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ACTION IN SELF-AWARENESS:
Evidence from Ansognosia for Hemiplegia and from Somatoparaphrenia

FINAL DISSERTATION

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To my Dad

Contents

Abstract

Conscious awareness is a fascinating psychological function of the human mind. It describes a subjective first-person phenomenon (Damasio, 1998), that consists in both the cognitive processes of the self and its interactions with the external world.

Therefore the construction of the self-awareness includes all the experiences related to the body (James, 1980), in order to process and to represent the perceptual, motor, emotional and cognitive states as own bodily states.

This function results to be impaired in several neuropsychological and neurological disorders (Flashman, 2002), causing interferences with the personal identity or the awareness about ourselves (Orfei, et al., 2007). These pathological conditions reveal insight to scientifically investigate the cognitive processes and the neuroanatomical networks involved in awareness of the bodily self (Fotopoulou, 2012).

The self-awareness include both the 'sense of agency' as the feelings of the authorship and control of our actions and of the following changes on the external world and the 'sense of ownership' as the appreciation of the body as belonging to me (Gallagher, 2000) and they can be selectively or simultaneously impaired.

The specific disorder of body agency is the Anosognosia for hemiplegia (Babinski, 1914), as the apparent unawareness of own sensorimotor deficits or the inability to acknowledge and appreciate the severity of the paralysis and other sensorimotor deficits following stroke (Cocchini, Beschin, Cameron, Fotopoulou, & Della Sala, 2009)

Indeed the disturbances affecting the body ownership are the inability to recognize one's own body ('asomatognosia', Cutting, 1978) and the misattribution of ownership of own arm to another person ('somatoparaphrenia', Gerstmann, 1942).

This thesis aims to investigate the possible influences of bodily aspects in self-awareness, by focusing on the specific role of actions.

In Chapter 1 and 2, I introduced the disturbances of self-awareness of the Anosognosia for Hemipleia, and Somatoparaphrenia with neuropsychological and neuroanatomical accounts. Subsequently I wanted to highlight the importance of planning an action in these deficits in order to enhance the degree of motor awareness through both bottom-up and top-down mechanisms.

My main projects focused on the investigation of the role of the Action in Anosognosia for Hemiplegia. In details in Chapter 3, 4 and 5 my experiments based on evaluating the fluctuations of motor awareness in patients with Anosognosia for Hemiplegia during the request to execute an action. I investigated this issue in some different tasks: in the attempts to act, in third-perspective view and in automatic bodily activation by measuring skin conductance responses. In addition I modulated the affective resonance of these tasks by using dangerous stimuli, so that I could evaluate the influences of both bottom-up sensorimotor and top-down emotional and cognitive components in awareness' fluctuations. I also integrated brain lesion-analyses to understand the neural networks underneath.

In Chapter 6, I integrated the thesis with a single-case study of a patient with Crossed Somatoparaphrenia. This rare disorder gave me the possibility to investigate some aspects related to the body image and the body schema. I studied this patient in different situations assessing: multisensory integration and spatial components of proprioception and third-perspective view, in order to evaluate both sensorial and higher-order possible effects relating to the body representation.

In addition, I also enclosed two single-case studies. The first was a young patient with Balint's syndrome, which was evaluated in a cross-modal task, the second a man affected by Tactile Agnosia, whit whom I applied a rehabilitation program with transcranical direct-current stimulation. These studies are included as extra experiemental studies not belonging to the main PhD topic.

Chapter 1

Self-Awareness

1.1. Conceptualizing Anosognosia

The term Anosognosia (from the Greek, α = without, νόσος = disease, γνῶσις = knowledge) defines a disorder of the awareness of one's own disabilities, consequent to a brain lesion. These patients are incapable to recognize or to appreciate the severity of a deficit in sensory, motor, affective or cognitive functions (as memory or language) (Bisiach & Geminiani, 1991; Prigatano, 1996, 2010).
Babinsky (1914) coined the term Anosognosia for Hemiplegia (AHP), which indicates the pathological denial of contralesional motor deficits, following a right brain damage (but see Cocchini et al., 2009 for left hemisphere cases; Jehkonen, Laihosalo, & Kettunene, 2006). Specifically, AHP is a deficiency of awareness of the paralysis and of other possible concomitant sensorimotor impairments (Cocchini et al., 2009). In this condition, patients declare an unrealistic degree of autonomy, since they assume to be capable to act, to use their hand, or to walk (Vocat, Staub, Stroppini, & Vuilleumier, 2010).

1.1.1. Epidemiology of Anosognosia for Hemiplegia

Empirical studies of AHP after stroke report different frequencies of incidence of the disorder. From the classical range of prevalence of about 33-58% (Bisiach, Vallar, Perani, Papagno & Berti, 1986; Cutting, 1978), more recent studies have reported an occurrence from 10 to 17% (Baier & Karnath, 2005). This variability can mainly be attributed to differences in both diagnostic criteria of assessment and time since stroke onset (Jehkonen et al., 2006, Orfei et al., 2007). As a matter of fact, a meta-analysis of studies about AHP reported a prevalence range between 20 and 44% depending upon the time passed from the neurological event (Pia, Neppi-Modona, Ricci & Berti, 2004). For instance, it has been documented in 58 right brain damaged patients that the presence of AHP decreases from 38% in an hyperacute stage at 3 days from onset, to 18% in 1 week (subacute stage), and to 5% in a chronic condition after 6 months (Karnath, Baier and Nägele, 2005). Although AHP appears to change and evolve over time and to be often a transient dysfunction, it can affect the rehabilitation of all perceptual and cognitive deficits (Gialanella, Monguzzi, Santoro & Rocchi, 2005; Jehkonen et al., 2006), and it may result in poor general recovery (Jehkonen et al., 2000).

Finally, only a few studies investigated anosognosic disorders in hemiplegia after a left hemispheric stroke. Thus, their incidence might be underestimated due to a dependency on language in awareness' assessments and a consequent restriction of diagnostic tools (e.g., VATA-m, Della Sala, Cocchini, Beschin & Cameron, 2009).

1.1.2. Characteristics of Anosognosia for Hemiplegia

AHP is a specific neurological disorder that cannot be explained by a mere sensorimotor loss, a confusional state or a general cognitive deficit (Coslett, 2005). Although an intellectual impairment may be a predisposing condition for major severity, it does not appear to be the main causal factor of unawareness (Marcel, Tegnér, & Ninno-Smith; 2004, Vuilleumier, 2004).

Furthermore, AHP manifests in frequent co-presence with other deficits (e.g., personal and visual spatial neglect, Jenkinson, Preston, & Ellis, 2011), but double dissociations of AHP have been demonstrated with confabulation and deficits of frontal lobe functions (see, Heilman & Harciarek, 2010 for a review), proprioceptive (Cocchini et al., 2010) and personal or spatial visuo-motor impairments (Vocat et al., 2010).

These evidences of double dissociations indicate that anosognosia is a definite and independent deficit of awareness (Jehkonen et al., 2000), but in clinical practise

AHP appears as a heterogeneous phenomenon (Besharati, Crucianelli, & Fotopoulou, 2014; Orfei, et al., 2007), that manifests itself in several ways (Heilmann & Harciarek, 2010; Marcel, et al., 2004; Vocat et al., 2010).

In the more general cases, AHP patients are unaware of the presence of their deficits occurred after the stroke and also declare to be able to move their limbs as like as healthy individuals. Instead, in some partial clinical manifestations of AHP, these patients declare to suffer of some motor impairments and they sometimes justify with causes other than hemiplegia (i.e., tiredness, sprained ankle, arthritis, etc.) (Orfei, et al., 2007), or someone even claiming bizzare explanations to contradictory evidences (Bisiach, et al., 1986; Bisiach & Germiniani, 1991).

Furthermore, the affective resonance of the syndrome may reveal itself in various expressions. AHP patients can indeed remain optimistic about their prognosis or they can minimize and disclose abnormal attitudes towards their limb weakness (additionally related 'anosognosia phenomena', Cutting, 1978), up to a form of indifference to the problem, namely 'anosodiaphoria' (Babinski, 1914). Instead, other patients can express delusional components (Turnbull, Jones, & Reed-Screen, 2002; Vuilleumier, 2004), with abnormal beliefs or approaches towards their affected limbs, including excessive dislike or hatred ('misoplegia', Critchley, 1955).

The appearance of awareness can also appear independently in a behavioural or a verbal level. Some patients verbally admit the paralysis during a conversation, but attempt to move their plegic limb. Vice versa, other patients deny the presence of hemiplegia, but request constantly to remain in bed (Jehkonen et al. 2006; Marcel et al. 2004; Nimmo-Smith, Marcel, & Tegnér, 2005).

These features of partiality can also be very persistent and lead to different subtypes of AHP's manifestations. For instance, the syndrome can be explicitly affirmed, or can show some implicit forms of awareness. In these last cases, motor impairments are denied, but some degree of awareness about them is unintentionally expressed in task performances (Schacter, 1990).

Finally, other body delusions concerning the sense of body ownership may co-occur with AHP. In spite of the fact that behavioural and anatomical double dissociations with other body representation's disordered have been reported (Gandola et al., 2012; Invernizzi et al., 2013; Moro & Pernigo, et al., 2016, Vallar & Ronchi, 2009), some AHP patients cannot recognise one’s own body ('asomatognosia'), or they attribute its ownership to somebody else ('somatoparaphrenia', Gerstmann, 1942).

This clinical variability confirms that AHP is a multifaceted syndrome, which manifests itself in several sub-types (Jehkonen et al. 2000; Marcel et al. 2004), and suggests that different assessment methods, and likely, of rehabilitation trainings, need to be used in clinical and experimental practices (Jehkonen, et al., 2011; Nurmi & Jehkonen, 2014).

1.1.3 Disorder of the sense of ownership

Somatoparaphrenia can also independently occur as a specific neuropsychological disorder of body representation (Vallar & Ronchi, 2009; Invernizzi et al., 2013), as a form of misattribution of the paralyzed limbs to another person in the room, such as a doctor or a relative (Bottini, Bisiach, Sterzi, & Vallar, 2002), or even someone not physically present (Pugnaghi, Molinari, Panzetti, Nichell, & Zamboni, 2012).

Since it can manifest in different clinical behavioural and emotional forms and with possible co-present symptoms (Vallar & Ronchi, 2009), a broader classification includes all abnormal feelings and beliefs related to the hemiplegic limbs as the 'disturbed sensation of limb ownership' (DSO) (Baier & Karnath, 2008). This term is used in this thesis in order to avoid ambiguity.

1. 2. Neuroanatomy of Self-Awareness

1.2.1. Lesions beyond Anosognosia for Hemiplegia

AHP is frequently associated with a damage in perisylvian area of the right hemisphere. Several studies tried to analyse the specific lesion associated to the syndrome, despite the presence of high variability of manifestations and assessments (Jehkonen, et al., 2011).

In a first meta-analysis, a wide fronto-parietal network was found to play a crucial role in AHP, identifying a combination of both cortical (frontal, parietal, but also temporal and occipital regions), and subcortical (mainly basal ganglia and thalamus) structures. More in detail, the right premotor cortex in Brodmann's areas (BA) 6 and 44 and the inferior frontal cortex in BA 46 (Berti et al., 2005; Kortte, et al., 2015), joined to somatosensory and primary motor cortex (BA 4) (Berti, et al., 2005) are specifically associated with AHP, due to their role in motor monitoring.

In particular the premotor cortex and the surrounding superior longitudinal fasciculus are involved in detecting and monitoring incongruent sensorimotor feedbacks (Enriquez-Geppert, Huster, Figge, & Herrmann, 2014; see also for further details section '2.1 Theoretical account' in Chapter 2 about the computational model of motor control).

Another crucial area for motor awareness seems to be the right insular cortex (Karnath, et al., 2005). Indeed, according to a parallel model of self-awareness (Craig, 2009; 2010), the insula is implicated in all subjective feelings as interoceptive representations, perceived agency, and in more general aspects of body ownership (Karnath et al., 2005; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007).

It is important to notice that the temporal dynamic of the deficit seems to depend upon the lesion site: in more acute phases, subcortical structures seem to be crucially damaged, most of all the insula (Moro & Pernigo, et al., 2016; Vocat & Vuilleumier, 2010) and the basal ganglia (Moro & Pernigo, et al., 2016), but it appears that only a wider impairment of more cortical frontal-temporal areas is relevant for the persistence of the symptoms, mainly involving the rolandic operculum (ventral premotor cortex) and the superior temporal gyrus (Vocat & Vuilleumieri, 2010, Moro & Pernigo, et al., 2016).

Nevertheless, this wide cortical lesion in chronic AHP patients seems to be an evidence of the important role played by the fronto-temporal-parietal network in motor awareness. Thus, the specific deficits of the multisensory body representation in the insula (Karnath et al., 2005) or of the sensorimotor components in premotor cortex (Berti et al., 2005) are not sufficient as they need to be associated to other broader areas (Moro & Pernigo, et al., 2016).

Given the heterogonous characteristics of AHP, some studies have combined experimental and lesion analysis to investigate the anatomical networks of the specific subtypes of AHP. Notwithstanding the small sample size, it has been recently reported that the brain region associated with signs of implicit awareness are the inferior motor areas, insula, basal ganglia and limbic structures (Fotopoulou, Pernigo, Maeda, Rudd, & Kopelman, 2010) and subcortical with matter connected to the basal ganglia (Moro, Pernigo, Zapparoli, Cordioli, & Aglioti, 2011). This evidence is important to highlight that AHP is a multi-componential disorder. Finally, AHP is typically reported after a damage in the right hemisphere rather than after a left one, which are often excluded and likely underestimated due to the presence of combined language impairments (See Cocchini et al., 2009, Della Sala et. al., 2009).

1.2.2. Lesions beyond the Disturbed Sensation of limb Ownership

Right hemispheric stroke can also cause disorders of the sense of ownership, besides the anatomical double dissociation between AHP and DSO.

In classical studies, the right posterior insular cortex has been considered as a crucial area for subjective feelings and self awareness (Craig, 2009; 2010) and for a link between body and action awareness (Baier & Karnath, 2008). However, DSO does not selectively correlate to the inferior frontal gyrus (including the insula) as like as AHP does, but to more subcortical structures and white matter connections (Gandola et al., 2012; Invernizzi et al., 2013, Moro & Pernigo et al., 2016).

A lesion of DSO is indeed reported to be shifted to more medial and subcortical areas than in AHP, in particular with lesion of basal ganglia and thalamus and the surrounding white matter (Gangola et al., 2012; Invernizzi et al., 2013; Moro & Pernigo et al., 2016). These recent accounts underline the importance of subcortical structures in body ownership, that may be connected to higher cortical areas for other aspects of bodily awareness, as like as the sense of agency and self-other peculiarities (Blanke, 2012; Tsakiris, Longo & Hagard, 2010).

Even though DSO has been mainly described as following right brain lesions, in those few cases occurring after a left hemispheric damage, the involved areas are the ventral and medial frontal cortex with the posterior insula and the subcortical nuclei (Perren, Heydrich, Blanke, & Landis, 2015) similarly to some right brain damaged patients (Baier & Karnth, 2008; Gandola et al., 2012).

Chapter 2
Action in Self-Awareness

2.1. Theoretical accounts

AHP is a peculiar neurological deficit, when the patients present an impaired level of awareness referring to their contralesional hemiplegic arm and/or leg and they declare to be able to move (Babinsky, 1914; Cocchini et al., 2009), although the absence of any real action and of following sensory feedbacks (Bottini et al., 2010).

As mentioned above in Chapter 1, this syndrome manifests itself in different sub-types (Marcel et al., 2004, Orfei et al, 2007), due to the combination of some various clinical disorders and some different forms of spared degree of awareness. But despite the multi-componential character of the AHP, this syndrome allows us to specifically investigate the characteristics of the functioning of the sensorimotor system related to the motor awareness.

Focusing on the sensory aspects, in a early 'Discovery Theory' the combination of the deficit of proprioception and a more general cognitive impairment is assumed to cause the loss of personal perception and consequentially the decrease of degree of motor awareness (Levine, Calvanio, & Rinn, 1991). Since double dissociations with these deficits (proprioception and general cognition) are documented (Cocchini et al. 2010, Marcel et al., 2004), this hypothesis on primary sensory deficits could be excluded.

Instead, a computational model of the motor system (Wolpert, 1997) comes from a description of the mechanisms underlying the motor control system in healthy population. Normally, the intention to move is a motor command that produces both a prediction about the sensory consequences of movement and the occurring sensory feedbacks. In case of errors between the command and the real outcomes, a 'comparator' detects the discrepancy between the predicted and the actual action so to adjust it accordingly (Figure 1).

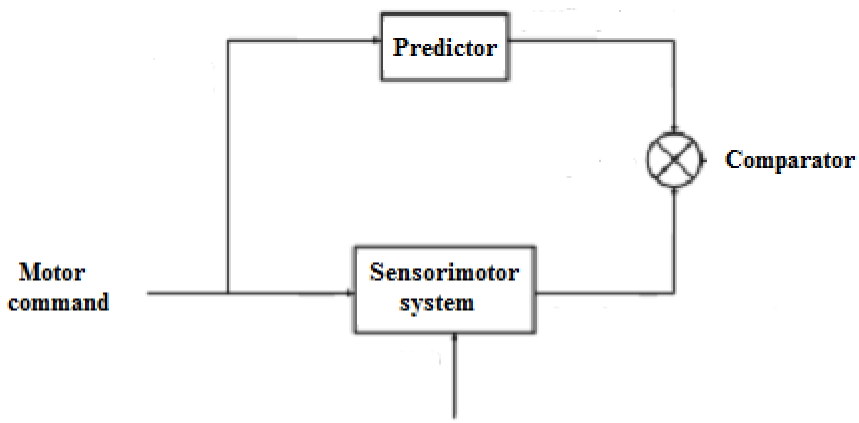

Figure 1. Computational model of the motor system. A simple schema of the motor model system in healthy population (from Blakemore, Wolpert, & Frith 2002).

After the first hypothesis about the failure to compute motor intention in AHP ('Feed-forward hypothesis', Heilman, 1991, Heilman, Barrett, & Adair, 1998), recent assumptions (Firth, Blakemore, & Wolpert, 2000) have focused on the connection between intention and prediction of action.

AHP patients seem to be able to form proper motor commands and the representations of their actions (Jenkinson, Edelstyn, & Ellis, 2009), which are the basic steps of motor awareness (Fourneret & Jeannerod 1998). In fact, patients with hemplegia (HP) in presence of motor awareness involve the intention to move, in order to predict its outcomes, but at the exact moment of execution they are able to detect the absence of movements thus preserving a good level of awareness. On the contrary, AHP patients maintain their erroneous beliefs about moving and assume to have acted accordingly to their will (Vuilleumier, 2004).

This aspect of unawareness can be reinterpreted as a deficit in the cognitive system devoted both to the intention and the motor execution, rather than to a general lack of acknowledgement about the motor deficit per se (Frith et al., 2000). In specific, the mechanism between the construction of a motor intention and the analysis of the consequent feedbacks may be the impaired point of the motor computational model with AHP ('Forward model') (Blakemore et al., 2001, 2002; Frith et al, 2000). Thus, the damage results to be at the level of the comparator mechanism, that causes poor awareness of discrepancy between the absence (or the impairment) of movements and the absence of a real sensory feedback (Bottini et al., 2010; Fotopoulou et al., 2008, but see Berti et al., 2007 for discussion).

Since the heterogonous nature of AHP, in recent hypothesis, it has been underlined that the AHP may emerges from a combination of different deficits (Saj, Vocat, & Vuilleumier, 2015, Vocat & Vuillemieur, 2010). In the 'ABC model', Vuilleumier (2004) proposed three main deficits, respectively, of the Assessing, Belief and Control operations, that may contribute in the phenomenon. In fact, in a more general model (Fotopoulou, 2014; 2015), some higher-order cognitive, emotional and motivation components (e.g. Turnbull, Fotopoulou, & Solms, 2014) are suggested to play a role in patient's inability of updating their 'prior belief' about themselves to the new 'prediction errors' about their movements, which may lead to a greater degree of awareness specifically for the motor domain (see Besharati, et al., 2014 for experimental results).

Inherently the importance of the actions in this phenomenon, some studies have systematically investigated the relation between the monitoring of intended actions and the actual movements with AHP (see, Jenkinson & Fotopoulou, 2010, for review). For example, AHP patients report an intact system of motor intentions through the plegic limbs, that interfere with their performance in spatial (Garbarini, et al., 2012) and temporal domains (Pia, et al., 2013) and their perception of unrealistic feedbacks (Fotopoulou, et al., 2008; Piedimonte, Garbarini, Pia, Mezzanato, & Berti, 2016).

Furthermore, it is important to stress that a request to act can enhance some residual forms of awareness, as an implicit unintentional adaptation of the movements to the presence of a paralyzed limb (Cocchini et al., 2010) or as an upcoming form of declarative awareness during the monitoring of the actual attempts to execute (Moro, et al., 2011; Moro, Scandola, Bulgarelli, Avesani, & Fotopoulou, 2015).

In conclusion, the real attempts to act reveal some aspects of the dysfunctional mechanisms beyond AHP and provide some possible insights in rehabilitation (see the next section 2.2 'Emergent awareness').

2.2. Emergent Awareness

The various manifestations of AHP and the presence of residual forms of awareness are current topics of debate, due to their possible contributions in understanding the mechanism of AHP and its possible clinical and rehabilitative approaches (Marcel et al., 2004).

Hitherto, there is no single model that can encompass all the multi-componential and heterogeneous features of AHP and explain its different sub-types.

In a hierarchical model of AHP (Crosson et al., 1989), three levels of deficit are detected: i) Intellectual awareness as a general acknowledgement of the deficit without remarkable compensations, ii) Emergent awareness when patients, in addition to a spontaneous denial of paralysis, may fluctuate to a declarative form of awareness during the attempt to perform an action, and iii) Anticipatory awareness, when the patients are able to anticipate the deficits and to search for compensatory strategies. It is worth noting that these different type of unawareness can be selectively spared.

Within an experimental paradigm, Emergent Awareness has been firstly described by Moro and colleagues (Moro et al., 2011, Moro et al., 2015). When AHP patients are required to execute an action and to judge their proficiency during their attempts to act, they become to some extent linguistically aware about their own deficit.

According to the 'forward model', these processes seem to influence the 'comparator' mechanism, thanks to a previous spared motor command (Moro 2013). Thus the role of action appears to have a relevant role in the mismatches between patient's intention and prediction to be able to move, without real sensory feedbacks (Blakemore et al., 2001; Fotopoulou et al., 2008). In fact, the motor command may have a crucial role in the prediction of feedbacks (More et al., 2011), while the judgments of their own proficiency during the attempts to act may influence the detection of discrepancy of the real outcomes and enhance the level of awareness (Moro, et al., 2015). In this way, such a process induces the presence of Emergent awareness and the implementation of behavioural strategies that are not usually employed in AHP or only at an implicit behavioural level (Cocchini et al., 2009; Moro et al., 2011).

These results can be placed also within other more general models. Firstly, in the 'ABC model' (Vuilleumier, 2004), AHP is a combination of three components of Assessment, Belief and Control operations, where the monitoring of the sensory feedbacks may have a crucial role in modifying incorrect beliefs of someone's abilities (Vocat, Saj, & Vuilleumier 2013). Secondly, based on a Bayesian 'predictive coding' framework (Friston, 2005; 2010), the lack of motor awareness in AHP may be a dysfunctional link between the 'prior beliefs' as acquired internal representations about the self, and the 'prediction errors' of actual situations (Fotopoulou, 2014; 2015), due to both interoceptive and exteroceptive signals (e.g. Schultz & Dickinson, 2000).

From these models, the required monitoring of movements induces the patients to check (control operation) their performance and their simultaneous explicit experience of failure may lead the patients to rethink about their own beliefs. Despite these models try to understand even more complex sensory and cognitive aspects of AHP, we may suppose that the direct confrontations of abilities during actions execution may contribute in the process of reaching temporary (Moro et al., 2011) or more long-lasting (Moro et al., 2015) declarative awareness, by changing previous beliefs into the new pathological condition (Fotopoulou, 2014; Fotopoulou et al., 2009).

In these potential processes, the role of memory seems to be crucial, as reported in anosognosia for other cognitive deficits as like as Alzheimer's disease (Morris & Mograbi, 2013). In fact, it has been hypothesized (CAM model, Agnew and Morris, 1998; Morris & Mograbi, 2013) that all long-lasting representations of the self are stored in a specialized Persona Database, that need to be updated in case of contrasting immediate experiences after the occurrence of a deficit.

Thus, we can suppose that the request of monitoring the actions' executions might contribute to an implicit updating of the autobiographical memory and to a following improvement of awareness (Moro et al., 2011; Moro, 2013).

It is relevant that in the process involve cognitive and metacognitive functions (like motor command and monitoring), but also executive functions of action, memory and speech, which are needed to integrate both implicit and explicit components of awareness and to store them into personal memories (Moro, 2013). As a matter of fact, Emergent awareness seems to require the white matter connections between parieto-temporal and frontal cortex in a spread neuronatomical network influenced by all those cognitive functions (Moro, et al., 2011).

In addition, Emergent awareness appears to have some rehabilitative evidences (Moro, et al. 2014). In fact, the role of attempting actions and the consequent analysis of occurring motor errors might be crucial in restoring this syndrome overtime (Moro et al., 2015) in a lack of effective training in the present literature (Kortte & Hillis, 2011; Jenkinson et al., 2011).

In conclusion, the rehabilitation of AHP appears to be insufficient as long as patients become explicitly aware and implement some strategies (Gialanella & Mattioli, 1992). The possible role of emergent awareness is to link tacit forms of awareness to declarative and behavioural improvements (Moro 2013) thus becoming a relevant field of investigation.

Chapter 3

Modulating Anosognosia for Hemiplegia: the role of dangerous actions in Emergent awareness

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Anosognosia for hemiplegia is a lack of awareness of motor deficits following a right hemisphere lesion. Residual forms of awareness co-occur with and explicit denial of hemiplegia. The term emergent awareness refers to a condition in which awareness of motor deficits is reported verbally during the actually performance of an action involving the affected body parts. In this study, two tasks were used to explore the potential role of i) attempting actions which are impossible for suffers of hemiplegia and ii) attempting actions which are potentially dangerous. Sixteen hemiplegic patients were asked to perform both potentially dangerous and neutral actions. Our results confirm an increase in emergent awareness in anosognosic patients during the execution of both of these types of actions. Morevoer, actions that are potentially dangerous improved the degree of awareness. However, lesions in the fronto-temporal areas appears to be associated with a reduced effect of action execution (emergent awareness), while lesions in the basal ganglia and amygdale and the white matter underlying the insula and fronto-temporal areas are associated

with a lesser degree of improvement resulting from attempting to perform dangerous actions.

3.1. Introduction

The term Anosognosia (from the Greek,α=without,νόσος=disease, γνώσις = knowledge) refers to a lack of awareness of sensory, motor or cognitive (i.e. language, memory) deficits. Babinski (1914) described a specific form of unawareness, known as Anosognosia for Hemiplegia (AHP), that selectively involves an incapacity to admit motor deficits and that mainly occurs as a consequence of right hemisphere lesions (Pia et al., 2004; Vocat et al., 2010; but see Cocchini et al., 2009; Jehkonen et al., 2006). Anosognosic patients fail to acknowledge or recognize their paralysis and they claim that they are able to carry out everyday activities, which are in reality impossible for them.

Sensory loss, intellectual impairment or a combination of thee cannot fully explain the syndrome (Marcel et al., 2004). Furthermore, double dissociations have been demonstrated between AHP and proprioceptive impairment (Cocchini et al., 2010), spatial or personal neglect (Vocat et al., 2010),confabulation and deficits in frontal lobe functions (Heilman & Harciarek, 2010 for review) and other disorders in body representation, in particular somatoparaphrenia and feeling of disownership of the affected limbs (Moro, Zampini, & Aglioti, 2004; Moro & Perngio et al., 2016).

AHP is indeed an heterogeneous and multi-componential phenomenon which may occur in a variety of clinical manifestations (Heilmann & Harciarek, 2010; Orfei et al., 2007; Marcel, et al., 2004; Vocat, et al., 2010).

A crucial role in the syndrome was initially attributed to lesions in the parietal lobe (Bisiach et al., 1986; Heilman, 1991) and in the wide networks of fronto-temporo-parietal integration (Pia et al., 2004). More recently, the premotor cortex (Berti et al., 2005) and the insula (Karnath, Baier, & Nägele, 2005) have been identified as

the core systems in AHP, with lesions associated with the symptoms in subcortical structures (the basal ganglia and the amygdale) and in white matter tracts (Vocat et al., 2010; Fotopoulou e al., 2010; Moro et al., 2011; Moro & Pernigo, et al., 2016).
Damages in different parts of these networks has been linked to various expressions of the syndrome, where specific anosognosic symptoms occuring along with residual forms of awareness. For example, in case of explicit anosognosia and implicit awareness, patients verbally deny their paralysis but act as if they know about their paralyzed body parts (Cocchini et al., 2010; Moro et al., 2011; Fotopoulou et al., 2010). This may have a significant impact as these implicitly aware patients will not try to stand up or to act alone (with the risk of hurt) and will ask for help when necessary. In these cases rehabilitation is generally more efficacious.
Another dissociation has been reported between deficits in awareness which refer to the self and to other patients. Although the majority of people suffering from AHP fail to acknowledge paralysis both in themselves and in other people, some patients deny the motor deficits only when answering questions which refer to themselves. This may indicate that in the former situation the motor awareness deficits relate to actions per se, while in the latter they are specific to patients own body actions (Marcel et al., 2004; Ramachandran, 1996; Ramachandran & Rogers-Ramachandran, 1996; Moro et al. 2011).
A form of Emergent Awareness has been previously described (Moro et al., 2011, Moro, 2013; Moro et al., 2015). In this condition, when the anosognosic patient are asked to actually perform an action using the affected body parts they are able to verbally state that they cannot perform the action due to their otor deficits (Moro et al., 2011). This indicates that intention to act (and/or actually acting) may modify any explicit, verbal knowledge of deficits. More generally, this suggests that a modulation in AHP may be induced by ad-hoc experimental manipulations.
We investigated this topic by means of an experiment in order to establish whether there is a relationship between the top-down processes of requiring to carry out specific actions and the effects of the characteristics pertaining to that action, in

particular if they are of an emotional as compared to neutral nature. In fact, fluctuations of awareness in AHP are influenced by both sensory-motor and high cognitive functions (Fotopoulou, 2014 for review) and a role of emotional components has been previously reported (Besharati et al., 2014; Nardone, Ward, Fotopoulou, & Turnbull, 2008).

In the present study, anosognosic and hemiplegic non-anosognosic patients (HP) were asked to execute a number of everyday actions, which were impossible for them due to the paralysis. Their judgements regarding their proficiency in carrying out the actions were asked at various times: i) in a preliminary interview which focused on the specific actions to be performed (Semantic awareness); ii) before starting to execute the action (Anticipatory awareness); iii) during the execution (Emergent awareness) and iv) after the attempt to act (Post-error awareness) (Moro et a., 2011). Moreover, the experiment was devised to determine whether the nature of the action had in itself an impact on awareness. To this end, half of the actions were neutral (i.e. they could be executed in safety, without risks of injury) and the other half were dangerous (i.e. patients could potentially hurt themselves).

We expected that the real attempts to carry out actions would increase awareness in AHP patients, with more realistic judgments expressed during the execution and/or after the failure. Moreover, we expected that this Emergent Awareness effect would be stronger in dangerous as compared to neutral actions. A detailed analysis of the patients' lesions (Bates, et al., 2003; Rorden, Karnath, & Bonilha 2007) was also carried out in order to integrate behavioural and anatomical data associated with AHP and in particular with possible modulations due to emergent awareness and the characteristics of the actions they performed.

3.2. Materials and Methods

3.2.1. Participants

Sixteen patients suffering from severe left hemiplegia (absence of movement) as a consequence of a right hemisphere stroke were recruited at the Rehabilitation Unit, Sacro Cuore Hospital (Negrar, Verona) over a period of one year. They were divided into two groups basing on the presence or absence of AHP. This was assessed by means of the Bisiach scale (Bisiach, et al., 1986) and the Berti interview, which investigates symptoms related to upper and lower limbs separately (Berti, Làdavas, & Della Corte, 1996).

In this way eight patients were diagnosed as being affected by AHP (scores ≥1 at the Bisiach's scale and/or at least in one section of the Berti's Interview). The other eight patients did not present any signs of anosognosia (all scores=0) and these constituted the control group (HP, Table 1).

The two groups were matched for age, gender, education and intervals between lesion onset and dates of: the assessment, the CT/MRI exams and the experimental task (Table 1). The patients did not have a prior history of psychiatric or neurological diseases. They gave their consent to participate in the study, which was approved by the local ethics committee (CEP prot. N. 39216) and was carried out in accordance with the guidelines of the Declaration of Helsinki (2013).

Pt	Age	G	Educ	Test Int	CT/MRI Int	Exp Int	Lesion	Sens	Motor	Berti UL[1]	Berti LL[1]	Bisiach[2]	DSO UL[3]
AHP 1	64	M	18	66	86	99	FP Th	+	-	**1**	**1**	**1.5**	+
AHP 2	74	F	5	103	124	123	FP Th	-	-	**1**	**2**	**2**	-
AHP 3	47	M	8	34	77	49	TO	-	-	0	**1**	0	-
AHP 4	53	F	8	48	31	52	F	-	-	**1**	**1.5**	**3**	+
AHP 5	63	M	13	13	16	17	TP	-	-	**1**	**2**	**3**	+
AHP 6	57	F	10	61	61	62	FTP	-	-	**1**	**2**	**2**	-
AHP 7	83	M	5	11	11	20	FP Th	-	-	**1**	**1**	**1.5**	-
AHP 8	76	M	5	Na	Na	Na	FTP	-	-	**1**	**2**	**3**	-
Mean (Median)	*64.6*		*9*	*48*	*58*	*60.3*				*(1)***	*(2)***	*(2.5)***	
St.dev.	*12.3*		*4.6*	*32.4*	*41.2*	*39*							
HP 1	64	M	5	70	Na	85	Na	+	-	0	0	0	-
HP 2	55	F	13	76	71	77	FTP Th	-	-	0	0	0	-
HP 3	54	M	8	52	85	65	F, Th	-	-	0	0	0	-
HP 4	72	F	5	91	100	102	FTP	+	-	0	0	0	-
HP 5	66	F	17	103	Na	106	Na	-	-	0	0	0	-
HP 6	75	M	5	33	30	55	FP	-	-	0	0	0	-
HP 7	70	M	17	45	46	53	Th	+	-	0	0	0	-
HP 8	64	M	5	36	30	50	FTP	-	-	0	0	0	-
Mean (Median)	*65*		*9.3*	*63.2*	*60.3*	*74.1*				*(0)*	*(0)*	*(0)*	
St.dev.	*7.5*		*5.4*	*25.8*	*29.5*	*22*							

Table 1. Demographic and clinical data of patients with (AHP) and without (HP) anosognosia for hemiplegia. Pt= patient, G= gender, Educ= years of education. Test Int= interval days between lesion onset and assessment, CT/MRI Int= interval days between lesion onset and the CT/MRI scan, Exp Int= interval between lesion onset and experimental task. Sens= sensory deficits; Motor= motor deficits. [1]Berti's Interview, [2]Bisiach's Scale (The additional score of 1.5 refers to the conditions when patients report impaired abilities in moving the arm, but not the presence of hemiplegia), DSO= Disturbed sensation of limb ownership [3](Moro & Pernigo et al., 2016). UL= Upper, Limb LL= Lower Limb. Na= not available. T= temporal, O= occipital, F= frontal, P= parietal, Th= thalamus. - = deficits present; + = deficits not present. Pathological scores are in bold. For each group *Mean* or *(Median for Berti's Interview and Bisiach's Scale)* and *St.dev.*(Standard deviation) values are reported. **= Mann-Whitney Tests show significant differences ($p<0.01$) between two groups (no other significant results between the two groups).

3.2.2. Preliminary neuropsychological examination

Although some patients had scores under cut-off in the assessment of general cognitive profile (MMSE, Folstein, Folstein, & McHugh, 1975), this was mainly due to visuo-spatial problems (Table 2). Indeed, all patients were well oriented in space and time at the time of the experimental task.

All of the patients (except one in the HP group) failed in tests assessing frontal functions (Frontal Assessment Battery - FAB; Apollonio, et al., 2005), while short and long verbal memory (Forward digit span and Story recall; Spinnler, & Tognoni, 1987) was spared in the majority of the participants.

The AHP group showed more symptoms of extrapersonal neglect than HP group (Line Bisection, Albert Test and Copy Test; Wilson, Cockburn, & Halligan, 1987), while personal neglect (Comb and Razor Test, McIntosh, Brodie, Beschin, & Robertson, 2000) was present in both groups. Finally, only two HP patients were over cut-off on the Hospital Anxiety and Depression Scale (Zigmond, & Snaith, 1983).

	General and Frontal		Memory			Neglect					Mood
Pt	MMSE	FAB	Story recall ST	Story recall LT	Digit Fw	Bisection	Albert	Copy	VE	Comb	HADS
AHP 1	**22.2**	**7.2**	7.5	9	8	**0**	**18**	**1**	**-**	**-0.42**	14
AHP 2	**14.7**	**3.3**	**0**	**0**	**2**	**0**	**10**	**0**	-	0	13
AHP 3	**16.62**	**11.7**	6.5	6.5	8	**2**	*32*	**1**	Imp	**-0.36**	10
AHP 4	27	**11.9**	4.8	7.8	9	9	**34**	**2**	+/-	**-0.29**	5
AHP 5	**21.27**	**4**	**3.3**	4.4	**4**	**0**	**12**	**0**	**-**	**-0.125**	Na
AHP 6	27	**4.1**	5.5	5.5	**4**	**6**	**24**	**0**	-	**-0.8**	Na
AHP 7	*24.4*	**8**	6.3	5.3	**2**	**4**	**12**	**0**	-	**-0.47**	Na
AHP 8	**18.7**	**3.5**	6.5	6.4	7	**3**	**18**	**0**	-	**-0.4**	13
Mean	*21.5*	*6.7*	*5*	*5.6*	*5.5*	*3*	*20**	*0.5*		*-0.36*	*11*
St.dev.	*4.6*	*3.6*	*2.4*	*2.7*	*2.8*	*3.2*	*9.2*	*0.7*		*0.2*	*3.7*
HP 1	24.9	**8**	**0**	4.4	4	**6**	36	3	**-**	**-0.6**	Na
HP 2	24	**9.3**	9	8.5	7	8	36	**1**	+	0	Na
HP 3	28.74	**10.2**	6.5	7.7	6	9	40	**0**	+	0	8
HP 4	**21**	**1**	**3.1**	2.3	**5**	**0**	**12**	**0**	Imp	**-0.2**	11
HP 5	25.2	18	6.6	7.7	Na	9	36	4	Na	Na	Na
HP6	**19**	**7.9**	6.4	4.7	Na	**1**	**24**	**0**	-	**-0.21**	Na
HP 7	25	**11.9**	5.3	6.4	7	7	36	4	Na	**-0.5**	**18**
HP 8	**18.9**	**6.8**	3.8	3.8	9	**0**	**22**	**1**	+	**-0.13**	**20**
Mean	*23.3*	*9.1*	*5.1*	*5.7*	*6.3*	*5*	*30.2**	*1.6*		*-0.23*	*14.25*
St.dev.	*3.4*	*4.8*	*2.7*	*2.2*	*1.7*	*4*	*9.8*	*1.8*		*0.2*	*5.7*

Table 2. Neuropsychological data. Neuropsychological assessment of general functions, memory, neglect and emotional state in the patients with (AHP) and without (HP) anosognosia for hemiplegia. ST= short term, LT= long term, FW= forward, VE= visual extinction, - = deficit present, + = deficit not present. Imp = Impossible to assess, Na= not available. All scores are corrected for age and/or education. Pathological scores are in bold. Scores at cut-off are in *italic*. For each group *Mean* and *St.dev.*= Standard deviation values are reported. * = Significant differences (p<0.05) between the two groups at T-Test.

3.2.3. Lesion mapping

In order to analyze the neural correlates of AHP and compare the two groups, we analyzed the patients' lesions by means of a voxel-based lesion symptom mapping (VLSM) technique. Patients' structural MRI scans were mapped with the MRIcron software (http://www.cabiatl.com/mricro/mricron/index.html) (Rorden & Brett, 2000), by drawing on the standard T1-weighted MRI template (ICBM152) of the Montreal Neurological Institute (MNI) coordinate system, approximately oriented to match the Talairach space (Talairach & Tournoux, 1988). For the procedure, the template was oriented on the midsagittal and midcoronal axis to match each original MRI scan orientation as closely as possible. Successively, an experienced clinician (SB) traced each lesion manually onto the rotated template, while another expert clinician (VM) checked all the drawings in a double-blind procedure. For each patient, the outcome was a map of the damaged areas with each voxel labelled as 0 (intact) or 1 (lesioned). Finally, all the lesion maps were rotated back to the canonical orientation to align them to the standard sterotaxic MNI space (in 2mm x 2mm x 2mm voxel) and they were filtered with a custom masks based on the ICBM152 template, to exclude the voxels of lesions outside the white and gray matter brain tissues.

An analysis of lesions' volumes were computed with Non-Parametric Mapping (NPM) software (Rorder, et al., 2007). In order to investigate the neural correlates of AHP, we compared the lesions maps of the two groups, by means of a subtraction technique and a voxel based lesion comparison based on the Libermeister binomial test (False discovery rate - FDR corrected, Benjamini & Hochberg, 1995).

In addition, in order to analyzed the neural correlates of the disorder in case of emergent awareness and the effects of potentially dangerous actions in AHP we carried out a VLSM with t-test statistics, using the performance during the experiment as continuous predictors (Bates, et al., 2003; Rorden, et al., 2007).

It is to be noted that, while the behavioural results at our tasks inform the reader about the improvement in awareness due to experimental manipulations, these analyses of lesions provide data regarding the patterns of lesions associated with the lack of such improvement. In fact, all of these statistics were implemented for each voxel in the brain (Rorden et al., 2007) and the outcomes indicate the voxels damaged in patients with statistically worst performance (at p-value < 0.05 and corrected for multiple comparison by using a FDR - False Discovery Rate).

The outcome of the subtraction and the significant lesion maps of the voxel-based lesion techniques were superimposed onto T1 templates to calculate the amount of lesioned voxels in various cerebral areas and the centre of the mass of each damaged area. This was then overlapped onto the Automatic Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002) to provide information on the gray matter, and onto the Tractography based Atlas of human brain connections Projection Network (Natbrainlab, Neuroanatomy and Tractography Laboratory) (Catani & de Schotten, 2012; de Schotten et al., 2011) for the white matter.

3.2.4. Experimental Task

In order to investigate the role of attempting to perform actions in modulating patients' awareness (Emergent awareness) and the effects of actions which were potentially dangerous, an ad-hoc task was devised.

The patients were asked to judge their proficiency in the execution of specific actions (neutral or dangerous) in four different situations: i) during an interview, ii) before the attempt to act, iii) during and iv) after the actual attempt to act.

As this main task was executed in the first-person perspective, another task (*Judgment of Others' actions*) was administered in which the patients had to judge the abilities of another hemiplegic patients with regard to the same actions (for Method and Results, see as supplementary materials in the Chapter 4). This control task allowed us to evaluate any potential dissociation in AHP patients in their judgments relating to themselves and to other people.

3.2.4.1 Stimuli

20 bimanual or full body actions which were impossible for hemiplegic patients were selected. Another 4 unimanual actions involving the healthy hand were used as a control to check the consistency of patients' responses and their attention to the task.

The 20 experimental actions were divided into two blocks. The first block consisted of 10 actions that involved the full-body (FB e.g. going downstairs, using a wheelchair). The second block was consisted of 10 upper-body actions (UB e.g. cutting nails with scissors, using a ruler to draw a line). The realistic nature of the setting was guaranteed by the choice of everyday actions.

In order to test the impact of actions which were potentially dangerous, in each block there were 5 neutral (N) and 5 potentially dangerous (D) actions. In the FB block, actions were dangerous because the patients were at risk of falling or getting hurt (e.g. moving from a wheelchair to a bed). Actions in the UB block were potentially dangerous for everybody regardless of paralysis (e.g., cutting one's own nails with scissors). The actions were selected so that each D action corresponded to a N action in terms of similarity of execution (e.g. moving a full pot from a gas ring - Lifting up a tray with glasses) or purpose (e.g. walking – using the wheelchair) (see Table 3).

Control actions		Full-body (FB)	Upper-body (UB)
Looking at the side		Walking	Putting a nail in a wooden block
Blowing the nose		Moving from the wheelchair to the bed	Lighting up a candle
Drinking from a glass	*D*	Going down the stairs	Cutting his nails with scissors
Tilting the bust		Lifting up a heavy box	Washing a big knife at the sink
		Standing up from sitting	Moving a full big pot from a gas ring
		Using the wheelchair	Using a ruler to draw a line
		Snuggling on the bed	Sharpening a pencil
	N	Going into the elevator to use it	Opening a big tube of cream
		Scratching both knees	Washing a big spoon at the sink
		Holding the sitting position	Lifting up a tray with glasses

Table 3. Experimental actions. The 24 actions are shown. Left column, the 4 control actions; Central column: the 10 Full-body actions; Right column: the 10 Upper-body actions. The 20 experimental actions are divided into two blocks of dangerous (D) and neutral (N) actions. D actions are listed in order to link to its corresponding N action (e.g. Walk - Use the wheelchair).

3.2.4.2 Procedure

The order of the two blocks (FB and UB) was counterbalanced between the participants with breaks of 20-30 minutes between the two blocks.

The task was executed in four steps. The participants were first asked Yes/No answer questions to judge whether they could perform the actions ("Can you do it?", for the answer "No" the score was 0). In the case of a positive answer, they had to rate their ability on a 10-point Likert scale ("How well can you do it?" - with scores ranging from 1 = "I cannot do it" to 10 = "I can do it without any problems"). This score represented the measure of Semantic awareness.

Next, the patients were put in a real situation, they were given the necessary told and were then request to perform each of the action. Before starting to move, the same general question ("Can you do it?") was asked. Again, in case of positive answer, participants were requested to predict their proficiency in that specific action on the10-point Likert scale ("How well can you do it?"). This was considered a measure of Anticipatory awareness.

In the third step, the patients were asked to carry out the action and the same two questions were asked during the attempt. This provide a measure of Emergent awareness.

Finally, after the failure in the attempt, the questions were asked again. This was a measure of Post-Error awareness.

The attempts to act were realized in absolute safety and the patients were stopped before any eventual risks of injury might occur . The FB actions were executed in the gym of the rehabilitation department, where patients could try to act under the supervision of the physiotherapist. The UB actions were executed in a room, at desk (or sink) under the supervision of the experimenter. Any potential disturbance or distraction (e.g. the presence of other people or environmental noises) were removed.

3.2.4.3. Comparison with the judgment of the physiotherapists

In order to measure patients' unawareness regarding their ability to execute the specific experimental actions, their judgments (Semantic awareness) were compared to those expressed by their physiotherapists (Pht judgement) with references to the same actions and with the same criteria of response (Yes/No question and in the case of positive answer giving a score from 1 to 10 on a Likert scale).

3.2.4.4. Modulation of AHP

Finally, in order to investigate potential general fluctuations in AHP due to the experimental manipulations, a general measure of awareness (General awareness) was recorded at the beginning and at the end of each of the two blocks (4 measures in total).

This scale was developed from a previously validated assessment (Marcel et al.'s modified interview; Marcel, et al., 2004; Moro et al., 2011) with the participants being asked: one standard question on general awareness ("Do you feel something unusual on your body?", scores 0= completely aware, 5= slightly aware and 10= completely unaware), two questions on general sensory-motor abilities of their upper and lower body parts (e.g. "Do you feel something unusual on your left arm?", scores 0= completely aware, 5= slightly aware and 10= completely unaware) and 7 questions regarding their proficiency in bimanual or bipedal everyday actions different from those used in the experimental task (e.g. "Can you clap your hand?" requiring a Yes/No question and in the case of a positive response allocating a score on a 10-point Likert scale). In this way the score ranged from 0 to 100.

The same procedure was repeated for the second block (see timeline in Figure 1).

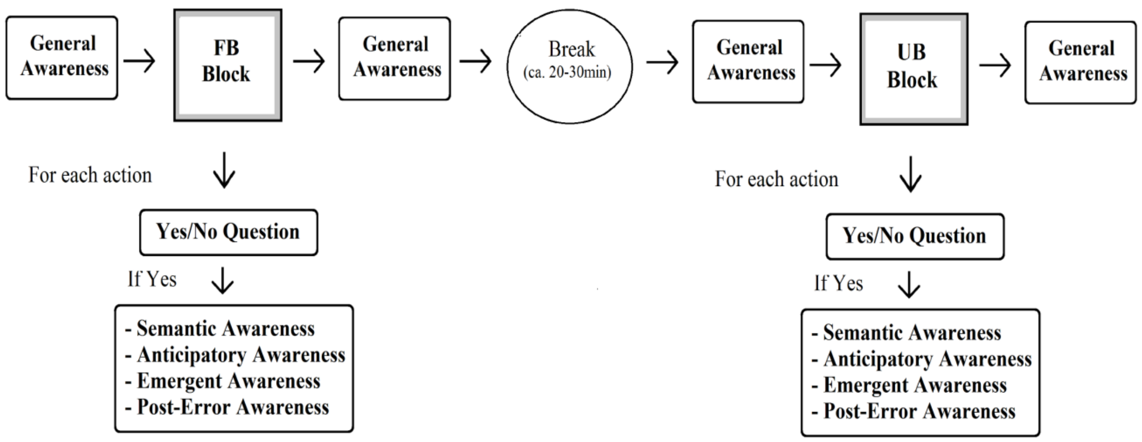


Figure 1. Experimental task. The general timeline of the First person-perspective task. The two blocks were counterbalanced between subjects. The measure of General awareness was recorded before and after each block. For each action, the questions about proficiency assessed semantic anticipatory, emergent and post-error awareness.

3.2.4.5. Statistical Analyses

According to the Likert scale, the score range was from 0 to 10, with 0 when the action was judged impossible and 10 when the patient or the physiotherapist (Pht) declared that the action was possible without any difficulties. Given the ordinal nature of the data, these were analysed by means of a cumulative logit model (Agresti, 2002) in R (R Development Core Team, 2015 with cumulative link mixed model - clmm function of the ordinal package, Christensen, 2015). The cumulative logit model allows us to compare several factors in an ANOVA-like way using the ANalysis Of DEviance Test (ANODE, McCullagh & Nelder, 1989). For all analyses, the random intercept of the model was the subject due to the small sample (Bates, Kliegl, Vasishth, & Baayen, 2015).

In order to evaluate patients' degree of awareness, the judgment of the Phts were compared to those expressed by the patients in the first step of the task (Semantic awareness), by means of a 2 (Evaluator: Pht vs. Patient) x 2 (Group: AHP vs. HP) ANODE Test.

The modulation of awareness induced by the experimental task was computed in a 2 (Group: AHP vs. HP) x 4 (Time: Semantic, Anticipatory, Emergent, Post-Error) x 2 (Action: Dangerous vs. Neutral) x 2 (Block: FB vs. UB) ANODE Test.

Finally, to investigate any potential generalization of the experimental effects on actions other than those executed, the partecipants' scores in the General Awareness Assessment were analyzed across time in a 2 (Group: AHP vs. HP) x 2 (Interval: Before vs. After block) x 2 (Block: FB vs. UB) ANODE Test.

All the post-hoc analyses were computed by means of Least-Square Means (lsmeans) Test (Lenth, 2016), a specific analysis for ordinal data, with Bonferroni corrections for multiple comparisons (Bonferroni, 1936).

3.3. Results

In the trial involving the control unimanual actions, all of the patients (AHP and HP) declared to be able to perform the actions and showed a good level of attention to the task giving consistent responses.

3.3.1. Behavioural data

The results of the comparison between the judgments given by Patients and Phts indicate a main effect of Evaluator ($LR\chi^2_{(1)}$= 43.62, $p<0.01$) and the Evaluator*Group interaction ($LR\chi^2_{(1)}$= 64.73, $p<0.01$). Post-hoc analyses show that only in the AHP group there is a difference between Pht and patient's judgments ($p<0.01$) (Figure 2).

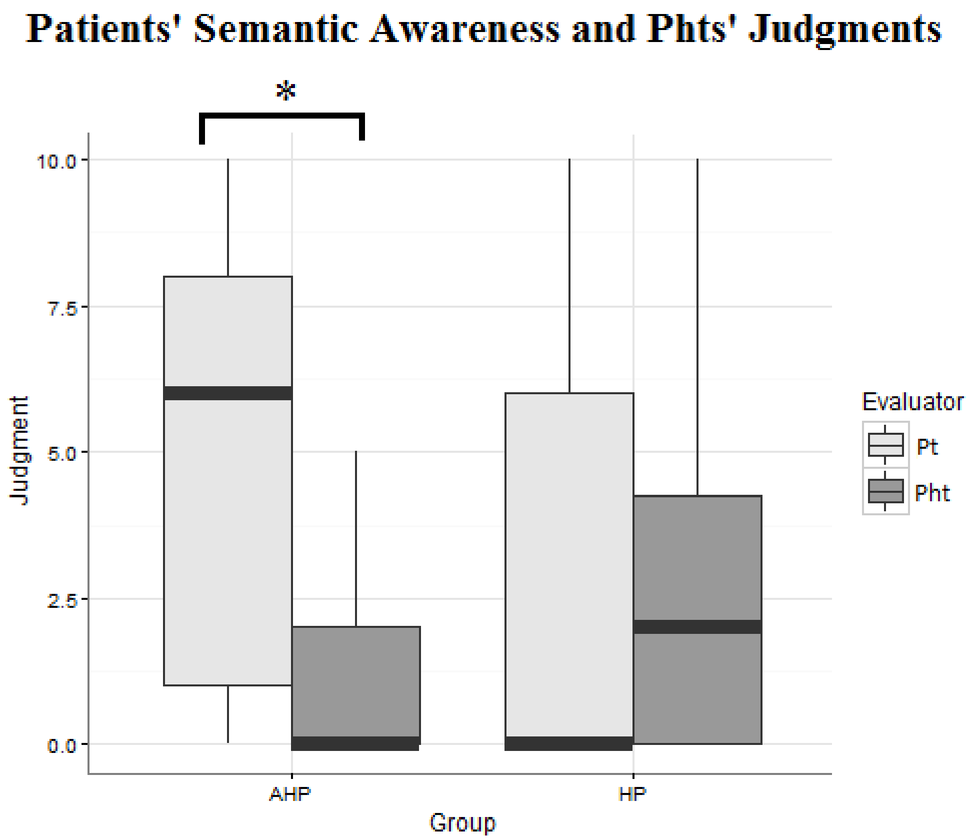


Figure 2. Patient's Semantic Awareness of their proficiency in experimental actions and Phts' Judgments. The judgments of Pt (Patients) and PhT (Physiotherapists) are reported for the two groups (AHP and HP). The Judgment's range on the y-axis is between 0 to 10 as recorded during the task. The box represents the first and the third quartile of

data, and the darker line inside is the median. The bottom and the top whiskers are respectively 1.5* Interquartile range lower and 1.5* Interquartile range higher.

The analysis of the modulation in awareness induced by the task shows that the main factors of Group ($LR\chi^2_{(1)}$=9.01, p<0.01), Time ($LR\ \chi^2_{(3)}$= 31.29, p<0.01) and Action ($LR\chi^2_{(1)}$= 19.24, p<0.001) and the Group*Time ($LR\chi^2_{(3)}$==10.08, p=0.02), Group*Block ($LR\chi^2_{(2)}$=13.77, p<0.01) and Action*Block ($LR\chi^2_{(2)}$=49.62, p<0.01) interactions are significant.

Post-hoc tests of the Group*Time interaction indicate that in AHP group awareness improved in Emergent versus Semantic (p<0.01) and versus Anticipatory Awareness (p=0.05), and in Post-Error versus Semantic (p<0.01) and Anticipatory Awareness (p<0.001). In contrast, there are no statistical differences for the HP group (Figure 3a).

In the Group*Block interaction only the AHP group shows a significant difference between FB and UB (p<0.01) with greater awareness in actions involving the full body with respect to those of upper body (Figure 3b).

Finally, in the Action*Block interaction, post-hoc analyses indicate significant differences between dangerous and neutral for each of the FB and UB blocks (both p<0.01) with a greater awareness for dangerous as compared to neutral actions in both groups (Figure 3c).

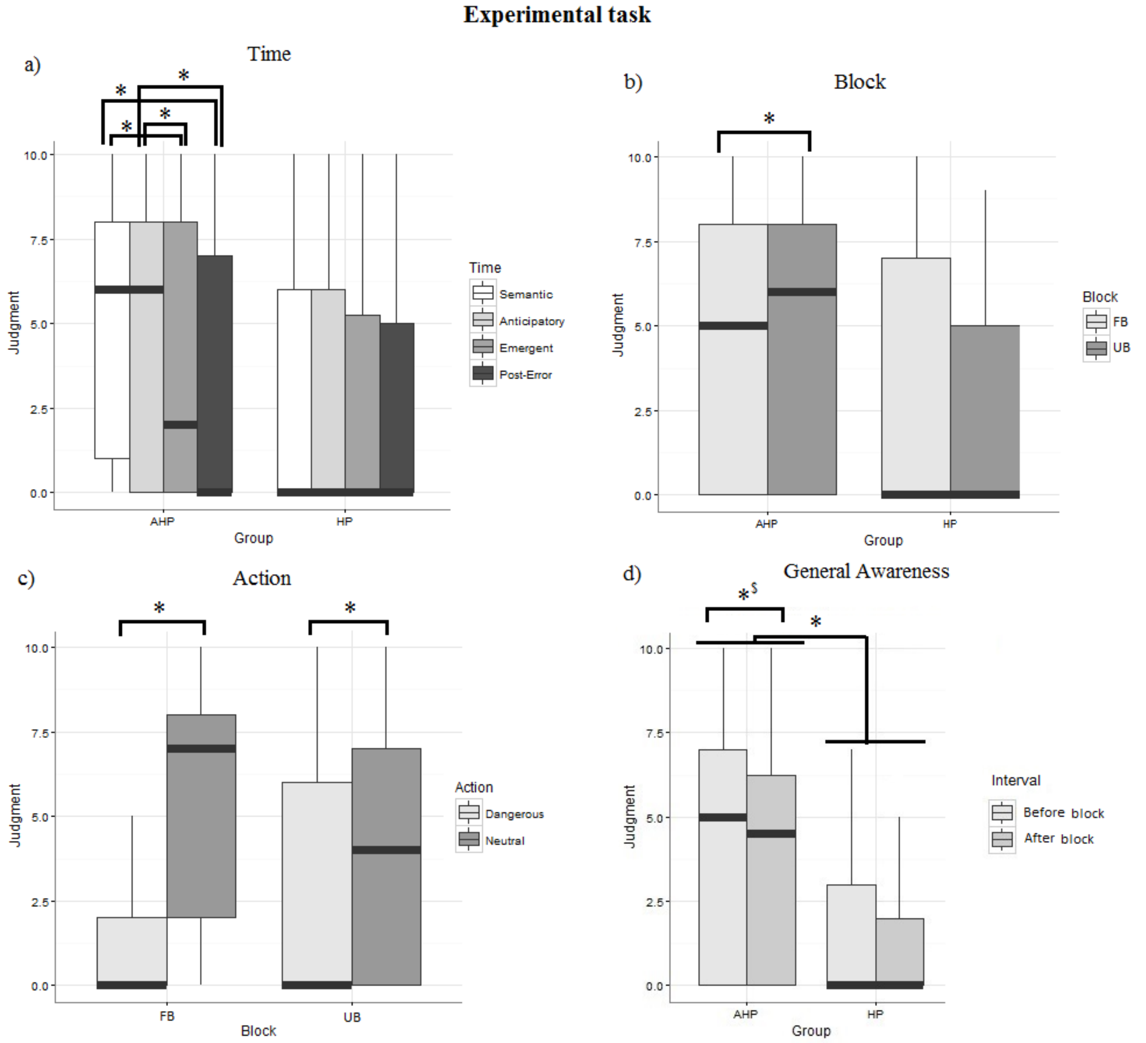


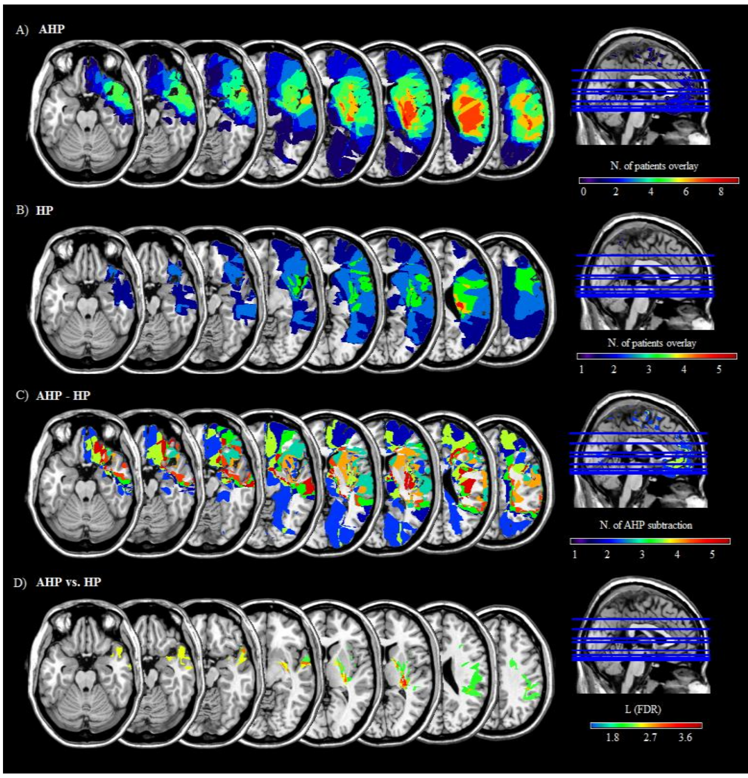
Figure 3. Results at the experimental task. The judgments of patients in the range between 0 to 10 as recorded during the task are reported.Lower judgments refer to higher awareness and vice versa higher judgments refer to lower awareness. The box represents the first and the third quartile of data, and the darker line inside is the median. The bottom and the top whiskers are respectively 1.5*Interquartile range lower and 1.5*Interquartile range higher. a) Judgments of the two Groups are reported according to Time, b) Judgments of the two Groups are reported according to Block, c) Judgments of the Blocks are reported according to type of Actions (not separated for Group), d) scores at General Awareness Interview. *= Significant result, $*^{\$}$=Significant results, not Bonferroni corrected.

The results regarding the modulation of General Awareness show the main effects of Group ($LR\chi^2_{(1)}$= 7.91, $p<0.01$) and Interval ($LR\chi^2_{(1)}$= 5.49, p=0.02), without significant interactions. With the aim of conducting a limited exploration, we computed a post-hoc analyses between Group and Interval. Only in the AHP group there is a difference ($p=0.04$) in awareness between the Before and After blocks (regardless of the order of the blocks). However, the difference does not resist to Bonferroni correction ($p=0.07$) (Figure 3d).

3.3.2.Voxel Lesion Symptoms Mapping

3.3.2.1. Comparison between groups

There were no significant differences between the AHP and the HP groups in the extent of lesions (AHP mean= 241.49cc, SD= ±122.88cc; HP mean= 123.00cc, SD= ±123.31cc; $t_{(12)}= 1.78$, $p=0.09$) (see Figure 4). The statistical comparison between the two groups (Figure 4D) showed that the cortical areas which were mainly compromised in AHP are the right supramarginal gyrus, the inferior parietal cortex the superior temporal pole, the insula, the rolandic operculum and the prefrontal gyrus. In addition, the basal ganglia (in particular the putamen and the amygdale) proved to be damaged in the AHP group. The lesion extended into the white matter, involving in particular the long segment and anterior segments of the right arcuate and the cortical spinal tract.



AHP v. HP L(FDR)

E) GREY MATTER

Area	N Voxel	N% Voxel	x	y	z
Precentral Gyrus	2367	8.75	45	-13	47
Rolandic Operculum	980	9.13	51	8	-1
Insula	472	3.34	30	11	-18
Amygdala	165	8.40	32	-6	-11
Inferior Parietal	1805	16.77	37	-50	38
SupraMarginal Gyrus	3866	24.51	43	-37	23
Angular Gyrus	1528	10.92	47	-45	23
Putamen	560	6.58	29	-19	5
Pallidum	396	18.10	20	-3	8
Heschl	62	3.20	37	-22	8
Superior Temporal	1219	4.83	61	2	-10
Superior Temporal P	1658	15.56	54	21	-18
Middle Temporal Po	524	5.53	53	8	-31

F) WHITE MATTER

Area	N Voxel	N% Voxel	x	y	z
Anterior Commissure	542	10.23	31	-5	-11
Arcuate Anterior Segment	3400	40.61	40	-36	21
Long Segment	95	29.30	37	-36	21
Arcuate Posterior Segment	669	8.02	31	-33	10
Cortico Ponto Cerebellarun	298	5.88	28	-27	7
Cortico Spinal	3173	14.38	27	-21	6
Internal Capsule	1019	5.83	29	-27	5
Optic Radiations	405	11.10	30	-24	6
Uncinate	1263	16.78	28	-3	-11

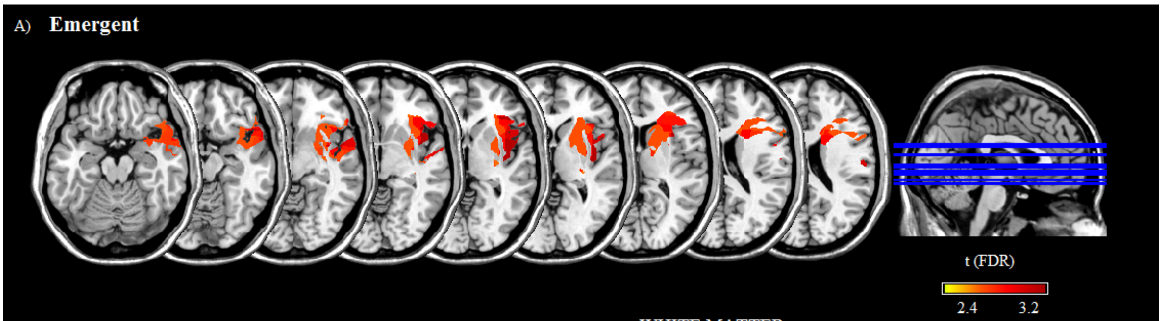
Figure 4. Lesion mapping between groups. Mapped lesions displayed in axial view and in a central sagittal slice for: Overlay images of A) AHP patients (center of mass= x 30, y -10, z 20), with bar of index of number of total patients overlaid and B) HP patients (center of mass= x 34, y -10, z 24), with bar of index of number of total patients overlaid. Comparison between the two groups: C) subtraction of the HP groups from the AHP group (center of mass= x 29, y -9, z 19), with bar of index indicating the number of AHP patients who survive to subtraction; and D) results from comparison between two groups at the Liebermeister (L) binomial analysis (center of mass= x 39, y -16, z 17), with bar of L value (FDR corrected) of significant areas (p-value<0.05). Statistical results from L comparison for E) gray and F) white matter, with number, percentage (%) of voxels for each area and MNI coordinates (only areas with impaired percentage of voxel bigger than 5%). All lesions are in the right hemisphere. The same axial sections are shown in A-D.

3.3.2.2. Lesions associated with lack in Emergent awareness

In order to identify the networks specifically involved where there was no modulation in awareness, we calculated an index of Emergent awareness [(Anticipatory awareness /Emergent awareness)/Anticipatory awareness]*100. This was computed on the sum of the Likert-scale scores for each subject in order to detect the fluctuation between the different kinds of awareness (the ratio between Anticipatory and Emergent awareness), which had been modulated with respect to the initial level of awareness.

Lesion mapping results indicated which damaged area was related to a lower index value, i.e., a lesser degree of Emergent awareness. This index was used as an independent predictor in a VLSM involving all the of the patients (t-test statistics).

It was evident that a lack of Emergent awareness can be associated with lesions involving a wide fronto-temporo-parietal network, in particular with the insula, the ventral inferior frontal area and the temporal lobe. In addition, the basal ganglia, amygdale and white matter around them are damaged (Figure 5).



GREY MATTER

B)

Area	N Voxel	N% Voxel	x	y	z
Inferior Frontal Operculum	1218	10.90	52	22	-1
Inferior Frontal Triangularis	2440	14.24	43	29	-1
Orbital Inferior Frontal gyrus	1314	9.56	51	20	-5
Insula	5889	41.68	40	10	-12
Amygdala	140	7.12	31	-7	-10
Caudate	1640	20.65	22	23	10
Putamen	3493	41.06	26	17	11
Pallidum	457	20.87	28	-5	-5
Superior Temporal	931	3.68	45	0	-8
Superior Temporal Pole	2661	24.98	46	18	-14
Middle Temporal Pole	594	6.27	56	8	-18

WHITE MATTER

C)

Area	N Voxel	N% Voxel	x	y	z
Cortico Spinal	695	3.15	13	-1	6
Inferior Occipital Frontal Fasciculus	1474	11.73	36	4	-9
Internal Capsule	2099	12.01	23	22	10
Uncinate	965	12.82	35	2	-8

Figure 5. Lesion mapping with behavioural data in Emergent awareness. A) Lesions associated with lack in Emergent awareness are displayed in axial view and in a central sagittal slice. t value (FDR corrected) of significant areas (p>0.01) are reported (center of mass= x 36, y 14, z 6). Table of significant lesions with number and percentage of voxels for each area for B) grey and C) white matter (only areas with impaired percentage of voxel bigger than 3%).

3.3.2.3. Lesions associated with reduced effects resulting from attempts to perform actions of a dangerous nature

To evaluate damaged areas were involved when the partecipant's level of awareness did not increase as a result of attempting a potentially dangerous action, the index was computed as: [(Neutral /Dangerous)/Neutral]*100. Again, we considered the fluctuations between different kinds of actions (the ratio between Neutral and Dangerous actions), modulated with respect to the initial level of awareness in Neutral actions.

The index was calculated firstly on the sum of each parent's scores for Anticipatory awareness and then on the sum of the scores for Emergent awareness. We computed two different VLSM (t-test statistics) in order to identify the damaged area (lower index) related of a reduced influence of Dangerous on, respectively, Anticipatory and Emergent awareness.

The results regarding the reduced influence of Dangerous on Anticipatory awareness indicated that this lack of effect is associated with cortical and subcortical lesions in frontal areas, the insula, the rolandic operculum and the basal ganglia (Figure 6a-c).

The reduced influence of Dangerous on Emergent awareness is associated with damage to the insula, the basal ganglia and amygdale, and the white matter around these structures (Figure 6d-f).

A) **Dangerous in Anticipatory Awareness**

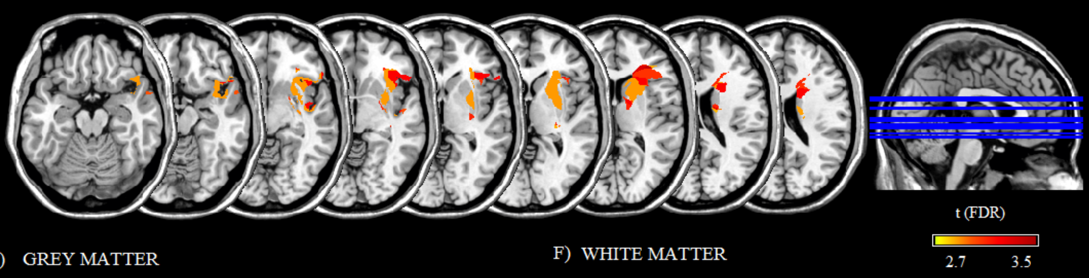
B) GREY MATTER

Area	N Voxel	N% Voxel	x	y	z
Orbital Inferior Frontal gyrus	1278	9.30	51	20	-5
Rolandic Operculum	3153	29.38	51	7	-1
Insula	7230	51.17	40	10	-12
Supramarginal gyrus	1269	8.05	41	-30	25
Caudate	1209	15.22	13	8	8
Putamen	3552	41.74	29	-16	10
Pallidum	154	7.04	19	0	7
Heschl gyrus	658	33.98	45	-12	5
Superior Temporal	773	3.06	45	0	-8
Superior Temporal Pole	1009	9.47	46	18	-14

C) WHITE MATTER

Area	N Voxel	N% Voxel	x	y	z
Arcuate Anterior Segment	3985	47.60	43	-3	15
Long Segment	138	35.29	35	-29	22
Cortico Spinal	1297	5.88	27	-11	10
Inferior Occipital Frontal Fasciculus	1064	8.47	36	4	-9
Internal Capsule	1604	9.18	26	4	21
Uncinate	328	4.36	35	2	-8

D) **Dangerous in Emergent Awanreness**



E) GREY MATTER

Area	N Voxel	N% Voxel	x	y	z
Inferior Frontal Triangularis	1544	9.01	38	38	5
Orbital Inferior Frontal gyrus	1225	8.91	42	19	-14
Insula	2735	19.36	41	14	-13
Amygdala	71	3.61	30	-8	-11
Caudate	1773	22.33	14	13	16
Putamen	3146	36.97	26	17	11
Pallidum	297	13.57	28	-8	-5
Superior Temporal Pole	542	5.09	45	18	-14

F) WHITE MATTER

Area	N Voxel	N% Voxel	x	y	z
Cortico Spinal	740	3.35	15	2	10
Inferior Occipital Frontal Fasciculus	1153	9.17	36	-25	-5
Internal Capsule	1963	11.24	26	29	15
Uncinate	346	4.60	25	-2	-7

Figure 6. Lesion mapping with behavioural data in emotional/dangerous nature of actions. Two different VSLM s separate analyses of lack of Dangerous effect in Anticipatory and Emergent actions showed similar results: A) Lesions of lack of Dangerous effect in Anticipatory awareness (center of mass= x 37, y 0, z 11). B) Table of significant lesions with number and percentage of voxels for each area for B) grey and C) white matter. D) Lesions of lack of Dangerous effect in Emergent awareness (center of mass= x 30, y 16, z 5). Table of significant lesions with number and percentage of voxels for each area for E) grey and F)white matter. For both VLSM analysis: The statistical lesions are shown in axial view and in the middle sagital slice, t-value (FDR corrected) are reported only for significant areas ($p>0.01$) and only areas with impaired percentage of voxel bigger than 3%.

3.4. Discussion

Nowadays, it is widely accepted that AHP is a multifarious syndrome (Orfei 2007; Vuilleumier et al., 2004; Fotopoulou, 2014) and that residual forms of awareness may be spared in anosognosic patients (Cocchini et al., 2010; Moro et al., 2011). Very recent studies also suggest that modulation of the symptoms is possible by means of specific manipulation, for example changing the patient's perspective of self- observation (Fotopoulou, Holmes, & Kopelman, 2009; Besharati, Kopelman, Avesani, Moro, & Fotopoulou, 2015), activating the intention to act (Moro et al., 2015) or inducing specific emotions (Besharati et al., 2014).

The purpose of this study was to investigate the possibility of activating residual forms of awareness by asking the patients to execute everyday actions in specific conditions.

In particular, we focused on: i) the potentially positive influence of attempts to act on patients' awareness of their deficits (Emergent awareness) and ii) the potential impact on anosognosia of attempting to perform actions with dangerous characteristics (Actions of a dangerous nature). Our results support and expand previous data (Moro et al., 2011) indicating that AHP patients may show signs of a form of emergent awareness. In fact, the patients' degree of awareness increases during the actual attempts to act, in comparison to the Anticipatory awareness (before execution). In addition, the attempt to perform potentially dangerous actions positively influences these effects, inducing an improvement in awareness in both the AHP and control groups.

Finally, an improvement (although not statistically significant) in the degree of General Awareness (which does not directly relate to the experimental action) is recorded after the execution of the task. This may be important in terms of devising rehabilitation strategies.

3.4.1 The assessment of Anosognosia for Hemiplegia

The categorization of our patients as anosognosics or non-anosognosics was initially done based on their scores on the Bisiach scale and Berti interview, which are two well known and widely used instruments in the AHP diagnosis.

This first assessment was also confirmed by the results of the two groups in the experimental task. In fact, the comparison between the judgments of the patients and that of their Physiotherapists judgments regarding their proficiency confirmed the preliminary classification. It is worth to note that an assessment based on this kind of comparison is particularly sensitive in term of identifying the presence of anosognosia (e.g. the VATAm, Della Sala, Cocchini, Beschin, & Cameron, 2009).

Finally, we administered a further ad-hoc questionnaire where specific items regarding self-reported proficiency in bimanual and bipedal actions (different from those of the task) were used as a measure of General Awareness (Marcel et al.'s modified interview, Marcel et al., 2004; Moro et al., 2011). As the scores in this interview ranged from 0 to 100, it offered us the possibility to detect any fluctuation in participants' awareness occurring before and after the experimental task.

We can thus assume that the two groups of patients really differed in terms of awareness. A comparison of their lesion confirmed this, as in AHP patients it was possile to detect the involvement of a wide right fronto-temporo-parietal network in AHP (Pia et al., 2004), with a main role of ventral frontal areas (Berti et al., 2005; Fotopoulou et al., 2010; Kortte et al., 2015), the insula (Fotopoulou et al., 2010, Karnath, Baier, &Naegele, 2005; Vocat et al., 2010, Moro & Pernigo et al., 2016), but also of subcortical structures, such as the basal ganglia and amygdale (Fotopoulou et al., 2010; Moro et al., 2011; Vocat et al., 2010) and the white matter around them (Moro & Pernigo, et al., 2016).

We also found lesions in the supramarginal gyrus and inferior parietal cortex. This indicates that in this AHP group the damage was spread in a more posterior and cortical direction with respect to previous studies (Karnath et al., 2005; Berti et al., 2005; Fotopoulou et al., 2010; , Moro et al., 2011; Moro & Pernigo et al., 2016).

The cortical parietal damage also explains the presence of visual spatial neglect, which was recorded in all of the patients in the AHP group (Bartolomeo, de Schotten, & Chica, 2012; Moro & Pernigo, et al., 2016 supplementary materials in Chapter 4).

The hypothesis of more general disorders in the ability to evaluate has been advanced in AHP (Saj, Vocat, & Vuilleumier, 2016). As the comparison between the AHP group's judgements referring to themselves as compared to others (Chapter 4) did not show significant differences, we cannot totally exclude this interpretation.

Nevertheless, observing the performance of each individual patients provided confirmation of the results of a previous concerning the existence of a dissociation (Moro et al., 2011). In fact, although four out of seven patients in this study (one of them did not perform the ther-reffered task) showed symptoms of AHP both in the self- and other-referred conditions, two patients displayed a significantly greater degree of anosognosia in the self-referred condition and one in other-referred condition.

Finally, the FB actions were judged to be more difficult than the actions involving only the upper limbs (UB). This may be at least in part explained by the fact that the motor deficit in lower limbs was more evident at the patients, who were in a wheelchair. In addition, the patients were given daily training in FB actions during the rehabilitation sessions, while most of the bimanual actions were not performed by the patients during their stay in hospital. Thus, we cannot exclude the possibility that some learning mechanisms relating to their difficulty in performing those actions might contribute to an implicit updating in autobiographical memory (the Personal Data Base in Morris & Mograbi, 2012).

However, these everyday experience in rehabilitation training were not enough to make AHP patients aware of their paralysis, as they were anosognosic with regard to both upper and full body actions.

Hence it is important not to consider AHP as an all-or-nothing phenomenon, but as a multifaceted complex syndrome that needs to be assessed in a variety of contexts, at different times and with several different methods (Nurmi & Jehkonen, 2014 for review). When well investigated, the issue of fluctuations in symptoms may be addressed in order to help patients to increase awareness (Besharati et al., 2015; Moro et al., 2015).

3.4.2. Emergent Awareness

Emergent Awareness in AHP has been described (Moro et al., 2011, Moro et al., 2015) as the explicit awareness that emerges during an attempt to act. It may be detected when AHP patients become more aware of their own deficits when they are asked to actually perform actions or to explain the reasons why they fail.

The concept originates from the hierarchical model of awareness devised by Crosson and colleagues (Crosson et al., 1989; Orfei, et al., 2007; Moro et al., 2011). This describes three levels of awareness: (1) intellectual awareness, i.e. the generic ability to recognize a deficit (e.g. “I suffered a stroke”); (2) emergent awareness, in which a patient becomes declaratively aware of his/her deficits only when asked to perform an action with the affected body part (i.e. by means of “confrontation”; e.g. “I thought I was able to do this action, but now I’m realizing it is impossible for me”); and (3) anticipatory awareness, i.e. the ability to anticipate the effects of a deficit, i.e. admitting the inability to perform an action before it becomes evident in a real situation (e.g. stating beforehand “I cannot jump because of my paralysis”). This model posits a hierarchical relation between the three levels so that anticipatory awareness is thought of as the highest level (and thus the first one to be affected in AHP), which is followed by emergent and then intellectual awareness. However, in cases of AHP it is possible that individual patients may show varying degrees of deficit in these three forms of awareness (Marcel et al., 2004; Moro et al., 2011).

The first study which tested this theory in AHP demonstrated empirically that when patients were asked to perform movements with their affected body parts, emergent awareness was manifested in a group of patients who were more generally unaware of their deficits (Moro et al., 2011). This finding suggests that intellectual and perhaps even anticipatory awareness may increase as a result of failed attempts to perform an action.

The efficacy of this approach has also been confirmed in a study of rehabilitation where a specific error-based program was administered to four AHP patients (Moro et al., 2015). Unfortunately, the number of patients involved in both of these previous studies was small and in addition only bimanual actions were employed. Thus, further data were necessary in order to confirm and expand the first evidence.

In line with the data resulting from these two studies, the AHP patients in the present study judged their ability to perform actions as being worse they when they were actually placed in the real condition to act in comparison to the judgement that they gave during an preliminary out-of-context interview (Semantic Awareness) or before being placed in the situation where they were required to act (Anticipatory Awareness). This improvement in awareness was also present after the execution of the action, when patients compared their previous judgements with their failures to perform (Post-Error awareness).

The Forward Dynamic model helps to explain our results. According to this model, motor awareness is based on the congruence between action planning and the prediction of the sensory consequences of the same action. When a given movement does not occur as intended and planned, a mismatch between predicted and actual sensory feedback is detected by a brain comparator that brings about conscious awareness of an error (Blakemore, Wolpert, & Frith, 2002; Fotopoulou et al., 2009). In AHP, the symptoms derive from a defective functioning of the comparator which for some reasons is incapable to detect this mismatch (Bottini et al., 2010; Fotopoulou et al., 2008). In this framework, we consider that intention to act combined with the request to evaluate performance may have an important role in the activity of monitoring any discordance between the original intention and the sensory feedback and contribute towards an improving in Emergent awareness (Moro et al., 2011). The process induces the use of cognitive and metacognitive strategies and executive processes (necessary for the intention, the monitoring and the evaluation of performance), which are not spontaneously activated in AHP patients and can be very important resource for recovery.

3.4.3. Effect of potentially dangerous actions

It is well known that the characteristics of a stimuli and the emotions these characteristics arouse have an impact to individual's responses. For example, the emotional content of facial expressions strongly influences the process of face perception for both healthy subjects and neurological patients (de Gelder, Frissen, Barton & Hadijikhani, 2003; Vuilleumier & Schwartz, 2001; Vuilleumier, 2004; Moro et al., 2011). The presence of dangerous objects interferes also with movements by evoking a specific aversive affordance (Anelli, Borghi, & Nicoletti, 2012; Anelli, Nicoletti, Bolzani, R., & Borghi 2013), which probably has the main purpose of preparing the motor networks to act in order to protect the self (Bradley, Codispoti, Cuthbert, & Lang, 2001). Dangerous stimuli may also be efficacious as they improve the impaired motor control of involuntary movements, as shown in a patient suffering from anarchic hand and magnetic apraxia, where involuntary grasping and groping significantly reduced in the presence of dangerous (e.g. a piece of broken glass) but not neutral (e.g. a glass) objects (Moro & Pernigo, at al., 2015).

This modulation of the emotions is thought to be based on the direct modulatory effects of subcortical structures (in particular the amygdale), that promote the processing of emotionally salient events (Amaral & Price, 1984; Sah, Faber, Lopez de Armentia, & Power, 2003; Vuilleumier et al., 2004).

The role of emotional and motivational components in AHP has been investigated a number of times (Bisiach & Geminiani, 1991; Ramachandran 1996; Vuilleumier, 2004) and the difficulty which AHP patients have in accepting and tolerating an aversive emotional status has been interpreted as a problem concerning the emotional-regulation system of negative feelings relating to the self (Kaplan-Solms & Solms, 2000; Turnbull et al., 2002; Turnbull, Evans, & Owen 2005).

According to the 'defense' theory (Weinstein & Kahn, 1955), the misattribution of negative emotions would be related to a refusal to explicit acknowledge own deficits. However, when spared, a certain degree of implicit knowledge of deficits could induce a process of repression (Anderson & Green, 2001). This latter hypothesis has been confirmed in recent studies showing that AHP patients can evoke implicit negative emotional reactions when given information regarding their hemiplegia and this interferes with their performance in attentional (Nardone et al., 2007) or verbal-inhibition tasks (Fotopoulou, et al., 2010).

Our results confirm these data and expand them by providing evidence of the positive effect of the potentially dangerous actions resulting in a greater temporary degree of explicit awareness of hemiplegia. Interestingly, the effect of potentially dangerous actions was seen in both groups in the present study, suggesting that the processes underlying protective activation or alerting may be spared in AHP patients. Emotional negative stimuli has been found to have an activating role in a recent study (Besharati et al., 2014), that investigated the influence of emotions on explicit awareness. In this outstanding paradigm, negative or positive self-referential emotions were induced by giving, respectively disapproving or approving social feedbacks to the patients about their performance. Although the AHP patients were capable of experiencing both negative and positive feelings, only the former induced a temporary improvements in explicit self-awareness (Besharati, et al., 2014).

Another interesting result is that actions with dangerous attributes have an effect on all kinds of awareness, not only when the action is in progress (Emergent awareness) but also before the action starts (Semantic and Anticipatory awareness). It is thus possible that, in addition to the subcortical emotional processes linked to the action planning, more top-down, semantic factors (i.e. the knowledge about the danger involved in a action) influences the effect.

In a similar way, neuro-anatomical studies have shown that he representation of actions involving dangerous stimuli is associated with a cortical activation in a general network (Baumgartner, Willi, & Jäncke, 2007; Hajcak et al., 2007; Oliveri et al., 2003), that integrates emotional information with behavioral and cognitive motor responses (Pessoa and Adolphs, 2010). Both subcortical areas, such as the basal ganglia (Butler et al., 2007, Phelps et al., 2001), amygdale and putamen (Romano, Gandola, Bottini, & Maravita, 2014), and cortical regions probably contribute in a fronto-insula/limbic inhibitory regulation (Phelps et al., 2001). Our analyses of the lesions are mainly explorative, due to the small number of patients, but they support this hypothesis. In fact, the lack of an improving effect resulting from a request to perform a potentially dangerous action, (in particular with reference to the responses relating to Emergent awareness), is significantly linked to a damage to the basal ganglia and amygdale (Hornigo, Vega-Flores, & Castro-Alamancos, 2016) and in the white matter underlying insula and fronto-temporal areas.

In the present study, the awareness of the AHP patients increased to a greater degree with FB as compared to UB actions. This is particularly interesting since FB actions (e.g. standing up or walking) are in fact potentially dangerous only for patients suffering from paralysis, while UB actions may be dangerous for everybody (i.e. putting a nail in a wooden block or lighting up a candle). This might represent an index of some residual forms of implicit awareness (see also Nardone et al., 2007; Fotopoulou et al., 2010).

An implicit bodily response to potentially dangerous stimuli has been found in a recent study (Romano et al., 2014), where the anticipatory reaction of skin conductance to threatening stimuli was recorded in hemiplegic and somatoparaphrenic patients, subjects with hemiplegia and anosognosia for hemianesthesia and hemiplegic patients without deficits in body representations. Crucially, the authors found a reduced conductance response in somatoparaphrenic patients, specifically relating to the contralesional arm, which they considered as not belonging to their body. In contrast, anosognosic patients showed implicit responses which were analogues to those of patients who only suffered from paralysis.

3.4.4. Limitation and conclusions

This study has some limitations. As with most studies on AHP, the number of patients is small. This is mainly due to the rarity of the syndrome and the difficulty of finding patients with a sufficient degree of attention, which was necessary to complete the task. Unfortunately we could not examine in depth the level of anxiety and depression in the patients and the data from the HADS were not available for all of them. Nevertheless, clinicians did not identify specific problems relating to mood or anxiety in the patients recruited for the study.

Taking everything into consideration, our results confirm the existence of various different forms of awareness and the possibility of activaing residual emergent awareness in order to restore an explicit recognition of his/her motor deficits. Attempting actions and the consequent analysis of the patient's motor deficits (with adequate emotional support) might be crucial in the recovery from anosognosia (Moro et al., 2015), especially in contexts which do not offer effective training programs (Kortte & Hillis, 2011; Jenkinson, Preston, & Ellis, 2011, but see Besharati et al., 2015).

Our experiment brings some new evidences regarding the influence of emotional and motivational components of action on AHP (as in Besharati, et al., 2014), and it is thus potentially useful in rehabilitation.

Chapter 4

Modulating Anosognosia for Hemiplegia: the Judgment of Other's actions (Supplementary materials)

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4.1. Control task: The Judgment of Others' actions: a third-person perspective

In order to collect data regarding the dissociation in motor awareness deficits, which may refer exclusively to the self or also to other people, a second task was administered. The patients were asked to judge the ability of another hemiplegic patient to carry out the same actions as those used in the main experimental task.
This chapter is in integration to the previous experiment (in Chapter 3), thus the theoretical framework and the information related to the patients are present in the introduction and the discussion of Chapter 3.

4.1.1. Stimuli

The patients were asked to view a series of very short video-clips (ca. 3-4 seconds long), showing a young man suffering for left hemiplegia. The list of 24 actions he had to perform were the same as those used in the main experiment in Chapter 3. Crucially, the video never showed the whole action, but stopped before the action started, so only the situation in which the patient was asked to do the actions, but not his attempts to act were seen. This allowed us to investigate other-referred awareness only in the Anticipatory (and not the Emergent) condition. The patient was shown from a frontal perspective and his hemiplegia was always clearly visible.

4.1.2. Procedure

The participants sat at a table and a computer was placed in front of them (at around 40 cm) or in a right position (in case of neglect), in which it was easily visible. The examiner sat close to the patient and the video-clips were shown. After each video, the subjects were asked (by means of Yes/No questions) to judge the capacity of the patient in the video to realize the action seen ("Can he do it?" the score for No was 0). In case of positive answer, they then had to judge the other's proficiency ("How well can he do it?") using the 10-point Likert scale (from 1 = "He cannot do it" to 10 "He is very good at it"). FB and UB blocks were presented in a counterbalanced order between participants.

To prevent that this other-referred perspective task influences the self-referred awareness (Besharati, et al., 2014; Fotopoulou, et al., 2009), this task was always administered after the main experimental task.

In addition, the potential general effect of the videos in the General Awareness Interview (Moro et al., 2011) was measured at the beginning and at the end of the whole task.

4.1.3. Statistical analyses

In order to assess any fluctuations of Awareness from a self-referring or other-referring perspective, these analysis were carried out only for the AHP group. The data from seven subjects were available, since 1 patient did not execute this task for practical reasons. The differences between judgments of self or another patient's action were analysed by means of a 2 (Perspective: Self vs. Other) x 2 (Action: Dangerous vs. Neutral) ANODE Test. All post-hoc analyses were executed with lsmeans Tests (Bonferroni corrected).

To investigate the potential effects on awareness, the scores at the General Awareness were analysed across time in a 2 (Interval: Before vs. After task) lsmeans Test.

4.2. Results

In the judgment of others' actions, the results showed significant statistical differences in AHP in the main factor Action ($LR\chi^2_{(1)}$=35.30, $p<0.01$), but not in Perspective ($LR\chi^2_{(1)}$= 1.68, p=0.19) and in the interaction Action*Perspective ($LR\ \chi^2_{(1)}$= 1.20, p=0.27) (Figure 1Sa). Thus, analysing the whole group, the dissociation self-other does not emerge (but see below for individual results).

In the General Awareness assessment the AHP group showed a difference between the assessments pre and post task ($p<0.01$) (Figure 1Sb).

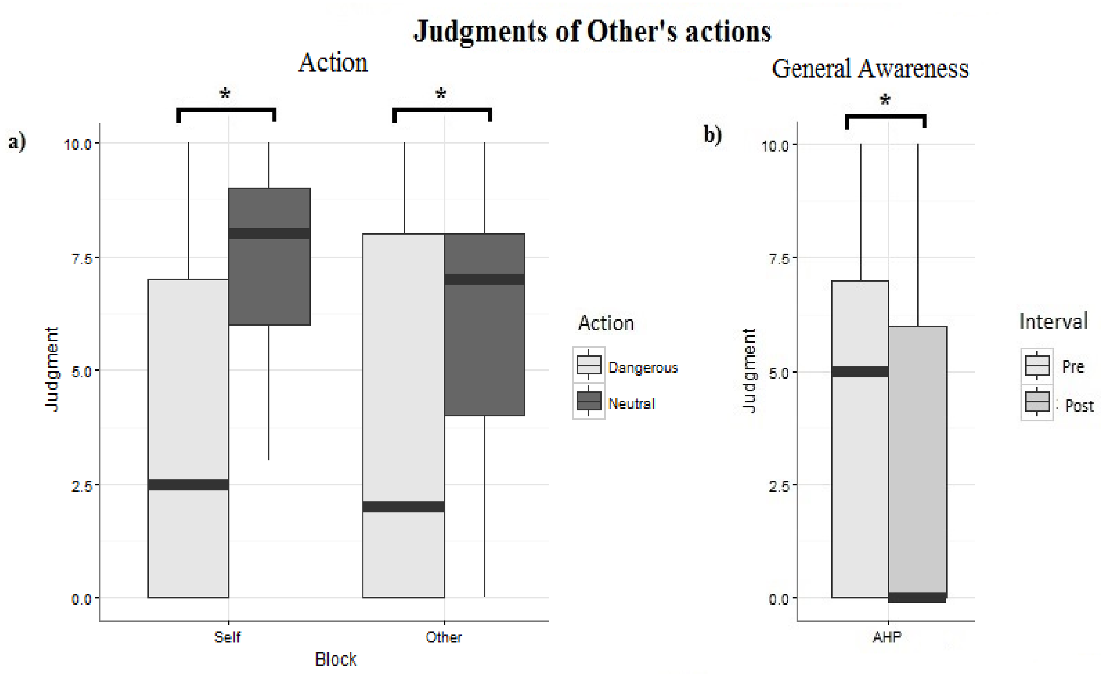

Figure 1S. Results for AHP group at *The Judgment of Other person's actions* task. The judgments of patients are expressed in the range between 0 to 10 as recorded during the task; lower judgments indicate that the action are judged as more difficult (i.e. better awareness), and vice versa higher judgments refer to actions perceived as easier (i.e. worse awareness). The box represents the first and the third quartile of data, and the darker line inside is the median. The bottom and the top whiskers are respectively 1.5* Interquartile range lower and 1.5* Interquartile range higher.

a) Judgments are reported according to the Perspective (Self and Other) and the type of Actions (Dangerous and Neutral), b) Judgments at the measure of General awareness pre and post the other-referred experimental task.

4.2.1. Individual performance

As in the previous literature on the subjects, the dissociation between self- and other-referred anosognosia is reported only in some of AHP patients, we analysed the individual performance (Figure 2S), in order to calculate the number of patients really manifested this dissociation. For each subject we computed a repeated 2-way (Perspective: Self vs. Other) Wilcoxon Test.

Statistical differences are detected for participant n. 2 ($Z=-2.07$, $p=0.04$) and subject n. 4 ($Z=-3.34$, $p<0.01$), who showed greater awareness in other-referred condition as they judged the other patient's proficiency as being worse than their own(Self)..

In contrast, the subject n. 3 showed a contrary effect (Z=-2.87, $p<0.01$) with more severe judgments for the Self than for the Other patient's actions.

All of the other patients did not show differences in judgment, confirming that the dissociation between Self and Other is present only in some AHP patients.

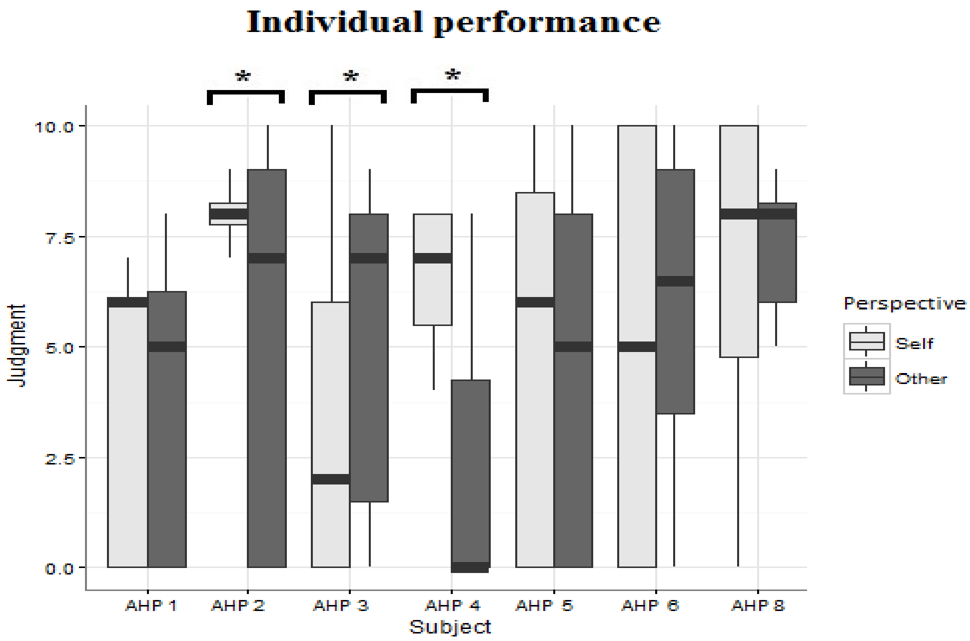

Figure 2S. Individual results of the AHP patients in *The Judgment of Other person's actions* task. The judgments of patients are expressed in the range between 0 to 10 as recorded during the task; lower judgments indicate that the action are judged as more difficult, and vice versa higher judgments refer to actions perceived as easier. The box represents the first and the third quartile of data, and the darker line inside is the median. The bottom and the top whiskers are respectively 1.5* Interquartile range lower and 1.5* Interquartile range higher.

Chapter 5

Modulating of Skin Conductance responses in Anosognosia for Hemiplegia

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Anosognosia for hemiplegia is a deficit of motor awareness that is characterized from heterogeneous and multi-componential factors. From previous evidence, it has been suggested that a real attempt to perform an action might enhance some residual form of awareness.

In this experiment, we investigate whether some residual forms of awareness might be detected in measurements of automatic bodily responses of skin conductance during actions with or without the affective resonance of danger. From the results the skin conductance responses of patients with Anosognosia for hemiplegia appear to be enhanced by vicarious actions, but not specifically from dangerous objects used during these actions. We suppose that some more specific type of stimuli and processes might be needed to induce sensorymotor and top-down modulations of awareness, but further investigations are suggested.

5.1. Introduction

The neurological disorder of Anosognosia for Hemiplegia manifests itself as a lack of awareness of motor impairments in patients affected by a right brain damage (Babinski, 1914). Namely, these patients fail to acknowledge or recognize the motor deficit of their upper and/or lower limbs and report being able to move them. AHP has heterogeneous and multi-componential manifestations (Heilmann & Harciarek, 2010; Orfei et al., 2007; Marcel, et al., 2004; Vocat et al., 2010), that consist of both sensory-motor and high cognitive functions (Fotopoulou, 2012; 2014).

Several studies have systematically investigated the relation between monitoring of intended actions and actual movements with AHP (Jenkinson & Fotopoulou, 2010 for review). For instance, it has been demonstrated that AHP patients have an intact intention to move, which influences their performance during bimanual actions. Despite only one of their hands is actually moving, the intention and the plan of bimanual actions incide to the performance of the spared hand(Garbarini, et al., 2012; Pia, et al., 2013) and to the perception of the incoming feedbacks (Piedimonte et al., 2016). Furthermore the presence of AHP affect the automatic bodily responses, as the electrodermal and muscle responses are observed during mental imagery of movements of the hemiplegic limb (Hildebrandt & Zieger, 1995). Similarly, when AHP patients are instructed and trained to program a reaching action as it would be really performed, they show muscles activation through electromyography of their paralyzed arm (Berti et al, 2007). These results demonstrate that these patients preserved intentions to move and that they can produce the motor commands of the affected hemiplegic limb.

In a recent study (Romano et al., 2014), the automatic electrodermal activity was investigated in right-brain damaged patients affected by hemiplegia. These patients were divided into different groups: subjects with somatoparaphrenia (deficit of the sense of ownership of their own arm), subjects with anosognosia for hemianestesia (lack of awareness of the controlateral sensory impairments) and subjects without deficits in their body representation. Crucially, the authors found that the anticipatory skin conductance reaction after the threatening stimuli was reduced specificaly in the somatoparaphrenic group referring to the affected arm which they felt as not belonging to their body. In other words, a deep detachment of the arm from the body representation influences the implicit response to potential dangerous stimuli. Vice versa, there are no significant differences in the other groups of hemiplegic patients. Even the presence of anosognosia for the hemianestesia does not appear to implicitly modulate the perception of sensory stimuli. These results suggest that the body representation can be implicitly influenced in different ways by the sense of ownership or the degree of awareness (Romano et al., 2014). We may hypothesize that some somatoparaphrenic patients might show some spared electrodermal reaction as an implicit form of ownership of their arm and that the automatic reaction of skin conductance might be a useful method to detect the fluctuations in awareness.

Instead the AHP patients show a deficit in sense of agency, meant as the feeling of authorship and control of their own actions (Gallagher, 2000). Despite the absence of actual limbs' movements due to hemiplegia, these patients do not appear to be aware about such a lack or at most they show it only in some tacit forms of awareness. For example, some patients can implicitly adapt their movements to compensate for the paralyzed limb without claiming the presence of hemiplegia, namely a form of Implicit awareness (Cocchini et al., 2010). Other patients reach instead an upcoming form of declarative awareness during the actual attempt to execute the movement, which is known as Emergent awareness (Moro, et al., 2011; Moro et al., 2015).

In this framework, we suppose that these residual forms of awareness might be detected in measurements of automatic bodily responses both in relation to actions (Berti et al., 2007; Hildebrandt & Zieger, 1995) and to their emotional resonance. Since dangerous stimuli appear to improve the level of awareness in AHP during the request to act (D'Imperio, Bulgarelli, Bertagnoli, Avesani, & Moro - Chapter 3 of this thesis), the skin conductance responses (SCR) might provide an implicit

automatic measure of awareness during actions with threatening and neutral stimuli (Armel & Ramachandran, 2003; Guterstam et al., 2011; Romano et al., 2014).
In this new experiment, right-brain damage patients with and without AHP are request to perform a 'go-like' task, while the skin conductance responses (SCR) are constantly recorded. In the task some images of an arm during actions' executions are displayed in a first-perspective view so to make the patients feel as if their own arm is moving. After a few seconds, these images are covered by a big coloured square that is the 'go-signal' to answer. Patients are instructed to state its colour and the accuracy of responses is recorded. In order to detect possible fluctuations of awareness, these images are divided in accordance to the left or right hand and to the active action of reaching or the passive situation of being threatened by an approaching stimulus. In this way, we measure the behavioural and electrodermal bodily responses in relation to both the presence of the hemiplegia and the type of action. Furthermore, the stimuli are also differentiated by means of their affective resonance, since half of them have implied dangerous meaning while the other half are neutral. In particular, the dangerous actions feature objects implying the risk of being hurt and may trigger protective reaction.
Finally, we also request the patients to declaratively judge their proficiency to realize the same actions, with the aim to evaluate a possible dissociation between implicit and explicit forms of awareness.
In this study, we evaluate both the sensory-motormechanisms associated to different types of stimuli and the possible higher cognitive modulation of awareness associated to changes in emotional state after a potential threat (Besharati et al., 2014; Nardone et al., 2007).

5.2. Materials and Methods

5.2.1. Participants

Ten neurological patients following a right-brain damaged and suffering from severe contralateral hemiplegia were recruited among 1 year. The deficits of language comprehension and production and an history of brain injuries or psychiatric disease were considered as exclusion criteria. The two groups were matched for age, gender, education and the interval from the lesion onset and the experimental task (Table 1).

Pt	Age	G	Educ	Exp Int	Sens	TE	Motor
AHP 1	75	M	5	< 1	+	+	-
AHP 2	72	F	5	1 - 3	-	Imp	-
AHP 3	49	F	5	< 1	-	Imp	-
AHP 4	41	F	Na	3 - 6	+	Na	-
AHP 5	46	M	8	3 - 6	+	-	-
Mean	*56.6*		*5.8*				
St.dev.	*15.7*		*1.5*				
HP 1	83	F	5	< 1	+	-	-
HP 2	47	M	9	> 6	-	Imp	-
HP 3	37	M	8	> 6	-	Imp	-
HP 4	53	M	13	1 - 3	+	Na	-
HP 5	Na	F	Na	3 - 6	-	Imp	-
Mean	*55*		*8.8*				
St.dev.	*19.8*		*3.3*				

Table 1. Demographic and clinical data of patients with anosognosia for hemiplegia (AHP) and without anosognosia for hemiplegia (HP). Pt= patient, G= gender, Educ= years of education. Exp Int= interval between lesion onset and experimental task classified in periods of: < 1 Month, form 1 to 3 Months, from 3 to 6 Months, > 6 Months. Sens= sensory deficits, TE= tactile extinction, Motor= motor deficits. -= deficits present; += deficits not present. Imp= impossible to assess, Na= Not available. For each group *Mean* and *St.dev.*= Standard deviation values are reported

All the patients were divided into two different groups basing on the presence of AHP. For the categorization, AHP was assessed in upper and lower limbs by means of the Bisiach scale (Bisiach et al., 1986) and the Berti interview (Berti et al., 1996). For the diagnosis of AHP, the scores were ≥ 1 at both the Bisiach scale and the Berti interview (Table 2).

In order to verify the normal reactions of SCR to the task, we compared their performances to a control group of group of 10 healthy people, which matched for age, gender and education. All the participants gave their consent to participate in the study (approved from the local ethics committee -CEP prot. N. 39216- and carried out in accordance with the guidelines in the Declaration of Helsinki, 2013).

All patients were well oriented in space and time at the time of the experimental task. Although some patients had scores under cut-off in the assessment of general cognitive profile (MMSE, Folstein, Folstein, & McHugh, 1975), this was mainly due to visuo-spatial problems (Table 3). Half of the patient from each group failed in tests assessing frontal functions (Frontal Assessment Battery - FAB; Apollonio, et al., 2005).

Finally both groups showed more symptoms of extrapersonal (Line Bisection, Albert Test and Copy Test; Wilson, Cockburn, & Halligan, 1987), and personal neglect (Comb and Razor Test, McImtosh, Brodie, Beschin, & Robertson, 2000).

Pt	Berti UL[1]	Berti LL[1]	Bisiach[2]	MMSE (30)	FAB (18)	Bisection (9)	COMB
AHP 1	1	2	3	**11**	**5**	Na	**-0.3**
AHP 2	1	2	1.5	**17**	**1**	**0**	**-0.2**
AHP 3	1	2	1.5	**23**	12	9	0
AHP 4	2	2	1.5	**20**	15	**0**	Na
AHP 5	1	1	1	*24*	15	6	**-0.4**
Mean				*19*	*9.6*	*3.75*	*-0.22*
St.dev.				*5.24*	*6.31*	*4.5*	*0.17*
HP 1	0	0	0	25	14	**6**	-0.06
HP 2	0	0	0	**16**	**11**	**2**	**-0.29**
HP 3	0	0	0	**16**	**11**	**2**	**-0.36**
HP 4	0	0	0	26	12	**4**	**-0,31**
HP 5	0	0	0	29	14	**0**	**-0.33**
Mean				*22.4*	*12.4*	*2.8*	*-0.32*
St.dev.				*6.02*	*1.52*	*2.28*	*0.01*

Table 1. Neuropsychological data of patients with anosognosia for hemiplegia (AHP) and without anosognosia for hemiplegia with Right damage (HP DX) and after left damage (HP SX). Pt= patient. UL= Upper Limb LL= Lower Limb. Na= not available-= deficits present; += deficits not present. Pathological scores are in bold. Scores at cut-off are in *Italic*. For each group *Mean* and *St.dev.*= Standard deviation values are reported.

5.2.2. Stimuli

The stimuli consisted of single images in which two arms were displayed while interacting. In these images, the two arms were placed in front of each other, so that whomever was watching the screen saw an arm at the front, in a first-perspective view, as if it was making the movement and reaching out for the other arm, pointed in the opposite direction in an interactive situation.

The other arm in the opposite view was always holding an object. Thus, to create the stimuli, 16 different objects were chosen that were easy to handle with one hand and common in everyday life activities.

Three different types of images were designed for the experiment to characterize different features of the first-perspective movements: i) the moment before the interaction in an undetermined pre-action moment (Pre-action Block), ii) the arm in first-perspective actively reaching the opposite objects (Active Block) and iii) the other arm with the object approaching the arm in first-perspective, which is meant to move away or escape (Passive Block). It is relevant to notice that these actions were never completed. Indeed, in the Active Block, the arm in first-perspective was in a middle frame while reaching the other arm with the object. While in the Passive Block the opposite arm was in the middle of approaching the closer arm in first-perspective.

Each object was used to realize a stimulus image for each Block, so that there were 16 different kind of stimuli for every block.

Furthermore, these stimuli were divided according to their affective resonance: half of the images were dangerous and half neutral (see section *Validation of affective resonance of stimuli*). This subdivision was based on the type of object hold from the opposite hand, which characterized the action. For the Dangerous Actions (D), we used some threatening objects that normally elicit the risk of getting hurt (i.e. a shard of glass or a knife). Dangerous objects in Active Block were then placed in a manner that would cause an injury if it is reached (e.g., ending on the sharp point of the knife pointing towards the reaching hand). Instead in the Passive Block the dangerous objects were used to approach the arm in a first-perspective in a threatening way (i.e. trying to hit the arm with the sharp end of the knife) (see Figure 1). Vice versa, the objects used for Neutral Actions (N) were harmless (i.e., a whole glass or a plastic comb). In addition, the objects were selected so that each dangerous object corresponded to a neutral object for similarity of shape and size (e.g., the knife and the comb) (see Figure 2).

All the images were repeated during the task and presented once for each hand, so that in total we presented 96 stimuli for hand (divided in 32 stimuli for each block: Pre-action, Active and Passive) and repeated for the other hand.

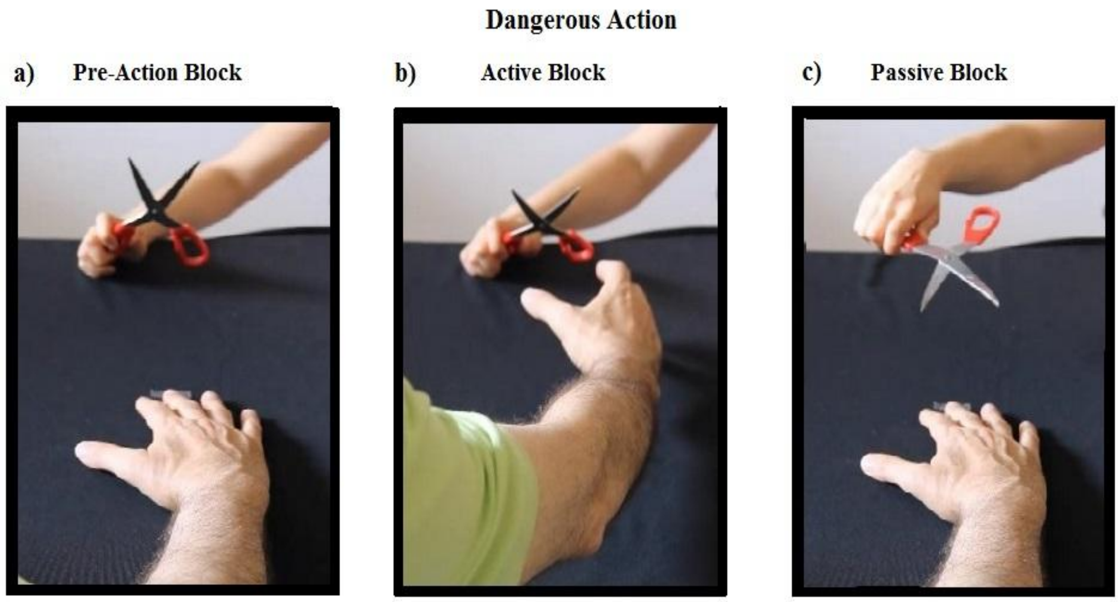

Figure 1. Example of Dangerous Action. Experimental stimuli of a dangerous action is displayed separately for the movements in the a) Pre-action, b) Active and c) Passive Block. They are displayed only for the right hand. But they are repeated for the left hand.

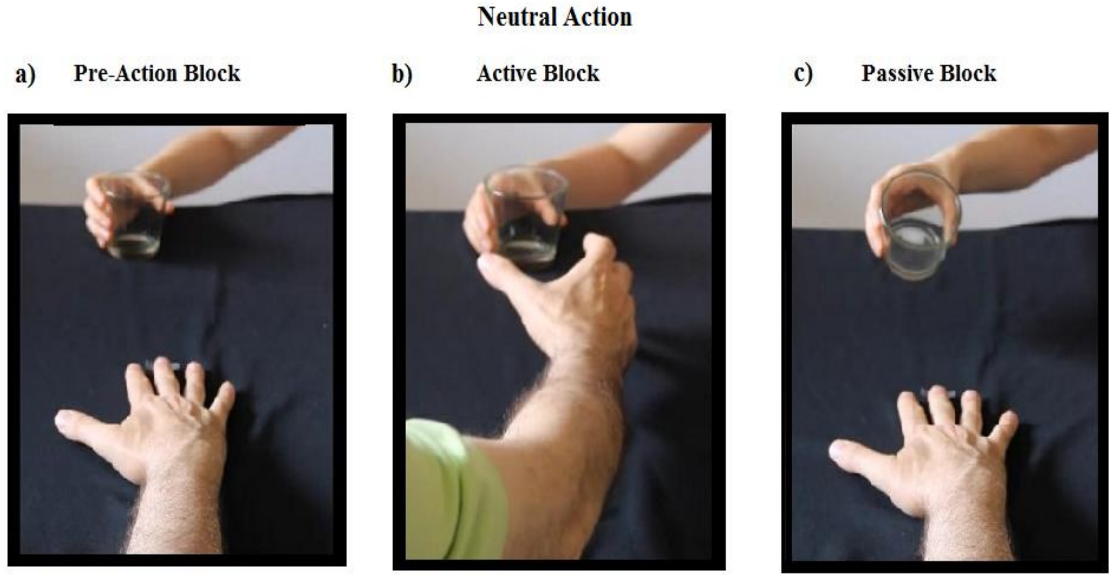

Figure 2. Example of a Neutral Action. Experimental stimuli of a Neutral action is displayed separately for the movements in the a) Pre-action, b) Active and c) Passive Block. They are displayed only for the right hand. But they are repeated for the left hand.

5.2.2.1 Validation of affective resonance of stimuli

In order to ensure the affective resonance of the stimuli, 12 health subjects (6 males and 6 females, mean of the age = 52.58 ±18.36, that were not involved in the experimental task) were recruited to judge their saliency.

These subjects sat at the table and the computer was placed in front of them (ca. at 40 cm). All the 96 images of the the experiment were individually shown in the middle of the computer screen, exactly as in the experimental procedure. The subjects were asked to judge the dangerousness of each image by means of a visual analogue scale (VAS) displayed below the image with the mouse (with the right button). The VAS gave a value in a range from 0 ("Not dangerous at all") to 100 ("Very dangerous").

For the experimental images the medians under the first quartile were qualified as neutral and over the third quartile as dangerous. Across all patients, the medians for the selected images were respectively 8.5 for Neutral and 87 for Dangerous Actions and they were considered as suitable for the experiment.

5.2.3. Procedure

In the experimental task, the subjects sat on their wheelchairs at a table and a computer was placed in front of them (ca. at 50 cm). The images were shown in the middle of the screen, so that they were well visible for all patients (also in cases of neglect).

Before the beginning of the experimental procedure, the subjects were left quite for a few minutes so that they could relax and feel comfortable. Subsequently, they were gently introduced to the experimental setting.

The experiment consisted of a go-like task, while SCR was recorded. In each trial, after a fixation cross (2000 ms), a stimulus was shown on the screen randomly for 4.5 or 5 seconds so that subjects could not get used to stimulus timing. Then, a big coloured square appeared on the screen and completely covered the stimulus. This was the "go signal" to which subjects were instructed to answer by saying its colour ("Yellow" or "Green") as soon as they could. The images disappeared after the answer and another trial started. Accuracy at the task was recorded.

In order to familiarize with the task before the start, an instruction block was administered. For which, 8 images of a single hand (without objects) were shown randomly for 4.5 or 5 seconds and then the yellow or green square form appeared. The subject was instructed to pay attention to the hand and trained to answer only at the appearance of the square form by saying its colour. In this introductive part the subject was also asked to recognize which hand was displayed ("Which hand is it?" - Left/Right answer). This question was asked randomlly a couple of times during the task, to ensure that the subjects were aware about it.

As abovementioned, the experiment was composed of three different Blocks (of 32 stimuli each) associated to the different moments of actions (Pre-action, Active and Passive Blocks) and they were run in counterbalanced order between subjects. In each block, stimuli were presented randomly so that half were Neutral and half were Dangerous Actions (as suggested for SCR measurements, e.g. Romano et al., 2014) (see timeline in Figure 3).

The task was administered in two separate days, respectively one day for all the blocks referring to an hand, in order not to tire the subjects out. For all the patients, we always started the experiment with the Blocks referring to the impaired hand, to avoid the possibility that the level of AHP might be influenced by the experiment routine.

E-prime 2.1 Software (Psychology Software Tool Inc., Pittsburgh, A) was used to control timing and randomisation of the task and the measurement of SCR was constantly recorded for the entire duration of the experiment by means of a Biopac. In addition at the beginning and at the end of the task, the level of explicit awareness of the same actions were measured by a self-reported judgment of proficiency on a 10 Likert-points scale ("How well can you use your hand with this object?" - from 0 "I am not able to do it" to 10 "I can do it without any problems", namely the Explicit Awareness)

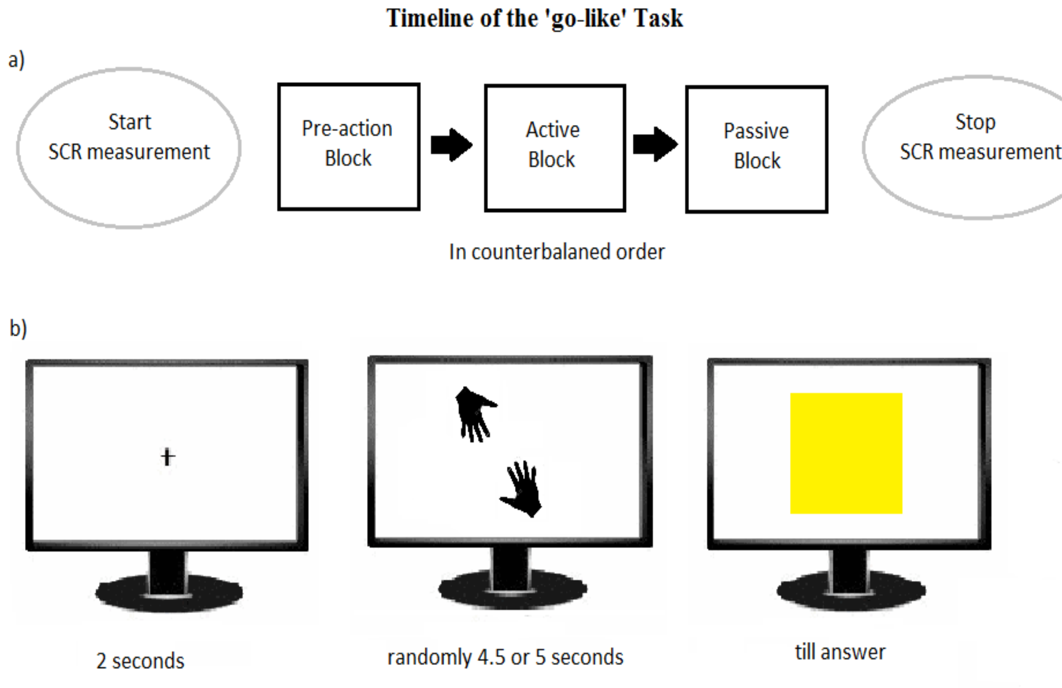

Figura 3. Timeline of the 'go-like' task. a) General timeline of the task for each hand. b) Specific timing for each trial of the task (the object is not displayed for space issue).

5.2.3.1. Skin conductance responses' measurement

Skin conductance responses (SCR) were recorded using a specific acquisition amplifier for skin conductance activity EDA100C (Biopac System Inc.). The amplifier was connected to the computer through a serial port. The gain parameter was set at 5 µmho/V and the signal sampled at 100 Hz.

Two snap electrodes (EL507: 2.7 cm x 3.6 cm, 1.5 mm thick) were used to acquire the signal. They were placed on subject's shoulder (as in Cacioppo, Tassinary, & Berntson, 2007), after that the skin was carefully cleaned with spirit. In case of patients the electrodes were placed on the ipsilateral shoulder. The electrodes were self-adhesive and pre-gelled with isotonic cream, that ensures a good signal-to-noise ratio. At the beginning of each stimuli a trigger was digitally send from the E-prime Software to the signal to sign the stimulus timing.

The analysis of SCR was computed using Acqknowledge 4.0 Software (provided by Biopac System). At first we filtered the signal at a cut-off of 40Hz, then an automatic continuous decomposition analysis (CDA; Benedek & Kaernbach, 2010) permitted to separate the phasic components form the tonic activity, by means of a high pass digital filter at 0.05 Hz.

The SCR was analyses on a peak-to-base measurements (similar to Romano, et al., 2014), by computing the difference between the maximum (peak) value in the interval between 0.3 s to 5 s post-stimulus (limit of the trials' time presentation) and the average value in the 0.3 s pre-stimulus.

To overcome the intersubject variability (Lykken & Venables, 1971), the SCR responses were normalized within subjects into z-scores before being analysed.

5.3. Results

5.3.1. Accuracy

The performance of all patients at the go-like task was extremely high in the accuracy (mean=91.72%). It confirmed both that the task was easy to perform and that all patients paid attention at it.

The analyses were computed by means of a 2 (Group: AHP v. HP) x 2 (Hand: Hemiplegic v. Healthy hand) Chi^2 Test, and post-hoc analysis with pairwise comparison tests for proportions with False discovery rate (FDR) correction (Benjamini & Hochberg, 1995).

Despite the high level of accuracy, the result indicates a statistical difference of responses ($\chi^2_{(1)}=8.50$, $p<0.01$), with a specific lower frequency of correct answers for the AHP group about the Hemiplegic hand than the Healthy hand ($p<0.01$). Instead the HP group do not present any differentiations in performance according to the hand (Figure 4).

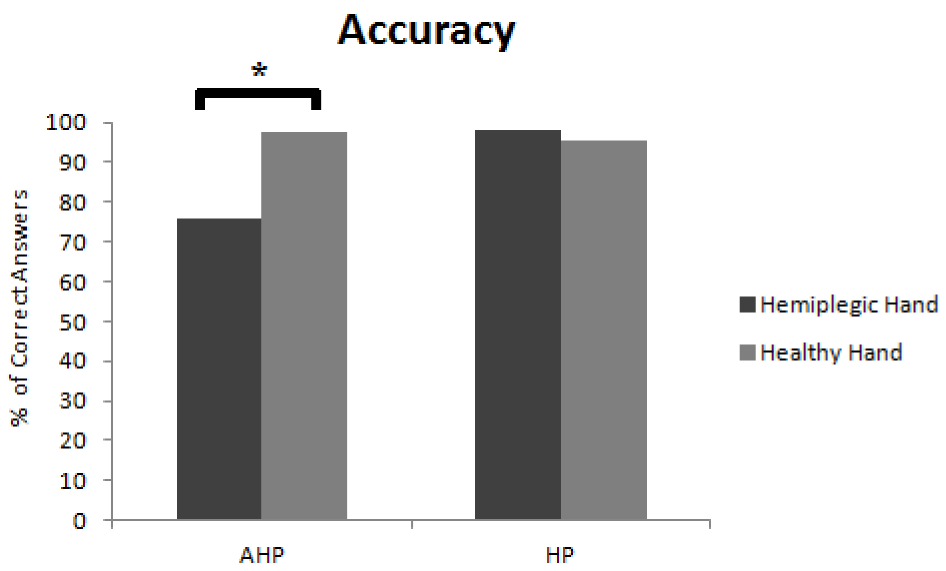

Figure 4. Accuracy at the 'go-like' Task. Percentage of Correct Answers are shown in accordance to the Group and to the Hand.

5.3.2. Skin Conductance Reponses

The z-scores of peak-to-base measure of the SCR were analyzed separately for the control group of healthy subjects and for brain-damaged patients.

For the SCR of the healthy control group, the analyses were computed by means of Linear Mixed Models. The fixed factors were the Block (Pre-action v. Active v. Passive) x Type (Dangerous v. Neutral actions), while the random intercept of all the model was the subject due to the small sample (Bates, Kliegl, Vasishth, & Baayen, 2015).

For the analysis reffering only to the brain-damaged patients, we added to the model two fixed factors of Group (AHP vs. HP) and Hand (Hemiplegic v. Healthy) and the covariate factor of Anosognosia (the value of the External awareness before the experiment). Post-doc analysis are computed by means of t-test with FDR correction (Benjamini & Hochberg, 1995).

For the control group of healthy subjects, the results indicate a statistical difference of the Interaction Type*Block ($F_{(1,1)}$=5.72, p=0.01), but not statistical effects of Type ($F_{(1,9)}$=0.08, p=0.78) and Block ($F_{(1,9)}$=0.63, p=0.49). In direct t-tests, there is only a statistical difference of Type in Pre-action Block ($t_{(1,9)}$=1.90, p=0.05), with higher SCR for Dangerous (mean=0.16) than Neutral (mean= -0.02) actions (Figure 5).

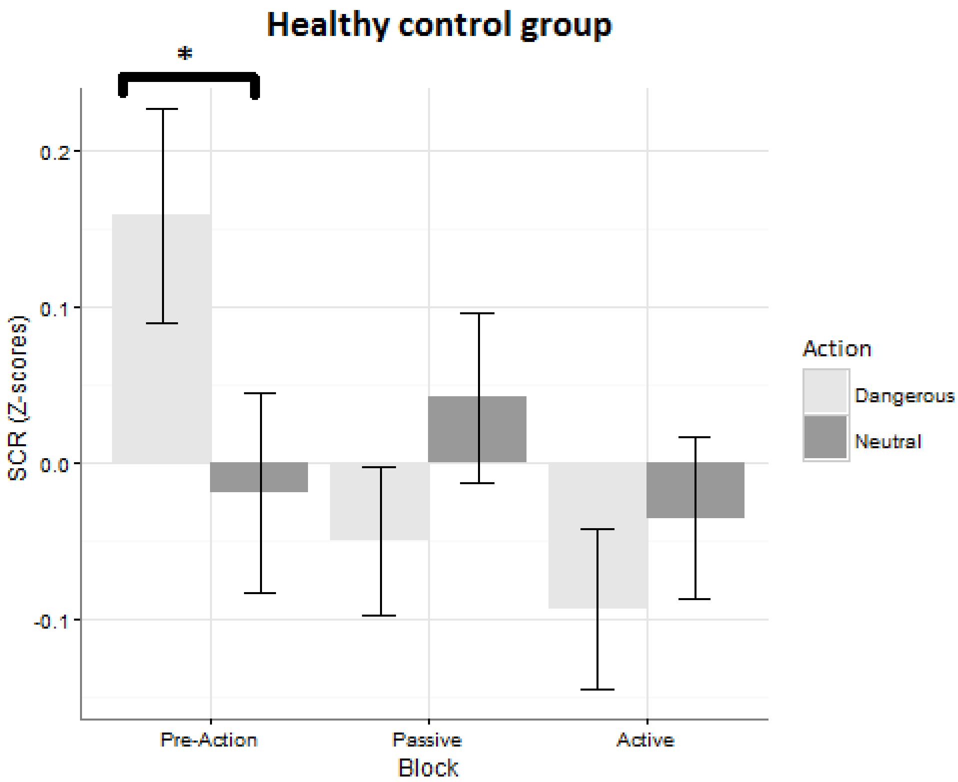

Figure 5. SCR of healthy control group. Z-scores of SCR measurements of the control group of healthy subjects. The results indicate that the task elicits an affective automatic responses for Dangerous Actions. In case of possible movements to avoid the danger, the enhancement is not present. * for p≤0.05.

For the two groups of patients, the results indicate a statistical difference of the covariate Anosognosia ($F_{(1,1)}$=4.77, p=0.03) and the main factors Type ($F_{(1,1)}$=4.31, p=0.04) and Hand ($F_{(1,1)}$=15.21, p<0.01), but not other main factors Group ($F_{(1,1)}$=4.13, p=0.07) or Block ($F_{(1,2)}$=2.57, p=0.08). There is a significant Interaction of Group*Hand*Anosognosia ($F_{(1,1)}$=6.97, p=0.01) and a tendency to significant of Group*Type*Hand ($F_{(1,1)}$=3.55, p=0.06). There are no other effects (Figure 6 and 7).

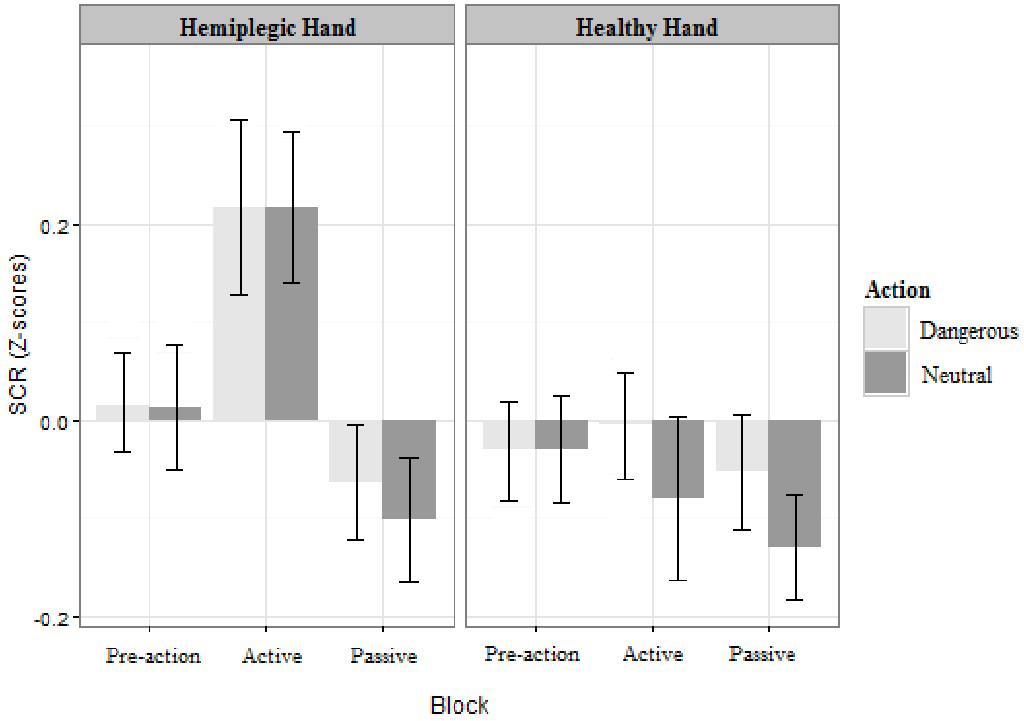

Figura 6. SCR of the brain-damaged groups. The means of the Z-scores of the peark-to-base SCR for both AHP and HP group are shown, in order to show the average responses for the brain-damaged patients

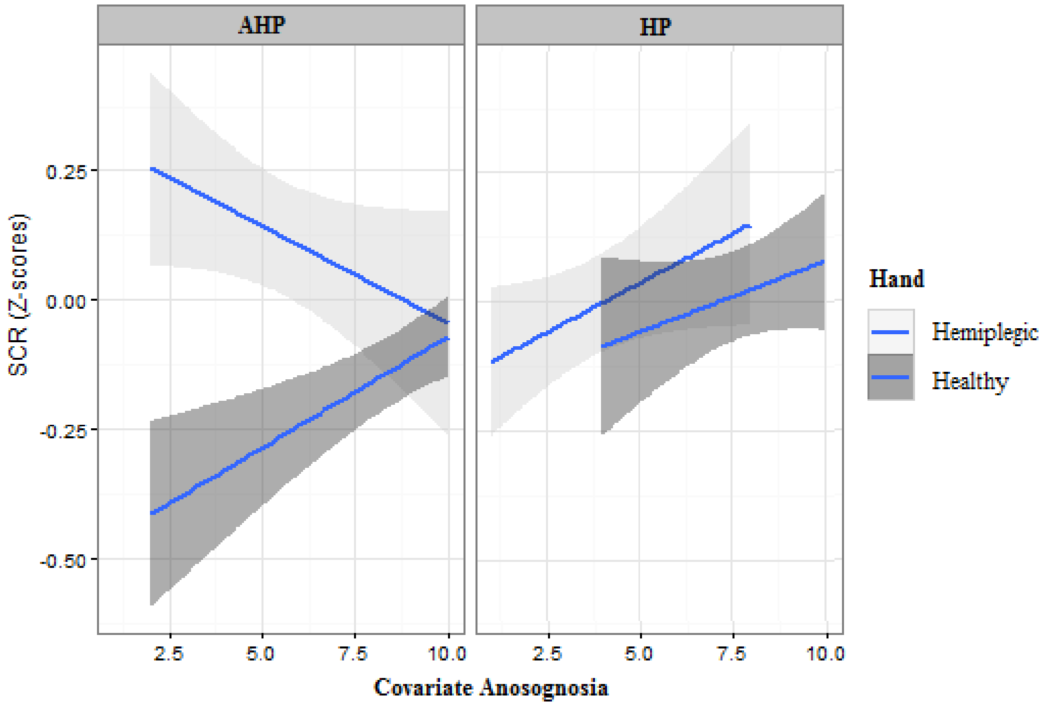

Figura 7 Covariate Anosognosia. Trend of the Z-scores of SCR for the covariate Anosognosia according to the Group and the Hand.

In order to investigate the role of the Hemiplegic hand, we provided divided the analysis according to the hand. We included all factors mainly for a descriptive reason. For instance only the results on the Hemiplegic hand show statistical differences of the main of Block ($F_{(1,2)}$=9.40, p<0.01, FDR corrected), but not of the other main effects of Group ($F_{(1,1)}$=1.22, p=0.33), or Type ($F_{(1,1)}$=0.12, p=0.72). There is a significant Interaction of Group*Block ($F_{(1,2)}$=3.98, p=0.03, a tendecy with FDR correction).

There are no significant results for the Healthy hand.

Finally, for more descriptive aims, a separate analysis was performed for each group only for the Hemiplegic hand.

For the AHP group, the results indicate only the main effect of Block ($F_{(1,2)}$=6.47, p<0.01, FDR corrected), but not of Type ($F_{(1,1)}$=0.06, p=0.79), or of Interactions. In post-hoc t-tests, higher SCR values appear for the Active Block (mean=0.35) than the Passive (mean= -0.15) ($T_{(1)}$=-3.97, p<0.01, FDR corrected) and lower Passive to the Pre-action (mean=0.11) Blocks ($T_{(1)}$=-2.22, p=0.4, FDR corrected).

For the HP group, the results indicate the main effect of Type ($F_{(1,1)}$=7.05, p=0.02, FDR corrected), but not of Block ($F_{(1,2)}$=3.33, p=0.04), or for Interactions. Higher SCR values appear for the Dangerous Type (mean=0.01) than the Neutral Type (mean= -0.03) (Figure 8).

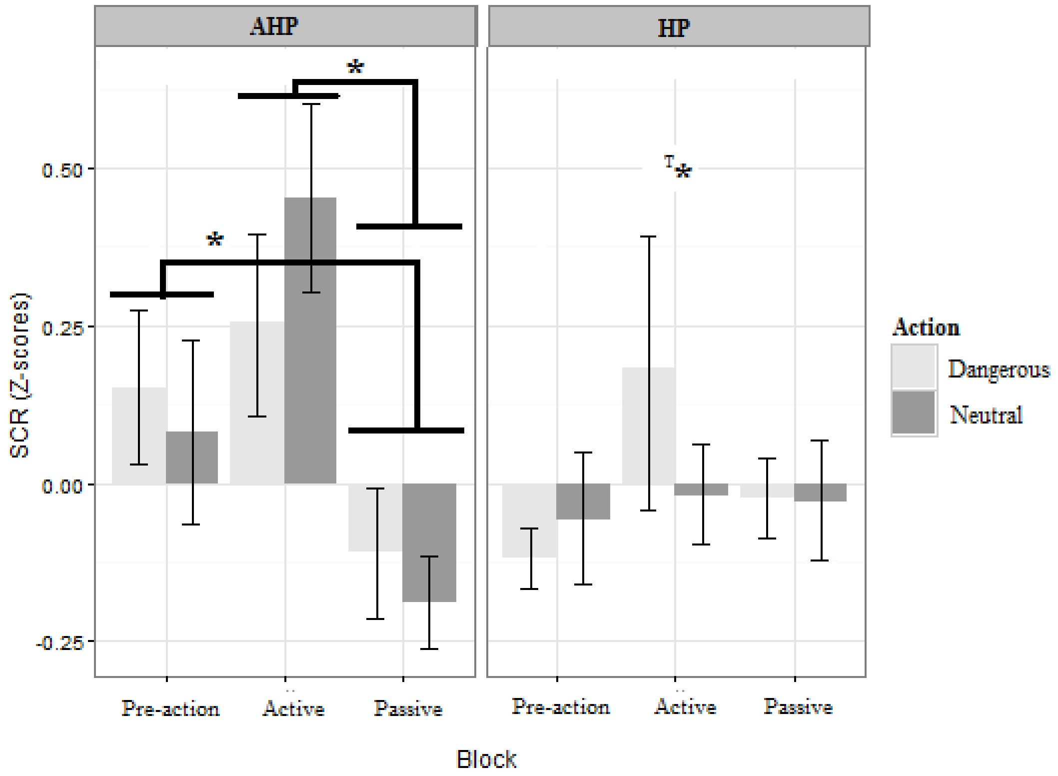

Figura 8. SCR for the Heiplegic hand. The means of the Z-scores of the peark-to-base SCR for both AHP and HP group are shown. * for p≤0.05. ^{T}* = Significance of factor Type.

5.3.3. External awareness

Given the ordinal nature of the data from the Likert scales, these data were analysed by means of a cumulative logit model (Agresti, 2002) by the ANalysis Of DEviance Test (ANODE, McCullagh & Nelder, 1989). For all analyses the random intercept of the model was the subject, for the theoretical reason that the sample was small (Bates, Kliegl, Vasishth, & Baayen, 2015).

The modulation of External awareness for the Hemiplegic hand was computed in a 2 (Group: AHP v. HP) x 2 (Interval: Before v. After task) ANODE Test. All the post-hoc analyses were computed by means of Least-Square Means (lsmeans) Test (Lenth, 2016), that it is a specific analysis for ordinal data, with the Bonferroni corrections for multiple comparisons (Bonferroni, 1936).

Results indicate a main effect of Interval ($LR\chi^2_{(1)}$= 12.96, $p<0.01$) and the interaction Interval*Group ($LR\chi^2_{(1)}$= 15.15, $p<0.01$). Post-hoc analyses show that only in the AHP group there was a difference between the higher measurement before than after the task ($p<0.01$, Bonferroni Corrected) (Figure 9). No other post-hoc comparisons are significant.

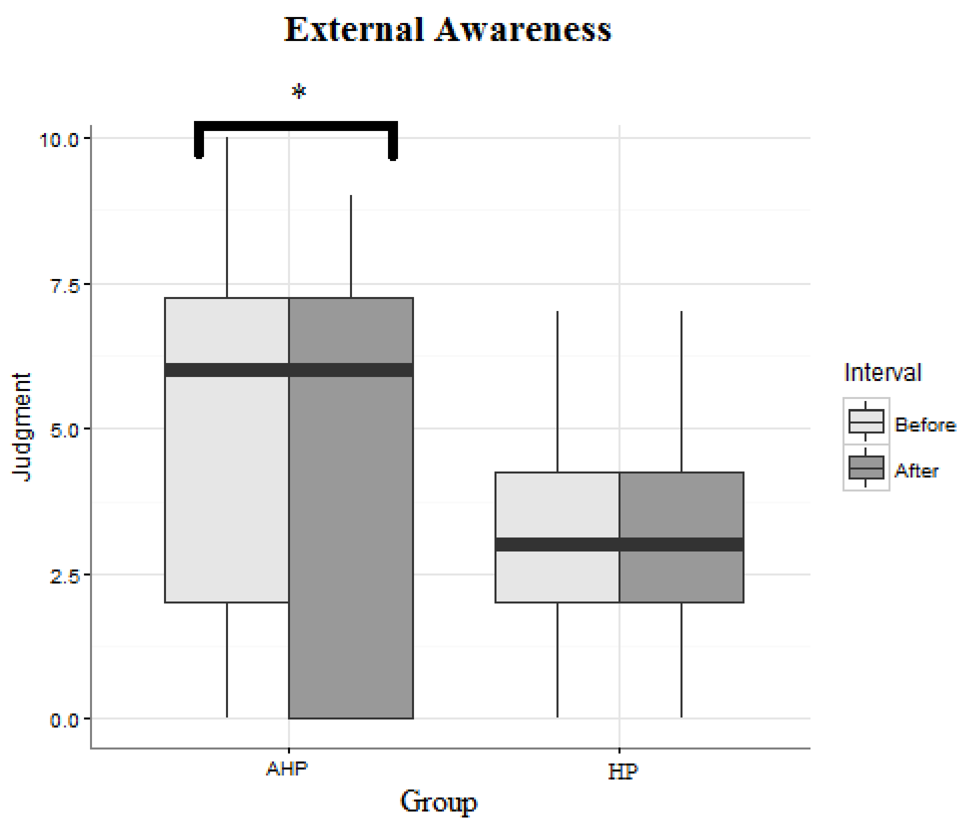

Figure 9. External awareness. The judgments of self-reported proficiency are reported for the two Groups and the two Intervals before and after the task. The Judgment's range

on the y-axis is between 0 to 10 as recorded during the task. The box represents the first and the third quartile of data, and the darker line inside is the median. The bottom and the top whiskers are respectively 1.5* Interquartile range lower and 1.5* Interquartile range higher.

5.4. Discussion

In clinical and experimental practices, AHP is considered as a multi-componential syndrome (Orfei et al., 2007) and is a relevant source of insight in the investigation of residual forms of awareness (Nurni & Jehkonen, 2014). For instance, some AHP patients reported implicit aspects of awareness during bimanual actions (Cocchini et al., 2010; Moro et al., 2011) or temporal (or long-term) explicit awareness by asking them about their motor proficiency during the actual attempt to execute (Moro et al., 2011, Moro, et al., 2015).

The main purpose of this study was to investigate the potential relation between implicit forms of awareness by means of SCR and the vicarious action excution. The SCR was measured during the vision of in-time actions in a first-perspective view. In particular, SCR to dangerous stimuli in Active actions of reaching and Passive actions of escaping were evaluated in right brain damaged patients with hemiplegia or with hemiplegia and AHP.

5.4.1. Implicit forms of awareness during actions

AHP reveals some latent processing of motor information that may lead to an explicit insight of the deficit (Cocchini, et al., 2010). It has been long acknowledged that some patients with AHP declaratively deny any motor impairments, but report some apparent implicit knowledge of the paresis during movements' attempts (Cocchini, Beschin & Della Sala, 2002; 2009, Moro et al., 2011).

Recent evidence has shown the dissociation between explicit and implicit aspects of AHP. Indeed, although some patients fail to recognize the motor deficit only in first-perspective, yet they are still able to verbally assess the performance of other paralyzed patients (Fotopoulou et al., 2011; Marcel, et al., 2004) orn to admit their own deficits while whatching themselves in a third-perspective view in a mirror or in a video-clip (Besharati, et al., 2015; Fotopoulou, et al., 2009).

Other possible dissociations between implicit and explicit types of awareness have been reported in relations to actions' executions. For instance, some patients, who verbally deny their paralysis, are able to adjust their actions to compensate for the impossibility to move the hemiplegic arm, as they would know about their impairments (Cocchini et al., 2009).

Taken together, in our experiment we aim to detect implicit awareness through the observation of some acions, by means of the automatic bodily activations. Infact SCR were already used to prove disturbances of body representation (Romato et al., 2014) and it might be an implicit measure of motor awareness. SCR seemed to be similar between our AHP andHP groups, adnd they may be considered as a conflict between the visual perceived actions (on the screen) and the absence of real movements which could be plan (Berti et al., 2005).

This conflict might be similar for both the AHP and the HP groups, but only the former presented an inability to explicitly acknowledge their motor deficits in the same actions (Explicit awareness) and showed a reaction similar to an avoidance of attention to left-hand's movements (Accuracy). Although in our experiment this dissociation was not clearly shown (see below for some differences between groups of patients), these outcomes suggested that the automatic responses of skin conductance could provide information about an implicit form of awareness during ations that may be otherwise hard to detect.

5.4.2. Modulation of awareness during actions

The explicit awareness that emerges in AHP during an attempt to act is known as Emergent Awareness (Moro et al., 2011, Moro et al., 2015). Based on the hierarchical model of awareness by Crosson and colleagues (Crosson et al., 1989; Orfei, et al., 2007), the Emergent awareness appears to be in a middle position between the Intellectual awareness of the presence of a global deficit (i.e. 'I know I had a stroke') and the Anticipatory awareness of the specific motor deficit and the ability to anticipate its effects by adjusting the performance before to act.

Since AHP can be selectively impaired in these three forms, only some AHP patients show to improve their motor awareness when they are requested to attempt to act (Moro et al., 2011) and to explain the reasons of their failures in those movements (Moro et al., 2015).

In fact, the first study about this theory has empirically demonstrated that when some AHP patients are asked to perform some actions with their affected limbs, the Emergent awareness may manifest as an improvement of verbal degree of awareness of their paralysis (Moro et al., 2011), with a possible restoring effect (Moro et al., 2015). These results have been confirmed in a similar study where the degree of awareness was influenced by both the attempts to act and the general emotional features of the actions (D'Imperio et al., Chapter 3), suggesting the presence of top-down processes in recovery from AHP (Fotopoulou et al., 2010).

In this study, we aimed to investigate the possible relation between these three levels of AHP by analysing an automatic aspect of actions related to the body and the level of explicit awareness during vicarious actions' execution (Moro, 2015).

In our experiment, what it is worth to notice that the activation from the SCR for both AHP and HP groups seemed to be specifically associated to the actions in which a movement is displayed in first-perspective view (Active Block), in comparison to the situation in which the action of escaping might be the natural reaction but it is not yet present in the stimuli (Passive Block). Furthermore, in all patients the automatic responses were mediated from the level of explicit awareness of the same actions, as a confirmation of the heterogeneous attribute of the syndrome (Marcel at al., 2004), and its different levels of awareness.

Interestingly, the control group of health subjects presented an activation for the Dangerous stimuli, but only when the actions was not shown. This outcome might suggest that they might plan and monitor adequate actions in the Active and Passive Blocks in order to not get hurt, so thus the affective responses about them might be suppressed.

5.4.3. Affective resonance of actions

The possible modulation of awareness through dangerous stimuli has been reported in Chapter 3, where it has been suggested that the motivational/emotional aspects of actions may modulate the degree of AHP before and during actions.

In fact, the dangerous graspable objects interfere with the movements, by evoking some specific aversive affordances and bodily motor responses to escape or to avoid the danger (Anelli, et al., 2012; 2013) in order to protect the self (Bradley, Codispoti, Cuthbert, & Lang, 2001). Therefore, the dangerous objects can play a role in modulating the sense of agency and of its awareness. For instance, this kind of stimuli can effectively increase an impaired motor control of movements, as in a patient suffering from anarchic hand, who improved her performances in presence of dangerous objects by showing a decrease of involuntary grasping (Moro & Pernigo, at al., 2015).

In AHP patients the bottom-up aspects of bimanual actions' requests may elicit some residual implicit levels of awareness (Cocchini et al., 2010; Moro et al., 2011), which may then be combined with higher order processes of action processing (D'Imperio et al., Chapter 3; Fotopoulou, 2015), as in an attentional study in which the reaction to motor related words is influenced by the presence of motor awareness (Nardone, et al., 2007). This evidence suggested the possible influences of action and dangerous situation in AHP.

In our experiment, indeed, AHP patients presented an enhancement of the SCR during the movements of reaching (Active Block) in comparison to Passive movements, but for both Dangerous and Neutral Actions.

We might consider this result as an automatic affective implicit reaction during the execution of actions, but with a tendency of over-activation, which is not related to actions' features. We cannot complitely exclude that it may relates to a more general deficit of awareness in monitoring the actions (Vuilleumier, 2004; Saj, Vocat, Vuilleumier, 2014).

In the HP group the SCR appeared to increase progressively as the level of Anosognosia, which was instead not explicitly expressed during the neuropsychological assessment. Furthermore the level of SCR of the HP patients reached a similar activation to the AHP patients. But later on, when the evaluation of Anosognosia in the AHP group was even higher, the SCR decreased, as a possible sign that the implicit awareness was not more present.

Despite the differenciation in groups' SCR values, it is important to stress that the two groups do not show any clear distinction, but the results might be driven from the level of Explicit awareness of the same experimental actions. Thus, we can confirm the multi-componential heterogeneous aspect of AHP (Orfei et al., 2007), that implies possible fluctuations of the syndrome and some peculiar manifestations of residual forms of awareness, which can be selectively impaired (Moro et al., 2011). Furthermore, we might suppose that a potential residual form of awareness, which might be detected in skin conductance measurements during the attempt to act, can be described only in a sub-group of patients as already reported about Emergent and Implicit motor awareness (Moro et al., 2011).

The HP patients without anosognosia have a similar tendency of enhancement of SCR specifically for the Active Block, that supports the hyphotesis of importance of the attempts of actions in better realize paralysis' consequences and recovery (Moro et al., 2015). But in the HP group the increasing of SCR appeared to be specific for Dangerous actions as a selective arousal with Dangerous Actions for a more protective reaction to these stimuli.

These outcomes might put emphasis on the theoretical hypothesis, that the spared motor command is not sufficient to explain the lack of acknowledge the absence of sensory feedback in AHP (Berti et al., 2007 for discussion; Fotopoulou et al., 2008; Jenkinson & Fotopoulou, 2010). Therefore, the sense of agency might combine both a good level of awareness during the motor command and the integration of the predicted consequences during the execution (Desmurget et al., 2009).

Considering all these theoretical accounts, these results might be a first experimental insight, that the HP patients with preserved explicit awareness are able to combine their conscious intention to the absence of movement and thus of feedbacks, so they might generate a protective alerting reaction to danger. Instead, the AHP patients do not show a complete different activation according the affective resonance of the stimuli during the movement, but a general enhancement of arousal. So this result might indicate a spared ability or a probable dominance of motor command (Jenkinson & Fotopoulou, 2010), although they do not completely adjust their motor representations to feedbacks.

Nevertheless, our results seem to be in accordance with the tendency of AHP patients to report self-generated movements, but they fail to integrate adequately the consequential feedbacks in order to become (Jenkinson et al., 2009, Fotopoulou et al., 2008), and consequently they do not reach explicitly awareness about their deficits.

5.4.4. Limitation and conclusions

The sample was quite small, as like as many studies about AHP, but more patients might be needed to understand the results better and to overcome the high variability of the measurement of skin conductance. The difficulty was to find patients with a sufficient degree of attention, which was necessary to complete the task. Furthermore the task appeared to be complex to administrate and the results might be interpreted as not very strong. For example there were not huge responses for the HP group, which were not very influenced by the stimuli. But, despite we did not control for the perception of dangerousness for the experimental subjects, the validation of the stimuli reported a clear division of actions according to their affective meanings.

Notwithstanding these limitations, our results confirmed the existence of heterogeneous forms of awareness and the important role of attempting actions in modulating the degree of motor awareness (Moro et al., 2011). We showed some small signs of improvements of External awareness after the task, but we underlined the import role of specific and consistent feedbacks in possible restoring processes of AHP (Moro et al., 2015). In conclusion, with this study we supported the evidence about the attempting actions in eliciting the Emergent Awareness (Moro et al., 2011) and the consequent analysis of occurring motor errors as a crucial method in recovery from anosognosia (Moro et al., 2015).

Chapter 6

Modulation of Somatoparaphrenia following left hemisphere damage

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Somatoparaphrenic symptoms after left hemisphere damage are rare. To verify the potential role of body-related sensory (proprioceptive, visual and somatosensory) manipulation in patients experiencing sensations of hand disownership, the symptoms of a patient suffering from crossed somatoparaphrenia were monitored and clinical and neuropsychological variables were controlled. Four types of manipulation were administered: changes in spatial position of the hand, multisensory stimulation and self-observation (using video and mirrors). Multisensory visuo-tactile stimulation was effective in reducing somatoparaphrenia and changes in the position of the hand produced some positive effects. Third person perspective self-observation, however, did not result in any changes.

6.1. Introduction

Disorders in body representations following brain damage have been reported since the first half of the twentieth century (Head & Holmes, 1911). Gerstmann (1942) described body ownership disturbances citing patients who were unable to recognize contralesional body parts as belonging to their own body. Later, various classifications were suggested (e.g. Critchley, 1953; Hécaen, 1972) and a distinction was made between patients showing a lack of recognition of the existence or ownership of their limbs (asomatognosia/disownership) and the condition where this is accompanied by delusions regarding the affected limbs, such as the belief that the affected limb belongs to another person (somatoparaphrenia).

Somatoparaphrenia may in fact take several clinical forms (Vallar & Ronchi, 2009) and in order to classify all abnormal feelings and beliefs regarding paralyzed limbs, a definition entitled 'the disturbed sensation of limb ownership' (DSO) was proposed (Baier & Karnath, 2008; Moro & Pernigo, et al., 2016).

The specificity of the syndrome and the contribution of other functions in its onset (in particular, somato-sensory information and neglect) is still being debated (Vallar & Ronchi, 2009). Furthermore, DSO is usually associated with Anosognosia for Hemiplegia (AHP), although clinical and anatomic dissociations have been found. While AHP occurs after damage to the right insula, rolandic operculum and superior temporal gyrus, a shift in the latero-medial direction (involving the basal ganglia) emerges when DSO co-occurs with AHP (Moro & Pernigo et al., 2016).

Only a few cases of DSO after left hemisphere lesions have been reported (Perren, Heydrich, Blanke, & Landis, 2015) but even though the incidence of this pathology is rare, these cases may help us to understand the theories underlying neurocognitive mechanisms of body-ownership better.

It has been proposed that crossed somatoparaphrenia is less strongly associated with AHP and personal neglect than somatoparaphrenia after right brain damage. In contrast, it seems rather to depend upon a combination of extra-personal neglect and sensory-motor deficits, with concomitant verbal capacities which allow the patient to express delusional ideas (Perren et al., 2015).

In this context, if by means of experimental procedures a change in symptoms can be effected, this would constitute a contribution towards a better understanding of the syndrome. To date experimental results are not exhaustive and almost exclusively refer to DSO after right hemisphere lesion (but see Spitoni et al., 2015).

With the aim of investigating the potential role of body-related sensory information in modulating DSO after left hemisphere damage, we compared the effects of four different types of manipulation in one individual patient (AS). Changes to the spatial position of the contralesional upper limb were made in order to evaluate proprioceptive and spatial components. Multisensory visuo-tactile stimulation served to investigate the role of sensory integration in the syndrome, while self-observation of the hand in a video clip or a mirror allowed us to assess the effects on the patient of changes in perspective.

These procedures have been recently demonstrated to be efficacious in reducing DSO following right-hemisphere lesion. In particular, it has been suggested that there is a visuo-spatial component of the syndrome as changes in the observation perspective (Fotopoulou, Rudd, Holmes, & Kopelman, 2009) or in the position of the examiner (Salvato et al., 2015) induce a modulation. Moreover, it has been demonstrated that multisensory visuo-tactile stimulation produces an effect (Bolognini, Ronchi, Casati, Fortis, & Vallar, 2014). To the best of our knowledge, these manipulations have not been applied in crossed DSO and there have been no comparisons of their effects on an individual patient.

6.2. Methods

6.2.1. Case report

AS is a 78 year-old, right-handed woman with 13 years of education. She suffered a hemorrhagic left hemisphere stroke involving the fronto-temporal-insular cortex, the underlying white matter and basal ganglia (Figure 1). She was examined 3 days after the lesion onset and then daily for three months. During this period, she remained unable to move her right limbs. She showed disorders in tactile perception and her sense of position. There were signs of right side personal and extra-personal neglect and deficits in calculation, praxic abilities and frontal functions, while language and memory were preserved (Table 1). AS was unaware of her hemiplegia (AHP) and showed signs of somatoparaphrenia (DSO): in a number of clinical interviews she repeatedly denied that her right side was paralyzed and when she looked at her right upper limb (UL), she declared it was not hers and that it belonged to the doctor or examiner.

Due to the unusual side of the lesion, an extensive assessment of body representation was carried out one month after the onset of the lesion (Moro, Pernigo, Urgesi, Zapparoli, & Aglioti, 2009). This showed disorders in left-right orientation, the denomination of body parts and finger agnosia (Table 1). While the DSO resolved itself in 6 weeks, AHP was still present six months after the lesion onset.

AS gave written, informed consent to her participation in the study (CEP prot. N. 39216).

	3 days		1 month		2 months	
Motricity	Right	Left	Right	Left	Right	Left
MRC[1]	0	5	0	5	0	5
Tactile Perception (9)	**0**	9	**0**	9	**3**	9
Proprioception (9)	**0**	9	**0**	9	**3**	9
Handedness						
Handedness Questionnaire[2]	19	2	19	2	19	2
Edinburgh Inventory[3]	19	0	19	0	19	0
Right Spatial Neglect						
Line Crossing[4]	**0**	18	**0**	18	**0**	18
Star Cancellation[5]	Np		**8**		**6**	
Line Bisection[5]	**9**		**9**		**9**	
Figure and shape copying[5]	**0**		**0**		**0**	
Representational drawing[5]	**0**		**0**		**0**	
Comb and Razor test[6]	**0.78**				**0.28**	
Double stimulus Extinction %[7]	**0**	100	**0**	100	**0**	100
Body Representation						
Anosognosia for Hemiplegia (UL)[8]	**2**		**2**		**2**	
Anosognosia for Hemiplegia (LL)[8]	**2**		**2**		**2**	
Somatoparaphrenia[9]	**-**		**-**		**-**	
Left-right disorientation (10)[10]	**6**		n.a.		**6**	
Indication of body part s (verbal command)[11]						
One's own body with closed eyes(18)			17			
Examiner's Body open eyes (18)			17			
On a manikin (21)			*16*			
Spatial localization of body parts (13)			*10*			
Spatial localization of bicycle parts (13)			12			
Semantic Knowledge[11]						
Denomination of body parts (18)			***9***			
Definition of body part functions (10)			10			
Finger agnosia[11]						

Indication of her fingers (30)		**18** np	
Indication on a drawing of a hand (30)		25 25	
Denomination of fingers (30)		**18** **18**	
Definition of finger functions (10)		**2**	
General Functions (MMSE)[12]	*24*	Na	na
Language	+	+	+
Memory[13]	np	+	+
Praxic functions[14]	**-**	**-**	**-**
Calculation[15]	np	**-**	**-**
Frontal Functions[16]	np	**7.5**	na

Table 1. Neuropsychological assessment. The scores at the neuropsychological assessment at intervals of 3 days, 1 and 3 months from lesion onset are shown. Assessments in: Motricity ([1]Florence, et al., 1992), Handedness ([2]Briggs & Nebes, 1975; [3]Oldfield, 1971*)* and Neglect ([4]Albert, 1973; [5]Wilson, Cockburn, & Halligan, 1987; [6]Beschin & Robertson, 1997; [7]Karnath, Baier, Nägele, 2005). Assessment of Body representation: Anosognosia for hemiplegia ([8]Berti, Làdavas, & Della Corte, 1996)*;* Somatoparaphrenia (*[9]*Moro et al., 2004); Left/Right Disorientation ([10]Benton, 1959); Identification of body parts, semantic knowledge of body and finger agnosia ([11]Moro et al., 2009). General functions ([12]Folstein, Folstein, & McHugh, 1975); Language, Memory ([13]Spinnler & Tognoni, 1987); Praxic functions ([14]De Renzi, Motti, Nichelli, 1980); Calculation abilities ([15]Miceli, & Capasso, 1991); Frontal Functions ([16]Apollonio, et al., 2005). UL= Upper Limb, LL= Lower Limb. na= not available. np= not possible. += not impaired, -= impaired. The number of total stimuli assessed is in parenthesis. Scores at cut-off are in *italic.* Pathological scores are in bold.

c)

Area	% Voxels	N. Voxels
Temporal Middle L	87.56	34458
Temporal Inferior L	85.62	21958
Putamen L	84.88	6741
Insula L	84.43	12686
Heschl L	83.54	1507
Temporal Superior L	77.89	14259
Temporal Pole Middle L	76.50	4578
Temporal Pole Superior L	62.56	6399

Area	% Voxels	N. Voxels
Rolandic Oper L	58.40	4636
Amygdala L	53.95	935
Pallidum L	48.88	1117
Frontal Inferior Oper L	26.91	2226
Caudate L	25.18	1934
Fusiform L	23.53	4313
Hippocampus L	18.53	1384
ParaHippocampal L	15.17	1197

d)

Area	% Voxels	N. Voxels
Sagittal Stratum	100	2228
Superior Fronto-occipital	100	507
Uncinate Fasciculus	100	380
External Capsule R	95.65	5367
Retrolenticular Part of Internal Capsule	95.51	2402
Posterior Limb of Internal Capsule	72.80	2733
Posterior Thalamic Radiation	60.22	2392
Anterior Limb of Internal Capsule	50.30	1861

Area	% Voxels	N. Voxels
Tapetum R	57.55	343
Superior Corona Radiata	57.39	4304
Superior Longitudinal Fasciculus	42.02	2776
Posterior Corona Radiata	31.30	1167
Anterior Corona Radiata	25.45	1743
Fornix	24.64	277
Body of Corpus Callosum	6.82	935
Ceerebral Peduncle R	1.18	27

Figure 1. Lesion analysis. AS's lesion was traced on a standard MRI template from the Montreal Neurology Institute (MNI) using MRIcron software (Rorden & Brett, 2000). The final drawing was superimposed on an Automatic Anatomical Label (AAL) template and the JHU (Johns Hopkins University) DTI-based white matter atlas in order to analyze the damage to grey and white matter, respectively. a) A representation of the traced lesion on a 3D brain, b) Real neurological CT in Axial view, c) Percentage and number of voxels damaged for grey and d) white matter areas.

6.2.2. Procedure

To verify the role of visual and sensory components in the modulation of disownership, four experimental manipulations were repeatedly administered during the first 6 weeks. These included: i) changes in the spatial position of the patient's right hand; ii) multisensory stimulation; and changes in the patient's visual perspective of her hand by means of self-observation in iii) a video-clip or iv) a mirror.

In each session, at least two different manipulations were carried out (Table 2), in random order and with intervals of 45 minutes. The number of manipulations and the duration of each session depended on AS's conditions, in particular on her attention and fatigue. In fact, AS's cognitive functions fluctuated and were influenced by clinical variables (e.g. pain, quality of sleep) and manipulations were only administered when she felt well enough. A daily diary of symptoms potentially related to DSO was kept (Table 2).

Session number/	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Task	M,4th	M,5th	M,6th	M,7th	M,8th	M,11th	M,12th	M,13th	M,14th	M,15th	M,19th	M,20th	M,21st	M,23rd	M,28th	J,1st	J,3rd	J,5th	J,7th	J,8th	J,15th	Jl,15th	A,15th
Spatial position		x			x	x	x	x	x	x	x	x	x	x		x	x	x	x	x			
Multisensory	NT		NT	NT				x		x				x	NT			x	x		NT	NT	NT
Mirror					x		x				x		x					x					
Video									x			x		x		x	x						
Session number/	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Symptom	M,4th	M,5th	M,6th	M,7th	M,8th	M,11th	M,12th	M,13th	M,14th	M,15th	M,19th	M,20th	M,21st	M,23rd	M,28th	J,1st	J,3rd	J,5th	J,7th	J,8th	J,15th	Jl,15th	A,15th
AHP (b/a)	-	-/-			-/-	-/-		-/-		/-	-/-		-/-		-	-		-/-	-/-	-/-	-	-	-
Neglect (b/a)	-	-/-			-/-	/-			/-		/-				-	-		-/-		-/-	-	-	-
Attention	1	2	1	1	2	2	1	3	4	3	5	4	5	4	4	4	4	4	4	4	4	4	4
Fluency	1	3	1	1	5	4	1	5	4	4	4	4	3	5	3	3	3	3	5	3	3	3	3
Confabulation	2	4	2	2	2	3	2	4	4	4	2	3	2	4	3	3	3	3	5	5	5	5	5
Avoidance	5	5	5	5	5	5	5	3	3	2	1	1	1	3	5	5	5	3	2	4	5	5	5
Referred Pain	5	5	5	5	5	5	1	3	2	1	1	1	1	4	5	5	4	4	1	4	5	5	5
Fatigability	1	4	3	3	3	2	1	3	4	3	2	4	4	4	4	4	4	3	4	4	4	4	4
Gaze deviation	L	L	L	L	L	L	L	L	L	L													

Table 2. Timetable of the experimental sessions and the evolution of the symptoms. All the experimental and clinical sessions are reported. In the upper section, x= administration of the experimental task; NT= not testable. In the lower section, the evolution of clinical symptoms over time. AHP= Anosognosia for hemiplegia; b/a= assessment done before and after the experimental manipulations;. -= presence of deficit. Scores for clinical symptoms: Attention= scores from 1 (no attention) to 5 (normal attention), Fluency= scores from 1 (mute) to 5 (loquacious), Confabulation= scores from 1 (inconsistent language) to 5 (consistent language), Avoidance= scores from 1 (very frequent) to 5 (not present at all), Referred Pain= scores from 1 (excessive complains) to 5 (not reported pain); Fatigability= scores from 1 (high degree) to 5 (absent). L= Presence of gaze deviation towards the left side.

AS was tested in a quiet room with the examiner standing on her right. She sat at a table, The position of her hands and the direction of her gaze were controlled. To assess any potential modulation in DSO due to experimental procedures, we recorded the patient's responses to two questions regarding DSO before and after each manipulation: "Is this hand your hand?" (Response: Yes/No); and if the response was "No", "Whose is this hand? ". All of the patient's responses were manually recorded. In the multisensory and mirror manipulations (see below), the questions were also asked during stimulation. The same questions were asked again 5 minutes later to check how long the modulation lasted and to avoid any carry-over effects.

Whenever it was possible, any potential modulation in AHP and neglect was assessed before and after the experimental task (Table 2). Finally the same experimental procedures were repeated once on the left hand as a control.

6.2.2.1. Changes in spatial position.

While she was being distracted by general questions, AS's right hand was placed palm down, in one of four positions (counterbalanced order, Figure 2B): a) raised in front of her eyes; resting on the table to her b) left, c) in the middle and d) to her right. When her hand was still, questions regarding its ownership were asked (25 assessments for each position).

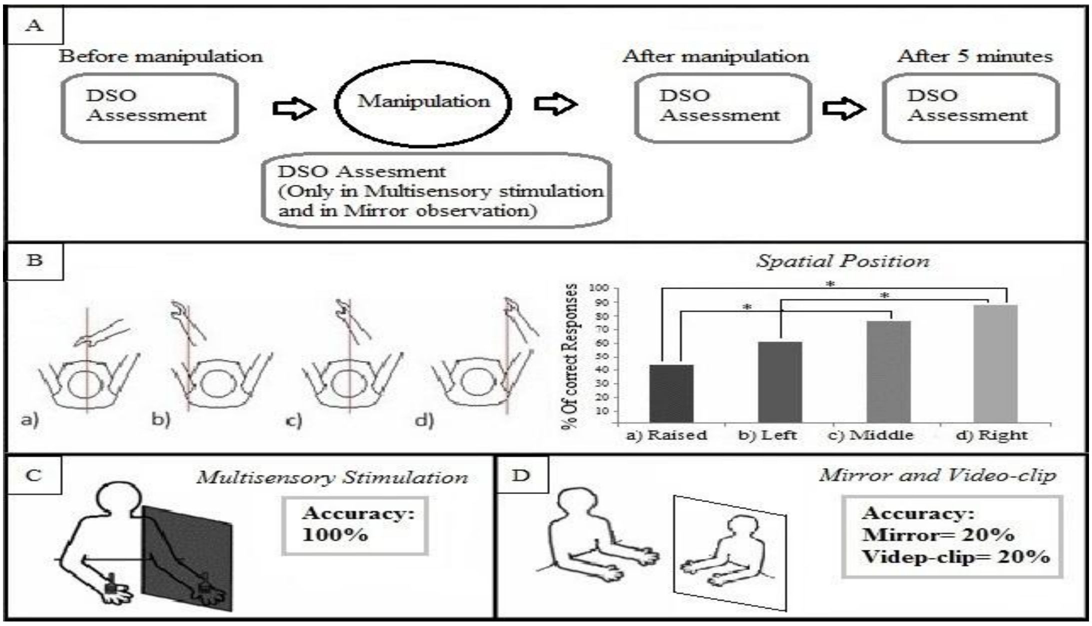

Figure 2. Experimental Procedure: A) The timeline for the experimental procedure for all tasks. B) The positions of AS's right hand in *Spatial Position* manipulations. a: Raised; b: to the Left; c: in the Middle; d: to the Right. A graph with the percentage of correct responses is shown with *= significant direct post-hocs (χ^2, FDR corrected, Benjamini & Hochberg, 1995: Raised vs. Middle: $\chi^2_{(1)}$=4.083, p=0.053; Raised vs. Right: $\chi^2_{(1)}$=8.912, p=0.008; Left vs. Right: $\chi^2_{(1)}$=3.742, p=0.053). C) AS's position in the *Multisensory Stimulation* experiment and the percentage of correct responses. D) AS's position in the *Mirror* (similar to *Video-clip*) stimulation and the percentage of correct responses for the mirror and video-clip manipulations.

6.2.2.2. Multisensory stimulation

AS's hands lay on the table in front of her, elbow bent, palm down and in a symmetrical position (Figure 2C). Following Bolognini and colleagues' procedure (2014), we simultaneously stroked the dorsum of AS's right hand (which she could see) and left hand (hidden from view) with a soft cosmetic brush for 2 minutes. Throughout the stimulation, we made sure that AS was looking at her right hand, recalling her attention whenever necessary, and we asked questions relating to DSO (5 measures).

6.2.2.3. Video-clip

A video (recorded during the first assessment of AHP and DSO) showed the patient while she was answering DSO-related questions (Besharati, Kopelman, Avesani, Moro, & Fotopoulou, 2015). In the video, a frontal view of the upper part of the patient's body was visible. and the examiner was shown standing to the right of the patient holding her right arm. Over 5 sessions, the video-clip was shown to AS and the DSO questions were asked.

6.2.2.4. Mirror

The procedure was similar to that used in the video-clip experiment with the only difference being that AS responded to the DSO questions while she was sitting at a table looking at her right hand reflected in a mirror (on-line measure, 5 measures).The mirror was placed in front of AS and it showed her right hand from a 3rd person visual perceptive (Fotopoulou et al., 2009).

6.3. Results

AS always recognized the left hand as her own during the control tasks.

In contrast, the sense of ownership of right hand was modulated to different degrees by the experimental manipulations. There were immediate strong effects resulting from the multisensory stimulation, minor benefits from the changes in the hand position and no improvement from the changes in visual perspective. Since whenever the patient denied the ownership of her hand she was very consistent in attributing it to the doctor, we exclusively analyzed the Yes/No responses to the first question ("Is this hand your hand?").

6.3.1. Spatial position

Changing the position of AS's hand modulated her sense of disownership ($\chi^2_{(3)}$=12.438, p=0.006), with the central/raised position resulting in the worst performance. A progressive increase in accuracy was present in the positions with the hand lying on the table to the left, in the centre and to the right (Figure 2B).

6.3.2. Multisensory stimulation

There was an immediate and ameliorating effect on DSO during the multisensory stimulation sessions with the patient referring to the hand as her own in all five sessions (Figure 2C). Unfortunately, 5 minutes after manipulation, AS went back to denying ownership.

6.3.3.Video-clip and Mirror sessions

No effects were found. When AS was asked to look at her hand from a different perspective, she merely became confused.

No change in AHP and neglect was recorded either before or after experimental sessions.

6.4. Discussion

Somatoparaphrenia is a rare syndrome after right brain damage and it is almost unknown in left-side lesions. Only a few patients have been described (Perren et al., 2015) and for this reason our patient is particularly interesting. The neuropsychological assessment excluded the possibility that AS presented with reversed hemispheric lateralization and thus her case is even rarer. Indeed, she showed symptoms typically associated with both left (calculation disorders, left/right confusion, finger agnosia, apraxia) and right hemisphere lesions (neglect, AHP, DSO). For this reason, we consider that her case involves a co-occurrence of Gerstmann's syndrome (Mayer et al., 1999). A similar combination of symptoms was previously reported in a patient suffering from Gerstmann's Syndrome following right lesion (Moro et al., 2009). Although rare, these cases lead us to consider that a definitive version of the distinction between body schema and body image, normally connected with right or left hemispheric lesions respectively, is not totally adequate in terms of describing the neural correlates of body representation.

AS was in the acute phase of the illness and her attention fluctuated. This precluded the possibility of devising complex experimental paradigms, which are generally very demanding in terms of attention. Nevertheless, the continuous, daily monitoring of her clinical and neuropsychological symptoms (in particular, neglect and AHP) enabled us to exclude the possibility that the modulation of DSO was mediated by factors other than those relating to our experimental procedure. Indeed, we noted a progressive increase in attention over time, but this did not correspond to any change in DSO. In contrast, this increase in her attention capacity appeared to be associated with a temporary aggravation of other symptoms such as fatigue and avoidance (Fotopoulou, Pfaff, & Conway, 2012). Confabulations did not change over time. Our results confirm that it is in fact possible to modulate DSO symptoms by means of simple manipulation (Fotopoulou et al., 2009; Bolognini et al., 2014; Spitoni et al., 2015).

A comparison between the four types of intervention indicates that for this patient the most efficacious was multisensory stimulation. This procedure had immediate effects, although only temporary, on the patient's self-attribution of the disowned hand. As expected due to her sensory deficit, AS did not report any sensation of being touched when her hand was stroked. Thus, we consider that the combination of contralateral (left hand) tactile stimulation and visual input from the affected right hand provided an integration of the sensations from the unimpaired hand onto the disowned hand, with resulting increase in the sense of ownership (Bolognini et al., 2014).

Changes in spatial position also had some positive effects. That there is a spatial component to DSO is supported by the observation that vestibular stimulation ameliorates neglect and DSO (Rode et al., 1994). However, our result is in this respect counterintuitive. In fact, one might expect that the sense of ownership would increase when the hand is placed in the non-neglected hemi-space. In contrast, AS identified the hand as her own more frequently when it was on her right, neglected side. This suggests that neglect and DSO are largely independent. A similar dissociation between DSO and neglect has been documented in other two somatoparaphrenic patients (Moro, Zampini, & Aglioti, 2004). In that study, moving the spatial position of the hand towards the non-neglected hemi-space induced a recovery in tactile extinction (symptom of neglect) but did not affect DSO.

We consider that in AS it was the congruency between visual information and the position of the hand in the canonical representation of the body, rather than the spatial position itself, that facilitated the integration of her hand in her body, thereby increasing the sense of ownership. This is also consistent with the frequent clinical observation that somatoparaphrenic patients often look for “their” supernumerary hand in the canonical position (precisely on the neglected side of the space), where the hand is expected to be.

A limited impact of vision is confirmed by the absence of modulation found in visual perspective manipulation, both in the on-line (mirror) and off-line (video-clip) conditions. This contrasts with previous results involving DSO and AHP after right lesion where these manipulations were efficacious in terms of reducing symptoms (Fotopoulou et al., 2009; Besharati et al., 2015; Moro, Scandola, Bulgarelli, Avesani, & Fotopoulou, 2015).

Thus, in the case of AS, stimulation of multisensory integration and top-down (canonical) representations of the body have ameliorative effects on DSO. In contrast, visuo-spatial components do not impact directly on the sense of ownership. We can thus conclude that, although all these multiple factors probably co-occur at the onset of the syndrome, the possibility of modulating them differs.

Finally, we do not know whether our experimental manipulations impacted on AHP. Unfortunately, awareness was only checked before and after the sessions and we never asked specific questions regarding this issue during the manipulations, meaning that any potential changes went unrecorded.

All things considered, it is clear that these factors and the difference in sensitivity to experimental manipulations after right and left hemisphere lesions deserve further investigation.

Chapter 7:
General Discussion

AHP is not an all-or-nothing phenomenon, but as a multifaceted and complex syndrome. Our studies confirmed the heterogeneous and multi-componential features of AHP (Orfei 2007; Vuilleumier et al., 2004; Fotopoulou, 2014), that may occur in a variety of clinical manifestations (Heilmann &Harciarek, 2010; Orfei et al., 2007; Marcel, et al., 2004; Vocat, et al., 2010) and some residual forms of awareness may be shown (Cocchini et al., 2010; Moro et al., 2011). Furthermore these possible fluctuations in AHP can support patients' rehabilitation (Besharati et al., 2015; Moro et al., 2015), and thus they are worth to be investigated.

In recent studies about AHP, it has been suggested that specific tasks could contribute in influencing its symptoms, such as the evaluation of own motor proficiency during the real attempts to act (Moro et al., 2015), the presentation of visual feedbacks of own abilities in third-perspective (Fotopoulou et al., 2009; Besharati et al., 2015) or inducing specific emotions (Besharati et al., 2014).

In the first study in Chapter 3, we investigated the possible fluctuations of AHP in the attempts to act in relation to some potentially dangerous actions. Changes of awareness in AHP are influenced by both sensory-motor and high cognitive functions (Fotopoulou, 2014 for review) and a role of emotional components has been previously reported (Besharati et al., 2014; Nardone, Ward, Fotopoulou, & Turnbull, 2008). Therefore we investigated the possible relation between the effects of actions' characteristics, in particular its emotional valance (neutral and dangerous nature of stimuli) and the top-down processes of requiring to carry out specific actions, in order to integrate both sensory aspects of an action and its possible cognitive, motivational and emotional components (Fotopoulou, 2015).

In this study, we devised a task where AHP and HP patients were asked to execute some everyday actions, that had a dangerous or a neutral meaning and we assessed their level of awareness in different timing: before, during and after the action and in an extra out-of-context moment.

Our results showed that the explicit level of awareness of our patients changed in a on-line moment of executing the actions and recognizing some motor problems. Thus we confirmed the presence of Emergent awareness in our group of AHP patients, as a residual form of awareness during the actually perform of an action with the affected body parts when patients become linguistically awareness. In fact the Emergent awareness was already previously described (Moro et al., 2011, Moro, 2013; Moro et al., 2015) as a possible modulation in AHP induced by ad-hoc experimental manipulations and based on the presence of intention command and a possible modulation of the successive motor execution by verbally declaring self proficiency during the performance.

According to the Forward Dynamic model, when there is mismatch between intended and planned actions and actual sensory feedback, a cognitive 'comparator' should detect the error and construct conscious awareness about it (Blakemore, Wolpert, & Frith, 2002). This process may be defective with AHP and they do not update their belief about actions' outcomes according to the real discrepancies. Thus, we suppose that intention to act combined with the request to evaluate performance may have an important monitoring role and support the enhancement of Emergent awareness (Moro et al., 2011; 2013).

In addition we explored the potential role of dangerous actions in this process. The emotional feature of stimuli seemed to improve the degree of awareness of hemiplegia in both the groups of hemiplegic patients with and without Anosognosia. But if in HP patients the improvements appeared mainly before to start the action, in AHP patients continued to contribute in improving the level of awareness during the attempt to act.

In fact it has been long known, that dangerous objects interfere also with movements, for example by evoking a specific aversive affordance (Anelli, Borghi, &

Nicoletti, 2012; Anelli, Nicoletti, Bolzani, R., & Borghi 2013), that probably has the main purpose of preparing the motor networks to act in order to protect the self (Bradley, Codispoti, Cuthbert, & Lang, 2001).

In addition AHP shows some emotional and motivational components (Bisiach & Geminiani, 1991; Ramachandran 1996; Vuilleumier, 2004), while these patients show difficulty in accepting and tolerating aversive emotional status as a problem in the emotional-regulation system of negative feelings referred to the self (Kaplan-Solms, 2000; Turnbull et al., 2002; Turnbull, Evans, & Owen 2005). Some experimental evidences suggest that AHP patients can evoke implicit negative emotional reactions in relation to their hemiplegia, that could interfere with their performance in cognitive tasks (Fotopoulou, et al., 2010; Nardone et al., 2007) and even play a role in temporary restoring the degree of motor awareness (Besharati, et al., 2014). We suggested that the dangerous resonance of actions may enhance explicit awareness probably due to bottom-up processes of protective activation or alerting and top-down emotional and semantic aspects, as both components in the complex phenomenon of motor awareness (Vuilleumier, 2004; Fotopoulou, 2014;2015).

From the brain lesions analysis, a broad front-temporal network and subcortical structures may be important in these processes. At first we confirmed a similar association between Emergent awareness, temporal lobe and white matter connections. In addition in processing potentially dangerous actions the related areas are basal ganglia, amygdale and in white matter underlying insula and fronto-temporal areas, as in the general cortical activation with dangerous action (Baumgartner, Willi, & Jäncke, 2007; Hajcak et al., 2007; Oliveri et al., 2003) and in the fronto-insula/limbic inhibitory regulation (Phelps et al., 2001).

In Chapter 4 we investigated the same actions in third-perspective view, while asking the patients to judge the abilities of another hemiplegic patients. This control task allowed to evaluate the possible dissociation in AHP patients in judgments referred to the self and to other people. But we saw that our group of patients did not improve their abilities to detect the motor impairments in third-perspective view (only two patients out of seven). These performances could indicate that in the previous task of attempting the actions, the motor awareness deficits relate to specific for one's own body actions, while in the latter it would consider the actions per se (Marcel et al., 2004; Ramachandran, 1996; Ramachandran & Rogers-Ramachandran, 1996; Moro et al. 2011). Furthermore only some AHP patients take advantages from the third-person perspective and deny the motor deficits only when answering to self-referred questions. Indeed, our result is an evidence that different forms of residual awareness can be selectively spared (Moro et al., 2011).

Successively in Chapter 5 we tried to evaluate different aspects of the actions' executions. Therefore we analyzed whether an active action of reaching or a passive reaction of escaping may contribute in AHP in relation to their affective resonance and we tried to detect some residual forms of awareness measurements of automatic bodily responses. In fact skin conductance responses were already reported as a sign of spared motor intention in AHP (Hildebrandt & Zieger, 1995), and we hypnotized they may provide an implicit automatic measure of awareness during actions. In addition since dangerous stimuli appear to improve the level of awareness in AHP during the request to act (Chapter 3), we expected to find some automatic modulation according to affective features of actions with threatening and neutral stimuli (Armel & Ramachandran, 2003; Guterstam et al., 2011; Romano et al., 2014). From our results the experience of a vicarious active action in first-perspective view enhanced in AHP the automatic responses of skin conductance. In addition our AHP patients showed a similar SCR activation to those of the other HP group, despite their deficit of explicit declarative awareness and even some possible avoidance reaction to the experimental actions (in accuracy). This dissociation may suggest an implicit form of awareness of these AHP patients and that skin conductance may be a useful method to detect them.

In our experiment, however, active actions of reaching enhance automatic skin responses in AHP patients, but for both Dangerous and Neutral Actions. It may be considered, that the automatic affective implicit reaction of AHP patients during the actions is linked to a general enhancement of arousal. This result may indicate a spared ability or a probable dominance of motor command (Jenkinson & Fotopoulou, 2010), although they do not completely adjust their motor representations to feedbacks. Finally, so we supposed that the residual forms of awareness probably need to be integrated with some higher-cognitive processes, in order to fill the discrepancies between the visual and the experiences actions (in this study) and to enhance an explicit level of awareness (Moro et al., 2015).

The last Chapter finally gave some evidences of fluctuations in Crossed Somatoparaphrenia by means of different experimental approaches with the aim of investigating the potential role of body-related sensory information in modulating body ownership's deficit. In this study we compared the effects of different types of manipulation: i) Changes to the spatial position of the contralesional upper limb were made in order to evaluate proprioceptive and spatial components, ii) Multisensory visuo-tactile stimulation served to investigate the role of sensory integration in the syndrome, while ii) self-observation of the hand in a video clip or a mirror allowed us to assess the effects on the patient of changes in perspective.

Our patient seemed to improve her sense of ownership thanks to a multisensory stimulation, and to possible influences of changes of body position, but not to task of third-perspective view. These results highlights that even the disturbances of body ownership present some various clinical manifestations and they might be influenced from different types of bottom-up and top-down stimulations.

In conclusion the general construction of self-awareness appears to be a very complex phenomenon and both its aspects of sense of agency and sense of ownership (besides their peculiarities) appear to be influenced by different levels of components in a consistent and adequate updating of the Self (Fotopoulou, 2015). Finally, in case of deficit, Self-awareness requires to be extensively evaluated to underline both preserved and impaired mechanisms, in order to lead to possible rehabilitation programs.

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Visual and Cross-modal cues facilitate the discrimination of overlapping visual stimuli in Balint's Syndrome

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Abstract

Introduction: Cross-modal interactions improve the processing of external stimuli, particularly when an isolated sensory modality is impaired. When information from different modalities is integrated, object recognition is facilitated. This cross-modal facilitation probably bases on bottom-up and top-down processes. Aim of this study is the investigation of potential effects of cross-modal facilitation in simultanagnosia.

Methods: We report a detailed analysis of clinical symptoms and a 18F-FDG Brain PET/CTs study of a patient affected by Balint's Syndrome, a rare and pervasive visual-spatial disorder following bilateral parieto-occipital lesions. In addition, we experimentally investigated the effects of visual and non-visual cues in the facilitation of overlapping pictures. Four modalities of sensory cues were used: visual, tactile, olfactory and auditory.

Results: Data from neuropsychology showed the presence of Ocular Apraxia, Optic Ataxia and Simultanagnosia. The experimental results indicate a positive effect of the cues in the discrimination of overlapping pictures, not only in the identification of the congruent cued stimulus (target) but also in the identification of the other, non-cued stimulus. All the sensory modalities analysed (except the auditory stimulus) were efficacious in increasing visual recognition.

Conclusions: We consider that in this patient cross-modal facilitation induced the activation of both top-down (attentional and short-term memory) and bottom up (sensory systems) processes able to improve the recognition of complex overlapping images. This is potentially useful in the devising of rehabilitation training for attentional and visual-perceptual deficits.

Introduction

Experimental evidence indicates that objects characterised by redundant multisensory cues are identified more rapidly than the same objects presented in a unimodal condition. This suggests that object identification in one modality is influenced by input from other modalities.

To date, this effect of cross-modal integration has been mainly investigated in visuo-acoustic modalities (Chen & Spence, 2011; Fort, Delpuech, Pernier, & Giard, 2002; Pascucci, Megna, Panichi, & Baldassi, 2011; Schneider, Engel, & Debener, 2008). However, cross-modal facilitation has also been demonstrated for synchronous auditory-tactile (Gillmeister & Eimer, 2007), visuo-tactile (Helbig & Ernst, 2007) and visuo-olfactory (Gottfried & Dolan, 2003) integration. In addition, an effect of cross-modal facilitation in the detection of emotional stimuli has been described (Dolan, Morris, & de Gelder, 2001; Seubert et al., 2010).

Cross-modal interactions are modulated by both the nature of the perceptual task and the sensory skills of individuals (Fort et al., 2002). This type of interaction is particularly efficient in terms of improving perceptual performance when an isolated modality is deficient (Caclin et al., 2011). For this reason, the study of cross-modal facilitation in patients affected by perceptual and attentional diseases may offer important information for clinical assessment, rehabilitation and compensatory strategies.

Balint's syndrome (BS) is a specific disorder affecting visuo-spatial attention (Hécaen & de Ajuriaguerra, 1954). It is usually the result of lesions in the bilateral parieto-occipital area, but has also been reported after damage involving frontal areas (Hausser, Robert, & Giard, 1980) and pulvinar areas (Ogren, Mateer, & Wyler, 1984). BS was initially described in a patient suffering from "progressive cerebrovascular complications" (Balint, 1909; Rizzo & Vecera, 2002) and later reported after traumatic brain injury, posterior cortical atrophy, tumours and prion disorders (e.g. Creutzfeldt-Jakob disease) and viral infections such as HIV (for a review, see Rizzo & Vecera, 2002).

Three deficits (not always associated) represent the core of BS symptoms: ocular apraxia, optic ataxia and simultanagnosia (Rizzo & Vecera, 2002).

The term Ocular Apraxia indicates a lack of organisation in voluntary eye movements, with prolonged static fixations and dysfunctional gaze shifting (Rossetti, Pisella, & Vighetto, 2003). When Optic Ataxia occurs, oculo-motor coordination is impaired, in the absence of motor, sensory or visual acuity or visual field disorders (Karnath & Perenin, 2005). This makes it very difficult or impossible to execute visually goal-directed movements of the hands, such as reaching and grasping objects in the peri-personal space. Finally, Simultanagnosia (Wolpert, 1924) refers to an inability to explore complex visual images and to perceive multiple objects and the relationship between them. The processing of individual items and local features is however spared.

Literature on BS mainly refers to single-case reports. This is due both to the low frequency of the syndrome and to the fact that typically there are bilateral large lesions, usually responsible for extensive sensory and cognitive symptoms, all of which hinder specific assessments.

We had the opportunity of carrying out extensive research on a young man affected by BS (stable over time) as a consequence of anoxic cerebral damage. He was keen to participate in our study. In addition to an in-depth neuropsychological assessment and an (18)F-FDG PET/CT study, we devised an experimental procedure in order to investigate the potential effects of cross-modal facilitation in the identification and denomination of two objects shown in overlapping images.

Previous studies have investigated the role of visuo-tactile facilitation in spatial representation (Valenza, Murray, Ptak, & Vuilleumier, 2004). Nevertheless, to the best of our knowledge, the effects of cross-modal processing in simultanagnosia have never before been investigated. Starting from the data indicating that the perception of external stimuli is supported (through bottom-up and top-down processing) by cross-modal integration, when isolated sensory modalities are impaired (Pascual-Leone, Amedi, Fregni, & Merabet, 2005), we hypothesized that cross-modal facilitation enhances MR's ability in detecting and recognizing overlapping visual images.

In order to test the effects of facilitation induced by various different sensory stimuli, we devised an experimental paradigm very similar to a matching-to-sample task. A single stimulus (cue) was first presented in one of four sensory modalities (visual, tactile, olfactory and auditory). Then, an image showing two overlapping objects was presented in the visual modality and the subject was asked to identify and denominate both objects. In this way, we were able to measure not only the direct effect of congruent facilitation on the cued stimulus, but also whether the recognition of one of the two overlapping elements helped the visual system to identify the other object.

2. Methods

2.1. Case report

MR was a 40 year old, right-handed man who worked as a manual worker (8 years of education). As consequence of cardiac arrest (30-40 seconds) which occurred 5 days after a surgical operation, he suffered an anoxic brain injury. A CT scan (3 days from onset) revealed hypodensity in the cortical and subcortical bilateral parieto-occipital transition, in the right fronto-parietal and left rolandic areas.

A month after the onset of the lesion, MR appeared to be not totally oriented in time and space and not fully aware of his condition. The left side of his body was weak but there were no paralysis or sensory deficits. There were massive disorders in ocular motricity and when he reached for objects using his hands, in addition to non-testable difficulties in exploring the left visual field and minimal deficits in object recognition. During conversation he showed anomies and phonemic paraphasias, with alexia and agraphia.

The procedure of the study was approved by the local ethics committee (CEP, Verona) and informed written consent concerning the participation in the experiments was obtained by the patient.

2.2. General Neuropsychological Assessment

Two months after the stroke, a computerized campimetric examination indicated only a few small patches of reduced sensitivity in the visual field. Horizontal and vertical ocular movements were normal. General cognitive functions and temporal orientation appeared to have been spared, although a global slowness in verbal and motor responses was evident. Initial signs of spatial neglect and apraxia had recovered. He complained of difficulties in object discrimination. As a result of this, a first assessment of visual agnosia was carried out (Table 1, second column).

	2 months	4 months	Cut-Off
Agnosia Battery[1]			
Efron Test (20)	20	18	16.51
Figure-ground discrimination (33)	**16**	**24**	29.03
Overlapping images test (Ghent) (40)	**4**	**24**	36.51
Incomplete images test: short (Gollin) (75)	**imp**	**38**	58.56
Matching objects (40)	**23**	*30*	30.79
Chimeric images (48)	**32**	*41*	41.99
Colour naming (40)	**35**	*36*	36.16
Associative match task (20)	**12**	19	17.92
Semantic Test: short (240)	236	235	234.09
Picture naming (40)	**35**	*37*	37.67
Object denomination (33)[2]	30	-	-
BORB[3]			
Length match (30)		*24*	24
Size match (30)		*23*	23
Orientation match (30)		21	20
Position of gap (40)		34	27
Letters (36) (sec.)		36 (**1.58**)	(0.4)
Paired non-overlapping (36) (sec.)		35 (**1.42**)	(0.4)
Paired overlapping (36)(sec.)		35 (**0.97**)	(0.4)
Triples non-overlapping (36) (sec.)		32 (**2.5**)	(0.4)
Triples overlapping (36) (sec.)		28 (**3.47**)	(0.4)
Geometrical shape (36) (sec.)		32 (**5.05**)	(1.0)
Paired non-overlapping (36) (sec.)		35 (**3.08**)	(1.1)
Paired overlapping (36)(sec.)		33 (**2.75**)	(1.1)
Triples non-overlapping (36) (sec.)		30 (**4.05**)	(1.2)
Triples overlapping (36) (sec.)		34 (**3.97**)	(1.3)

Table 2. Neuropsychological assessment of Visual Agnosia. [1]Battery Test for Agnosia (It. Vers. Barletta-Rodolfi, 1996) at 2 and 4 months ([2]Additional clinical test of denomination of real objects). [3]BORB (Riddoch & Humphreys, 1993) at 4 months; imp = impossible. Pathological scores are in bold; in *Italic* the score at cut-off or where the time of execution is slower than normative data.

Four months after onset, at the time of the experimental procedure, MR underwent a further assessment for visual agnosia, neglect, language, memory and executive functions (Tables 1 and 2). His deficits in visual discrimination were confirmed, in particular in a subtest involving the discrimination of multiple and overlapping images (Table 1) and in the examination of visual extinction of double stimuli. In addition, MR showed deficits in executive functions in tasks involving short-term memory, phonemic fluency (FAB, subtest score = 1) and task planning (Table 2).

		Cut-Off/ES
Neglect		
Reading	+	
Writing	+	
Barrage	+	
Coping with drawing	+	
Clock Test[1] (13)	13	7.57
Visual extinction	**-**	
Language		
Denomination of pictured compound nouns (30) (AAT[2])	30	
Denomination of pictured sentences (30) (AAT[2])	27	
Memory		
Short-term spatial memory (9) (Corsi[3])	**2.5**	3.75
Long-term spatial memory (29.16) (Corsi[3])	17.2	10.25
Short-term verbal memory (16) (Word Span[3])	**2.5**	3
Story Recall[3] (16)	11.1	4.75
Executive Functions		
FAB[4] (18)	16.85	12.03
BADS[5] (24)	**11**	18.6
Rule shift cards (ES 0-4)	*3*	3
Action program (ES 0-4)	*3*	3
Key search (ES 0-4)	**2**	3
Temporal judgement (ES 0-4)	**1**	3
Zoo map (ES 0-4)	**0**	3

Modified six elements (ES 0-4)	**2**	3
Verbal Judgement[3] (60)	42.5	33
Tower of London[6] (36)	**24**	26.54

Table 2. General Neuropsychological Assessment. MR's scores in batteries that assess Neglect ([1]= Caraffa et. al, 2011), Language ([2]= Luzzatti, Willmes, & De Bleser, 1991), Memory ([3] =Spinnler & Tognoni, 1987) and Executive Functions ([4] =Frontal Assessment Battery, FAB test – Apollonio et al., 2005; [5] =Behavioural Assessment of the Disesecutive Syndrome – BADS, it. version Spitoni, Antonucci, Orsini, D'Olimpio & Cantagallo, 2002; [6] =Tower of London, ToL - Shallice, 1982) are reported. ES= Equivalent Score, += normal performance, - = pathological performance, pathological scores are in bold; in *Italic* the scores at cut-off.

2.3. Balint's Syndrome

Following the seminal case report by Balint (Balint, 1909, reported in Vallar & Papagno, 2007), three main symptoms were investigated separately: ocular apraxia, simultanagnosia and visuo-motor processing.

Ocular Apraxia: In the acute phase, ocular apraxia was manifested in MR's inability to read, write and visually follow lines. These disorders recovered during the first few months. At the time of our second evaluation (four months from the onset), MR was able to follow specific directions with his eyes on verbal command, though with some minimal hesitation on the left side. Nevertheless, MR was not able to voluntarily gaze the surrounding space. In addition, he failed to pursuit eye movements and he could not move his eyes properly in order to identify small differences in the length of two or more objects (e.g. the length discrimination of two sticks task, Table 3) or to single out one object among others (Table 3).

	% correct responses
Ocular Apraxia	
Sorting the length of multiple objects (sticks) (10)	**50**
Length discrimination of two sticks (19)	**31.58**
Simultanagnosia	
Identification of the numerosity of objects (5)	**0**
Discrimination of the reciprocal position of two objects (47)	**57.48**
Visuo-motor processing	
Optic ataxia R (8)	100
Optic ataxia L (13)	84.61
Pointing at objects RH (45)	**73.33**
Pointing at objects LH (45)	**48.89**
Pointing with a tool RH (15)	**33.33**
Pointing with a tool LH (15)	**26.67**
Pointing at overlapping objects RH (15)	**66.67**
Pointing at overlapping objects LH (15)	**73.33**
Grasping with RH (15)	**80**
Grasping with LH (15)	**60**

Table 3. Clinical assessment of Balint's Syndrome. MR's scores in tasks assessing Optic Apraxia, Simultanagnosia and Visuo-motor processing are reported. Pathological scores are in bold.

Simultanagnosia: The patient complained that he found it difficult to explore space and complex, multipart objects, in comparison to normal abilities to recognize and name simple, single objects, real or represented in pictures. At the first assessment, MR failed in the task of visual extinction of double stimuli, where he always missed one of the two stimuli presented simultaneously. In contrast, he detected the single stimulus (the right or left one), indicating that he perceived only one stimulus at once. At two months from lesion onset, he still failed in a task of identification and counting objects closely placed (i.e. identification of the numerosity of objects, Table 3). Moreover, MR could not discriminate the reciprocal position of two real objects superimposed (e.g. identifying whether a spoon was in front of or behind a fork). He also failed in discrimination of the two parts of chimeric images. Finally, he could not describe a complex scene as a whole, stating that he saw some separate sets of images without being able to integrate them into one image (see video in Supplementary Materials).

Visuo-motor processing: MR could grasp moving objects that were placed in his right or left hemifield (Optic Ataxia - Karnath, 2005) without problems. In contrast, he failed to point at and grasp static objects (e.g. a pen or a fork) with either his right or left hand, and his performance worsened when he pointed at objects using an instrument of some sort (e.g. a pencil).

2.4. Neuroimaging data from (18)F-FDG Brain PET/CT

The examination was carried out by a highly experienced physician of nuclear medicine (MaS) two months after the lesion onset (for technical details, see Figure 1). Results indicated reduced metabolism in the parietal areas and at the parieto-occipital transition bilaterally, while occipital lobes appeared spared. In addition, hypo-metabolism involving the dorsal frontal areas were present bilaterally, but more extended in the right hemisphere. Note that the Lateral Occipital Complex (LOC) turned out to be spared from lesion (Figure 1).

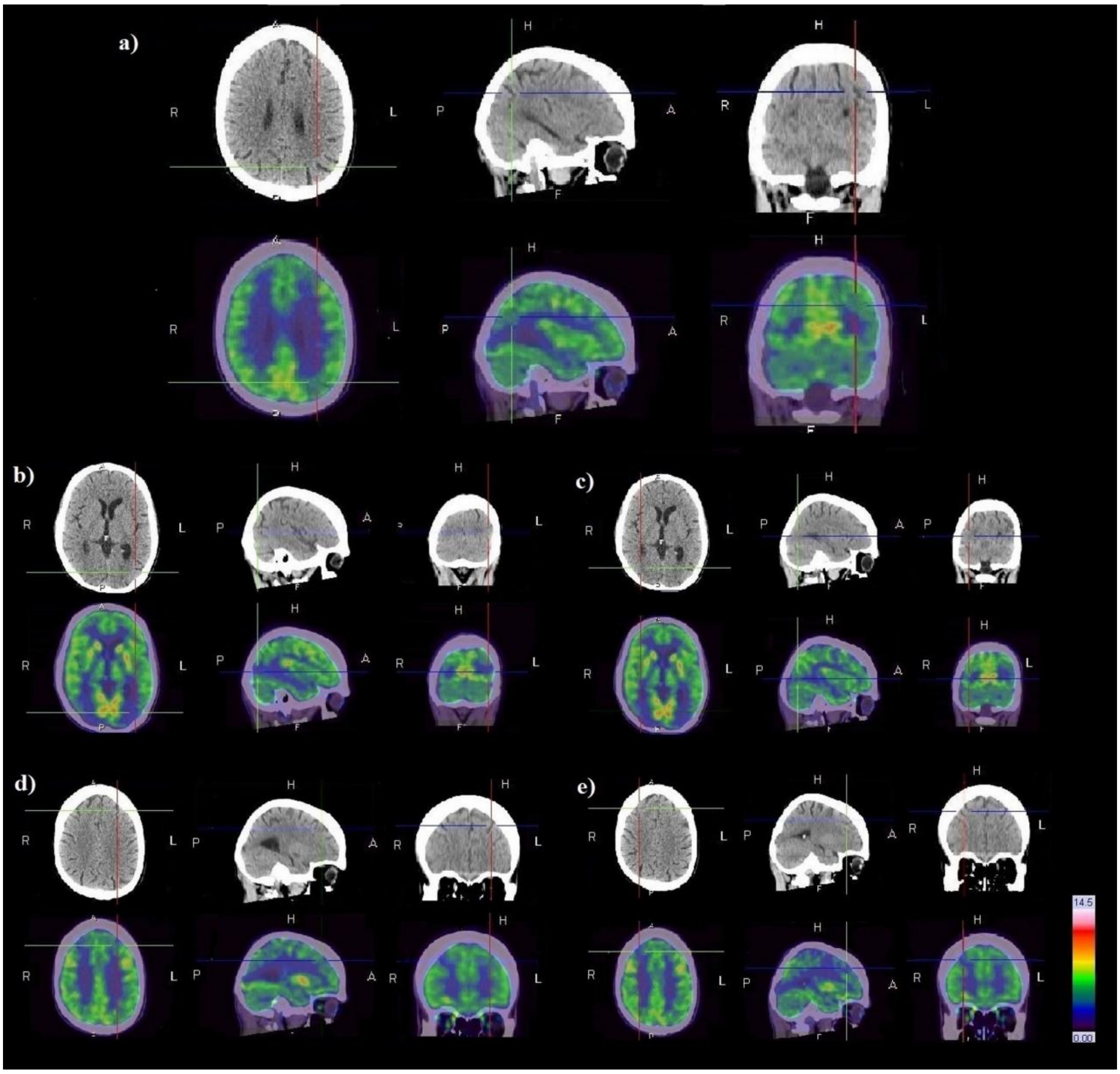

Figure 1. (18)F-FDG Brain PET/CT. The patient was asked to fast for at least 6 hours before the examination. The blood glucose level of the patient was determined before the examination. Scanning was not performed until the blood glucose level was less than 140 mg/dL. The test was performed using a hybrid PET/CT scanner (Siemens mCT Biograph, Germany). The Brain CT scanning was performed using a continuous spiral technique on a 64-slice helical CT, and the PET scanner had three detector rings. No contrast medium was administered during CT scanning. After the CT scan, an emission scan was performed from the head to the thigh after the intravenous injection of 0.08 mC/kg (2.96 MBq/kg) FDG.CT and PET scan data were co-registered. The standardised uptake value (SUV) was acquired using the attenuation-corrected images, the amount of injected FDG, the body weight of the patient, and the cross-calibration factors between PET and the dose calibrator. The images are displayed following the neurological standard (left to right side) and are based on an SUV scale (from red = activation to blue = no activation). Reduced metabolism is evident in: a) temporo-parietal areas, b) left and c) right parietal-occipital junctions; d) left and e) right frontal areas.

3. Experimental design: Cross-modal matching in the discrimination of overlapping figures

A new experimental task was devised to investigate the potential influence of multisensory facilitation on the identification of multiple overlapped visual stimuli. First, a preliminary stimulus (cue) was presented in one of four sensory modalities: visual, tactile, auditory or olfactory. Next, a stimulus consisting of two overlapping images was shown in visual modality and MR was requested to identify and denominate both the objects shown in the overlapping images. Only in half of the overlapping images the cue corresponded to one of the two images (target), while in the other half there were no objects corresponding to the cue (two non-target stimuli).

3.1. Stimuli

In order to ensure that the degree of difficulty was comparable in each of the conditions, all the stimuli were selected from the BORB subtests (Riddoch & Humphreys, 1993), with the exclusion of those that had been used during the neuropsychological assessment.

The visual cues were outlines of objects drawn in black (10.6cm x 10.6cm) and they were identical to the target stimulus showing overlapping figures in all but the rotation (see below). For the other non-visual cues, realistic stimuli were used. Real objects served as tactile stimuli (e.g. a comb, a balloon). Naturalistic sounds were played in the headphones as auditory cues (e.g. a bell, a match being struck). Real odours were used for the olfactory stimuli (e.g. an onion, a cigarette).

Each cue was followed by the stimulus showing two overlapping images, 45 degree rotated in opposite directions, (the cued and the distractor images or the two non-target images). Each overlapping stimulus was presented twice for each of the two rotation positions (see Fig 2).

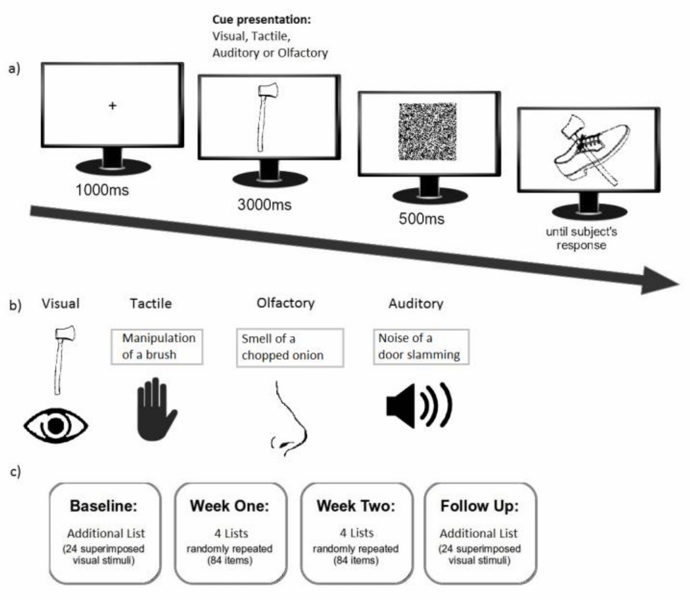

Figure 2.**The experimental task.** a) Timeline regarding the procedure for each individual item. b) Examples of sensory primes used in the four conditions. c) The general timeline of the experiment.

4 separated lists of stimuli were created for the various sensory modalities used in the cued stimuli (visual= n.36, tactile= n.24, auditory= n.12, olfactory= n.12, the number of trials for each modality depended on how difficult it was to match the stimuli of the BORB with real objects which were useful for the auditory and olfactory modalities).

An additional list of 24 different overlapping images without any cues (baseline and follow-up lists) was presented before and after the experimental procedure as a general measure of the ability to recognise overlapping images.

3 healthy subjects (mean age= 39.66, DS= ±7.50, education and gender matched to MR) were recruited to verify whether the lists compared in terms of the degree of difficulty. Their accuracy and response time for denominating the two objects in the overlapping images were recorded and analysed.

3.2. Procedure

MR sat approximately 55 cm away from a 15-inch LCD monitor (resolution 1024 x 768 pixels; refresh frequency 60Hz). After observing a central fixation point

(1000 ms), a cue (visual or non-visual: auditory, tactile or olfactory) appeared for 3000ms. A black and white random-dot-mask (10.6cm x 10.6cm in size, duration 500ms) was then shown followed by the overlapping image stimulus, which remained until the subject responded (Figure 2a). Crucially, in half of the trials, the cues (n. 84) were consistent with one of the objects (target) shown in the overlapping images, while the other image represented a different (non-target) object. In the other half of the trials (the non-cued stimuli), both the objects in the overlapping images were non-target, namely different from the cue. MR was requested first of all to click the computer mouse in order to indicate whether or not the overlapping images included the previous shown cue (*Identification task*, response: Yes/No). He was then asked to denominate both of the objects represented in the overlapping images stimulus (*Denomination task)*.

In the baseline list, there were not any cues and the central fixation point (1000ms) was followed by an overlapping image showing two objects which remained until MR had denominated them.

Accuracy in the Identification task was automatically recorded by the software, while in the Denomination task an examiner manually annotated MR's answers.

The 4 experimental lists were randomly repeated in two consecutive sessions, with an interval of a week between the sessions (total= 168 items). The additional baseline list was presented before (baseline) and after (follow-up) the whole experimental procedure.

E-prime 2.1 Software (Psychology Software Tool Inc., Pittsburgh, A) was used to control timing and randomisation.

3.3. Statistical analyses

The trials where MR failed to recognise the cue were excluded from the analyses (7 out of 168). For the Identification task, in order to test whether there were differences in accuracy between the various conditions, a 4x2 log-linear model was computed with sensory Modality (visual, tactile, olfactory, auditory) and Answer (correct/error) as factors.

In the Denomination task, three scores were possible (correct denomination: both objects= 2; one object= 1; neither of the objects= 0). Responses were initially analysed separately for each sensory modality by comparing the frequency of cued and non-cued items with a 2 (Cue: present/absent) x 3 (Response: 0,1,2) log-linear model. Then, in order to specifically assess the effects of the cue in each modality, the frequency of correct responses in the cued and not cued trials, post-hoc analyses were computed with χ^2 tests, all False Discovery Rate (FDR) corrected (Benjamini & Hochberg, 1995). In all of these comparisons, Cramer's V effect size was adopted ($V<0.1$= negligible effect, $0.1 \leq V<0.2$= weak effect, $0.2 \leq V<0.4$= moderate effect, $0.4 \leq V<0.6$= relatively strong effect, $0.6 \leq V<0.8$ = strong effect and $0.8 \leq V \leq 1$= very strong effect; Rea & Parker,1992).
We also tested the efficacy of the cues by computing a log-linear model for each modality on the frequencies of the cued items versus the frequencies in the baseline with 2 (Condition: baseline vs. cued items) x 3 (Response: 0, 1, 2) factors. Analogous 2x3 log-linear models were executed for non-cued stimuli.
In conclusion, to verify any potential effects of general improvement, the baseline and follow-up lists were compared in a 2 (Time: baseline vs. follow-up) x 3 (Response: 0,1,2) log-linear model.

4. Results

The performance of the controls confirmed that the stimuli lists were balanced for difficulty. No differences between the lists in terms of accuracy ($\chi^2_{(2)}$=3.831, p>0.05) or response times ($F_{(1,4)}$=0.919, p>0.05) were found (general accuracy in denomination of overlapping figures = 94.59% , range=200-209/216).

4.1. Identification task

In this task MR's rate of accuracy was 93.17% overall (with a mean of 92.62, ±5.52 across lists). He failed to identify 7 cues in the overlapping images and there were only 3 false alarms (i.e. when he indicated a cue which was not shown in the target). An accuracy analysis showed no significant effects for Modality ($\chi^2_{(3)}$=4.262, p=0.234), Answer ($\chi^2_{(1)}$=2.972, p=0.085) or Modalities*Answer interaction ($\chi^2_{(3)}$=2.344, p=0.504).

4.2. Denomination task

Results indicated that the cue enhanced MR's performance although to different degrees depending on the sensory modality (Figure 3).

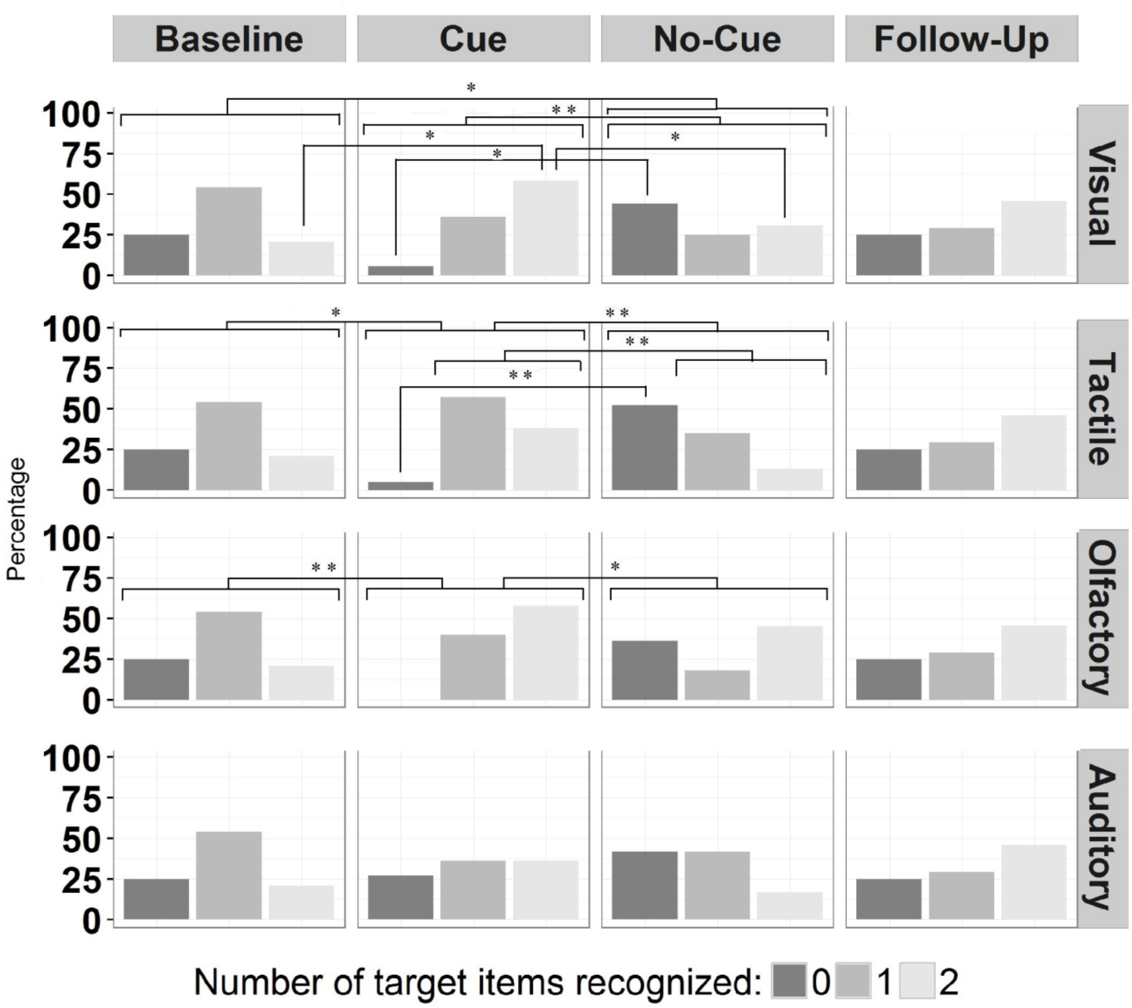

Figure 3. MR's results in the experimental task. For each cue modality (as shown on the right) the frequency of responses in the cued condition (second column) is compared with the baseline (left column) and the non-cued condition (third column). The follow-up condition (right column) is compared with the base-

line condition. (Baseline and follow-up on the additional list, see text). *:<0.05, **:<0.01

The *Visual cue* significantly improved MR's performance. We found significant effects of Cue ($\chi^2_{(1)}$=12.395, p<0.001), Response ($\chi^2_{(2)}$=18.418, p<0.001) and the Cue*Response interaction ($\chi^2_{(2)}$=16.305, p<0.001). Direct χ^2 analyses showed that there were more type 2 responses ($\chi^2_{(1)}$= 4.556, p=0.049, V= 0.251) and fewer type 0 responses ($\chi^2_{(1)}$= 12.518, p=0.001, V= 0.417) in cued as compared to non-cued trials. The efficacy of cued stimuli was also confirmed in the Condition*Response interaction ($\chi^2_{(2)}$=10.264, p=0.006) in the comparison between cued stimuli and baseline (no effects of Condition $\chi^2_{(1)}$= 2.093, p=0.148 or Response $\chi^2_{(2)}$= 4.471, p= 0.107). Direct χ^2 analyses showed that there were more type 2 responses in the case of visual cued stimuli than in the baseline ($\chi^2_{(2)}$= 6.790, p=0.027, V= 0.336).
Finally, in the comparison between non-cued visual stimuli and the baseline there was a main effect of Condition ($\chi^2_{(1)}$= 4.7166, p=0.030), but not other effects (Response: $\chi^2_{(2)}$=4.471, p=0.107 or Condition*Response interaction ($\chi^2_{(2)}$= 5.338, p=0.069).

The *Tactile cue* also significantly improved MR's performance. A comparison showed significant effects of Cue ($\chi^2_{(1)}$= 10.971, p<0.001) and Response ($\chi^2_{(2)}$=12.293, p=0.002) and the Cue*Response interaction ($\chi^2_{(2)}$= 14.509, p<0.001). In a direct comparison between cued and non-cued stimuli, type 0 responses were significantly fewer for cued stimuli ($\chi^2_{(1)}$= 10.206, p=0.004, V=0.476). Although there were no other direct differences, the sum of type 1 and 2 responses was higher for cued than for non-cued trials ($\chi^2_{(1)}$= 10.206, p=0.001, Cramer's V=0.476).
The comparison between cued stimuli and the baseline showed a main effect of Condition ($\chi^2_{(1)}$= 3.9624, p=0.046) but no effects of Response ($\chi^2_{(2)}$=4.4710,

p=0.107) or of the Condition*Response interaction ($\chi^2_{(2)}$= 4.501, p=0.105). Finally a comparison between non-cued tactile stimuli and the baseline did not reveal any differences (Condition $\chi^2_{(1)}$= 2.039, p=0.153, Response $\chi^2_{(2)}$=4.471, p=0.107, Condition*Response interaction $\chi^2_{(2)}$= 3.725, p=0.155).

The *Olfactory cue* significantly improved denomination in cued trials. We found main effects of Cue ($\chi^2_{(1)}$=5.545, p=0.018), Response ($\chi^2_{(2)}$=8.512, p=0.014) and the Cue*Response interaction ($\chi^2_{(2)}$=6.268, p=0.043). No differences between cued and non-cued stimuli were found in direct χ^2 contrasts.

Nevertheless, denomination after olfactory cues was significantly better than at baseline as indicated by the main effect of Condition ($\chi^2_{(1)}$=8.317, p=0.004) and the Condition*Responses interaction ($\chi^2_{(2)}$=7.486, p=0.024) but with no effect of Response ($\chi^2_{(2)}$=4.471, p=0.107). Direct χ^2 did not show any significant effects.

Finally a comparison between non-cued stimuli and baseline indicated that there were no differences (Condition $\chi^2_{(1)}$= 0.403, p=0.526, Response $\chi^2_{(2)}$=4.4710, p=0.107, Condition*Response interaction $\chi^2_{(2)}$= 4.471, p=0.107).

In the denomination task no specific advantage of *Auditory* cue was found (Cue: $\chi^2_{(1)}$=0.505, p=0.477, Responses: $\chi^2_{(1)}$=0.188, p=0.910, Cue*Responses interaction: $\chi^2_{(2)}$=1.253, p=0.534). Furthermore, there were no differences either between cued stimuli and the baseline (Condition$\chi^2_{(1)}$=1.019, p=0.313, Response $\chi^2_{(1)}$=4.471, p=0.107, Condition*Response interaction $\chi^2_{(2)}$=1201, p=0.548) or between non-cued stimuli versus the baseline ($\chi^2_{(1)}$= 0.0910, p=0.762, Response $\chi^2_{(2)}$=4.471, p=0.107, Condition*Response interaction $\chi^2_{(2)}$= 1.025, p=0.599).

4.3. Baseline and follow-up lists

A comparison between the baseline and follow-up lists did not show any significant differences (Time: $\chi^2_{(1)}$=0.0001, p~1.00, Response: $\chi^2_{(2)}$=4.471, p=0.107, Time*Responses: $\chi^2_{(2)}$=4.134, p=0.127) .

Discussion

In this study the potential effects of different types of sensory cues in reducing simultanagnosia were investigated in a patient with Balint's syndrome. The diagnosis was formulated based on the results from a detailed neuropsychological assessment and supported by an accurate analysis of underlying lesions by means of a (18)F-FDG Brain PET/CT. We found that the ability to recognise overlapping pictures may be improved by presenting a congruent stimulus (cue) prior to the task. This stimulus was presented using a visual modality and also other sensory modalities. Crucially, the sensory cue improved not only the target object, but also the non-target object. This suggests that the facilitation effect produced by the presentation of a cue acts on the visual system, allowing the patient to disambiguate the two overlapping images and thus separate them. In fact, although MR's discrimination of the (cued) target was obviously influenced by the fact that he recognised it from the previous equivalent cue, his improvement in terms of recognition of non-target objects can only be due to the visual identification of the overlapping objects in the image. In addition, the fact that there were very few false alarms (i.e. the trials with an incongruent cue where the patient incorrectly indicated the cue as an object present in the stimulus) rules out the possibility that MR was basing his discrimination of objects in the overlapping images exclusively on his previous recognition of the cue.

Balint's Syndrome

The patient here described showed certain specific signs of BS. The initial symptoms of neglect had totally disappeared at the time of the experimental study and MR did not suffer from visual acuity or serious visual field deficits. Ocular apraxia had been present exclusively in the acute phase, when MR was totally unable to voluntarily move his gaze which appeared fixed and vacuous (the "psychic paralysis of gaze" originally described by Balint, 1909). At the time of our assessment, his inability to compare object size or lengths remained, probably at least in part due to simultanagnosia. MR was able to grasp moving objects but failed to point at or grasp unmoving objects or pick out one object from among others (Optic Ataxia).

As previously described in other cases (Chechlacz & Humphreys, 2014; Dalrymple, Barton, & Kingstone, 2013), the most evident symptom was certainly MR's simultanagnosia, (i.e. his inability to interpret complex visual displays due to a difficulty in processing multiple items and the relations between them) (Wolpert, 1924). MR complained that he saw a chaotic and incoherent picture of the surrounding world and this was confirmed by the assessment which showed that he was unable to see more than one object, or even a piece of an object, at a time. He appeared to be totally unaware that what he was looking at was only part of a larger image and he was unable to synthesise the elements of a scene in order to produce the overall scene (Rafal, 2001). Two forms of simultanagnosia have been described (Farah, 1990). In "dorsal simultanagnosia" attentional limitations preclude the detection of multiple objects, while in the "ventral" form the main symptom is a slowdown in visual processing that causes disorders in recognising the individual parts of a multipart object (Rizzo & Vecera, 2002). The dorsal subtype is associated with bilateral lesions in parieto-occipital areas, including the cuneus, the intraparietal sulcus and visuospatial white matter pathways (Chechlacz & Humphreys, 2014). The ventral subtype, less frequent, results from left inferior occipital-temporal damage (Farah, 1990).

Damage resulting from anoxic etiology generally causes multi-focal lesions and areas of hypodensity which are not easy to identify with traditional neuroimaging techniques. The double imaging method (PET/CT) here employed provided a valid support in the identification of the functional damage of MR. Areas of hypometabolism were found in bilateral parietal areas across both the parieto-occipital and temporo-parietal transitions. These areas have been previously described in patients suffering from BS (Phan, Schendel, Recanzone, & Robertson, 2000; Rizzo & Vecera, 2002). A specific investigation on the site of the lateral occipital complex (which is specialised in recognition of single objects), confirmed that this area was spared. In fact, MR did not show any disorders in his perception of individual objects. Finally, the damage to the right dorsolateral frontal cortex explains MR's impairment in planning tasks (FAB, London Tower, BADS).

Although this is compatible with both the dorsal and ventral forms of simultanagnosia, we consider that MR mainly suffered from object-based disorders. Indeed, he could identify multiple objects in space (although slowly) and he did not present with spatial or topographic deficits. In contrast he failed to identify multipart, complex, overlapping objects, even when these occupied the same spatial coordinates as an object that he could see (Rafal, 2001). Actually, MR manifested two apparently opposite deficits: he was unable to integrate individual picture-parts to make them into a whole but he was also unable to identify the individual elements of a complex image. For example, he was at the same time unable to realise that a complex image showed a coffee-bar (with typical furniture and objects, a waiter and a customer) and unable to identify in a chimeric image the presence of two elements (e.g. a dunk and a key). Rather than an isolated inability to focus his attention across a wider area (the Restriction of Visual Attention hypothesis, Rizzo & Vecera, 2002; Rafal, 2003), we suggest that MR's disorders involve an interaction mechanism between spatial attention and processes of perceptive grouping (Shalev et al., 2004; Chica, Bartolomeo, & Valero-Cabré, 2011).

It has been shown that the features of a stimulus can modify the expression of simultanagnosia, for example the distance between local elements in compound forms (Dalrymple, Kingstone, & Barton, 2007; Huberle & Karnath, 2006; Montoro, Luna, & Humphreys, 2011) as can the significance of a stimulus or its familiarity (Coslett & Saffran, 1991; Shalev, Mevorach, & Humphreys, 2007). In addition, the salience of a stimulus may influence the symptoms (Dalrymple et al., 2007; Montoro et al., 2011). Mevorach and colleagues (2014) found that manipulating local and global shapes so that either the former or the latter were salient changed the patient's performance, showing an effect of local or global "capture" which was simply dependant on the relative salience of the shape. This capture effect may be also associated with the inability to disengage attention from a stimulus (Farah 1990). MR's symptoms only in part support the Integrated Competition Hypothesis (Duncan et al., 1997) which explains simultanagnosia as the result of an all or nothing competition between objects (Jackson, Swainson, Mort, Husain, & Jackson, 2009). In fact, he recognised only one element at a time in complex scenes and omitted (or neglected) the others. Nevertheless, following this theory, the patient would be expected to systematically recognise one of the two overlapping images, while in the baseline and the non-facilitated condition MR failed to identify either of the two objects represented in the stimuli.

In effect, it is probably impossible to identify one single disorder underlying simultanagnosia due to variability in the symptoms as a result of different aetiologies and the co-occurrence of other deficits. Discordant findings probably reflect the existence of distinct subtypes (Coslett & Lie, 2008) associated with at least partially different lesions.

Disorders in recognizing a whole object is reported even in the integrative visual agnosia (Humphreys & Riddoch, 1987). This is a particular type of apperceptive visual agnosia involving deficits in recognition of single objects, but preserved abilities in the analysis of their single parts. We exclude this possibility as MR showed spared abilities in processing single drawings and real objects. Furthermore, integrative agnosia is reported after lesions in bilateral posterior and ventromedial occipital-temporal areas, including inferior temporal, fusiform and lingual gyri (Riddoch, et al. 2008). These ventral areas were spared in MR.

Facilitation effects induced by a visual cue

Our results indicate that a visual cue helped MR to discriminate the elements in two overlapping figures. Crucially, when the stimuli were cued this facilitated the recognition not only of the target but also of the not-target stimuli. In other words, when the patient was able to match the cue with the target in the overlapping figure (Identification task) and to identify one object in the double stimulus (Denomination task), he was then also able to separate this object perceptively from the other object and to distinguish each of these as one single object. In terms of visual attentional processes, we can hypothesise that the cue induced a generic increase in brightness contrast in the limited space depicted in the images. This might enhance both bottom-up and top-down attentional processes. With regard to the potential bottom-up mechanisms, we suggest that the cue facilitated a disengagement of attention from the global stimulus (global "capture"), allowing the identification of the two separate objects of the overlapping figures. In other words, the cue would potentially represent an instrument that allow the patient to overcome the global capture effect. To at least partially support this hypothesis , at the denomination task, in the trials with a false cue (i.e., when the cue was not present in the following overlapped images) the performance decreased significantly in comparison to the baseline.

As the significance of stimuli influences in the attention to the same stimuli in simultanagnosia, we suggest that top-down, semantic memory processes were also involved in our experimental results. Previous results support this hypothesis. In a single-case study, Coslett and Saffran (1991) found that their patient was better at identifying two simultaneously presented words when these were components of compound words (e.g. BASE and BALL) or were semantically related (e.g. HOT and COLD) than when they were unrelated. Better recognition was also found for pairs of line drawings that were semantically related (e.g. both animals) than those that were unrelated (e.g. an animal and a tool) (Coslett and Saffran,1991).

Recognising the object used as a cue may also have induced an effect of "familiarity" for the stimulus which was subsequently presented. In an interesting study, Shalev et al. (2007) demonstrated that their simultanagnosic patient perceived only the global shape of a compound letter as long as its local elements were unfamiliar; however, after that the patient was trained to identify the local (previously unfamiliar) elements, it became difficult to perceive global forms containing the now-familiar local elements. Thus, familiarity changed the stimulus saliency.

That said, we suggest that the facilitation in our experiment did not act separately on the visuo-spatial attentional or semantic systems, but rather enhanced the integrative processes of spatial attention and visual discrimination.

Cross-modal facilitation in the perception of overlapping images.

In everyday situations, people perceive the surrounding complex environment as a unique, coherent whole thanks to the integration of multiple sensory systems such as the olfactory, auditory, visual, gustatory and tactile systems. The likelihood and speed of detection and identification of events is certainly higher when inputs come from two or more sensory channels as compared to only one (Demattè, Sanabria, & Spence, 2006, 2009; Gottfried & Dolan, 2003).

Cross-modal integration is certainly supported by neuronal networks at multiple levels. A first level acts relatively early in subcortical brain structures (e.g. the colliculus) and in the primary sensory cortices. Here, there are bimodal neurons that at the same moment respond to stimuli presented in two different modalities, in particular when those two stimuli occur in close spatial and temporal proximity (Diaconescu, Hasher, & McIntosh, 2013; Fort et al., 2002; Gottfried & Dolan, 2003). A second step involves the associative cortices. For example, synchronous auditory-tactile stimulation induces cross-modal facilitation effects and increases the auditory intensity rating thanks to the auditory-tactile multisensory neurons in the auditory associative cortex (Gillmeister & Eimer, 2007). In addition to these sensory areas, multisensory integration in humans is supported by a complex, widespread network. This involves the superior temporal sulcus which is associated with the integration and labelling of objects and the intraparietal sulcus, involved in spatial information processing (Calvert, 2001; Stein & Stanford, 2008). In these areas an overlapping activation related to three different senses (tactile, auditory and visual) has been recorded (Beauchamp, Yasar, Frye, & Ro, 2008; Bremmer et al., 2001; Langner et al., 2012). Furthermore, the retro-medial orbito-frontal cortex and hippocampal areas have been identified as neuronal correlates of multisensory integration involving the olfactory and gustatory domains (Gottfried & Dolan, 2003; Price, 2008). Finally, the amygdala and the insula have also been found to be involved in the integration of cross- or multisensory information related to emotional perception (Dolan et al., 2001; Freiherr, Lundström, Habel, & Reetz, 2013).

This suggests that, in multisensory integration, high cognitive functions such as attentional and memory processes are also involved (Rizzo & Vecera, 2002). The improvement that our patient showed in his ability to discriminate the two objects in the overlapping images after non-visual cues probably made use of these widespread networks. Certainly, these interacted with and enhanced the more specific spatial-attentional processes (as mentioned earlier for visual unimodal facilitation). In addition, research on multisensory interaction has demonstrated that this is more efficient at improving perceptual performance when an isolated modality is deficient (the principle of "inverse effectiveness"; Caclin et al., 2011; Hairston, Laurienti, Mishra, Burdette, & Wallace, 2003).

Nevertheless, in the case of MR cross-modal integration was not as efficacious as visual facilitation in terms of reducing simultanagnosia and neither did the auditory modality have any notable effects. The delay between the cue and the presentation of stimuli showing overlapping objects may have contributed to this reduction in efficacy. There may also be other factors. The *visual* cue was perceptively identical (although not rotated through 45° like the target stimuli) and for this reason represented the most salient cue, thanks to the possible integration of bottom-up and top-down processes. In contrast, non-visual cues only matched the target stimuli semantically, probably inducing top-down attentional and short-term memory processing (Shinn-Cunningham, 2008). In addition, while the temporal proximity between cue and target was identical for all of the modalities, spatial congruency was only respected in the visual modality (Frassinetti, Bolognini, & Làdavas, 2002; Valenza et al., 2004).

The tactile and olfactory cues were efficacious in improving MR's recognition and denomination of overlapping objects, but the auditory cues did not have any influence. A possible explanation is that the acustic cue was too difficult to identify and thus did not provide useful information. In fact, MR made many mistakes in recognizing acoustic cues (33.33% errors: 1 excluded and 3 missed in the *Identification* task).

Nevertheless, this result was unexpected, considering the importance that auditory inputs have in the context of daily life and in terms of object recognition. One could speculate that auditory stimuli are more connected to linguistic than visual information about objects. Thus, these stimuli might facilitate verbal recall more than visual recognition. Unfortunately, we did not investigated this possibility in MR.

A hypothesis regarding the enlargement of the attentional window by means of a priming task (with a procedure similar to ours and a delay between the stimuli) has been suggested in a single-case study involving a patient affected by BS (Shavel, et al., 2004). The patient showed an improvement in the visual recognition of compound letters following a preliminary task in which he had been asked to identify one of same letters. Nevertheless, it remains unclear if this effect was supported by implicit processes or short-term memory.

Another possible interpretation of our results refers to the effects of expectation of imminent stimuli. When sensory stimuli occur close together in time and space they are likely expected by individuals to be associated signals coming from a common source (top-down expectation; Gau & Noppeney, 2016; Körding, et al. 2007; Magnotti, Ma, & Beauchamp, 2013). In our task, immediately after exploring the cue, the patient could be in an expectation condition, awaiting the presentation of the same object, that is thus more easily detected. However, the effect of trial expectation does not explain the partial effect of improvement in the recognition of the second uncued stimulus in the overlapping images. In addition, it is important to consider that the patient was aware that the cue might or might not anticipate one of the objects shown in the overlapping images (50% of the probability). This probably reduced the expectation effect.

In conclusion, we consider that the identification of a previous stimulus influenced MR's capacity to perceive overlapping objects, probably thanks to a combination of bottom-up and top-down processing when the cue was visual, and to top-down facilitation in cross-modal cues. Unfortunately, the effects were only temporary and were not generalised to other stimuli, as demonstrated by the fact that there were no differences in MR's scores for the additional list administered before and after the experimental procedure. Thus, in terms of recovery, cross-modal facilitation does not seem to represent a useful strategy for rehabilitation. Nevertheless, the number of trials for each modality used in our experiment are probably too few to induce any long-term changes. Only more specific, prolonged programs will indicate the potential effects of cross-modal facilitation in simultanagnosia.

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Rehabilitation of Tactile Agnosia by means of Transcranial Direct Current Stimulation

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Abstract

Objective: The study aims to investigate the effects of transcranial Direct Current Stimulation (tDCS) in a rehabilitation programme for Tactile Agnosia and to understand the role of the stimulation site in the modulation of the symptoms.

Design: A single case study. Single blind pseudo-random trial in an ABABAB paradigm.

Subject: A patient suffering from Associative Tactile Agnosia following an ischemic stroke in the right front-parietal cortex.

Methods: Three blocks of occupational/neuropsychological and motor rehabilitation sessions with off-line a-tDCS were alternated with three blocks of rehabilitation sessions without tDCS (6 blocks in total). In order to assess the recovery, patient's performance was recorded in a tactile object recognition task before and after each of the 6 blocks and in two follow-up sessions (at 20 days and at 6 months). Furthermore during the blocks with a-tDCS, the stimulation was administered in counterbalanced order to two sites: i) the perilesional parietal area (specific stimulation) and ii) a far from lesion occipital area (non-specific stimulation).

Results: The rehabilitation programme was significantly more efficacious when associated with a-tDCS than when it was administered without stimulation. In addition, the patient performed better after stimulation to the specific perilesional area as compared to the non-specific site. This improvement lasted over time.

Introduction

Tactile Agnosia (TA) is a modality-specific deficit affecting the tactile recognition of objects, in the presence of adequate sensory, linguistic and cognitive functions.[1] Patients with TA are unable to identify simple objects when these are manipulated using their affected hand. In contrast, they easily recognise the same objects with the other hand and when they see them or hear their typical sound (e.g. the noise of keys).[2] Furthermore, TA is not due to linguistic or memory deficits, as patients can normally denominate the objects presented in non-tactile modalities.

Various different hypotheses have been advanced to understand the causes of TA. The first anecdotal descriptions of the syndrome did not clearly distinguish it from elementary somatosensory impairment,[3,4] but recent studies have focused on more detailed descriptions of the symptoms and associated cerebral damage.[5] In fact, the very first hypothesis that TA is the consequence of sensory disorders[3,6] has been replaced by more recent theories suggesting that the neural correlates of TA may be found in a disconnection between tactile modality specific encoding and processes of multimodal integration[7] or semantic memory systems.[8,9] In some cases,[4,10] the presence of non-efficacious exploratory motor procedures has suggested that perceptual-motor integration may contribute to the syndrome.[4] Finally, a theory concerning the role of general supra-modal disorders in spatial perception has also been advanced.[11-15]

After the encoding of an elementary sensory perception, the process of object recognition by touch may be compromised at two steps: i) when sensory elements are integrated (Apperceptive TA) or ii) when the semantic representation of an object is activated (Associative TA).[7] Apperceptive TA is reported following damage to the inferior parietal and insula cortex.[3,11,15,16] Associative TA is instead associated with lesions in the inferior parietal, supra-marginal[4,17] and angular gyri,[9] posterior insula and temporal cortex.[11] A patient suffering from TA after a lesion in the corpus callosum (trunk and splenium) has also been reported.[18]

In effect TA is a rare syndrome, often discussed in single-case reports (but see[11]). This is mainly due to its very low incidence and the difficulties involved in isolating TA symptoms from frequently co-present sensory and motor disorders.[3]

To the best of our knowledge, there have been no studies to date which specifically investigate the effects of rehabilitation programmes for TA. Transcranial Direct Current Stimulation (tDCS), however, offers a new method of rehabilitation training. It is considered to be a useful tool as it modulates brain plasticity by means of the polarization of neuronal populations.[19] Anodic tDCS increases cortical excitability with positive effects on learning processes[20] and facilitation in the acquisition of new skills.[21] On the contrary, cathodic tDCS has inhibitory effects, resulting in a decrease in neural activity. tDCS may be particularly useful in order to contrast post-lesional symptoms due to hyperactivity in some networks or to modulate inter-hemispheric activations.[22,23]

Here we report a single case study regarding a man with left hand TA following a vascular lesion in the right parietal cortex. Neurological and neuropsychological assessments were associated with an accurate analysis of his lesion. A rehabilitation programme using tDCS was then carried out in order to understand: i) whether brain stimulation can enhance the effects of a traditional rehabilitation programme and ii) if different stimulation sites impact on the efficacy of the programme. For this reason, we used an ABABAB paradigm alternating a tDCS plus behavioural training programme (blocks A) with a behavioural programme (blocks B). In addition, in the A blocks we compared the efficacy of tDCS stimulation to two different cortical areas: i) a specific perilesional area (P4) and ii) a non-specific, far from lesion area (Oz-O2). In this way, we were able to evaluate not only the efficacy of tDCS in behavioural training for TA, but also whether its effects are driven by an increase in neuronal excitability in specific perilesional areas or by a general cortical activation.

Methods

Case report

US is a right-handed, 56-year-old German man. He has a high standard of education (PhD), speaks fluent Italian and works as an agronomist. 15 days after an ischemic stroke in the fronto-parietal area of the right hemisphere, he was admitted to the Department of Rehabilitation. He was oriented in time and space and aware of his deficits. Motricity was spared although he suffered from very mild weakness in his left leg. He complained that he was no longer able to recognize objects with his left hand, although he could identify their shape and size. This deficit did not affect his right hand.

Neuropsychological assessment

1 month after the lesion onset, US's general cognitive functions appeared preserved (Mini Mental State Examination - MMSE=30/30[24]). An in depth neuropsychological assessment confirmed that the patient did not show any signs of neglect or language disorders. There were some difficulties regarding attentional flexibility, inhibition of automatic responses (Visual Elevator test, Stroop and PASAT) and planning (Tower of London, BADS). His score in a verbal short-memory test was under cut-off, but he did not show any other memory deficits. Although during the execution of intransitive gestures US made some minimal errors (perseveration, omission and conduit d'approche), he compensated well for these. He did not have any pathological scores in tests for apraxia. The details of the neuropsychological assessment are reported in Table 1.

	Score	Cut-Off (ES 0-4)
Attention		
Trail Making Test[25]		
Test A (sec.)	50	>93
Test B (sec.)	151	>282
Test B-A (sec.)	101	>187
Attentional Matrices[26]	46.5	30
Visual Elevator (TEA[27])	**8.3**	9.2
Stroop Test[28]		
Word (sec.)	44	<50
Colour (sec.)	74	<80
Colour/Word (sec.)	**143**	<120
PASAT[29]		
ISI 4000	**10***	≤6*
ISI 3000	**9***	≤6*
ISI 1800	**24***	≤9*
Spatial Neglect		
BIT[30]		
Conventional Subtests	141	129
Behavioural Subtests	80	67
Memory		
Short-term spatial memory[26]	*3.75*	3.75
Long-term spatial memory (Corsi[26])	13.9	5.75
Short-term verbal memory (Word Span[26])	**2.25**	3
Story Recall[26]	14.4	4.75
Rey 15-words Test[31]		
Immediate Recall	52.2	28.53
Delayed Recall	13	4.69
Rey Complex Figure Recall[32]	14.15	6.20
Imitation hand positions[33]	20	12
Apraxia		
Rey Complex Figure Copy[32]	*28.33*	28
Clock Drawing Test[34]	9	7.57

Ideational Apraxia Test[35]	14	(4)
Ideomotor Apraxia Test[36]	66	53
Constructive Apraxia Test[26]	10.50	(2)
Executive Functions		
FAB[37]	16.8	12.03
Raven's progressive Matrices[38]	36.75	20.72
Tower of London[39]	**23**	26.54
WCST[40]	97.8	90.50
BADS[41]		
Rule shift cards	0*	(4)
Temporal judgement	3	(3)
Key search	**6**	**(1)**
Zoo map	14	(3)
Modified six elements	5	(3)
Language		
AAT[42]		
Token test	49	(4)
Repetition	147	(4)
Writing	90	(4)
Naming	118	(4)
Comprehension	119	(4)

Table 1. Neuropsychological Assessment. US's scores in tests assessing Attention,[25,26,27,28,29] spatial neglect,[30] Memory,[31,32,33] Apraxia,[34,35,36] Executive functions[37,38,39,40,41] and Language are reported.[42] All scores (second column) are corrected for age and education. ES= Equivalent Score. * = tests where the score is based on the number of errors. Pathological ES are 0 (severe) and 1 (moderate). ISI= Inter-stimuli Interval in msec. Pathological results are in bold; scores at cut-off are in italics.

Tactile Agnosia

Somato-sensory perception

In order to isolate the presence of Tactile Agnosia with respect to other potential deficits, a detailed screening of somato-sensory perception was preliminarily administered by means of clinical tasks and the Evaluation of Somatic Sensation Test[43] (Table 2). US did not show any left hand deficits in the detection of tactile stimuli. In contrast, he failed to localise tactile stimuli with both hands and to imitate the position of his right hand with his left hand. However, this latter symptom seemed to be the result of a certain degree of awkwardness in the movements of his left hand rather than proprioceptive deficits. In fact, US carried out all the tests for somatic sensations and proprioception without errors (Table 2).

	At 1 month		At 6 month
	RH	LH	LH
Tactile Perception			
Lightly touch (12)	100	91.66	100
Touch with Pressure (12)	100	100	100
Vibration (8)	100	100	100
Temperature (12)	100	**75**	100
Tactile extinction (19)	94.7	84.5	-
Localization of the touch by other hand (12)	75	**66.66**	75
Imitation of other hand position (12)	91.66	**50**	75
Discrimination of movement (12)	-	91.66	-
Somatic Sensation Test[43]			
Joint Position Sense (0-51*)	-	11*	8*
Pressure Sensation (0-16*)	-	4*	0*
Motor Sequences (0-16*)	-	0*	0*
Thumb-index grip force control (0-316*)	-	16*	28*
Functional tests (0-40*)	-	0*	1*
Object recognition (15)	100	**26.66**	-
Tactile Recognitions[17]			
Geometrical shapes			
Discrimination (12)	100	83.33	-
Denomination (12)	100	83.33	-
Drawing objects after haptic exploration (5)	80	**40**	-

<u>*Praxic Abilities*[17]</u>			
Letters during active manipulation			
Discrimination (12)	91.66	83.33	100
Denomination (12)	75	**25**	50
Letters during passive manipulation			
Discrimination (12)	91.66	91.66	91.66
Denomination (12)	66.66	**41.66**	50
<u>*Supra-modal Spatial Representation*[17]</u>			
Tactile Spatial Representation (9)	77.77	66.66	-
<u>*Visual Spatial Imagery*</u>			
Imagery of letter shape[44] (40)	100		

Table 2. Clinical assessment of Tactile Agnosia and correlated functions. The results in the examinations at one and six months after lesion are reported in percentages of correct responses. Sensory perception was assessed by means of clinical tasks and the Evaluation of Somatic Sensation Test.[43] Clinical tests of Tactile Perception, Praxic Apraxia and Supra-modal Spatial Representation for diagnosis of Tactile Agnosia were administered following the procedure suggested by Veronelli and colleagues and Sartori & Job.[17,44] RH = right hand; LF = left hand. * = number of errors. In parentheses the number of items per task. For the task of imagery of letter shape the scores are not hand specific. Pathological scores are in bold.

The Assessment of Tactile Agnosia

In order to determine the nature of the subject's tactile agnosia (whether associative or apperceptive), we capitalised on the method of assessment proposed by Veronelli and colleagues.[17] This distinguishes three main functions: i) *tactile recognition,* which concerns the processing and integration of the basic sensory features of objects in order to determine its shape; ii) *praxic abilities*, which are necessary to explore objects and iii) *supra-modal spatial representation*, in order to exclude more general spatial deficits.

US was blindfolded during all of these tasks. The tests were first executed with the left hand and then with the right hand as control (Table 2).

Object recognition. A task involving the tactile recognition of a variety of objects was used to evaluate the presence of Tactile Agnosia. 15 different objects used in daily life activities (e.g. clothes peg, screwdriver) were presented at three different time intervals from the lesion onset.

While US could immediately name all the objects using his right hand (100%), he was totally unable to recognise them with his left hand. This task was repeated three times in the first 40 days after lesion onset in order to verify the stability of the symptoms (score at 15 days: 1/5; 25 days: 1/5; 40 days: 2/5). In addition, the patient was unable to give any information about object functions or to execute the pantomime of their use. Nevertheless, after manipulation with his left hand, he was able to describe the shape of the objects in detail in terms of their outline, texture and temperature (see Supplementary video materials - SM).

Tactile recognition. Two tasks were administered. In a task involving the Discrimination of geometrical shapes, US was asked to manipulate 12 pairs of three-dimensional geometrical shapes (i.e. triangles, squares, circles and rectangles; small= 1.5x1.5 cm; big= 3x3 cm) and to judge if they were the same size and shape (same/different response). In a Denomination task, the same geometrical shapes were presented individually and the patient was asked to name them.

In addition, in order to distinguish between US's abilities to perceive and represent the shape of the various objects from potential linguistic disorders, he was requested to do a drawing task after haptic exploration of the objects.[17] US manually explored 5 different objects (a birthday candle, a wooden spoon, a bottle of nail varnish, a pair of glasses and pincers) and was asked to draw them immediately afterwards (using is right hand). He was then asked to identify all the 5 objects previously drawn. The score was calculated on the number of objects which he had drawn and denominated correctly.

US did not show any particular difficulties in the discrimination and naming of the geometrical shapes after left hand exploration (Table 2) and this confirms his ability to recognise elementary features of shapes and objects. In contrast, he found it difficult to recognise his own drawings after left hand manipulation (but not after right hand manipulation (Left Hand: 2/5; Right hand: 4/5). This suggests that he was unable to integrate features pertaining to the shape in order to identify objects**.** The fact that he was able to name objects after right hand tactile exploration excluded any potential role of language and drawing abilities.

Praxic ability. A comparison between active and passive manipulation allowed us to distinguish between symptoms due to agnosic and apraxic deficits. In the active condition, US was asked to identify 12 3D-letters that he was permitted to manipulate freely. In the passive condition, the same 12 letters were written by the experimenter on the palm of US's hand (graphesthetic function). In both tasks US was requested to: i) identify two letters as being the same or different from each other (Discrimination task) and ii) name one of the letters (Denomiantion task).

An isolated deficit in identification abilities after active manipulation may be an index of praxic disorders,[10] while in the presence of tactile agnosia, patients are expected to fail in both the active and passive conditions. Nevertheless, in the case of associative tactile agnosia, only passive naming would be impaired with spared passive discrimination.[17]

Although US's movements appeared slightly clumsy, he was easily able to recognise whether the pairs of letters were the same or different (based on the elementary features of the shapes). Nevertheless he failed at the Denomination task.

Supra-modal Spatial representation. A specific assessment excluded the presence of spatial neglect (Table 1). Nevertheless, due to the fact that the cerebral lesion was on the right hemisphere, we assessed S*upra-modal spatial representation* after tactile exploration.[17] A 30x30cm base with 36 nails in it was placed in front of the patient. He was asked to move his hand touching the tops of the nails according to 9 different sets of directions given by the examiner (e.g. "Please move your hand 3 nails to the left").

No considerable difference was found between the two hands in this task (right hand:77.78%; left hand: 66.66%) ruling out a main role of disorders in spatial representations in US's tactile agnosia. Finally, we excluded disorders in mental imagery by means of a letter imagery task.[44]

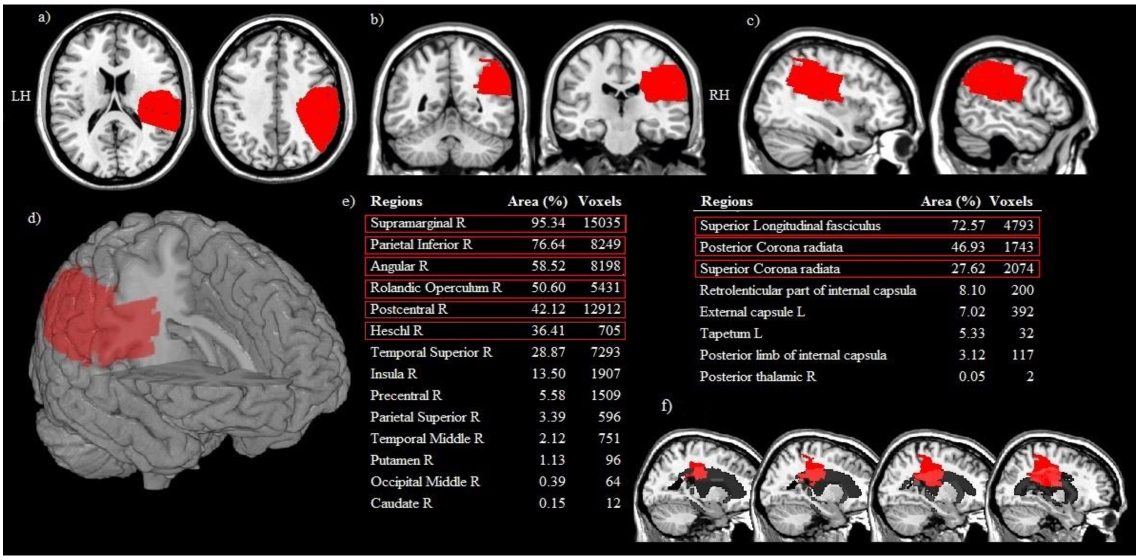
Analysis of lesion

A structural MRI was carried out 3 days after the lesion onset and the patient's lesion was mapped by mean of the MRIcron software[45] on the standard T1-weighted MRI template (ICBM152) of the Montreal Neurological Institute (MNI) coordinate system, approximately matched to the Talairach space.[46] We first oriented the template on the midsagittal and midcoronal axis to match the original scan of the patient. Then, a blind expert clinician manually traced the lesion using the MRIcron Software.[45]

The final image of the lesion was superimposed onto the Automatic Anatomical Label (AAL) template[47] in order to ascertain the number of voxels involved in the lesion in each area and the centre of mass of the lesion.

The main areas damaged in the right hemisphere lesion are the supramarginal gyrus (-x= 53, y=-22, z=18), the inferior parietal cortex (x= 37, y=-50, z=38), the angular cortex (x= 38, y=-53, z=22), the rolandic operculum (x= 53, y=-10, z= 11), the postcentral gyrus (x= 63, y= -15, z= 15), the Heschl gyrus (x= 40, y= -24, y= 12), the superior temporal gyrus (x= 60, y= -12, z= 11) and the insula (x= 41, y= -6, z= 11) (see Figure 1 for details). The same test repeated at 10 days from the stroke gave analogous results.

The same procedure was used by overlapping the lesion to the JHU (Johns Hopkins University) DTI-based white matter atlas[48] in order to analyse the white matter tracts. This indicates that the lesion involves the superior longitudinal fasciculus and the posterior and superior corona radiata (Figure 1f).



Regions	Area (%)	Voxels
Supramarginal R	95.34	15035
Parietal Inferior R	76.64	8249
Angular R	58.52	8198
Rolandic Operculum R	50.60	5431
Postcentral R	42.12	12912
Heschl R	36.41	705
Temporal Superior R	28.87	7293
Insula R	13.50	1907
Precentral R	5.58	1509
Parietal Superior R	3.39	596
Temporal Middle R	2.12	751
Putamen R	1.13	96
Occipital Middle R	0.39	64
Caudate R	0.15	12

Regions	Area (%)	Voxels
Superior Longitudinal fasciculus	72.57	4793
Posterior Corona radiata	46.93	1743
Superior Corona radiata	27.62	2074
Retrolenticular part of internal capsula	8.10	200
External capsule L	7.02	392
Tapetum L	5.33	32
Posterior limb of internal capsula	3.12	117
Posterior thalamic R	0.05	2

Figure 1. **US's lesion.** The lesion traced on MRI Template is reported (the right hemisphere is on the right). The lesion (in red) mostly involves the right supramerginal gyrus, inferior parietal, angular cortex rolandic operculum, post-central gyrus, Heschl area, temporal superior gyrus and insula. The lesion is shown in a) Axial, b) Coronal, c) Sagittal views and d) on a 3D brain representation. e) The tables show the percentage and number of voxels of damaged tissue in each area in the grey (left table) and white matter (right table). f) The lesion (in red) affecting the white matter.

Experimental design

A series of anodic-tDCS (a-tDCS) stimulation sessions was administered to US with the aim of investigating its potentially beneficial effects.

Three 5-day-blocks of off-line a-tDCS stimulation sessions blocks (A) were alternated with three 5-day-blocks of occupational/neuropsychological rehabilitation sessions without tDCS blocks (B). During the a-tDCS sessions (A), electrical stimulation was administered to both the perilesional parietal area (specific perilesional stimulation condition) and the right occipital area (non-specific stimulation condition). This was carried out in a counterbalanced order over the five sessions of each block, with an interval of at least 2.5 hours.

A task involving the recognition of real objects (executed by the subject before and after stimulation) served as a measure of the modulatory immediate effects of tDCS. A similar task but with different objects was employed as general measure of improvement between the blocks (Figure 2).

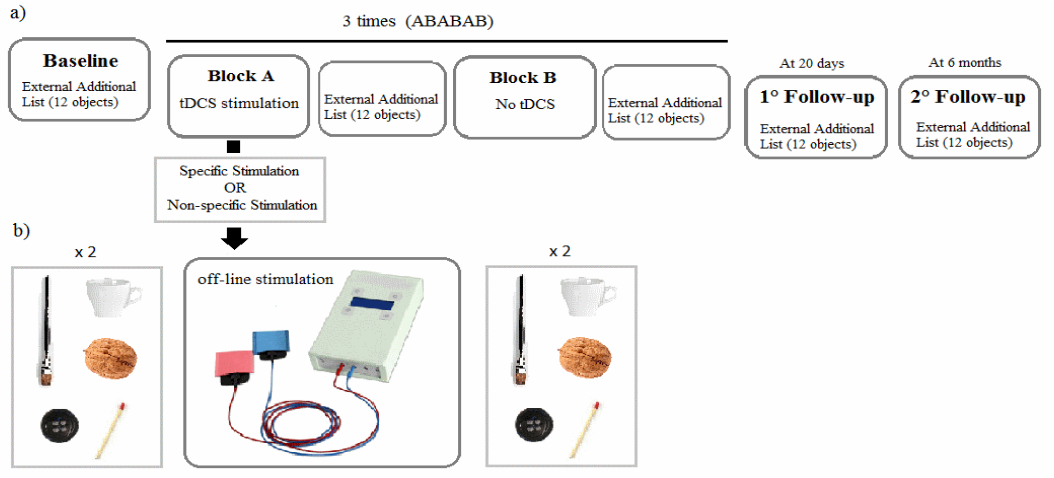


Figure 2. **Experimental Design** a) Timeline of the entire experiment, b) An example of the objects (5 objects repeated once) used in a single session involving specific or non-specific stimulation and presented to the patient before and after tDCS (block A).

The paradigm thus allowed us to investigate whether: i) a-tDCS stimulation induces a greater improvement in tactile recognition than occupational/neuropsychological therapy and ii) the specificity of the area stimulated impacts on the effects of this training.

tDCS

In accordance with safety guidelines,[49] off-line tDCS stimulation was administered by means of a constant current stimulator (BrainStim, EMS), using two saline-soaked sponge electrodes (5x7 cm; 35cm^2) at an intensity of 2mA for 20 minutes (with a fade-in and fade-out of 120s).[50,51] The sites of the electrodes were identified following the international 10-20 system coordinates.[52,53] In each session, the location of the anodic electrode was counterbalanced in two stimulation sites corresponding to the two experimental conditions: the perilesional parietal area on P4 (the specific stimulation condition) and the occipital area on Oz-O2 (the non-specific stimulation condition). The cathodic electrode was always located in an extra-encephalic position on the contralateral side of the forehead.

Object recognition pre and post a-TDCS. Before and after a-TDC stimulation, US was asked to recognize a series of simple, everyday objects, which he manipulated with his left hand. We built some lists of objects. In order to balance the difficulty of the lists and to avoid the learning effects due to the repetition of the same objects, various different lists were administered before and after the session following the order showed in Table 3.

Block and Day	Specific Parietal Stimulation	Non-specific Occipital Stimulation
A1 (5 objects repeated)	List	List
Day 1	A	F
Day 2	B	G
Day 3	C	H
Day 4	D	I
Day 5	E	L
A2 (5 objects repeated)		
Day 1	F	A
Day 2	G	B
Day 3	H	C
Day 4	I	D
Day 5	L	E
A3 (6 objects repeated)		
Day 1	M	N
Day 2	O	P
Day 3	N	M
Day 4	P	O
Day 5	Q	R

Table 3.The lists of objects used to assess the effects of a-tDCS and the order of administration is schematized. Capital letters indicate the different lists.

General measure of tactile recognition. An additional list of another 12 objects which were different from those previously used (the External Assessment List) was used as a general measure of tactile recognition before stimulation, between each block and in two follow-up assessments.

Procedure

As shown in Figure 2, the training programme lasted a total of 6 weeks. 3 weeks of tDCS stimulation associated with traditional occupational/neuropsychological and motor rehabilitation (Blocks A in Figure 2) were alternated with 3 weeks when the patient participated exclusively in occupational/neuropsychological and motor rehabilitation (Blocks B in Figure 2).

Each tDCS daily session was planned in six steps:

Step one: US sat in front of a table, blindfolded. An object was put into his left hand which was lying palm up on the table and he was asked to identify it. The object remained in his hand until he recognised it or in any case for a maximum of 2 minutes. When he found it impossible to name the object, an accurate description of it was accepted.

Step two: the first tDCS stimulation condition (i.e. specific – in P4 or non-specific – in Oz-O2) was administered. During stimulation, the patient did not perform any activities.

Step three: the subject did a recognition task involving the same objects as those used in Step 1.

Interval: between the two stimulation conditions there was an interval of around 2.5 hours during which US participated in physiotherapy and rested. Note that during the A blocks, the neuropsychological/occupational activities carried out (i.e. those focusing on attention, executive functions, proprioception and limb position recognition) were never executed during stimulation but always at different times in the day.

Step four: using an identical procedure as that used in Step 1, the patient was asked to execute a tactile recognition task with a new list of objects (table 3).
Step five: a-tDCS was applied to the second site (non-specific – in Oz-O2 or specific – in P4)
Step six: a further recognition task using the same objects as those used in Step 4 was carried out.
As the patient was blindfolded during these experimental sessions, he could not see the objects and did not receive any feedback regarding his performance. This was done in order to avoid any interference.
Only at the end of the whole training programme (i.e. after Block B3) did US use his right hand (i.e. the control hand) to explore all the objects previously used in the recognition tasks.
Furthermore, in order to measure any potential improvement in US's general ability in terms of tactile recognition, the External Assessment list (with 12 objects which were different from those used in training programme) was administered before training (baseline), between the A and B blocks and in two follow-ups, respectively 20 days and 6 months after the end of training programme (Figure 2).

Results

The fact that all of the objects used in the training programme were familiar to US was confirmed by the patient's post-training performance with his right hand (accuracy= 93%). US's performance was analysed on three levels, namely as general improvement, effects of stimulation and specificity of stimulation site.

General Improvement. The scores applying to the External Assessment list in the various different phases of the programme were compared to each other (Baseline, A1, B1, A2, B2, A3, B3, two follow-ups) by means of repeated Wilcoxon Tests. The raw scores obtained in task using the External Assessment List were used for analysis. All of the responses were sorted into three categories for each object: 1= Correct recognition of the object; 0.5= Recognition of the correct semantic category, but not of the specific object; 0= Failure to recognise the object.

Results indicated a significant difference between the baseline and A3 (Z=-2.385, p=0.017) and B3 (Z=-2.181, p=0.029). This improvement lasted until the first follow up (Z=-2.322, p=0.020) and the second follow up (Z=-2.060, p=0.039) (Figure 3a). In addition, significant differences emerged in a comparison between A1 (Z=-2.271, p=0.023) and B1 (Z=-2.251, p=0.024) versus the first Follow up (Figure 3a).

Effects of stimulation. The effects of rehabilitation in blocks A (tDCS) and B (without tDCS) were compared by computing the differences between the scores obtained using the post-block External Assessment list with those of the pre-block assessment (and corresponding to the previous post-block measure, i.e. the differences between post-A1v. Baseline, post-B1 v. post-A1, post-A2 v. post-B1, post-B2 v. post-A2, post-A3 v. post-B2, post-B3v. post-A3). For each object of the External Assessment list, we computed the differences between the patient's responses in the two assessments in order to obtain a performance index. We awarded a score of +1 or + 0.5 when the patient identified correctly or partially correctly an object which had not been identified in the list for a previous task (i.e. an improvement in performance), 0 when his performance did not change and -1 or -0.5 when he failed to recognise an object which had been previously correctly or partially correctly identified (i.e. a worsening performance).

The comparison by means of Wilcoxon tests showed that the blocks after tDCS (As) gave better results than those without tDCS (Bs) (Z=-1.943, p=0.052). However, direct contrasts for consecutive Blocks (A1 v.B1; A2 v. B2, A3 v. B3) did not show significant results (see Figure 3b).

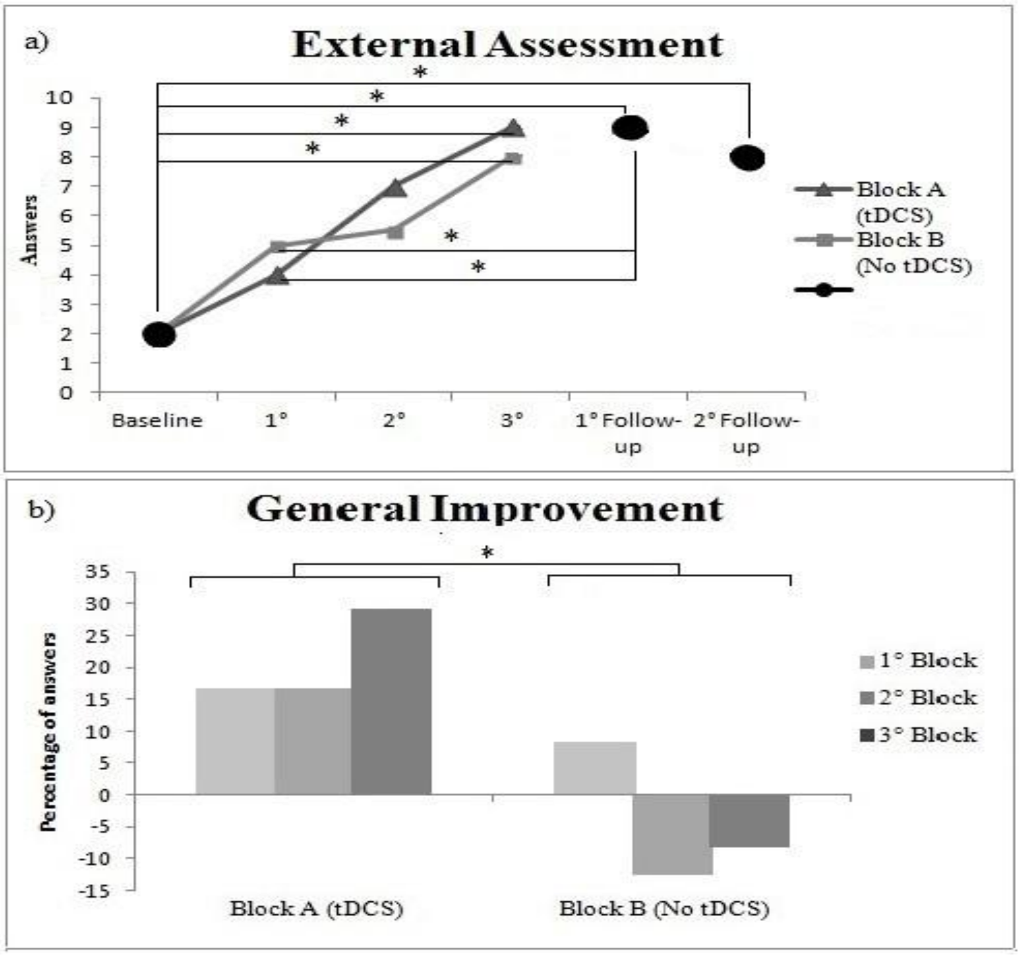


Figure 3. **Measures of General Improvement and Effects of stimulation.** a) External Assessment analysis on performance at Baseline after each training session and in the two Follow-ups. b) The comparison of General Improvement between Blocks A with tDCS and Blocks B without tDCS is shown; *:<0.05.

Specificity of the stimulation site. Taking into consideration only the A Blocks, a comparison was made between the number of objects recognised after specific and non–specific stimulation by means of a Mann-Whitney Test (Site: Parietal vs. Occipital). For each session, this analysis was computed on the differences between US's score in the recognition of objects task before tDCS stimulation and his score in the recognition task with the same objects after stimulation (the performance index was calculated with the same criteria described in section *Effects of stimulation*).

Results indicated that tDCS applied to the specific, perilesional Parietal area was more efficacious than non-specific stimulation applied to the Occipital cortex (Z=-2.072, p=0.038).

In addition, for each stimulation site (specific and non-specific), the 3 blocks were compared by means of a Friedman Test (Time: 1st; 2nd; 3rd), with direct Wilcoxon post-hoc analyses. Only in the specific Parietal Stimulation Condition was the improvement significantly different between the 3 blocks (Friedman $\chi^2_{(2)}$=5.801, p=0.055). In fact, the improvement was more impressive in the A1 (Z=-1.988, p=0.046) and A2 blocks (Z=-2.516, p=0.012) than in A3. In contrast, there were no differences between the three A blocks in the non-specific Occipital Stimulation condition (Figure 4).

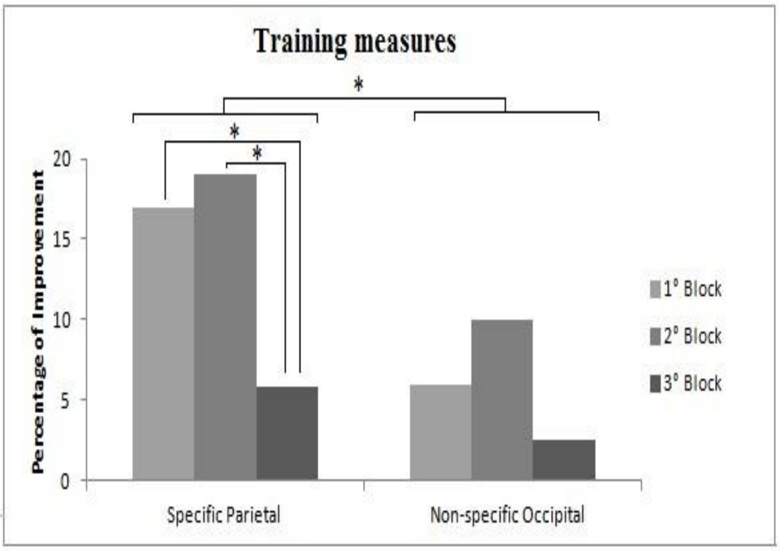


Figure 4. **Measure of Specificity of the stimulation site.** A comparison between the scores relating to Parietal (specific) and Occipital (non-specific) stimulation in the three blocks of stimulation to each site. Significant direct contrasts are reported. *:<0.05

Discussion

In this single case study, the effects of a tDCS programme on the recovery of a patient suffering from TA were investigated. Furthermore, specific perilesional stimulation was compared to stimulation applied to a site far from the patient’s lesion, i.e. a site which was not involved during the tasks performed. In a 6-week-ABABAB paradigm, the patient alternated a week of occupational/neuropsychological rehabilitation with a week where these activities were associated with anodal tDCS stimulation. This was repeated three times. Results indicate that tDCS enhanced US’s performance in tasks involving the tactile recognition of objects. Crucially, the patient's performance improved after specific tDCS stimulation in the perilesional Parietal area as compared to stimulation in a non-specific Occipital area. This recovery lasted until the follow up assessments at 20 days and 6 months after the end of the intervention. These results suggest that a-tDCS stimulation on perilesional areas can support the recovery of impaired abilities and supports traditional rehabilitation, facilitating processes of learning with long-term effects.

Phenomenology and neural correlates of Tactile Agnosia. To better understand the nature of US’s deficits, an in depth assessment of TA was carried out and the patient’s symptoms were compared with the information emerging from an analysis of his lesion. Disorders in the perception of touch, pressure, vibration and temperature were excluded. In addition, following assessment by means of Delay's categorization[54], it was established that US was not impaired in the recognition of the size and shape of objects (amorphognosia) or in the discrimination of specific features relating to objects, such as weight, texture or temperature (ahylognosia). The patient was also able to describe objects in detail after manipulation with his left hand, but he could not identify them in semantic terms or describe their function (tactile asymboly), that is, he was unable to name objects or mime their use. We excluded the possibility of language deficits as US was able to name the objects that he had manipulated or drawn after manipulation with his right hand. Even though he was able to draw (and also describe) all of the object's individual features, he was unable to identify the object manipulated with his left hand and thus also to represent it correctly in a drawing.

It is somewhat difficult to understand the role of motor ability in object recognition and to ascertain whether poor manipulation might lead to a failure to recognise an object or vice versa.[4] Nevertheless, US did not present with any specific motor disorders during manipulation. At times the subject reduced the speed of manipulation but this was exclusively in order to focus his attention on the task.

Another aspect to consider is that lesions in the right parietal cortex are often associated with spatial disorders. We excluded this possibility in US. Although in the first days after the stroke he found it difficult to explore the area of space to his left hand side, this deficit had totally resolved itself at the moment of this study.

Our hypothesis is that US presented with left hand unilateral Associative TA,[7] namely a specific problem regarding the recognition and semantic representation of the objects that he explored with his left hand. These symptoms are due to a disconnection between the primary somatosensory cortex and the networks involved in the superior processes associated with object identification[4] or between these latter and the semantic memory system.[8]

According to previously reported cases of Associative TA,[4,9,11,17] US's brain damage mainly involved the right hemisphere in the supra-marginal gyrus, the inferior parietal cortex, the angular cortex, the insula and the temporal cortex. In addition, the rolandic operculum and the post-central gyrus were damaged.

There was also a small amount of damage to the tapetum of the corpus callosum. A similar lesion (specifically in the splenium) was reported in a case of tactile anomia.[55] This is a deficit due to the disconnection between intact tactile and impaired verbal processes and it is characterised by difficulties in naming and verbally describing objects after manipulation. Nevertheless, this typically spares the ability to pantomime the use of an object. In contrast, as reported, US was able to describe in detail the features of an object, but he was unable to mime its use. Furthermore, he did not manifest any other deficits associated with tactile anomia, such as finger anomia[18] or dysgraphia.[6] US's lesions also included subcortical white matter, in particular the superior longitudinal fasciculus and the posterior and superior corona radiate. The superior longitudinal fasciculus is one of the intra-hemispheric white matter tracts that connect the posterior and anterior networks involved in attentional processes.[57,58] This might explain the dysfunctional signs relating to attention and executive functions that US showed in some attentional tests (TEA, Stroop, PASAT, Tower of London, BADS) and in everyday life activities where he showed hesitation (e.g. when approaching new tasks) and uncertainty (e.g. when planning and organising multiple tasks).

In addition, these subcortical lesions may have damaged the connections between parietal (SII, inferior parietal and posterior associative areas) and frontal (prefrontal, SMA, premotor, FEF) cortices, which are active in normal people during tactile recognition tasks.[4,10,59,60]

Finally, a ventral pathway (connecting SI, SII, insula and medio-temporal areas) is involved in the non-specific modality of object recognition, as shown in memory tasks regarding the shape of objects,[61] object discrimination [2] and the integration of different modalities in object recognition.[3] It is thus possible that US's lesion affects these connections between ventral, parietal and frontal areas.[60]

Taken as a whole these data suggest that US suffered from Associative TA.

The effects of a tDCS programme in the rehabilitation of TA. The application of tDCS in rehabilitation programmes is relatively recent and to date only a few studies have investigated the efficacy of this stimulation when associated with a specific rehabilitation programme for brain damaged patients (e.g. [22,64-66]). In line with these previous studies, we proposed a programme involving repeated tDCS sessions (over several days) in order to monitor the additive effects of stimulation.[22,66]

In addition, we analysed the potentially different impact of tDCS on US's performance comparing two different stimulation sites.

In the comparison between the B blocks (in which US only participated in occupational/neuropsychological therapy) and the A Blocks (in which standard rehabilitation was associated with brain stimulation) the latter produced better results.

We can thus conclude that for this patient, tDCS enhances the effects of rehabilitation, with prolonged long term effects as confirmed in the two follow-up checks.

We exclude the possibility of a spontaneous recovery as, although US was in the acute phase after the lesion onset, his deficits in object recognition were stable at the three measurements carried out before the experimental baseline. Moreover, his results were not influenced by other sensory-motor factors since the rehabilitation activities he carried out were identical in blocks A and B and the stimulation was administered off-line (i.e. not contemporary with occupational/neuropsychological rehabilitation).

The tDCS programme we devised was relatively long and this probably facilitated the resulting long term potentiation (LTP).[67] Specifically, off-line anodal tDCS stimulation affects the neuronal membrane depolarisation by means of the involvement of glutamatergic N-methyl-Daspartic (NMDA) receptors that, subsequently, activate LTP mechanisms.[68,69] In fact, off-line stimulation is usually applied for its neuroplasticity effects in experimental and clinical populations suffering from neuropsychiatric disorders (e.g. depression, chronic pain and stroke rehabilitation).[70]

Finally, we exclude any potential effects of adaptation to stimulation. Post stimulation effects have been reported elsewhere,[71] but the improvement gained by the subject in our study was maintained even though our paradigm included long intervals without tDCS (one-week blocks B1, B2 and B3).[72,73]

The results of the comparison we made between the two stimulation sites indicate that tDCS is more efficacious when applied to the perilesional Parietal area than the Occipital area. By analysing the subject’s performance in each condition, his improvement after P4 stimulation was more evident in the first two blocks (A1 and A2) than in the last week of training (A3). Nevertheless, it is worth noting that in week A3 US’s performance was quite good even before training and this might have reduced the possibility of recording further improvement in this specific block.

A smaller improvement, especially in the first two blocks, was also recorded with Occipital stimulation, indicating that non-specific stimulation may also affect neuro-modulation, although less than with specific perilesional stimulation.

We chose not to use a sham stimulation condition in this study since the patient was very sensitive to any changes in the intensity of the stimulation and quickly understood when the stimulation was not real. In any case we consider that it is useful to compare different areas of stimulation in order to understand the importance of a focused stimulation, as has recently been discussed in other studies.[74]

Our analysis of US's lesion indicated that the area corresponding to P4 is in a perilesional position in the right posterior parietal cortex (PPC). This was the site which was used in previous studies regarding tDCS stimulation with brain-damaged patients, in particular in rehabilitative training for neglect[65] and apraxia.[5] In fact, PPC corresponds to the area between the superior and inferior parietal cortices, in the parietal-frontal network - an area which is often disconnected in TA.[11,15,76,7715] For this reason, we suggest that stimulation to PPC might have modulated the increased activity in the spared tissue around the lesion.

It has been suggested that PPC has a role in supporting the recognition of objects in general since it is involved in the integration of the various different features which make up an object.[78] In addition, anodal tDCS on the right perilesional PPC enhances sensory-motor networks.[65] Thus, we cannot exclude the possibility that in our study tDCS stimulation affected the perception of the objects thereby increasing the efficacy of manipulation.[4]

PPC also plays a role in top-down attentional mechanisms,[79,80] in particular in the visuo-spatial network.[58] Nevertheless, US presented with very good attentional abilities and we therefore exclude the possibility that the progress he made depended on attentional factors.

The main limitation of this study is that it involves only one individual patient whose performance is not comparable with those of control subjects due to the ease of the task for healthy people. Thus, we do not know if stimulation applied to other patients with similar symptoms would have the same effect and it is in fact very difficult to find similar subjects due to the fact that the deficit is highly specific. Nevertheless, at the beginning of the rehabilitative programme carried out in a sub-acute phase, US's TA was stable thus excluding the hypothesis of a spontaneous recovery.

Another potential limitation is that this paradigm did not include a proper sham condition but compared two stimulation sites with each other and two conditions involving the presence or absence of tDCS stimulation and traditional rehabilitation. Even if this is not a typical administration, this procedure allowed us to identify the effects of specific perilesional stimulation.

In conclusion, the results of this study suggest that, at least in the case of this patient, specific perilesional stimulation can support rehabilitation by enhancing perceptual, representational object related processes. Further studies are needed in order to understand the potentially greater efficacy of paradigms involving online specific-stimulation administered during the execution of ad-hoc tasks.

Clinical messages

- anodic tDCS increases the efficacy of rehabilitation in a patient with Tactile Agnosia after ischemic stroke.
- Specific anodic tDCS on perilesional areas is more efficacious than non-specific stimulation for patients recovering from Tactile Agnosia and it represents a useful tool to be used in rehabilitation after strokes.

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