient showing also an extensive cortical damage, mapped in the stereotactic space and superimposed on brain regions (in white) involved in AHP (Berti et al., 2005). In spite of the large cortical lesion, it is clear the sparing of some of the brain areas associated with AHP by Berti et al. (2005).

5. Discussion

The sense of embodiment is a complex experience, which comprises more than one distinct component in sensation and action: we are normally aware that "the body we inhabit is our own" (Tsakiris et al., 2006) and that our limbs belong to us; this omnipresent sense is called sense of "body ownership". Awareness of the state of the motor system and the sense of being, rather than not, the cause of an action , are also a crucial aspect of our sense of "being us".[22]

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[22] In the domain of motor cognition, we limit our reflections on awareness for the state of the motor system without touching the domain of agency, the sense of awareness of who is the actor of an action; the present study has nothing to offer in this respect.

Even though these experiences have common elements, the underpinning neural systems, the way they operate and eventually interact are still far from being fully understood.

In normal circumstances, these experiences are strongly linked, even quite inseparable. Much to reinforce the intuitive notion that the underlying normal mental states should share cognitive causal mechanisms, the study of brain damaged patients has revealed a frequent co-occurrence of the disturbance of the sense of being able to move (e.g. AHP) and of the sense of body ownership (e.g. SP) (Baier and Karnath, 2008); this frequent co-occurrence of symptoms has justified the interpretation of AHP and SP as diverse manifestations of a common defect of body scheme representation, maybe due to insular damage (Baier and Karnath, 2008; Karnath et al., 2005).

The unitary interpretation of Bisiach accommodates, in functional terms, the multifarious repertoire of bodily based symptoms that one can observe in spatial neglect (Bisiach et al., 1990a). However, the unitary interpretation of certain syndromes does not necessarily imply that all symptoms should always coexist, nor it implies that they are explained by a single mechanism implemented in a single crucial brain region or network. Indeed, two disorders might be functionally independent impairments occurring together simply because brain damage tends not to be sufficiently specific (see Bottini and Toraldo, 2003).

Recently, the sense of body ownership and the sense of being causally involved in actions have been studied in behavioral (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Tsakiris and Haggard, 2005) and neurofunctional (Farrer et al., 2003; Tsakiris et al., 2007) experiments on healthy subjects. An "independence" model, which - contrary to the "additive" model - holds that the sense of agency and body ownership are qualitative different, has recently been supported by fMRI evidence showing different underpinning sets of brain regions, with no shared activations for these two component of the sense of self (Tsakiris et al., 2010). However, this study is based on the well known rubber hand illusion, an illusory perception of a prosthetic hand as part of the self: it remains to be established whether this experimental manipulation is sufficient to describe the human spontaneous sense of body ownership (Zeller et al., 2011). In addition, the sense of agency may not

necessarily fully correspond to the ability to monitor the power of the motor system, the cognitive ability tackled by the interviews for AHP.

Our anatomical observations may provide an initial contribution to disentangle sensory and motor aspects of body-representation in the brain. An explicit comparison of the lesion pattern associated with AHP and SP in anatomo-clinical correlation studies with different groups of patients has not been attempted yet because of the rarity of pure SP patients. However, our preliminary anatomical evidence speaks in favor of dissociable neural networks for the manifestation of SP and AHP: a comparison of the anatomical pattern previously associated with AHP by Berti et al. (2005) and the lesion distribution of each patient described here clearly shows that the pure SP patients had a sparing of most of the regions related to AHP.

Taken together, our behavioral and anatomical observations suggest that the frequent co-occurrence of AHP and SP might be most likely due to the limited specificity of naturally occurring brain lesions, rather than to a commonality of their central cognitive causal mechanisms.

Frontal premotor regions, together with the insula, seem to be crucial either for action representation (Baier and Karnath, 2008; Berti et al., 2005; Karnath et al., 2005) and multisensory integration processes allowing the construction of a coherent body representation (Ehrsson et al., 2005; Ehrsson et al., 2004; Zeller et al., 2011). However, while AHP seems to be tightly linked to this anterior damage affecting motor control processes embedded in the same neural network of the monitored primary function (Berti et al., 2005), anatomical data about SP show a more crucial involvement of grey subcortical structures and white matter bundles (Feinberg et al., 1990; Gandola et al., 2011). Indeed, the overlay lesion plot of our five pure SP patients clustered around subcortical grey nuclei and white matter fibers and does not share commonalities with the superimposed statistical map of regions associated to AHP (Berti et al., 2005) , as confirmed by the comparison with each single patient's lesion.

A possible explanation of the frequent concomitance of AHP and SP is that neglect patients usually have extensive lesions that may affect frontal areas and subcortical grey and white matter causing

both symptoms. Only in more rare cases, it may happen that, in the context of lesions leading to neglect and SP, the premotor frontal cortex is preserved to such an extent to allow action monitoring and, thus, awareness of hemiplegia. The ideal candidates for this situation are patients with haemorragic lesions confined to subcortical regions with direct damage of the internal capsule and the thalamus, and a variable degree of deafferentation of the cortical mantle: a variable degree of dysfunction of the overlying cortex may explain the concomitant presence/absence of anosognosia.

5.1 Explaining pure somatoparaphrenia?

The putative anatomical mechanisms discussed above are insufficient to provide a comprehensive description of SP. Indeed, cases of SP associated with, or dissociated from, AHP propose challenging dilemmas on the functional mechanism whereby a patient feels a sense of non-belonging for the paralyzed limb while producing a delusional belief that a limb can correctly move (the canonical case of SP with AHP) or while correctly appreciating the paralysis of the limb, as in the dissociated cases. Let's concentrate here on the dissociated cases. According to Heilman's or Frith et al.'s models of motor control (Heilman et al., 1991; 1998; Frith et al., 2000), the correct assessment of the motor status of a paralyzed limb should depend on the perception of a mismatch, by a comparator, between a motor plan and the lack of motoric consequences of the same plan. If this mechanism is valid for our dissociated cases, we should conclude that the correct assessment of the motoric status of a limb might not be sufficient to give a sense of ownership.

Further, it remains questionable which kind of feedback information is the patient using to appreciate the paralysis of the limb. Given the location of the lesion affecting the whole posterior limb of the internal capsule in all patients described here, a somatosensory feedback seems unlikely. On the other hand, are these patients making a better use of visual information and is their awareness limited to the "alien" limb through visual mechanisms? Would an interview of the patients while blindfolded modulate their reports? If this visual exploration hypothesis can explain the lack of AHP, why the same mechanism is insufficient to recognize the left limb as one's own?

Moreover, are patients talking about the same limb when assessing its motor power and the ownership?

Another interesting dissociation is the one between SP and personal neglect. In our series, only one patient had a severe form of personal neglect, being totally unable to localize his/her paralyzed limb. Four patients had a much milder form, being able to reach out the paralyzed limb after initial hesitations. Clearly, this represents a dissociation between some form of implicit knowledge, that permits the reaching behavior, and knowledge mediated by verbal descriptions, the one produced by the patients during the delusions of SP whereby *that* limb does belong to someone else[23].

These and many others remain outstanding issues in this area, something that we were unable to assess for this time, given the retrospective nature of our study, a limitation that we overtly admit.

A detailed analysis of the patients' verbalizations and further manipulations of the patients' interview may help to shed some additional light on this particular dissociation as well.

For example, during the interview for the evaluation of SP we noticed that our patients seem to judge the motor capacities with reference to the foreign hand; patient CT said, "this hand, that does not move, is not mine". An intriguing question is whether patients with SP and no AHP may refer to an alternative body schema of a foreign person, instead of their own corrupted bodily representation, to correctly evaluate actual motor performance. This possibility would be consistent with the evidence of Bottini et al. (Bottini et al., 2002), in which the dense hemianestesia of a somatoparaphrenic woman recovered when she was instructed to report touches delivered to "her niece's hand", rather than to her own hand.

Further behavioral investigations, where one attempts to verbally modulate the patients' awareness of hemiplegia, may be helpful to explore this issue: for example, one could explore awareness for hemiplegia by asking to report about the "alien" limb as much as about "their" limb.

These and other experimental manipulations may help to further develop our understanding on SP and the functional mechanisms underlying the sense of body ownership.

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[23] It may be interesting to recall that personal neglect is normally tested with the eyes shut.

6. Appendix.

6.1 Patient CT verbalizations

E: Close your eyes and tell me if you feel that I'm touching your hand. P: But.. that's not my hand!!. E: What? What's the problem with that hand? P: The problem is that it's not mine. I've already told it to the other doctor. Someone passed by and left it here but I don't know who he was. E: and what did the doctor tell you? P: He asked me whose hand was this one, but I don't know who attached it to my body. E: Can you move this hand? P: no, it does not move. E: Isn't it a little bit weird to have a foreign hand with you? P: no! - She takes the left hand, looks at it and says- my hand is not like this! This is shorter, it doesn't look like mine, plus, it does nothing!! E: What is this hand doing here with you? P: Nothing. It does not move. It does nothing. A second experimenter enters the room and asks: Good morning C., can you repeat me your problem? Whose hand is this? P: I've already told it. The problem is that this hand that cannot move is not mine. It's not like mine. E: Raise your arms up like me. Are you doing like me? P: No, how many times do I have to tell you? I'm raising up this arm (the right) only! E: Can you show me how you clap your hands? P: I cannot, this hand does not move.. But it is not mine. You can take it away.

E= examiner; P= patient.

6.2 Patient GB verbalizations

E. - Takes the left hand into the right hemispace and says- What is this? P: it could be my hand. E: Could?? Whose hand is this? P: mine or yours…it's a female hand.. it's of the nurse…but it wears my pajamas.. it's strange... E: - moves the pajamas away from GB sight and says - Whose hand is this? P: - GB continuously touches the hand and says - I don't know.. I feel nothing...if you pinch this one (right) I feel, but when I pinch that hand I can't feel I'm pinching.. obviously it's not mine.. it's yours... E: and where's your real hand? P: here on the bed (tries to find it out). E: so, if this hand isn't yours, I can take it away with me then... P: of course, if you want it, I'll give it to you as my gift, since I have no need for it. It doesn't work. Maybe you'll be able to get it working. E: Are you sad about having that hand with you? P: yes, a bit. Because I would like to understand why it does

not move and work like this other (the right). E: do you want to move this hand away? Wouldn't you be sad without it? P: yes if it was mine…but it's not. E: do you prefer that this hand was not so close to your body? P: yes, because it's not mine, it doesn't look like mine. My hand is more thin and dry. E: look at this hand, is it attached to your body or not? P: no.. I don't know.. I do not feel it. E: the nurses told us you woke up this night and called them, why? P: because there was this hand here and I thought that Nadia forgot it and I wanted to give it back her. She cannot work without it. Poor Nadia. E: Show me how you can clap your hands. P: Impossible. Let's try…No, I'm not doing it right, can't you see? I can make noise but I'm not really clapping. E: Look at me and do the same. Raise your hand up. P: It's the same. I'm raising up only my right arm, the good one.

E= examiner; P= patient.

6.3 Patient MA verbalizations

E: Why are you here? P: I had a stroke. E: How are you now? All right? P: No, I can't move this arm. E: Your left arm?. P: yes, but the same is for my left leg. All the left side of my body is paralyzed. Do you think I will ever be better? I don't think I will be able to move them anymore. E: Try to put your arms up in this way. P: That (the left) hand does not move. E: (the examiner brought M.A. left hand in front of his face). What is this thing in front of you? P: A hand. E: Whose hand is this? P: Yours! E: Mine? Are you sure? P: Yes sure, whose hand is it supposed to be? E: and where is your left hand? P: On my stomach. Can't you see? E: So this hand isn't yours.. P: No, my hand is on my stomach and cannot move. E: Whose hand could be this one? P: Yours of course. Are you joking?? Why should it be mine? My hand is different, not so heavy and it's not there, I always take it on my stomach. E: this is my right arm and this is the left. It couldn't be mine. P: Then maybe it's the hand of the doctor. He surely needs it. Call him.

E= examiner; P= patient.

6.4 Patient AS verbalizations

E: how are you Miss S.? P: not fine, it does not work. E: What does not work? P: this arm (she takes and touches her left hand), it does not move, it does not obey. E: I understand, but if I touch you there, can you feel it? P: yes yes, well. I do not know why but it does not obey. E: why are you here? P: for a stroke. E: try to get your hands in this way as you were holding a tray up. (She raises the right arm). E: Have you been able to do that? P: No, the other hand (the left) is not working, it does not obey!!. E: close your eyes (E. brings the patient's hand in front of her eyes), what's that? P: a hand of course. E: and whose hand is it? P: I do not know. E: Don't you know? And whose hand could it be? P: well, surely it is not mine. Take it away. E: if it is not yours, whose hand is it? P: Someone working here examined me before and hid his hand into my bed as a joke! Give it back! What a joke!! I would prefer my hand; this is too fat and puffy! E: Where is your real hand? P: I suppose he took my hand away and gave me this bad one! Go ask him!

E= examiner; P= patient.

6.5 Patient CP verbalizations

E: Hi, Mr. C. why are you here in this hospital? P: I had a stroke while I was on holiday. E: and what are your problems now? P: The main problem is with all the left part of my body. I cannot feel it nor move it anymore. E: Mr. C., look at this. What is this? P: your hand. E: my hand? Are you sure?. P: yes, of course. It couldn't be mine. E: and why? P:..it looks groomer than mine. E: From zero to ten, how much do you feel that this is not your hand? P: ten. E: and how much are you sure that it is mine? P: nine and a half. E: (after placing his left hand near the patient's one). Can you choose your own hand among these ones? P: They are both of you. E: (after placing both his right and left hands near CP's one). And now? P: They are yours. E: All of them three? P: yes. E: Don't you think they are too many hands for me? P: (smiling at the examiner).. You are a polyp!

5.Chapter 5. Residual premotor activity in patients with anosognosia for hemiplegia.

Preface

As already discussed in the Prologue and in Chapter 1 of this thesis, anosognosia for hemiplegia has been often conceived as a negative manifestation related to spatial neglect (see Vallar et al., 1998). However, the firm assertion of being moving a plegic body part as requested by the examiner in spite of any clear contrary evidence, is a clear productive delusion that grounds on a distorted representation of reality.

Abstract

The deficit of motor awareness showed by patients with anosognosia for hemiplegia is considered of great importance for the comprehension of the normal architecture of the motor system and motor awareness. Previous brain mapping studies proposed the right ventral premotor cortex, insula and somatosensory cortex as anatomical correlates of this syndrome (Berti et al., 2005, Karnath et al., 2005, Vocat et al., 2010). However, these studies have the limitation of not providing information about the anatomo-functional correlates of motor delusions, and they do not allow to fully test current cognitive models of anosognosia. The feed-forward theory explains anosognosia as a deficit of motor intention/planning (Heilman et al., 1991, 1998). Clearly this theory's prediction is a lack of activity within the whole motor system of the anosognosic patients. A second theory (Frith et al., 2000) predicts that some residual activity, implicated with the generation of motor plans, should be observed in spared brain premotor regions. While the mismatch between the predicted representation of the final state of the motor system and its actual state would be neglected because of the lesion, these intended plans would match with the predictions, hence the delusional belief of having correctly performed a movement.

In this study, we measured with fMRI the neural activity in hemiplegic patients with and without ansognosia, and in normal controls, during a motor task. This simple fMRI experiments permitted to provide the first neuroimaging assessment of the two main competing interpretations of anosognosia with opposite predictions about the residual activity within the motor system. Our neurofunctional observations of a residual activity of premotor regions in anosognosic patients is, to our knowledge, the first neuroimaging support to behavioural evidence that suggests a preservation of motor intention for the paralyzed limb in patients with anosognosia (Berti et al., 2007; Fotopoulou et al., 2008), in whom the delusional belief of having moved would ground on residual aspects of motor planning components in presence of a right premotor lesion.

1. Introduction

Among symptoms classically associated with spatial neglect, anosognosia for hemiplegia is the lack of awareness for the contralesional motor deficits that follows brain damage, typically in the right hemisphere (Babinski, 1914). Anosognosic patients do not spontaneously complain about their motor deficit and they may even deny their impairment, despite any explicit demonstrations of their hemiplegia. Several hypotheses have been proposed to account for this disorder (Bisiach, 1995; Vallar and Ronchi, 2006). Based on a large body of evidence (Adair et al., 1997a; Gold et al., 1994a), Heilman and co-workers framed anosognosia in a "feed-forward" theory of motor control, in which motor plans are constantly compared with the somatosensory consequences of the actions. In this conceptualization, anosognosia would be a consequence of a lack of motor intention for the paralyzed limb (Heilman, 1991; Heilman et al., 1998). In absence of motor plans/intentions, a putative "comparator" of prediction and actual results, would be unable to detect any mismatch between motor plans (not generated) and the sensory consequences of the non-performed action. As a consequence, anosognosic patients would deny the motor deficit. The main lack of this theory resides in not explaining the delusional component of anosognosia, whereby patients affirm to have performed a movement as requested by the examiner, in spite of the evidence that a movement did

not actually occur. To explain these false experiences of movement, Frith and co-workers (Frith et al., 2000) proposed a further level of analysis in classical models of motor control, the comparison between the desired state and the predicted state of the motor system. This level would be preserved in anosognosia, hence the delusion of having moved: the denial of the motor impairement would be caused by a failure in the detection of discrepancies between predicted positions and actual movements, "while representations of the desired and predicted positions of the limb are appropriate, the patient is not aware of the discrepant representation of the actual position of the limb". This because sensory information about the actual state of the system are "absent or neglected" (Frith et al., 2000).

Clearly, contrasting neurophysiological predictions derive from these two competitive theories: while the first hypothesis predicts a global damage or malfunction of the system involved in motor planning/intention, the second is consistent with a distributed anatomical system for motor control, with a possible sparing of some specific components.

Early studies associated anosognosia with parietal lobe lesions typical of spatial neglect (Critchley, 1953; Gerstmann, 1942). However, these were single case reports, lacking any comparison with control groups of hemiplegic neglect patients without anosognosia. More recent evidence from group studies based on the classical anatomoclinical inference, suggests that anosognosia is best explained by lesions of the lateral premotor cortex, the sensory-motor primary cortex and the insula (Berti et al., 2005, Karnath et al., 2005, Vocat et al., 2010).

Altought, the literature provides several investigations of motor functions in normal subjects, with explicit motor tasks, motor imagery tasks or motor awareness/attention to intention tasks (Lau et al., 2004a) - for a review about commonalities between motor execution, motor imagery, and motor preparation in Stephan and Frackowiak, 1996 (Stephan and Frackowiak, 1996a) - so far, no study has integrated information derived from healthy subjects with evidence derived from patients with anosognosia for hemiplegia.

Aim of this project is to investigate, with fMRI, the neurophysiology of illusory motor execution in right brain damaged patients with anosognosia for hemiplegia. We focused on the motor activity of the upper limb, in particular on hand's fingers. The task we used "involved" intact and paralyzed limbs in an explicit motor finger opposition task, with interleaved interviews of the subjects about their motor performance. The registration of a residual activity within the premotor system, while the patient believes to have moved, will support the Frith's et al. (2000) hypothesis. The opposite observation would favour Heilman's interpretation that the patients generate no motor plans. Null outcomes are difficult but not impossible to interpret. In our study we will take the conservative attitude to accept the null hypothesis if no activation within the motor system will ever be found even at lowest statistical threshold (p<0.05 uncorrected) and if this finding will be replicated across anosognosic subjects.

2. Materials and methods

From a series of right brain damaged patients admitted to the Stroke Unit Department of Niguarda Ca' Granda Hospital from 2010 to 2011, we recruited (i) 5 right brain damaged neglect patients with anosognosia for hemiplegia and (ii) 5 right brain damaged neglect patients without anosognosia for hemiplegia. Subjects with any history or evidence of multifocal cerebrovascular disease, dementia or psychiatric disorders, as well as subjects showing any of the usual contraindications to MRI execution, were excluded. 24 normal volunteers (12 males and 12 females, mean age 59 years) were also recruited in order to obtain normative data.

2.1 Behavioural assessment

All subjects were tested with a clinical neuropsychological battery including the Mini Mental State Examination (Folstein et al., 1975) to exclude a generalized cognitive decline. Neurological assessment of motor strength, somatosensory and visual functions was performed according to the methods proposed by Bisiach, Vallar and Cappa (Bisiach et al., 1983).

We recruited only patients with a complete hemiplegia at a clinical assessment (3/3 at the Bisiach'

scale and totally unable to execute the proposed motor task). This allowed us to avoid the

confounding effect that residual motor power may have on the patients' evaluation on the status of

their motor system. All subjects tested were right handed according to the Edinburgh Handedness

Inventory (Oldfield, 1971).

As for the identification of visuo-spatial neglect, we used a modified version of the Albert test

(Albert, 1973) and of the Diller test (Diller et al., 1980; Diller and Weinberg, 1977) and considered

as "neglect" patients with a pathological score in at least one of the proposed tasks. The criteria for

the diagnosis of spatial neglect were derived from the performance of a control group of healthy

subjects tested on the same tasks. In the control group (n = 25; mean age: 60.09, SD: 6.93; range

45-74), the maximum difference between the number of left-sided and right-sided omissions was 1

for both tests. Hence patients with a left-right difference in omissions of at least 2, and in at least

one of the tests, were classified as suffering from spatial neglect. All the selected patients, with and

without anosognosia, suffered from a severe hemispatial neglect that was evident at both the

proposed tasks.

Anosognosia was assessed according to Bisiach's (Bisiach et al., 1983) four point scale, where the

most severe patients (score 3/3) deny the motor deficit even in spite of any contrary evidence and

claim to have moved following the examiner's instruction.

Demographic and clinical data of the selected patients are available in Table 1.

2.2 fMRI experiment

fMRI scans were performed during the execution of cued hand movements with, alternatively, the

right or left hand. The movements implied thumb to fingers sequential opposition: thumb to index,

thumb to middle finger etc. at a frequency of about 2Hz. These conditions were alternated with

resting state scans, according to a block design. Each block lasted for 30" (10 scans in each epoch)

and was followed by 3 scans in which subjects were asked through earphones whether they did move the hand's fingers. Subjects responded by pressing a button on a keypad with their right hand. There were 3 motor blocks and 3 rest blocks for each hand in a counterbalanced order.

All our patients with hemiplegia and severe anosognosia, when asked to execute a movement with the plegic limb, affirmed to have performed the movement even if none has occurred (they systematically pressed the button with their right index finger, that corresponded to the "Yes" response, after each motor block, irrespective of whether it was a left or a right movement block; on the contrary, they correctly answered by pressing the button corresponding to "No", with the middle finger, after each resting state block). This allowed us to monitor the constant presence of delusions of movement during the task's execution.

2.3 fMRI methods

MRI scans were performed using a 1.5 T General Electrics Signa scanner, equipped with gradient-echo echo-planar (Flip angle 90°, TE=60msec, TR=3000msec, FOV=280x210 mm; matrix= 96 x 64). All subjects were also scanned with a MP-RAGE high-resolution volumetric scan to identify the distribution of the brain lesions.

All conditions were modelled as a block design analysis. We used the Statistical Parametric Mapping 8 package (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). This permits stereotactic normalization of the MRI scans followed by a statistical analysis based on an ad hoc implementations of the general linear model.

During the standard pre-processing phase, normalization could have been confounded by the lack of correspondence between the subject (with a structural brain lesion) and the standardized template image. To avoid this effect, in this phase we inserted a mask image consisting of voxels values of zero in the lesioned area (see Brett et al., 2001).

After the pre-processing phase, before entering pre-processed data into the analyses, we checked for the images' quality by evaluating the degree of amplitude of the realignment parameters. Patients have been excluded from the analysis on the basis of excessive head motion during scanning (greater than 5 mm within a run in any direction). This stringent selection reduced the number of patients to 3 anosognosic and 3 non-anosognosic subjects, whose characteristics are summarized in Table 1.

Given this small sample size, we performed a fixed-effect analysis for each single patient.

We included in the design matrix the estimated movement parameters as confound regressors. Guided by a strong a priori assumption about activity in motor and premotor regions, all these analyses were performed as ROI based, by using anatomical regions of interest derived from the AAL anatomical template included in MRIcroN (Tzourio-Mazoyer et al., 2002). From this atlas we isolated (i) the bilateral precentral gyri, (ii) the bilateral supplementary motor area, (iii) the bilateral postcentral gyri, (iv) the bilateral supramarginal gyri and (v) the bilateral angular gyri. These regions have been selected as known to be involved in neural circuits implicated in motor intention, planning and execution (precentral giry and SMA) (Lau et al., 2004a), illusory movements and awareness in patients undergoing electrical stimulation by intracerebral electrodes (supramarginal and angular gyri) (Desmurget and Sirigu, 2009) and processing of sensory feedbacks (postcentral gyri). Furthermore, the region corresponding to each patient's mapped lesion was eliminated from the ROI used as mask, in order to exclude damaged voxels from fMRI analyses.

A random effect analysis was not possible given the small sample size. We thus resorted for inserting all the patients' data into a single multi-subjects fixed-effect analysis that allowed us to perform conjunction analyses between the activation patterns of the individual patients.

All analyses were masked on the main effect of right and left hand movement of healthy subjects, at a statistical threshold of $p < .001$. The statistical significance of the reported activation foci for all these analyses is available in Tables 2, 3, 4 and 5.

Patients	Sex	Age	Education (years)	Oldfield test	MMSE	Onset-fMRI (days)	M	SS	V	AHP	SP
							Neurological deficits				
A+ P1	M	63	5	R	21	8	3	3	3	3	0
A+ P2	F	77	5	R	11	8	3	3	2	3	0
A+ P3	M	76	13	R	23	12	3	2	1	3	0
A- P1	M	56	8	R	22	8	3	3	1	0	0
A- P2	M	61	8	R	18	6	3	3	3	0	0
A- P3	M	71	10	R	27	8	3	3	1	0	0

Table 1. The table summarizes the demographic and clinical data of the selected patients with and without anosognosia.

3. Results.

3.1 Lesion mapping results.

By using a subtractive approach, we first checked for differences in the anatomical distribution of the lesions between the two groups of patients (5 AHP+ vs 5 AHP-). This analysis confirmed results of the previous work on the anatomical bases of anosognosia by Berti et al. (Berti et al., 2005), as it revealed BA 4, 6, 44 as the centre of overlap, defined as those voxels in the subtracted lesion overlap that were damaged at least 80% more often in the experimental group than in the control group.
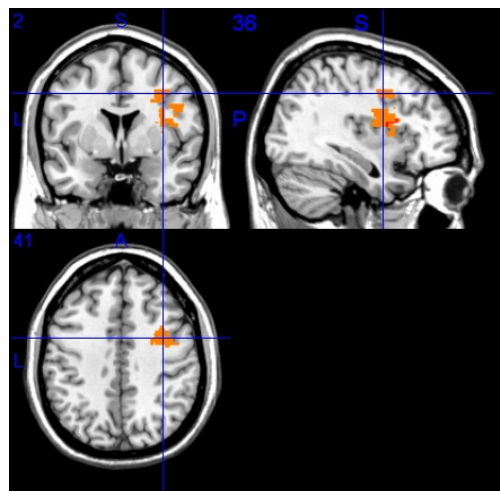
Figure 1: 5 AHP+ vs 5 AHP - . Subtractive method (MRIcroN): voxels in the subtracted lesion overlap that were damaged at least 80% more often in the experimental group than in the control group.

After the exclusion of the patients with excessive movement artefacts, the sample size was too small to perform any voxel-based analysis.

Figure 2 shows the lesions of each AHP+ and AHP- patient mapped in the stereotactic space and the overlay plots of the subtracted superimposed lesions (AHP+ patients vs AHP-patients).
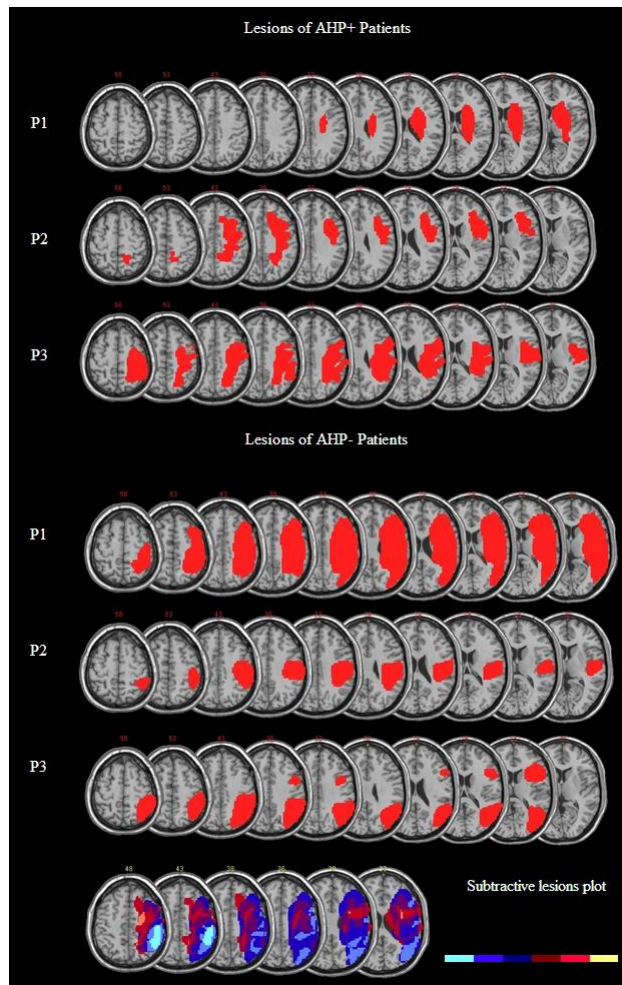
Fig 2. The figure illustrates the lesions of each patient with and without anosognosia, mapped in the stereotactic space. We also illustrate the overlay plots of the subtracted superimposed lesions (3 AHP+ patients vs 3 AHP- patients). Light blue colour in the scale indicates that the region is damaged in all of them AHP- patients and in none of the AHP+. Conversely, yellow indicates that the region is commonly damaged in all AHP+ subjects and in none of the AHP- .

3.2 fMRI results.

3.2.1 Right Hand.

As expected, the neural activations for the real movement of the intact right hand involved, in each AHP+ and AHP- patient, a mainly contralateral fronto-parietal network including primary motor

and premotor regions, the primary somatosensory cortex and, more posteriorly, the supramarginal and/or angular gyrus.

3.2.2 Left Plegic hand.

More notable were data emerging from the "movement" of the left plegic hand. As shown in Table 1 and Figure 3, in all of them AHP+ patients, it was detected a significant neural activity inside premotor regions spared by the lesion in the right hemisphere, and in premotor and parietal regions of the left intact hemisphere. This residual activity was particularly pronounced in the left hemisphere of the patients. The same pattern was activated in non anosognosic subjects, but it resulted to be less spatially extended than in anosognosic patients.

As patients were selected as having a complete hemiplegia (in particular a complete paralysis of the left hand), and given that they were monitored for any visually detectable residual motor capacities of the plegic hand, as well as for mirror movements of the right hand, during the tasks execution, this ipsilateral activity can not be explained by any real movement of the left or right hand.

Figure 3: Neural activations for the movement of the right and left hand in 3 AHP+ and 3 AHP- patients. Fixed-effect analysis. Contrasts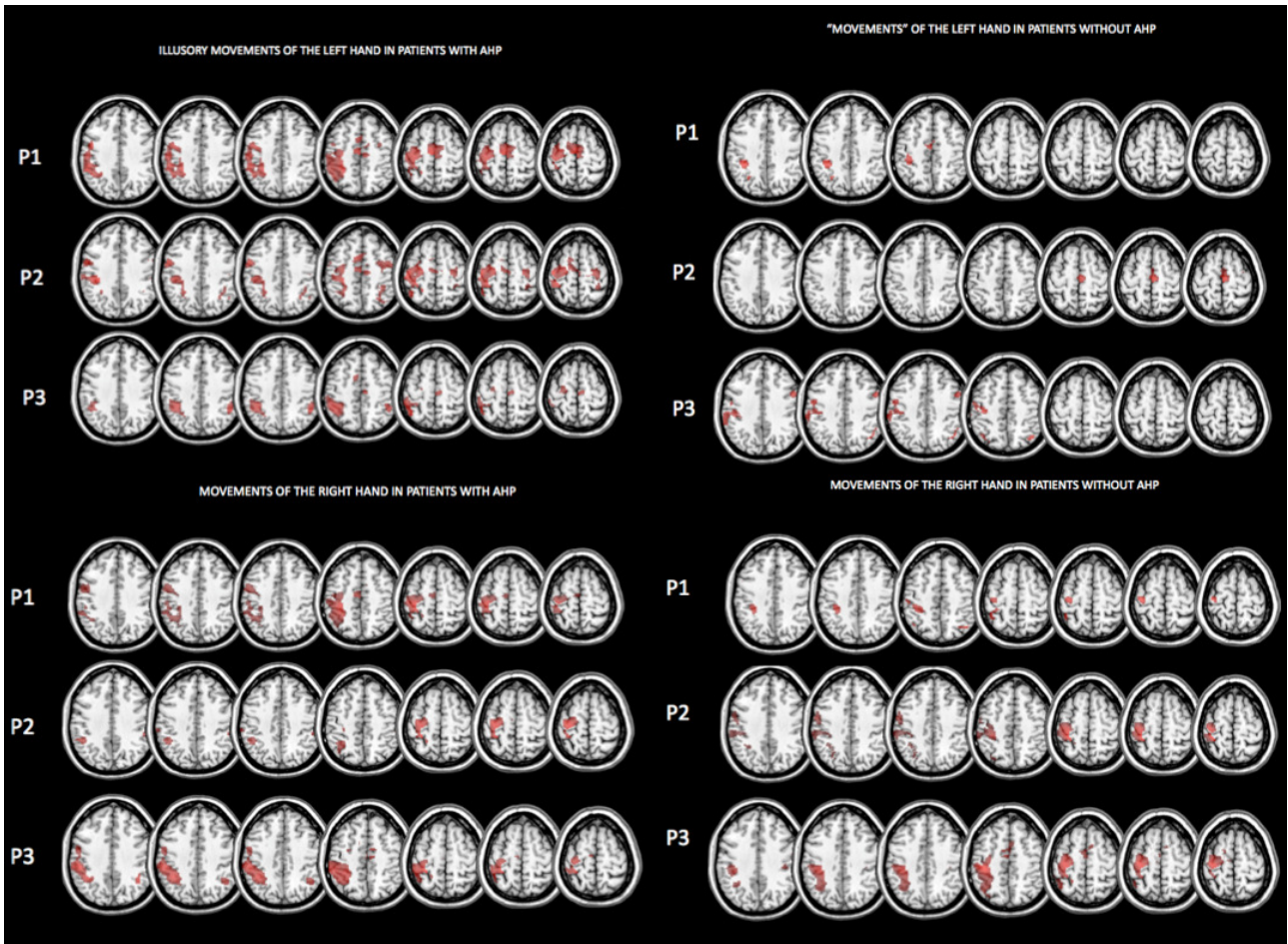 of interested have been masked on the main effect of movement of the right and left hand in healthy individuals, this mask has been thresholded at p<.001.

| | | AHP + Neural activations for illusory movement of the left plegic hand > rest | | | | | | | | | | AHP+ Neural activations for right hand movement > rest | | | | | | | | | | |
| | | Left brain hemisphere | | | | | Right brain hemisphere | | | | | | Left brain hemisphere | | | | | Right brain hemisphere | | | | |
		X	Y	Z	z-score	p=	X	Y	Z	z-score	P=		X	Y	Z	z-score	p=	X	Y	Z	z-score	p=
A+ patient 1	SMA (4/6)	-6	-18	62	5.6	0.000						SMA (6)	-4	-12	68	3.23	0.001					
	SMA (6)	-4	-12	68	5.4	0.000						SMA (6)	-10	2	66	2.38	0.009	10	0	54	2.71	0.003
	SMA (6)						14	4	68	2.3	0.010	Precentral gyrus (4)	-26	-24	70	4.42	0.000					
	Precentral gyrus (4)	32	-2	52	2.8	0.002						Postcentral gyrus (3)	-32	-30	56	7.14	0.000	64	-12	22	2.44	0.007
	Precentral gyrus (4)	-46	-2	22	2.6	0.005						Supramarginal gyrus (2)						68	-22	24	3.35	0.000
	Precentral/Postcentral gyrus (4)						12	-26	62	2.5	0.007	Supramarginal gyrus (40)	-60	-46	36	4.43	0.000	68	-30	26	3.07	0.001
	Postcentral gyrus (3)	-48	-4	18	2.4	0.009						Supramarginal gyrus (22)						66	-46	26	2.70	0.003
	Inf. parietal gyrus (40)	-32	-42	46	5.3	0.000																
A+ patient 2	SMA (6)	-6	6	46	3.0	0.001	14	-20	50	2.5	0.006	Precentral gyrus (4)	-28	-26	66	3.99	0.000					
	SMA (6)	-6	-18	52	2.8	0.002						Precentral gyrus (4)	-34	-20	66	3.70	0.000					
	Precentral gyrus (4)						24	-20	64	2.8	0.002	Postcentral gyrus (2)	-30	-40	60	3.51	0.000					
	Precentral gyrus (4)						38	-6	50	2.4	0.009	Supramarginal gyrus (2)						54	-34	38	2.62	0.004
	Precentral gyrus (4)	-42	-20	64	3.9	0.000	46	-6	52	2.6	0.005	Supramarginal gyrus (40)	-50	-48	36	2.56	0.005	58	-24	46	2.80	0.003
	Precentral/Postcentral gyrus (4)	-54	-2	40	3.4	0.000																
	Postcentral gyrus (3)	-48	-24	60	3.9	0.000	62	-2	24	2.6	0.005											
	Postcentral gyrus (3)						44	-26	40	2.5	0.006											
	Supramarginal gyrus (40)						64	-22	30	4.0	0.000											
	Inf. parietal gyrus (40)	-38	-32	38	3.9	0.000	34	-46	48	2.4	0.009											
	Inf. parietal gyrus (40)						36	-48	44	2.3	0.010											
A+ patient 3	SMA (6/4)						6	-24	52	3.4	0.000	SMA, (6)						8	-16	50	2.38	0.009
	SMA (6)						2	-20	72	3.2	0.001	SMA, (6)						10	-6	48	2.82	0.002
	SMA (6)						4	-24	64	3.2	0.001	Precentral gyrus (4)	-48	8	16	3.46	0.000	58	10	18	2.46	0.007
	Precentral gyrus (4)	-24	-20	70	2.4	0.008	12	-26	72	2.6	0.005	Postcentral gyrus (3)	-30	-38	60	4.04	0.000					
	Supramarginal gyrus (40)	-60	-22	20	2.9	0.002	58	-20	26	2.6	0.005	Supramarginal gyrus (40)	-54	-22	18	3.88	0.000	54	-24	20	3.03	0.001
	Supramarginal gyrus (42)	58	-48	26	3.5	0.000						Inf. parietal gyrus (2)	-52	-32	38	3.69	0.000					
	Inf. parietal gyrus (40)	-46	-44	54	3.5	0.000	50	-52	46	4.0	0.000	Angular gyrus (39)						42	-54	38	3.06	0.001
	Inf. parietal gyrus (40)	-38	-42	44	3.1	0.001																

Table 2.

		AHP- Neural activations for left hand "movement" > rest											AHP- Neural activations for right hand movement > rest										
		Left brain hemisphere					Right brain hemisphere						Left brain hemisphere					Right brain hemisphere				
		X	Y	Z	z-score	p=	X	Y	Z	z-score	p=		X	Y	Z	z-score	p=	X	Y	Z	z-score	p=
A- patient 1	SMA (6)	-10	-10	50	2.43	0.007	0	14	52	2.48	0.006	Precentral gyrus (4)	-38	-22	64	3.01	0.001					
	Precentral gyrus (4/6)	-24	-24	72	2.48	0.007						Postcentral gyrus (3)	-36	-38	54	2.65	0.004					
	Inf. Parietal gyrus (40)	-38	-40	40	3.55	0.000						Supramarginal gyrus (40)	-56	-30	26	2.72	0.003	60	-38	38	3.10	0.001
												Angular gyrus (39)						44	-62	50	2.96	0.002
												Inf. Parietal gyrus (40)	-34	-36	44	2.43	0.007					
A- patient 2	Precentral gyrus (4)	-48	-2	20	2.4	0.008	30	-28	70	2.5	0.006	Precentral gyrus (4)	-48	0	20	2.39	0.008					
	Precentral/Postcentral gyrus (4)	-40	-20	50	3.3	0.000						Precentral gyrus (4)	-46	-2	22	2.41	0.008					
	Precentral gyrus (4/6)						50	4	40	3.0	0.002	Precentral/Postcentral gyrus (4/3)	-56	-4	44	3.64	0.000					
	Postcentral gyrus (1,3)	-44	-22	42	2.4	0.008	26	-40	72	3.3	0.001	Postcentral gyrus (3)	-32	-36	60	6.22	0.000					
	Supramarginal gyrus (40)	-46	-28	30	3.0	0.001	68	-24	24	2.6	0.005	Supramarginal gyrus (40)	-54	-26	20	2.70	0.004					
	Inf. parietal gyrus (3)	-42	-24	40	2.4	0.008						Inf. parietal gyrus (40)	-58	-32	48	2.77	0.003					
	Angular gyrus (39)						46	-62	44	3.2	0.001											
A- patient 3	SMA (6)						4	-18	62	3.9	0.000	Precentral gyrus (4)	-30	-26	56	4.49	0.000					
	Postcentral gyrus (3)						28	-34	72	3.6	0.000	SMA (6)	-4	-6	54	3.57	0.000	6	8	56	2.83	0.002
	Angular gyrus (7)	-40	-66	54	2.4	0.008						Precentral gyrus (6)	-14	-12	70	2.54	0.006					
												Precentral gyrus (6)	-34	-22	64	4.81	0.000					
												Postcentral gyrus (3)	-40	-28	50	4.96	0.000	56	-10	30	2.49	0.006
												Supramarginal gyrus (48)	-52	-22	16	2.82	0.002	56	-24	30	2.80	0.003
												Supramarginal gyrus (3)						62	-24	42	2.49	0.006

Table 3.

Table 2 and Table 3 report, respectively for each single AHP+ and AHP- patients, MNI coordinates, Z scores and p values of the activation foci for the movement of the left hand (left side of the tables) and of the right hand (right side of the table).

As explained above, data from all the selected patients were then integrated into a single design matrix in a multi subjects and multi-run fixed effects analysis (Friston et al., 1999). This kind of analysis allows the identification of activations common to all subjects. Conjunction analyses performed by using a fixed-effect model are known to be very sensitive and allow the inference that each studied subject activate the resulting anatomical regions, and that "at least a certain proportion of the population would have shown this effect" (Friston et al., 1999). The contrasts of interest were masked using the main effect of movement of the right and left hand in healthy control subjects thresholded at p<.001(uncorrected). The statistical significance (p value) for the reported activation foci is available in Tables 4 and 5.
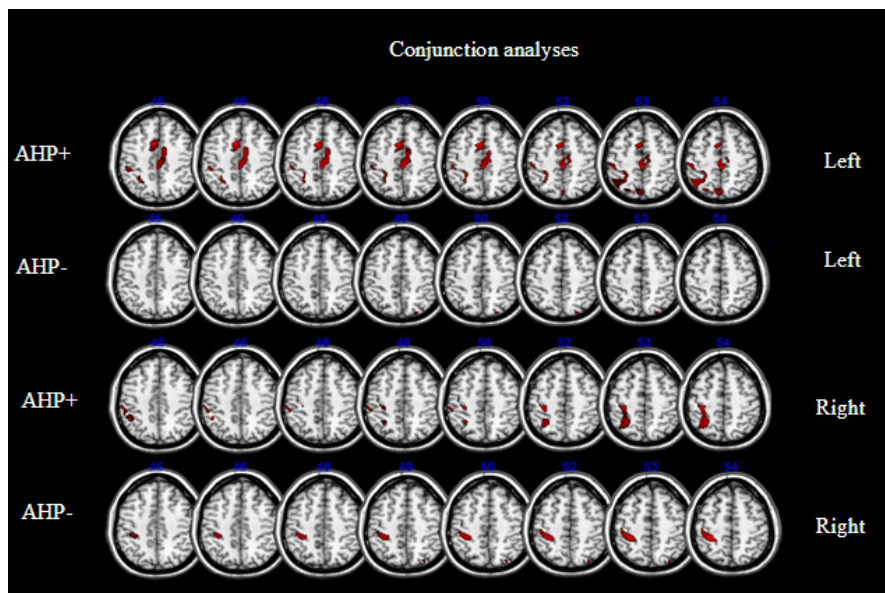

Figure 4. Multi-subjects fixed-effect analysis. In the upper part, the figure shows activations for the task "move the left hand" common to all of them 3 anosognosic (AHP+) and 3 non-anosognosic (AHP-) subjects. In the lower part, the figure shows activations for the real movement of the right hand common to all of them 3 AHP+ patients and 3 AHP- subjects (effects of interest are masked on the main effect of right and left movement in healthy subjects thresholded at p<.001).

Results, illustrated in Figure 4 and detailed in Table 4, still showed the expected contralateral motor activations for the right hand movement in AHP+ and AHP- patients. Notably, in confirmation of the single-patients fixed-effect analyses reported above, the illusory movement of the left plegic hand was consistently associated with a significant activation of the supplementary motor area and left parietal regions, while no activation was found in this analysis for non-anosognosic patients.

	Neural activations for movement of the right hand > rest in all AHP+ patients									
	Left brain hemisphere					**Right brain hemisphere**				
Brain regions	**X**	**Y**	**z**	**z score**	**p value**	**x**	**y**	**z**	**z score**	**p value**
Precentral gyrus (4)	-32	-28	60	4.74	0.000					
Postcentral gyrus (3)	-30	-38	60	3.96	0.000					
Superior parietal gyrus (7)	-28	-50	58	3.86	0.000	no voxels survived the statistical threshold				
Inferior parietal gyrus (40)	-44	-46	42	3.18	0.001					
Inferior parietal gyrus (40)	-54	-32	46	3.10	0.001					

	Neural activations for movement of the right hand > rest in all AHP- patients									
	Left brain hemisphere					**Right brain hemisphere**				
Brain regions	**X**	**Y**	**z**	**z score**	**p value**	**x**	**y**	**z**	**z score**	**p value**
Precentral gyrus (4/6)	-36	-24	66	4.51	0.000					
Postcentral gyrus (3)	-34	-38	56	4.78	0.000	no voxels survived the statistical threshold				
Postcentral gyrus (3)	-46	-28	54	3.15	0.001					
Precuneus	-2	-60	68	3.19	0.001					

	Neural activations for illusory movement of the left plegic hand > rest in all AHP+ patients									
	Left brain hemisphere					**Right brain hemisphere**				
Brain regions	**X**	**Y**	**z**	**z score**	**p value**	**x**	**y**	**z**	**z score**	**p value**
Precentral gyrus (4/6)	-22	-18	68	3.2	0.001					
SMA (6/4)	-2	-22	54	3.3	0.000	4	-32	54	3.9	0.000
SMA (6)	-6	8	50	4.3	0.000	8	-6	48	3.4	0.000
Postcentral gyrus (3)	-46	-30	58	3.5	0.000					
Thalamus	-6	-24	2	3.4	0.000					
Sup. parietal gyrus (7)	-30	-58	62	4.3	0.000					
Supramarginal gyrus (40)	-36	-38	38	3.4	0.000					
Inferior parietal gyrus (40)	-44	-36	42	3.4	0.000					

	Neural activations for illusory movement of the left plegic hand > rest in all AHP+ patients	
Table 4	No voxels survived the statistical threshold	no voxels survived the statistical threshold

Table 4. Conjunction analysis. Brain regions commonly activated in the 3 AHP+ patients, and , seprarately, activations common to all the 3 AHP- patients. The table reports the anatomical locations, Brodmann's areas (in brackets), stereotaxic coordinates of the activation foci in the MNI space, Z-scores and p values for the contrasts Movement of the right hand > rest and "movement" of the left hand > rest, for anosognosic and non anosognosic patients at the multi-subjects fixed effect analyses.

When directly compared with the three non-anosognosic hemiplegic patients, AHP+ subjects showed hyperactivations of this same network (supplementary motor area, left primary sensory-motor areas and left parietal regions) during the illusory movement of the paralyzed hand (Figure 5, Table 5).
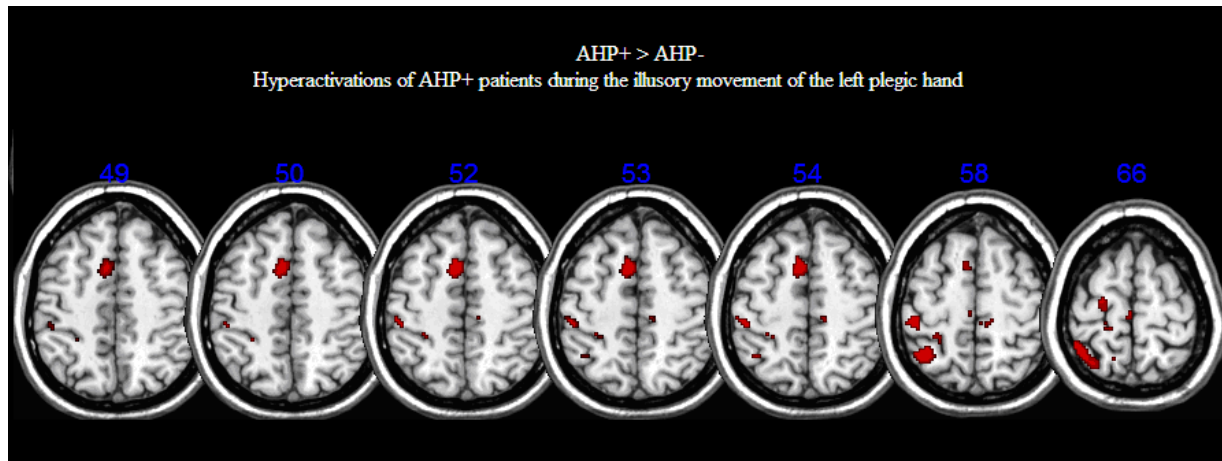

Figure 5. The figure shows brain regions that are significantly hyperactivated in AHP+ patients compared to AHP-patients, during the "*movement*" of the left plegic hand.

	Neural activations for "movement " of the left plegic hand in AHP+ patients > AHP- patients									
	Left brain hemisphere					**Right brain hemisphere**				
	X	Y	Z	z-score	p=	X	Y	Z	z-score	P=
Precentral/Postcentral gyrus (4)	-44	-24	62	5.0	0.000					
SMA (6)	-6	10	52	4.0	0.000					
Precentral gyrus/SMA (6)	-22	-14	68	3.9	0.000					
Precentral gyrus/Paracentral lobule (4)	-4	-24	62	3.5	0.000	2	-30	60	3.2	0.001
Postcentral gyrus (3)	-30	-38	54	3.5	0.000					
Inf. parietal gyrus (40)	-48	-34	44	3.5	0.000					
Sup. parietal gyrus (40)	-38	-52	62	4.5	0.000					

Table 5. The table reports the anatomical locations, Brodmann's areas (in brackets), stereotaxic coordinates of the activation foci in the MNI space, Z-scores and p values for the contrast "Movement" of the left hand > rest AHP+>AHP- patients.

4. Discussion

Aim of this research was to investigate with an fMRI study the neural bases of motor awareness in hemiplegia with or without anosognosia.

We measured, with fMRI, the neural activity in anosognosic patients and in hemiplegic non-anosognosic patients during a motor task. The fMRI experiment in these subjects permitted to provide the first neuroimaging assessment of the two main competing interpretations of anosognosia with opposite predictions about the residual activity within the motor system (Heilman et al., 1991, 1998, Frith et al., 2000). Our observation is in line with the Frith et al. (Frith et al., 2000) hypothesis and provides a neurophysiological basis to behavioural evidence (Berti et al., 2007; Fotopoulou et al., 2008) that, so far, suggested a preservation of the intention to move the paretic limb in anosognosic patients, in whom the non veridical belief of having moved would ground on residual aspects of motor planning components, in combination with a malfunction of the putative comparator.

The hyper-activation of motor regions of the left hemisphere is not as surprising as one may have thought at a first sight, given that evidence exists of a compensatory effortful of the intact motor regions in hemiplegic patients (see discussion in Pascual-Leone et al., 2005) and of a dominant role of this site of the brain in motor planning, with an also ipsilateral control of the left hemisphere on the left hand. However, in densely anosognosic patients, the activation of spared motor regions (precentral gyrus and supplementary motor area) confirms their possibility to intend to move and to generate motor plans. The concomitant presence of a damage to the right premotor cortex would prevent these patients from the possibility of correctly comparing predicted motor representations, though adequately generated, with sensory feedbacks of the non-executed action (Berti et al., 2005). These results represent the first direct neurofunctional evidence testifying a residual neural activity in brain circuits involved in motor intention and planning, suggesting that, inside premotor cortical regions spared by the lesion, the generation of a motor representation would still be possible. The

existence of such a residual motor representation, together with the consequent genesis of a predicted representation of the motor state (according to the Frith's model), would overcome sensory feedbacks of "no movement", thus triggering the non veridical awareness of having performed a movement with the plegic limb.

Of course much work still needs to be done to reach a full comprehension of motor awareness and its disorders. This evidence supporting the possibility of preserved motor intentions in anosognosic patients, although extremely relevant, is simply the first step towards a deep comprehension of this defect. It still remains to be fully clarified, for example, the role of the putative comparator in generating anosognosia. While Frith and colleagues (2000) proposed missing or neglected feedback information directed toward a still functioning comparator, Berti et al. (2005) suggested a damage of the comparator itself that, therefore, would be unable to detect mismatches even in presence of correct sensory feedbacks. Although anatomical lesions analyses showing damage of premotor regions, speaks in favour of Berti et al.'s (2005) hypothesis, a separate experiment would be needed to solve this question. Moreover, the observation of anosognosic patients (Bisiach et al., 1986; Ramachandran, 1995; Vallar et al., 2003) definitely shows several clinical manifestations, which suggest not only different degrees of severity of motor denial, but also a qualitative difference among these symptoms. A more detailed investigation of these symptoms could probably lead to a multifaceted classification including different kinds of motor denial, for example, with cases with and without an implicit knowledge of the deficit and different anatomical and neuro*dys*functional correlates.

6. Chapter 6. Conclusions.

To summarize, in this thesis, I concentrated on "positive" or "productive" manifestations that are usually observed in the context of unilateral neglect syndrome in patients with right brain damage. It was not clear whether these behaviours were functionally related, nor to what extent their anatomical bases could be disentagled from those of spatial neglect. Different strategies could have been considered to address this issue. Here we used anatomo-clinical correlation inference and anatomo-functional approaches, trying to witness discrete anatomical substrates for these different kinds of manifestations. In this way, we provided evidence for specific anatomical correlates of diverse productive behaviors associated with right brain damage, supporting that they are underpinned by different mechanisms and can be somewhat disentangled from spatial neglect [24].

In the personal space, somatoparaphrenia and anosognosia seem to be so closely interconnected that one might have wondered on whether specific anatomical substrates could ever be defined for these symptoms. However, we reported a number of cases of symptomatological dissociations and described the crucial role of a subcortical damage for the onset of somatoparaphrenia. Differently, anosognosic patients showed a specific involvement of cortical premotor regions. The observation of a preserved neural activity in the spared supplementary motor area suggests the preserved possibility of the generation of a motor intention/plan, the delusion thus deriving from a defective comparison between intended and predicted motor representations and the overcome of predictions on actual feedbacks.

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[24] Notwithstanding this effort toward the characterization of specific anatomical and cognitive mechanisms underlying these disorders, in line with the recent trend to the demonstration of symptomatological dissociations in the contex of the multi-componential disorder of spatial neglect, we also support that these defects are closely related to spatial neglect, and partially share its anatomical substrate (see for example the anatomical bases we showed for somatoparaphrenia and additional marks perseveration). The well known empirical observation of an amelioration of the entire spectrum of deficit commonly associated to neglect following diverse kinds of stimulation (caloric vestibular stimulation, prism adaptation etc.) strongly supports this association (see Vallar et al., 2003).

In the extrapersonal space, perseveration in cancellation tasks is the most common productive symptom. With respect to previous studies on the anatomical bases of perseveration, and its relation with neglect, which produced contrasting results, we covered a further step by isolating different behavioral patterns differently related with spatial neglect and underpinned by diverse anatomical substrates.

To conclude, we notice that, although the disorders described in this thesis are extremely different phenomena that, indeed, manifest as verbal or motor acts, in different spatial frames and in different side of the space (right or left, the "good" or "bad" hemispace), the damage of the opercular part of the inferior frontal gyrus is a common finding. This datum supports a link between these diverse phenomena, which may be all conceptualized as forms of defective monitoring of sensory-motor aspects of the self.

Oustanding issues..

Although results reported in the present thesis are, in my opinion, extremely relevant, a number of still open questions need to be given an answer to gain a deeper understanding of these symptoms. These are left for future experiments.

For example, as for the study of somatoparaphrenia, in our records of subjects, there was no sufficient data to permit a systematic evaluation of the time course of this disorder. Such a study will permit to evaluate the exact time course of somatoparaphrenia in relation to the time course of other sensory, motor or cognitive symptoms related to spatial neglect and AHP. Moreover, it could be useful to identify a particular lesion pattern associated with a greater likelihood of a persistent deficit and the physiological correlates of the remission of the disorder.

Symptomatological dissociation between somatoparaphrenia, personal neglect and anosognosia is another crucial point that deserves further investigations. In our series of pure somatoparaphrenic patients, only one subject had a severe form of personal neglect, being totally unable to localize the paralyzed limb. Four patients had a much milder form, being able to reach out the paralyzed limb after initial hesitations. Clearly, this represents a further dissociation between some form of implicit

knowledge, that permits the reaching behavior, and knowledge mediated by verbal descriptions, the one produced by the patients during the delusions of SP whereby *that* limb does belong to someone else[25] . A further intriguing question is whether patients with SP and no AHP are referring to an alternative body schema of a foreign person, instead of their own corrupted bodily representation, to correctly evaluate actual motor performance. Further manipulations of the patients' interview may help to shed new light on this uncommon dissociation. For example, one could try to induce a modulation of the patients' motor awareness, by asking, alternatively, to report about the "alien" limb as much as about "their" limb.

As for the dysfunctional cognitive mechanisms producing anosognosic motor delusions, the evidence for a preserved motor intention in anosognosic patients, although extremely relevant, is simply the first step towards a deep comprehension of this disorder. Indeed, it still remains to be fully clarified, for example, the role of the putative comparator in generating anosognosia. While Frith and colleagues proposed missing or neglected feedback information directed toward a still functionant comparator, Berti et al. suggested a damage of the comparator itself that, therefore, would be unable to detect mismatches even in presence of correct sensory feedbacks. A separate experiment would be needed to solve this question.

A recent model of motor control proposed by Desmurget and Sirigu (2009) introduce a further level of processing of the information leaving from the intact or dysfunctional comparator. A correct error message deriving from a preseverd mechanism of comparison between predicted motor representations and sensory evidence, could, however, be incorrectly processed in damaged parietal regions, preventing patients from a conscious error detection. The information about the motor failure, however, would be available at more implicit levels.

The observation of anosognosic patients (Bisiach et al., 1986; Ramachandran, 1995; Vallar et al., 2003) shows that there are several clinical manifestations. This does not only suggest different

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[25] It may be interesting to recall that personal neglect is normally tested with the eyes shut.

degrees of severity of motor denial, but also a qualitative difference amongst these manifestations. In the future, a more detailed investigation of these symptoms could probably lead to a multifaceted classification including different kinds of motor denial. For example, the study of the anatomical correlates of forms of complete anosognosia and forms in which an implicit knowledge of the deficit can be detected (it remains to be established how to detect it), could help to clarify the role of at least two of the main regions proposed as anatomical correlates of this deficit: the parietal and premotor cortices. This clarification would be also extremely relevant for the investigation of the neurofunctional correlates of normal processes of motor monitoring and motor awareness.

In summary, much work still needs to be done to reach a full comprehension of motor awareness and its disorders.

With regards to the extrapersonal space, our study on the different perseverative manifestation, their different relation with neglect, neglect related phenomena and anatomical bases, crucially needs to be expanded with the online registration of the patients' performance during cancellation tasks. This would permit to disentangle different behaviours that may produce the same final pattern of additional marks over the same target (a recurrent and a repetive mechanism, as proposed by Kim et al., 2009) and to investigate the plausible different nature of these behaviours maybe also linked to further distinguishable anatomical correlates. The use of different kinds of manipulation (such as for example vestibular caloric vestibulation or prismatic lenses) would also be useful in demonstrating the different relation of these manifestations with neglect if they will lead to the selective remission of one type of perseveration. This study also needs to be integrated with the observation of perseverative manifestations in non negect patients.

These and other experimental manipulations may help to further develop our understanding on productive symptoms and the functional mechanisms underlying the normal experience of these different aspects of sensory-motor monitoring and self awareness.

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You're in quest for more, to find the core,

Your journey still ain't over..

Your quest is your purpose, go on..!

You're in quest for more, to find the core,

It will be - never- over

Your quest is your purpose, go on ... !