

Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a systematic review of the literature

M. D. Orfei,¹ R. G. Robinson,² G. P. Prigatano,³ S. Starkstein,⁴ N. Rüsçh,¹ P. Bria,⁵ C. Caltagirone^{1,6} and G. Spalletta^{1,6}

¹IRCCS Santa Lucia Foundation, Laboratory of Clinical and Behavioural Neurology, Rome, Italy, ²The University of Iowa Carver College of Medicine, Iowa City, IA, USA, ³Barrow Neurological Institute, Phoenix, ⁴University of Western Australia and Fremantle Hospital, Fremantle, ⁵Catholic University of the Sacred Heart, Rome and ⁶Department of Neuroscience, University of Rome "Tor Vergata", Rome, Italy

Correspondence to: Gianfranco Spalletta, MD, IRCCS Santa Lucia Foundation, Laboratory of Clinical and Behavioural Neurology, Via Ardeatina, 306. 00179 Rome, Italy
E-mail: g.spalletta@hsantalucia.it

Anosognosia is the lack of awareness or the underestimation of a specific deficit in sensory, perceptual, motor, affective or cognitive functioning due to a brain lesion. This self-awareness deficit has been studied mainly in stroke hemiplegic patients, who may report no deficit, overestimate their abilities or deny that they are unable to move a paretic limb.

In this review, a detailed search of the literature was conducted to illustrate clinical manifestations, pathogenetic models, diagnostic procedures and unresolved issues in anosognosia for motor impairment after stroke. English and French language papers spanning the period January 1990–January 2007 were selected using PubMed Services and utilizing research words stroke, anosognosia, awareness, denial, unawareness, hemiplegia. Papers reporting sign-based definitions, neurological and neuropsychological data and the results of clinical trials or historical trends in diagnosis were chosen. As a result, a very complex and multifaceted phenomenon emerges, whose variable behavioural manifestations often produce uncertainties in conceptual definitions and diagnostic procedures. Although a number of questionnaires and diagnostic methods have been developed to assess anosognosia following stroke in the last 30 years, they are often limited by insufficient discriminative power or a narrow focus on specific deficits. As a consequence, epidemiological estimates are variable and incidence rates have ranged from 7 to 77% in stroke. In addition, the pathogenesis of anosognosia is widely debated. The most recent neuropsychological models have suggested a defect in the feedforward system, while neuro-anatomical studies have consistently reported on the involvement of the right cerebral hemisphere, particularly the prefrontal and parieto-temporal cortex, as well as insula and thalamus. We highlight the need for a multidimensional assessment procedure and suggest some potentially productive directions for future research about unawareness of illness.

Keywords: stroke; anosognosia; awareness; denial; hemiplegia

Received December 23, 2006. Revised March 9, 2007. Accepted April 12, 2007

Introduction

One of the most fascinating phenomena of the human mind is consciousness, that is, the psychological function by which all individual cognitive experiences about the self and the external world are integrated. In a number of neuropsychiatric disturbances this function is impaired (Flashman, 2002), causing interference with personal identity or altering attention or awareness. One such alteration is the apparent unawareness of impairment

which was referred to by Babinski (1914) as anosognosia (a-noso-gnosia Greek for 'non illness knowledge'). Anosognosia is generally and comprehensively defined as a disorder in which a patient, affected by a brain dysfunction, does not recognize the presence or appreciate the severity of deficits in sensory, perceptual, motor, affective or cognitive functioning (Bisiach and Geminiani, 1991; Prigatano, 1996; Antoine *et al.*, 2004). The term anosognosia is most frequently used to refer only to the unawareness of

Table 1 Conceptualizations and definitions of anosognosia

Authors	Anosognosia
Babinski (1914)	The apparent lack of awareness of hemiplegia following an acute brain lesion
Heilman <i>et al.</i> (1998), Prigatano (1996)	Clinical phenomena in which a brain dysfunctional patient is not aware of impaired neurological or neuropsychological function, which is obvious to the clinician and other reasonably attentive individuals. The lack of awareness appears specific to individuals deficits and cannot be accounted for by hyperarousal or widespread cognitive impairment
Antoine <i>et al.</i> (2004)	The impaired ability to recognize the presence or appreciate the severity of deficits in sensory, perceptual, motor, affective or cognitive functioning
Samsonovich and Nadel (2005)	Reversible alteration of the autobiographical memories related to a personal deficit, together with the awareness of these memories (and without any awareness of the alteration)

sensory-motor deficits following brain injury (Davies *et al.*, 2005) and can be observed in cases of hemiplegia, hemianopia and aphasia (Bisiach *et al.*, 1986; Rubens and Garrett, 1991; Heilman *et al.*, 1998; Coslett, 2005). In this review, we will focus on anosognosia for hemiplegia, exclusively in the study of stroke patients. However, we will review selected literature from traumatic brain injury (TBI) research and impaired self-awareness (ISA) in other patient groups for their potential sources of information for the understanding of anosognosia in hemiplegic stroke subjects and when considering methodological and theoretical issues in studying anosognosia for hemiplegia (Table 1).

The understanding of this disturbance is not only of theoretical interest, but also has clinical implications of great importance. First, it seems to represent a negative prognostic sign, as it can compromise the course of recovery and rehabilitation (Pedersen *et al.*, 1996; Gialanella *et al.*, 2005; Prigatano, in press); secondly, the study of anosognosia for hemiplegia following stroke can significantly contribute to our understanding of higher cognitive functions and consciousness (Pia *et al.*, 2004). Our goals are to compare different pathogenetic models, to examine assessment and diagnostic modalities, to clarify the relationship between anosognosia for hemiplegia in stroke patients and psychological denial and to illustrate issues which still remain unresolved and suggest some directions for future research.

Materials and Method

A detailed search of the literature was conducted. For our purposes, the database was selected using PubMed Services utilizing the keywords: stroke, anosognosia, awareness, denial, unawareness, hemiplegia. We also hand-searched relevant journals. In addition, the bibliographies of all important articles were searched for further publications.

The articles were restricted to English and French language and spanned the period from January 1990 to January 2007. We chose papers reporting sign-based definitions, relevant empirical neurological and neuropsychological data and results of clinical trials. Historically remarkable or conceptually related articles were included as well. All articles cited in this manuscript were judged by M.D.O and G.S. to be relevant and to meet the scientific and conceptual criteria listed.

Results

Matching the keywords 'stroke and anosognosia' 70 articles were selected; other combinations such as 'stroke and awareness' highlighted 566 papers, 'stroke and denial' 43 papers, 'stroke and unawareness' 22 papers and 'stroke and anosognosia and hemiplegia' 28 papers. Most of the papers were published in North America or Europe.

Babinski's work (1914) was the first to use the term 'anosognosia' to identify lack of awareness of a motor deficit, even though the phenomenon had been described by numerous clinicians prior to this time (Vallar *et al.*, 2003). Since that time, anosognosia has been examined primarily in hemiplegia following stroke and TBI. These patients deny their deficit, and overestimate their abilities, they state that they are capable of moving their paretic limb and that they are not different than normal people. If they partially admit impairments, they will ascribe them to other causes (i.e. arthritis, tiredness, etc.). Often, their false belief persists despite logical arguments and contradictory evidence and they may even produce bizarre explanations to defend their convictions (Bisiach *et al.*, 1986; Bisiach and Geminiani, 1991). Anosognosics usually do not show a catastrophic reaction, or desperation feelings about their condition and are unduly optimistic about their prognosis and medical illness. Notably, they may be aware of other illnesses or admit to some non-motor-related impairments. This is an indication of the modality-specific nature of anosognosia for hemiplegia (Ramachandran, 1996) which may also be present in other forms of unawareness of illness (Rüsch and Corrigan, 2002). Other phenomena which may be related to anosognosia for motor impairment include various forms of bodily delusions called somatoparaphrenias. For example, patients may disclaim ownership of their limb (Marcel *et al.*, 2004). Other manifestations include a lack of concern about the deficit, termed anosodiaphoria or a hatred towards it, termed misoplegia. Patients may also show an alteration of awareness in the direction of an overestimation of the extent of the deficit, with exaggerated complaints. These manifestations, however, may be affected by other factors, such as mood disorders, past experiences, current stressors, etc. The empirical research focusing on these disorders

is very sparse, therefore we will not include these phenomena in our definition of anosognosia.

Epidemiology

Empirical studies have reported wide ranging frequencies of anosognosia in patients with hemiplegic stroke.

Classical studies on prevalence rates for anosognosia for motor impairment have ranged from 33 to 58% in stroke victims (Cutting, 1978; Bisiach *et al.*, 1986). In other more recent studies, however, they ranged from 10 to 17% (Appelros *et al.*, 2002, 2003; Baier and Karnath, 2005). This variability is probably related to differences in diagnostic criteria used by different investigators, and differences in time since stroke (Pedersen *et al.*, 1996; Jehkonen *et al.*, 2006). For example, Pia *et al.* (2004) found prevalence rates ranging from 20 to 44% depending upon the time elapsed since brain injury. In fact, several authors noted a progressive recovery from anosognosia for hemiplegia following stroke within the first 3 months, making recovery more probable in the acute phase than in the chronic period (Cutting, 1978; Pedersen *et al.*, 1996; Jehkonen *et al.*, 2000; Marcel *et al.*, 2004). Thus, although one-third of hemiplegic patients may still show anosognosia during the chronic phase of the illness, the time of the assessment is crucial. Another factor in the variable prevalence rates for anosognosia for motor impairment after stroke may be the diagnostic criteria used. For example, Baier and Karnath (2005) found that a number of researchers diagnosed anosognosia when patients scored 1 on the Bisiach's scale, a score assigned when the disorder is reported by the patient only after specific questions. Therefore, the deficit is evident to the subject, but it may be relatively mild and subjectively less prominent to him than other co-occurring symptoms. As a consequence, these authors reported a lower rate of 10–18% of anosognosia in acute or subacute stroke patients based on a score of at least 2 on the Bisiach's scale (Bisiach *et al.*, 1986).

Finally, prevalence variations in epidemiological studies can be influenced also by patient selection bias. It occurs in non-randomized studies and limits their ability to generalize their results as well as understanding the study's outcome (Swenson, 1980; Mark, 1997). As it is evident from Table 2, different researches report findings from different settings, such as rehabilitation and acute hospitals or the community. Moreover, the variability of the data is striking not only among heterogeneous settings, but also among studies conducted in comparable settings. For example, Table 2 shows that anosognosia varies from 8 to 34% in acute hospital studies. It may depend on the breadth of the catchment area of each hospital and the number of beds available for acute stroke patients. The consequence could be that only patients with higher severity of stroke will be admitted. This can increase the probability of diagnosing anosognosia for motor impairment because severity of awareness deficit seems to be

positively correlated with the size of the lesion and therefore with the severity of the stroke and of the motor impairment (Hier *et al.*, 1983a, b; Pedersen *et al.*, 1996; Hartman-Maeir *et al.*, 2003). A good example of reduced patient selection bias is the Copenhagen Study (Jørgensen *et al.*, 1995; Pedersen *et al.*, 1996), where the rate of stroke patients admitted in the acute hospital is 88% of all cases regardless of age, severity and pre-stroke conditions. Thus, this study, although defined as hospital-based, *de facto* can be considered almost community-based. Inclusion criteria constitute another factor potentially influencing epidemiological data. Indeed, decision to include patients with different laterality of lesion, severity of aphasia and pre- and post-stroke dementia (Appelros *et al.*, 2007) may influence the rate of anosognosia for motor impairment. In contrast, no significant differences in frequency of anosognosia have been related to gender or age (Pedersen *et al.*, 1996; Pia *et al.*, 2004; Appelros *et al.*, 2007).

Pathogenesis

Most aetiological hypotheses about anosognosia for hemiplegia in stroke can be subdivided into three themes: neuropsychological models, hemispheric damage models and intra-hemispheric localization models (Frith *et al.*, 2000) (Table 3).

Neuropsychology

Some neuropsychological models consider anosognosia for hemiplegia after stroke to be the consequence of a global cognitive impairment (McGlynn and Schacter, 1989; Levine *et al.*, 1991). Although some relationships between cognitive function and awareness of motor deficit have been demonstrated, recent data do not associate anosognosia for motor impairment after stroke with either global cognitive impairment or a confusional or delirious state (Starkstein *et al.*, 1992; Coslett, 2005). Thus, although global cognitive impairment does not appear to be a major causal factor, it may be a predisposing factor or may lead to greater severity of anosognosia for hemiplegia following stroke (Marcel *et al.*, 2004; Vuilleumier, 2004).

Other researchers have focused on specific cognitive deficits. For instance, Starkstein and colleagues (1992) suggested that anosognosia for hemiplegia after stroke may result from memory impairment. As Marcel and colleagues (2004) argue, it could derive from a failure to transfer new information from working memory into long term memory. Anosognosic patients would be able to recognize their motor and/or sensory deficits when instances demonstrating these impairments occur, but they would fail to integrate them into their body self-image in long-term memory. Inconsistent forms of awareness are not rare in this population of patients. For instance, some subjects may complain they are paralysed and yet attempt bilateral actions, others deny paralysis but accept to stay in bed or in a wheelchair (Marcel *et al.*, 2004; Vuilleumier, 2004).

Table 2 Frequency of anosognosia among patients with hemiplegia

Authors	Setting	Sample	Time elapsed from stroke	Diagnostic tools	Rate of anosognosia
Cutting (1978)	Article not available	100 acute hemiplegic patients	Article not available	Cutting's questionnaire	58% RBD 14% LBD
Bisiach <i>et al.</i> (1986)	Acute hospital	36 RBD	1–37 days	Bisiach's Scale	33%
Starkstein <i>et al.</i> (1992)	Acute hospital	80 stroke patients	2–12 days	Anosognosia questionnaire	34% Total: 10% mild 11% moderate 13% severe
Stone <i>et al.</i> (1993)	Acute hospital	69 RBD 102 LBD	2–3 days	Standardized test battery (not available)	33%
Pedersen <i>et al.</i> (1996)	Acute hospital	566 acute stroke patients	Within 3 days	Bisiach's Scale	21%
Maeshima <i>et al.</i> (1997)	Acute hospital	50 RBD	Within 30 days	Unstructured questions about the deficit	24%
Jehkonen <i>et al.</i> (2000)	Acute hospital	56 RBD	Within 10 days	Cutting's questionnaire	7%
Hartman-Maeir <i>et al.</i> (2001)	Rehabilitation hospital	29 RBD 17 LBD	4–8 weeks	Unimanual and bimanual tasks plus explicit verbal measure	26% total: 17% RBD 9% LBD
Appelros <i>et al.</i> (2002)	Community	349 stroke patients	Within 30 days	Anosognosia questionnaire	17% (<i>n</i> = 48: 15 mild; 8 moderate; 25 severe)
Hartman-Maeir <i>et al.</i> (2003)	Rehabilitation hospital	36 RBD 24 LBD	4–8 weeks;	Patient Competency Rating Scale	77% total: 47% RBD 30% LBD
Farnè <i>et al.</i> (2004)	Rehabilitation hospital	33 RBD	Within 6 weeks	Cutting's questionnaire (adapted version)	31%
Marcel <i>et al.</i> (2004)	Rehabilitation hospital	65 stroke patients	55–79 days	Awareness interview	23% unaware of motor effect 80% unaware of somatosensory defect
Baier and Karnath (2005)	Rehabilitation hospital	72 RBD 56 LBD	Within 15 days	Bisiach's Scale	10%
Berti <i>et al.</i> (2005)	Not available	30 RBD	Within 60 days	Bisiach's Scale	3% affected by anosognosia without neglect; 57% affected by anosognosia with neglect
Appelros <i>et al.</i> (2007)	Community	272 stroke patients	1–4 days	Anosognosia questionnaire	17%

Abbreviations: RBD = right brain damaged patients, LBD = left brain damaged patients.

Table 3 Pathogenetic models of anosognosia in hemiplegia after stroke and TBI

Authors	Hypothesis
	Neuropsychology
Levine <i>et al.</i> (1991)	Hemisensorial deficits (proprioception) and general cognitive impairment (discovery theory)
Heilman (1991), Heilman <i>et al.</i> (1998), Adair <i>et al.</i> (1997)	Feedforward hypothesis: failure to compare planning and execution of an action
Starkstein <i>et al.</i> (1992)	Relationship with impaired attentional and arousal mechanisms; cognitive impairment is merely a predisposing factor
Ramachandran (1995)	Impairment of the right hemisphere 'anomalies detector' in self-perception deputed to set up new schemata for new data contrasting with old self-knowledge
Frith <i>et al.</i> (2000)	Impairment of a control system involving representations of desired and predicted states and models for generating these states
Vallar <i>et al.</i> (2003)	Unawareness of a deficit of intention or movement planning component, rather than, or in addition to, unawareness of a primary motor deficit
Marcel <i>et al.</i> (2004)	Failure to integrate awareness of episodic instances of the deficit in the long-term bodily representation; attentional dismissal leading not to experience parts of one's body as belonging to oneself (detachment, unconcern)
Pia <i>et al.</i> (meta-analysis; 2004)	Consequence of a damage to a fronto-parietal circuit related to motor and space representation (impairment of the spatial computation necessary for the execution of motor acts in space)
Vuilleumier (2004)	Defect in 'ABC' (Appreciation–Belief–Check) functioning
Coslett (2005)	Failure of intention to act in addition to a disruption of sensorial feedback
Davies <i>et al.</i> (2005)	Two-factor theory of delusions: anosognosia is a monothematic delusion, due to neuropsychological anomalies (first factor) and to a cognitive impairment (second factor) which contributes to maintaining the delusion in face of evidences.
	Hemispheric
Bisiach <i>et al.</i> (1986), Gilmore <i>et al.</i> (1992), Starkstein <i>et al.</i> (1992), Carpenter <i>et al.</i> (1995), Pia <i>et al.</i> (2004), Coslett (2005), Karnath <i>et al.</i> (2005), Turnbull <i>et al.</i> (2005)	Right-hemisphere damage
Geschwind (1965)	Disconnection (the lesion isolates the dominant hemisphere from the right non-dominant hemisphere that monitors the integrity of the left side of the body)
Friedlander (1964)	Handedness (the dominant side is more extended in cortical representations. Thus, anosognosia would be less probable following lesions in the left hemisphere)
Gainotti (1997), Davidson <i>et al.</i> (1999), Meador <i>et al.</i> (2000), Turnbull <i>et al.</i> (2005)	Failure of emotional perception and expression (damage of right-side negative emotion system)
	Key cerebral areas in anosognosia after stroke and TBI
Starkstein <i>et al.</i> (1992)	Superior temporal and inferior parietal cortex, basal ganglia, thalamus
Maeshima <i>et al.</i> (1997)	Thalamus, putamen, anterior limb of the internal capsule
Evyapan and Kumral (1999)	Medial or lateral part of the pons (medial or lateral pontine reticular nuclei)
Karussis <i>et al.</i> (2000)	Right thalamus
Pia <i>et al.</i> (meta-analysis; 2004)	Prevalence of fronto-parietal combination of lesions; frequent involvement of basal ganglia or insula
Berti <i>et al.</i> (2005)	Areas primarily involved: dorsal premotor cortex (BA6), BA44, somatosensory area, primary motor cortex
	Structures differentially involved: BA46, insula, inferior parietal lobule
Karnath <i>et al.</i> (2005)	Right posterior insula

This sort of cognitive dissociation is a very intriguing cue, particularly salient when the patient denies the motor deficit when asked to think in 1st person (e.g. 'In your present state, can you...?') but answers correctly when asked to think in 3rd person (e.g. 'If I were in your present

state, could I...?'). This evidence was recently investigated by Marcel and colleagues (2004), who found that nearly a half of stroke patients' answers examined seemed to depend on the form of the questions. The authors do not suggest a definite explanation for this phenomenon, rather they

confine themselves to speaking of an 'implicit knowledge' of the deficit (see also Ramachandran, 1996; Vallar and Ronchi, 2006). The inability to recall and use properly this knowledge, when present, could be traced back to motivational factors or a sort of cognitive dissociation depending on different viewpoints. If this last is the case, however, it is necessary to postulate a more general defect in monitoring one's own consistency in speech.

Focusing on the loss of proprioception, Levine (Levine *et al.*, 1991) developed the 'discovery theory'. In Levine's opinion, the patient cannot perceive himself, nor discover his own physical condition by self-observation due to loss of proprioception, but he also cannot construe this physical impairment due to a general loss of cognitive abilities and mental inflexibility (see also Marcel *et al.*, 2004). However, this model is not able to explain instances of patients showing anosognosia for motor impairment without proprioceptive loss and is inconsistent with the lack of association between anosognosia for hemiplegia and global cognitive impairment (Frith *et al.*, 2000; Davies *et al.*, 2005). The main problem with Levin's theory is that we do not discover our motor problems by self-observation and inference (e.g. a syllogism such as: weak limbs make poor movements, my limb moves poorly, I have a weak limb). The majority of patients are aware of the deficit and do not depend on cognitive deduction.

Other models suggest a defect in comparing the planning of an action and its execution. In healthy subjects, the premotor cortex sends a motor order to the motor, somatosensory and associated cortical areas which work as a comparator (Heilman, 1991; Lu *et al.*, 2000). So, expectations are compared with peripheral feedback during the execution of the movement (Heilman *et al.*, 1998). If feedback from the periphery lacks confirmation of movement, afferent signals would originate only from the premotor cortex and the comparator would interpret these afferents as a motor feedback, resulting in the illusion of movement. Analogous formulations of this model suggest that high-level brain structures produce two types of motor information (Wolpert *et al.*, 1995, 2001). The first consists of a specification of the sequence, force and timing of muscular contractions (*inverse model*); while the second predicts the trajectory of the movement and the final position of the limb (*forward model*). The latter also anticipates the sensory consequences of the movement. An impairment in the execution of the motor plan leads to a mismatch between muscular feedback and the anticipated sensory consequences of the action. This discrepancy usually provides awareness about features of movements. If the subject is unable to produce a motor plan, no muscular feedback would be generated and no mismatch would occur between predicted and actual experiences (Heilman, 1991; Coslett, 2005). According to this model, anosognosia for motor impairment in brain injured subjects should be reinterpreted as unawareness of a deficit in the higher level cognitive functions (intentionality/motor

planning), rather than a failure in realizing the motor deficit *per se* (Frith *et al.*, 2000; Vallar *et al.*, 2003). This theory is also compatible with the association between anosognosia and right-hemisphere lesions. In fact, the right hemisphere has been found to be dominant for intention (Heilman and Valenstein, 1979) for both the right and left sides of the body, while the left hemisphere generates programs only for the right half. Thus, we would reasonably expect a right-brain lesion to have a greater affect on overall motor awareness (Coslett, 2005). However, a sound theory of anosognosia for motor impairment should explain why patients deny or minimize their motor deficits even when not attempting any movement. This suggests that the mechanism of anosognosia for hemiplegia cannot be simply explained by disruption of sensory-motor mechanisms or problems with intentionality. Nor would this theory account for anosognosia in non-motor modalities (e.g. visual field deficit).

Hemispheric localization

The vast majority of patients with anosognosia for hemiplegia following stroke or TBI have a brain lesion involving the right hemisphere (Starkstein *et al.*, 1992; Pedersen *et al.*, 1996; Vallar *et al.*, 2003; Coslett, 2005; Turnbull *et al.*, 2005; Baier and Karnath, 2005). Moreover, when barbiturates are injected into one or the other carotid artery, so that one hemisphere is selectively anaesthetized and subjects suffer weakness of the side of the body opposite to the injection, a higher frequency of unawareness is evident when the barbiturate is injected into the right hemisphere (Bisiach *et al.*, 1991; Gilmore *et al.*, 1992; Adair *et al.*, 1997; Lu *et al.*, 2000; Pia *et al.*, 2004).

Forty years ago two models were proposed to account for this association of anosognosia for sensory-motor deficits with right-hemisphere dysfunction. Friedlander's *handedness hypothesis* (1964) suggested the dominant hemisphere had larger cortical motor and sensory representations. As a consequence, anosognosia for sensory-motor impairment would be less probable following lesions in the left (dominant) hemisphere, as the contralateral body percept would be less damaged. On the other hand, analogous damage in the right (non-dominant) hemisphere would destroy a larger proportion of the left body representation. Friedlander conducted some experiments to support his hypothesis, but they were inconclusive due to methodological problems (Coslett, 2005). On the contrary, Geschwind's *disconnection hypothesis* (1965) postulates an interhemispheric disconnection. The lesion would isolate the dominant (left) hemisphere from the non-dominant (right) hemisphere monitoring the integrity of the left side of the body. Without correct information from the right-hemisphere motor system, the left (verbal) hemisphere would not be aware of the impairment, could not report it verbally and might produce implausible explanations (i.e. confabulation). The same mechanism would be the

core of somatoparaphrenic delusions. Despite the attractiveness of this model, it does not account for various issues (Adair *et al.*, 1997). For instance, the patient does not realize the impairment although he can get information by visual feedback. Likewise, why does the patient not communicate about the deficit other than verbally? Furthermore, there are a minority of anosognosics with lesions of the left hemisphere (Coslett, 2005).

More recently, Ramachandran (1996) suggested that in normal conditions, the left hemisphere is concerned with managing small discrepancies in perception and thought, in order to make daily life consistent and predictable. When the discrepancies are so prominent that they cannot be ignored or adjusted, the right hemisphere creates new mental schemata or modifies the existing ones. In this view, anosognosia for motor impairment after brain injury would be a failure in this functional balance between the two hemispheres.

Other hypotheses focus on the role of the right hemisphere in perception and expression of emotion (Gainotti, 1972; Meador *et al.*, 2000; Borod, 2000). One of the remarkable aspects of anosognosia for hemiplegia is the associated lack of concern or negative emotional response to their deficit. In contrast, many left-side damaged patients display catastrophic reactions to their deficits or at least a low mood (Gainotti, 1972, 1976; Jorge and Robinson, 2002; Robinson, 2003; Turnbull *et al.*, 2005). Starting from these clinical observations, many authors have suggested a hemispheric asymmetry in the regulation of emotions (Sackeim *et al.*, 1982; Davidson and Irwin, 1999). As a consequence, in stroke patients, depression would result from disruption of the left-sided positive emotion system and anosognosia for hemiplegia from disruption of the right-sided negative emotion system (Davidson and Irwin, 1999; Turnbull *et al.*, 2005). This explanation, however, does not account for either the explicit denial of plegia, nor for the hatred sometimes observed in some right hemisphere damaged patients toward the paretic limb (misoplegia). It is also incompatible with cases of depression or fluctuations of mood in patients with right hemisphere injury. Alternatively, the right hemisphere might be preferentially involved in managing emotional behaviour, rather than specialized in negative emotions (Gainotti, 1997). This assertion is consistent with the finding that alexithymia, a particular form of impaired awareness of one's emotional state consisting of the inability to identify, decode or express feelings, is significantly associated with right-hemisphere stroke (Spalletta *et al.*, 2001, 2006).

Specific cerebral areas involved. Several studies have tried to identify characteristics of the lesion which correlate with anosognosia in stroke hemiplegic patients. Interesting data about the severity of stroke and specific cortical and subcortical areas involved in anosognosia emerged. First, significant correlations between anosognosia and size of the

stroke are described and preliminary data highlight the higher prevalence of anosognosia for hemiplegia in stroke patients with lesions with a mean diameter of 5 cm or more (Hier *et al.*, 1983a, b; Pedersen *et al.*, 1996; Hartman-Maeir *et al.*, 2003). Notably, a larger lesion size is correlated with anosognosia for hemiplegia only in right-hemisphere stroke patients, while no significant correlations with anosognosia and characteristics of the lesions were found in left-hemisphere stroke patients (Pedersen *et al.*, 1996; Hartman-Maeir *et al.*, 2003). Similarly, severity of hemiplegia appears higher in anosognosic patients (Appelros *et al.*, 2007). Given this evidence, we could speculate that anosognosia for hemiplegia is the result of impairment of a neuronal circuit involving more cerebral regions. However, an alternative explanation is that poor awareness would not be evident in patients with smaller lesions and milder deficits simply because the deficit itself is less salient and does not impair their daily functioning.

There are interesting suggestions about the role of specific cortical and subcortical structures in anosognosia for motor impairment. Most authors have found a significant correlation between anosognosia for motor impairment and lesions of the fronto-parietal or fronto-parietal-temporal areas (Pia *et al.*, 2004; Berti *et al.*, 2005; Samsonovich and Nadel, 2005). The involvement of frontal lobes in self-awareness has already been suggested by other authors. For instance, Prigatano and Schacter (1991) reported that damages to the anterior medial prefrontal cortex correlated with impaired self-awareness of appropriate social behaviour, judgement and planning and a lack of comprehension of others' mental states, thus enhancing the hypothesis about the role of prefrontal regions in the metacognitive function of self-reflection. Likewise, Samsonovich and Nadel (2005) hypothesized an 'egocentric map' in the prefrontal cortex and an 'allocentric map' in the hippocampus. Finally, Johnson *et al.* (2002) not only confirmed the role of medial prefrontal regions in self-reflection function, but also found that the posterior cingulate plays a role in memory, perception and evaluation of emotional stimuli as well as mediating memory retrieval and emotion in healthy subjects. Pia and colleagues (2004) reported on a meta-analysis of 23 studies published in the period 1938–2001 describing brain-damaged subjects and examining the presence of hemiplegia and anosognosia. Papers reporting on individual lesion sites were selected. The authors found that about 32% of cases with contralateral motor impairment showed anosognosia; 96.4% of these cases had an unilateral lesion (55% involving frontal areas, 55% parietal areas and 31% temporal areas). Although these cortical regions, without subcortical involvement, were all associated with anosognosia, the majority of the cases had multiple lobe involvement (56.2%) particularly fronto-parietal areas. Damage to the frontal system might be related to impairment of the monitoring system for action planning and execution. Thus, frontal involvement together with

concurrent parietal damage could be the core of a deficit in a cortical circuit related to space and motor representation (Berti *et al.*, 2005; see also Rizzolatti *et al.*, 1998).

Berti and colleagues (2005) examined a sample of 30 right-stroke patients with left hemiplegia. Three groups of patients were compared, those with both anosognosia for motor deficit and neglect, those with pure neglect and those with pure anosognosia. The authors found that the presence of anosognosia was characterized by damage to the dorsal premotor cortex [Broadman's areas (BA) 6], BA 44, and the somatosensory and primary motor areas. Other areas differentially involved were BA 46, the inferior parietal lobule and the insula. In particular, BA 3, 4, 6, 44 and the insula appeared to be significantly involved in pure anosognosia. Thus, the motor and premotor cortex, which are involved in the programming of motor acts, when damaged are also involved in anosognosia pathogenesis. Karnath and colleagues (2005) used a neuroimaging technique similar to Berti *et al.* (2005) to find differences in lesion location between anosognosics and non-anosognosics with right-hemisphere stroke and left hemiplegia. The two groups of patients were well-matched for a number of clinical and demographic characteristics which could influence their results. The authors found that the only lesions which discriminated the two groups were located in the right posterior insula. In particular, posterior insula was damaged in all 14 patients with anosognosia and only in 5 out of 13 patients without anosognosia. This result is not surprising, considering the connections between the posterior insula and the primary and secondary somatosensory cortex, premotor and prefrontal cortex as well as the superior and inferior temporal cortex. Karnath and co-workers (2005) hypothesized that lesions of the posterior insula may contribute to a deficit in integrating stimuli related to self-awareness and in determining bodily delusions. The authors specified that each single lesion in the insula was accompanied by variable brain damage surrounding this core pathogenetic area for anosognosia. Specifically they mentioned temporal and parietal cortical areas, basal ganglia and deep white matter. However, in contrast to the Berti *et al.* (2005) results, no lesions in the prefrontal or frontal areas are described.

Possible explanations for the partial discrepancy in the anatomical results of these studies may be differences in patient-selection criteria, and methods of comparison. For instance, Berti and colleagues (2005) grouped their subjects in three subgroups, according to the presence of anosognosia and/or neglect and they tested patients within 60 days from the acute event. In contrast, Karnath and co-workers (2005) matched two experimental groups (i.e. those with or without anosognosia) with respect to several variables, such as age, time elapsed from stroke, size of the lesion, neurological motor-somatosensory symptoms, extinction, hemianopia and presence of neglect and included only very acute stroke patients. Thus, differences in findings between these last two studies may be due to

inclusion criteria used and the time elapsed from the acute event.

Starkstein and co-workers (1992) reported a significantly higher frequency of superior temporal and inferior parietal cortical and thalamic lesions in stroke patients with mild or severe anosognosia for hemiplegia compared to patients with moderate or no anosognosia for hemiplegia, while patients with moderate anosognosia showed a higher rate of lesions involving the basal ganglia compared to patients without anosognosia. The role of the thalamus has raised considerable interest since some authors have noted a high incidence of thalamic stroke in anosognosics. In spite of this, the underlying mechanisms of anosognosia in thalamic stroke are still unclear (Karussis *et al.*, 2000). Furthermore, the medial and lateral parts of the pons may be involved in poor awareness of motor deficit following a brain insult (Evyapan and Kumral, 1999), perhaps based on connections between pontine structures and fronto-parietal cortical areas (Assenova *et al.*, 2006).

Thus, at present, the only hypothesis consistent with current data is that awareness of motor deficit is the product of a complex and wide neural network. It would be naïve to identify a single cerebral area as uniquely responsible for anosognosia for motor impairment following stroke (Appelros *et al.*, 2007).

Anosognosia for hemiplegia and neglect

Neglect (visual and tactile) often co-occurs with anosognosia for motor impairment, mostly following right-hemisphere damage (Caltagirone *et al.*, 1977; Rode *et al.*, 1992; Starkstein *et al.*, 1993; Rode *et al.*, 1998; Buxbaum *et al.*, 2004) and both are good predictors of negative outcome as well. The hemi-inattention syndrome may occur in different forms, such as perceptual, peripersonal, personal or motor (Rode *et al.*, 1998; Buxbaum *et al.*, 2004). Several authors have reported on the prevalence of anosognosia for motor deficit in patients with neglect following right-hemisphere injury. One of the first studies showing cases of double dissociations of anosognosia from personal and extra-personal neglect in stroke patients was published by Bisiach and colleagues (1986). The authors described that anosognosia for hemiplegia cannot be merely ascribed to a form of hemi-inattention to one's own left space, but has to be thought as a functionally independent deficit and that the co-occurrence of anosognosia and neglect should be traced back simply to the accidental involvement of neighbouring cerebral areas (Dauriac-Le Masson *et al.*, 2002). Subsequently, other studies have confirmed and enriched these hypotheses. For instance, Appelros and colleagues (2002) described a sample of 349 stroke patients, in which a sub-group of 279 subjects completed the neglect tests and a sub-group of 276 patients completed the Anosognosia Questionnaire by Starkstein. In the 279 group, 23% showed signs of extra-personal neglect and 8% of personal neglect, while in the 276 group

17% showed signs of anosognosia for motor impairment. The authors, though not specifying the overlap between the two diagnostic groups, asserted that neglect and anosognosia for hemiplegia co-occurred relatively often in the acute stage after stroke. The same authors, in a recent study (Appelros *et al.*, 2007), on the one hand confirmed the previous incidence rate (17%) of anosognosia for hemiplegia in stroke patients, on the other hand found no definite association between anosognosia and neglect. Furthermore, they listed the discrepancies between the two unawareness syndromes, with respect to typical lesion site, age, stroke severity, pre-stroke dementia and mortality rate. Berti and colleagues (2005) reported that 56.7% of their sample were affected both by anosognosia for hemiplegia and by neglect, while 40% were affected by pure neglect and 3.3% by pure anosognosia. The authors speculated that awareness of motor deficit and awareness of personal space were related to different components of a partially common frontoparietal network. As a consequence, if the lesion is large enough to involve both components, anosognosia for motor impairment and neglect would emerge together, while if the damage involves only one of the components, either anosognosia or neglect would emerge. Notably, clinical assessment of neglect usually relies on paper and pencil tests, including drawing, line bisection or cancellation tasks (Azouvi *et al.*, 2002) which do not distinguish different clinical forms of neglect (Azouvi *et al.*, 2003; Appelros *et al.*, 2003). The Catherine Bergego Scale (CBS; see Azouvi *et al.*, 2003), however, focuses on patients' functioning in 10 real-life situations by questions addressed to both the patient and the caregiver, including an evaluation of awareness. Studies on the psychometric properties of the CBS have confirmed its reliability and sensitivity (Azouvi *et al.*, 2002, 2003).

Anosognosia versus denial: behavioural manifestations in different patient populations

Weinstein and Kahn (1955) raised the issue of what role motivation and psychological defense might play in unawareness of physical deficits. In other words, might defective awareness of physical impairment protect patients from depression or other forms of reaction (House *et al.*, 1988)? Actually, refusal to acknowledge illness (i.e. denial of illness) is commonly observed in various medical conditions, such as coronary artery infarction, cancer and other life-threatening illness (Levine *et al.*, 1987; Bisiach *et al.*, 1986; Levine *et al.*, 1991; Fowers, 1992; Goldbeck, 1997; Korte *et al.*, 2003; Korte and Wegener, 2004). Thus, the failure to 'update' the body schema among hemiplegics could be due to a psychological unwillingness to accommodate the paralysed limb into the body image in order to preserve the sense of identity.

Recent clinical observations in this field have drawn a distinction between denial and anosognosia for motor

impairment. Indeed, they are both forms of unawareness with different sources and manifestations (Ramachandran, 1995, 1996; Korte and Wegener, 2004). Denial is presumably due to a psychological process, while anosognosia appears to be due to a neurological lesion. With regard to this issue, some interesting suggestions come from TBI research. Prigatano (Prigatano and Klonoff, 1998; Prigatano, 2005) studying primarily TBI patients admitted in a neuropsychological rehabilitation setting, noted that brain-injured subjects with anosognosia for cognitive deficits appear to lack information about themselves, show perplexity when receiving information about their deficits and even indifference when asked to manage it. On the contrary, patients with denial demonstrate a resistance and sometimes an angry reaction when given feedback about their disability. These findings indicate the importance to study anosognosia versus denial also in subjects with hemiplegia. Furthermore, anosognosia for motor impairment may be less chronic but more stable in its manifestations than denial. Indeed, denial patients tend to ignore for a longer period of time the threatening information about their motor deficit (Havet-Thomassin *et al.*, 2004). However, denial and anosognosia for motor deficit are not mutually exclusive and may interact and overlap over time. In a later stage, when at least partial cognitive functioning recovers, patients may show partial knowledge of the deficit, but they still resist feedback about their disabilities. Often this stage constitutes the rise of denial (Prigatano and Klonoff, 1998).

With respect to anxiety and depression, Fleming and colleagues (1998) found that patients with low awareness of deficits after TBI were less stressed and depressed, while patients with a higher awareness of the deficit were more anxious and depressed. Korte and colleagues (2003) suggested that a depressive reaction would be more likely if the TBI patient used avoidant as compared to denial coping strategies. Furthermore, some authors speculate that, although denial of illness has often been viewed as preventing recovery, in the early phases of recovery it can protect the patient from depression (Levenson *et al.*, 1984; Levine *et al.*, 1987; Godfrey *et al.*, 1993). In the long run, however, it becomes maladaptive, because it prevents the patient from developing more adaptive emotional and cognitive modalities to manage the chronic physical illness (Folks *et al.*, 1988, Goldbeck, 1997; Gialanella *et al.*, 2005).

Something similar to what has been described in TBI subjects could happen in stroke patients. Unfortunately, few studies have focused specifically on this distinction. In particular, Starkstein *et al.* (1992) in a study of the frequency of depression or anxiety among stroke patients with anosognosia for hemiplegia compared to those without showed no significant group differences. Therefore, patients with anosognosia for motor impairment might show perplexity and/or indifference about their motor deficit and denial patients might overreact with depression, anxiety or irritability. The actual presence of

these behavioural manifestations in stroke patients should be further studied.

Assessment

Physicians generally realize a lack of awareness of motor impairment when they ask the patients to use their paralysed or weak limb, or to compare their paretic movements with analogous movements of the healthy limb (Lu *et al.*, 2000; Marcel *et al.*, 2004; Nimmo-Smith *et al.*, 2005). These clinical observations, however, only allow clinicians to detect the presence of anosognosia for the motor deficit, but they do not give any information about its nature or extent. This, in part, led to the development of specific assessment tools for various patient groups (Table 4).

With respect to stroke patients, one of the first instruments for this purpose was Cutting's questionnaire (Cutting, 1978). It includes items about general awareness of the sensory-motor deficit and investigates other related phenomena, such as anosodiaphoria or misoplegia. This questionnaire may be useful at an early diagnostic stage after stroke, but its general questions and its dichotomous classification (aware/unaware) do not suffice to fully understand the phenomenon. Ten years later, Bisiach (Bisiach *et al.*, 1986) published a scale which allows clinicians to evaluate the presence and the degree of anosognosia for sensory-motor deficits on a 4-point scale. Anosognosia, if present, may be classified as mild, moderate or severe. This procedure, though more accurate, may be problematic in some cases. A score of 1 in the Bisiach's measure commonly indicates the mildest level of unawareness of illness. These patients, however, may still show adequate awareness of illness if asked specifically about their motor deficit (Baier and Karnath, 2005). Therefore, cut-off criteria must specify higher severity of sensory-motor anosognosia. In the Anosognosia Questionnaire, developed by Starkstein and colleagues (1992) the subject is asked to answer a series of questions and to perform some actions. The scoring is on a 4-point scale quite similar to Bisiach's procedure. Each question, however, requires the patient to do something which brings out a potential impairment. Feinberg (Feinberg *et al.*, 2000) developed a brief questionnaire quite similar to the previous ones, with initial general questions about the deficit and with progressively more focused items and additional clinical proofs. Other measures investigate self-awareness from a more multifaceted perspective, not focusing solely on patient's awareness of hemiplegic deficits. For instance, the Structured Awareness Interview (Marcel *et al.*, 2004) is a questionnaire consisting of eight main items which are specific and discriminative for unawareness phenomena. Moreover, the evaluation implies a double scoring: a score 1–3 describes the seriousness of the deficit as reported by the subject, and a classification as unaware/aware/inapplicable assesses the reliability of the patient's self-perception.

The questionnaire also asks the patient to estimate his/her ability to perform some unimanual, bimanual and bipedal activities (e.g. combing hair, tying a knot, jumping, etc.).

Some interesting suggestions can be borrowed from the assessment of awareness of deficit following TBI. Usually these scales are not focused on the motor deficit only.

With regard to the distinction between anosognosia and denial, some interesting suggestions are proposed by Prigatano and Klonoff (1998). They developed a double rating scale for patients with moderate to severe TBI: (a) the Impaired Self Awareness Scale to assess the presence/absence and severity of anosognosia for sensory-motor and cognitive deficits and (b) the Denial of Disability Scale to assess the presence/absence and severity of denial. Each subscale consists of a 10-item semi-structured interview regarding the patient's attitudes and behaviours, characterizing anosognosia or denial, respectively. The trait may or may not be present, and consequently a score ranging from 0 (full awareness) to 10 (full unawareness/denial) is assigned. It seems quite complete and discriminative, though a bit complex, since it encompasses various kinds of data, including neuropsychological performances and attitudes preceding the illness.

Levine (Levine *et al.*, 1987) also developed a semi-structured interview to detect a general denial of illness. This interview may be useful in a wide range of medical conditions. The Levine Denial of Illness Scale has been validated and shows good levels of reliability (Jacobsen and Lowery, 1992). It consists of a 24-item questionnaire; each item expresses a particular behaviour or attitude about denial. Some items are similar and consistent with Prigatano's Denial of Disability Scale (Prigatano and Klonoff, 1998). Therefore it could be integrated with other tools specific for anosognosia in hemiplegia following stroke.

Many questionnaires for self-awareness in TBI compare the patient's self-evaluation with the caregiver's or health professionals' reports. For instance, Prigatano and colleagues (1986; see also Borgaro and Prigatano, 2003) developed the Patient Competency Rating Scale (PCRS). It consists of 30 questions addressed both to the patient and to the caregiver. On each item, ratings are made as to 'how much of a problem' the subject would have in completing various activities, on a 5-point Likert scale, from '1—can't do' to '5—can do with ease'. The items cover a wide range of functional abilities, interpersonal skills and emotional status. Likewise, Sherer and colleagues (1998, 2003) developed the Awareness Questionnaire, a three-form interview to administer to the patient, a caregiver and the clinician. On each form, the abilities of the patient to perform various tasks after the injury as compared to before the injury are rated on a 5-point scale ranging from 'much worse' to 'much better'. It is made up of 17 questions spanning cognitive, physical and emotional areas. However, the caregiver may under/overestimate the patient's abilities (see also Starkstein *et al.*, 2006)

Table 4 Assessment of anosognosia in hemiplegia afterstroke and TBI

Areas of investigation	Scaling	Administration	Description
Awareness of the deficit in hemiplegia after stroke			
Cutting's Questionnaire (Cutting, 1978)	Dichotomous classification (having/not having anosognosia); different versions are described	Clinical rating scale	2 Items concerning general unawareness of illness, 7 items concerning unawareness of hemiparesis
Bisiach's scale (Bisiach <i>et al.</i> , 1986)	4-Point scale (0 = no anosognosia, 1 = mild, 2 = medium, 3 = severe)	Clinical rating scale	Three major areas of investigation (motor impairment, somato-sensory impairment and visual-field defect)
Anosognosia Questionnaire (Starkstein <i>et al.</i> , 1992)	4-Point scale (0 = no anosognosia, 1 = mild, 2 = moderate, 3 = severe)	Clinical rating scale	6 Main items plus 5 questions if the denial is elicited
Anosognosia for Hemiplegia Questionnaire (Feinberg <i>et al.</i> , 2000)	3-Point scale (0 = full awareness, 0.5 = partial awareness, 1 = complete unawareness)	Clinical rating scale	10 Items including some clinical tasks
Structured Awareness Interview (Marcel <i>et al.</i> , 2004)	Double scoring (the patient complains: 1 = a major deficit, 2 = a mild to moderate deficit, 3 = no deficit; A = aware, U = unaware, I = inapplicable),	Clinical rating scale	8 Items plus some unimanual, bimanual and bipedal tasks
Post Stroke Depression Rating Scale—Subscale of awareness of illness (PSDRS; Gainotti <i>et al.</i> , 1995)	3-Point scale (1 = full awareness, 2 = partial awareness, 3 = full unawareness)	Clinical rating scale	8 Items detecting awareness of cognitive and/or physical impairment
Assessment of awareness of deficit in TBI			
Patient Competency Rating Scale (PCRS; Prigatano <i>et al.</i> , 1986)	5-point Likert scale (1 = can't do, 5 = can do with ease)	Self-report	Patient/caregiver's form; 30 items to evaluate patient's competency in cognitive, physical and emotional domains
Change Assessment Questionnaire (Lam <i>et al.</i> , 1988)	5-Point Likert scale (1 = strong disagreement, 5 = strong agreement)	Self-report	Three areas of investigation (beginning of the treatment with no awareness, arise of awareness, full awareness and behavioural modification) with eight items each Patient/caregiver's form 20 items
Head Injury Behaviour Scale (Godfrey <i>et al.</i> , 1993)	4-Point Likert scale; double scoring (number of problems and level of distress)	Self-report	
Self-Awareness of Deficits Interview (Fleming <i>et al.</i> , 1996)	4-Point scoring (0 = adherence to reality, 3 = full unawareness)	Clinical rating scale	Three areas of investigation: (1) self-awareness of deficits, (2) self-awareness of functional implications of deficits, (3) ability to set realistic goals Patient's/caregiver's/clinician's forms; 17 items to evaluate a possible change in emotional, physical and cognitive domains after brain injury
Awareness Questionnaire (Sherer <i>et al.</i> , 1998)	5-Point Likert scale (1 = much worse, 5 = much better)	Self-report	
Anosognosia versus Denial			
Levine's Denial of Illness Scale (Levine <i>et al.</i> , 1987)	7-Point Likert scale (0 = no denial, 6 = severe denial)	Clinical rating scale	24 Items to detect behavioural cues of denial of illness
Clinician's Rating Scale for Evaluating Impaired Self-Awareness and Denial of Disability (Prigatano and Klonoff, 1998)	Double scoring (behavioural feature present/absent and 10-point scale: 0 = feature absent, 1 = light, 10 = severe)	Clinical rating scale	Two subscales: Impaired Self Awareness Scale and Denial of Deficit Scale, of 10 items each. Some items require the caregiver's contribution

undermining the reliability of patient versus caregiver ratings (Fleming *et al.*, 1996). Prigatano himself (Prigatano *et al.*, 2005) notes that relatives' reports may be altered by the distress due to the patient's condition and developed an additional questionnaire to get the caregiver's perspective about (a) the nature of the patient's problems (b) the level of distress experienced by the caregiver in helping the patient and (c) the level of the patient's awareness of his own difficulties (Prigatano *et al.*, 2005).

Another worthwhile scale is the Self-Awareness of Deficits Interview (Fleming *et al.*, 1996) in which three major areas of awareness are explored: the general awareness of deficit in its various forms, the functional implications of deficit and the ability to establish realistic goals projected in the future. The questions are a bit generic, but they may be improved by giving some prompts to the patients to focus on specific issues. The semi-structured interview uses a 4-point scoring for each area. Actually, it was developed for TBI patients, but it could be used in stroke patients, as it requires the subject to reflect on potential implications of his deficit.

Other instruments focus more on affective and emotional aspects. One such measure is the Neuropsychology Behaviour and Affect Profile (NBAP; Nelson *et al.*, 1989), which focuses on a range of non-cognitive symptoms: both pre-injury and post-injury self-reports and observer's ratings about behaviour and emotions (Mathias and Coats, 1999). Also the Head Injury Behaviour Scale (HIBS; Godfrey *et al.*, 1993) rates problematic behaviours and the distress they cause. They may augment the information from other instruments which are more specific for anosognosia for hemiplegia following stroke.

Prigatano (1999) has also suggested the need for a scale that assesses the various syndromes of impaired self-awareness. The scale would reflect specific problems of awareness associated with frontal versus parietal versus temporal versus occipital areas of dysfunction. This is a suggestion for future research which may help to solve the question of the cerebral areas damaged in different forms of anosognosia.

Treatment

Although no controlled treatment trials were identified in our search of the literature on anosognosia, Robinson (2004) published a secondary analysis of 24 stroke patients with anosognosia treated with either nortriptyline, fluoxetine or placebo in a double blind study of depression and cognitive recovery following stroke. Active and placebo patients were matched for severity of anosognosia. Mean scores on the Anosognosia scale (Starkstein *et al.*, 1992) prior to treatment were 3.8 ± 1.6 SD for active treatment and 3.8 ± 1.8 for placebo patients. Following 12 weeks of treatment, the placebo-treated patients had a mean score of 5.3 ± 1.5 , significantly greater severity of anosognosia than the active treatment group of 3.8 ± 0.8 (repeated measures

ANOVA $F=4.35$, $df=1, 22$, $P=0.049$). Thus, antidepressants prevented the worsening of symptoms that occurred over 12 weeks in the placebo group.

There is obviously a great need for further studies of treatment of anosognosia following stroke. The most effective treatment modality remains to be demonstrated.

Discussion

By examining and comparing contributions about anosognosia for hemiplegia in stroke patients, the description of a very complex and multifaceted matter emerges, in which different manifestations may be present to various degrees and prevent the development of a single diagnostic entity (Feinberg *et al.*, 2000; Marcel *et al.*, 2004). Thus, the phenomenon of anosognosia for hemiplegia needs further study in order to make the patient's rehabilitation easier and to enrich our knowledge of the processes of self-awareness. Current clinical descriptions emanating from various authors studying different patient groups who show some form of impaired self-awareness, particularly for motor deficit, are quite heterogeneous, because they involve various conceptual and clinical phenomena. For instance, the distinction between anosognosia in stroke hemiplegic subjects and denial has not been unravelled fully. Some hints about this issue are offered by TBI research, which highlights that anosognosia and denial are characterized not only by a different source, but also by specific behavioural manifestations. More research is needed to clarify if these differences can also be found in stroke patients and can therefore be used as diagnostic criteria.

The relationship between anosognosia for motor impairment in stroke patients and some other unawareness conditions (Carota *et al.*, 2005), such as neglect, is still a matter of debate. Most authors report a frequent but not necessary or causal link between anosognosia for hemiplegia and neglect. They hypothesized that different unawareness phenomena may be caused by damage to neighbouring cerebral areas sharing the same vascular distribution (Bisiach *et al.*, 1986; Starkstein *et al.*, 1993; Heilman *et al.*, 1998; Jehkonen *et al.*, 2000; Dauriac-Le Masson *et al.*, 2002; Vuilleumier, 2004; Marcel *et al.*, 2004; Coslett, 2005; Berti *et al.*, 2005). These findings demonstrate that we cannot merely ascribe anosognosia for hemiplegia to a failure in detecting contralateral events (Appelros *et al.*, 2007) as if anosognosia were an aspect of the neglect syndrome. Rather, these hypotheses suggest that anosognosia for hemiplegia and neglect are independent phenomenon based on anatomical correlates. The multilevel and complex nature of unawareness of motor impairment is witnessed by further clinical data. For instance, Ramachandran (1996) described some stroke patients with anosognosia for motor impairment seems unable to recognize similar deficits even in other people. The author (Ramachandran, 1995, 1996; Ramachandran and Rogers-Ramachandran, 1996) suggests that this

phenomenon is due to a double body-map in our mind: one for our own and one for others' body schemata, closely represented in our brain. These clinical observations could be linked to the functions of the mirror neurons (Rizzolatti *et al.*, 1996). This is a demonstration of the fertility of the study of anosognosia.

The neuroimaging studies reveal not only the strong association of anosognosia for hemiplegia with right-hemisphere damage, but also the frequent involvement of prefrontal and parieto-temporal cortical areas, as well as thalamus and insula. Despite these findings, the heterogeneity of neuro-anatomical correlations suggests that diffuse cerebral areas may play a role in self-awareness and that an individual lesion site cannot account fully for anosognosia for hemiplegia.

In addition to the neuro-anatomical studies, many other pathogenetic models have been proposed to explain anosognosia for motor impairment. Some authors have advocated a global cognitive impairment (Weinstein and Kahn, 1955; Levine *et al.*, 1991), others hypothesized a difficulty in integrating or transferring short-term memory experiences into long-term memory schemata (Starkstein *et al.*, 1992; Marcel *et al.*, 2004) and others have hypothesized a loss of proprioception (Levine *et al.*, 1991). Each single model, although pertinent and even intriguing, however, is valid only for a sub-population of anosognosic patients. None of the theories are able to account fully and exhaustively for the phenomenon in its complexity and phenomenological heterogeneity. One of the most advanced models is the feedforward hypothesis, whose original version by Heilman *et al.* (1998) has been repeatedly modified and improved by other researchers. The failure of expectations of an action with its sensory feedback is the core of this model, though, in the original version, it seems more suitable to account for phantom movements than for anosognosia for motor impairment *per se*. In sum, at the moment, no single model accounts for the varieties of clinical presentation and clinical correlates of anosognosia for hemiplegia.

In addition, further development is needed in the diagnostic criteria for anosognosia for motor deficit in stroke. Although a number of tools have been developed to assess this form of anosognosia, improved operational definitions to diagnose it are still needed. Given the high complexity and heterogeneity of awareness phenomena, it could be profitable to borrow suggestions from TBI procedures, such as the comparison between patient's and caregiver's answers. An important aim in clinical research now is not merely to detect the presence/absence of unawareness of motor impairment, but rather to understand the breadth of manifestations and the range of impairments which might be affected by this deficit. Thus, all aspects of unawareness need to be examined, not only from the physical impairment point of view, but also from the social/relational perspective, as well as discriminating

alterations in self-perception and anosognosia from psychological denial. Also, the variety of instruments makes comparisons between studies hard to analyse. For example, the reported rate of anosognosia for hemiplegia in stroke population varies between 8 and 73%. Obviously, as we discussed earlier in this paper, this may be caused by a variety of methodological problems, but more uniform diagnostic and selection/inclusion criteria would allow a greater consistency across studies and a more detailed assessment of anosognosic phenomena.

In conclusion, anosognosia for motor impairment following stroke is an interesting phenomenon which has attracted the attention of many investigators, but fundamental issues of diagnosis, cause, longitudinal course and treatment are all issues which deserve further research. Operational definitions should be defined more sharply and the procedures of assessment should be more comprehensive in order to grasp the multidimensional nature of the phenomenon. Progress in this field can be advanced by analysing hypotheses and data obtained from studies of patients with TBI which may broaden our view of impaired awareness and provide us with new methodologies and a theoretical basis for distinguishing between anosognosia and psychological denial. For instance, more reliable diagnostic tools would improve the recognition of peculiar aspects of the different awareness deficits and might ultimately allow us to treat them more efficiently. Furthermore, differences in diagnostic procedures have led to inconsistencies in our epidemiological data and complicate comparisons between studies. However, the current data base suggests that anosognosia for hemiplegia is a frequent phenomenon which presents a significant obstacle to physical rehabilitation therapy. Furthermore, treatment of awareness deficits is important to the care of patients with stroke and pharmacological, cognitive and behavioural approaches need to be studied in controlled trials. With respect to the etiopathogenesis, factors such as cognitive, behavioural and anatomical abnormalities, can interact and overlap. Studies which examine the interaction of these various factors may lead to the most comprehensive understanding of this disorder. Furthermore, neuro-anatomical substrates of anosognosia for hemiplegia still have to be clarified. In particular the role of single cortical and subcortical structures frequently reported as damaged in anosognosic patients, such as prefrontal, frontal and parietal cortical areas, insula and thalamus should be investigated in more detail. It is likely that unawareness of motor deficit derives from impairment of a cerebral circuit involving more than a single structure and this neuronal network needs to be identified. Thus, in this review, anosognosia for hemiplegia in stroke patients was the major focus, but results from other forms of brain injury could enrich the knowledge about awareness deficits related to hemianopia and aphasia for instance. A better understanding of anosognosia can shed light upon general self-awareness mechanisms and can be fertile for new paths

of research, for example about the role of mirror neurons (Rizzolatti and Craighero, 2004) and other mediators of this mechanism.

References

- Adair JC, Schwartz RL, Na DL, Fennell E, Gilmore RL, Heilman KM. Anosognosia: examining the disconnection hypothesis. *J Neurol Neurosurg Psychiatry* 1997; 63: 798–800.
- Antoine C, Antoine P, Guemouprez P, Frigard B. Awareness of deficits and anosognosia in AD. *Encephale* 2004; 30: 570–7.
- Appelros P, Karlsson GM, Seiger A, Nydevik I. Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. *J Rehabil Med* 2002; 34: 215–20.
- Appelros P, Nydevik I, Karlsson GM, Thorwalls A, Seiger A. Assessing unilateral neglect: shortcomings of standard test methods. *Disabil Rehabil* 2003; 25: 473–9.
- Appelros P, Karlsson GM, Hennerdal S. Anosognosia versus unilateral neglect. Coexistence and their relations to age, stroke severity and cognition. *Eur J Neurol* 2007; 14: 54–9.
- Assenova M, Beneciv Z, Logak M. Anosognosia for hemiplegia with pontine infarction. *Rev Neurol* 2006; 162: 747–9.
- Azouvi P, Samuel C, Louis-Dreyfus A, Bernati T, Bartolomeo P, Beis JM, et al. Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry* 2002; 73: 160–6.
- Azouvi P, Olivier S, de Montety G, Samuel C, Louis-Dreyfus A, Tesio L. Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego Scale. *Arch Phys Med Rehabil* 2003; 84: 51–7.
- Babinski J. Contribution à l'étude de troubles mentaux dans l'hémiplégie organique cérébrale. *Revue Neurol* 1914; 27: 845–7.
- Baier B, Karnath HO. Incidence and diagnosis of anosognosia for hemiparesis revisited. *J Neurol Neurosurg Psychiatry* 2005; 76: 358–61.
- Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, et al. Shared cortical anatomy for motor awareness and motor control. *Science* 2005; 309: 488–91.
- Bisiach E, Vallar G, Perani D, Papagno C, Berti A. Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 1986; 24: 471–82.
- Bisiach E, Geminiani G. Anosognosia related to hemiplegia and hemianopia. In: Prigatano GP, Schacter DL, editors. *Awareness of deficit after brain injury*. New York: Oxford University Press; 1991. p. 17–39.
- Bisiach E, Rusconi ML, Vallar G. Remission of somatoparaphrenic delusions through vestibular stimulation. *Neuropsychologia* 1991; 29: 1029–31.
- Borgaro S, Prigatano GP. Modification of the Patient Competency Rating Scale for use on an acute neurorehabilitation unit: the PCRS-NR. *Brain Inj* 2003; 17: 847–53.
- Borod JC, editor. *The neuropsychology of emotion*. Oxford: Oxford University Press; 2000.
- Buxbaum LJ, Ferraro MK, Veramonti T, Farnè A, Whyte J, Ladavas E, et al. Hemispatial neglect: subtypes, neuroanatomy, and disability. *Neurology* 2004; 62: 749–56.
- Caltagirone C, Miceli G, Gainotti G. Distinctive features of unilateral spatial agnosia in right and left brain-damaged patients. *Eur Neurol* 1977; 16: 121–6.
- Carota A, Diequez S, Boquosslavsky J. Psychopathology of stroke. *Psychol Neuropsychiatry Viel* 2005; 3: 235–49.
- Carpenter K, Berti A, Oxbury S, Molyneaux AJ, Bisiach E, Oxbury JM. Awareness of and memory for arm weakness during intracarotid sodium amytal testing. *Brain* 1995; 18: 243–51.
- Coslett BH. Anosognosia and body representations forty years later. *Cortex* 2005; 41: 263–70.
- Cutting J. Study of anosognosia. *J Neurol Neurosurg Psychiatry* 1978; 41: 548–55.
- Dauriac-Le Masson V, Mailhan L, Louis-Dreyfus A, De Montety G, Denys P, Bussel B, et al. Double dissociation between unilateral neglect and anosognosia. *Revue Neurol* 2002; 158: 427–30.
- Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci* 1999; 3: 11–21.
- Davies M, Davies AA, Coltheart M. Anosognosia and the two-factor theory of delusions. *Mind Lang* 2005; 20: 209–36.
- Evyapan D, Kumral E. Pontine anosognosia for hemiplegia. *Neurology* 1999; 53: 647–9.
- Farnè A, Buxbaum LJ, Ferraro M, Frassinetti F, Whyte J, Veramonti T, et al. Patterns of spontaneous recovery of neglect and associated disorders in acute right-brain damaged patients. *J Neurol Neurosurg Psychiatry* 2004; 75: 1401–10.
- Feinberg TE, Roane DM, Ali J. Illusory limb movements in anosognosia for hemiplegia. *J Neurol Neurosurg Psychiatry* 2000; 68: 511–3.
- Flashman LA. Disorders of awareness in neuropsychiatric syndromes: an update. *Curr Psychiatry Rep* 2002; 4: 346–56.
- Fleming JM, Strong J, Ashton R. Self-awareness of deficits in adults with traumatic brain injury: how best to measure? *Brain Inj* 1996; 10: 1–15.
- Fleming JM, Strong J, Ashton R. Cluster analysis of self-awareness levels in adults with traumatic brain injury and relationship to outcome. *J Head Trauma Rehabil* 1998; 13: 39–51.
- Folks DG, Freeman AM 3rd, Sokol RS, Thustine AH. Denial: predictor of outcome following coronary bypass surgery. *Int J Psychiatry Med* 1988; 18: 57–66.
- Fowers BJ. The Cardiac Denial of Impact Scale: a brief, self-report research measure. *J Psychos Res* 1992; 36: 469–75.
- Friedlander WJ. Body percept, handedness and anosognosia. *Cortex* 1964; 1: 198–205.
- Frith CD, Blakemore SJ, Wolpert DM. Abnormalities in the awareness and control of action. *Phil Trans R Soc London B: Biol Sci* 2000; 355: 1771–88.
- Gainotti G. Emotional behavior and hemispheric side of the lesion. *Cortex* 1972; 8: 41–55.
- Gainotti G. Disorders of the emotional behaviour during cerebral lesions. *Schw Archiv Neurol Neuroch Psychiatrie* 1976; 118: 215–29.
- Gainotti G. Emotional disorders in relation to unilateral brain damage. In: Feinberg TE, Farah MJ, editors. *Behavioral neurology and neuropsychology*. New York: McGraw Hill; 1997. p. 369–90.
- Gainotti G, Azzoni A, Lanzillotta M, Marra C, Rozzano C. Some preliminary findings concerning a new scale for the assessment of depression and related symptoms in stroke patients. *Ital J Neurol Sci* 1995; 16: 439–51.
- Geschwind N. Disconnection syndromes in animals and man. *Brain* 1965; 88: 237–94.
- Gialanella B, Monguzzi V, Santoro R, Rocchi S. Functional recovery after hemiplegia in patients with neglect: the rehabilitative role of anosognosia. *Stroke* 2005; 36: 2687–90.
- Gilmore RL, Heilman KM, Schmidt RP, Fennell EM, Quisling R. Anosognosia during WADA test. *Neurology* 1992; 42: 925–7.
- Godfrey HP, Partridge FM, Knight RG, Bishara S. Course of insight disorder and emotional dysfunction following closed head injury: a controlled cross sectional follow-up study. *J Clin Exp Neuropsychology* 1993; 15: 503–15.
- Goldbeck R. Denial in physical illness. *J Psychos Res* 1997; 43: 575–93.
- Hartman-Maeir A, Soroker N, Katz N. Anosognosia for hemiplegia in stroke rehabilitation. *Neurorehabil Neural Rep* 2001; 15: 213–22.
- Hartman-Maeir A, Soroker N, Oman SD, Katz N. Awareness of disabilities in stroke rehabilitation—a clinical trial. *Disabil Rehabil* 2003; 25: 35–44.
- Havet-Thomassin V, Gardey AM, Aubin G, Legall D. Several factors to distinguish anosognosia from denial after brain injury. *Encephale* 2004; 30: 171–81.
- Heilman KM. Anosognosia: possible neuropsychological mechanisms. In: Prigatano GP, Schacter DL, editors. *Awareness of deficits after brain injury*. New York: Oxford University Press; 1991. p. 53–62.

- Heilman KM, Valenstein E. Mechanisms underlying hemispatial neglect. *Ann Neurol* 1979; 5: 166–70.
- Heilman KM, Barrett AM, Adair JC. Possible mechanisms of anosognosia: a defect in self-awareness. *Phil Trans R Soc London B: Biol Sci* 1998; 353: 1903–9.
- Hier DB, Mondlock J, Caplan LR. Behavioral abnormalities after right hemisphere stroke. *Neurology* 1983a; 33: 337–44.
- Hier DB, Mondlock J, Caplan LR. Recovery of behavioural abnormalities after right hemisphere stroke. *Neurology* 1983b; 33: 345–50.
- House A, Hodges J. Persistent denial of handicap after infarction of the right basal ganglia: a case study. *J Neurol Neurosurg Psychiatry* 1988; 51: 112–5.
- Jacobsen BS, Lowery BJ. Further analysis of the psychometric properties of the Levine Denial Insight Scale. *Psychos Med* 1992; 54: 372–81.
- Jehkonen M, Ahonen JP, Dastidar P, Laippala P, Vilkki J. Unawareness of deficits after right hemisphere stroke: double dissociations of anosognosia. *Acta Neurol Scand* 2000; 102: 378–84.
- Jehkonen M, Laihosolo M, Kettunen J. Anosognosia after stroke: assessment, occurrence, subtypes and impact on functional outcome reviewed. *Acta Neurol Scand* 2006; 114: 293–306.
- Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP. Neural correlates of self-reflection. *Brain* 2002; 125: 1808–14.
- Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *Neurorehabilitation* 2002; 17: 311–24.
- Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støjer M, Olsen T. Outcome and time course of recovery in stroke. Part I: outcome. The Copenhagen stroke study. *Arch Phys Med Rehabil* 1995; 76: 399–405.
- Karnath HO, Baier B, Nägele T. Awareness of the functioning of one's own limbs mediated by the insular cortex? *J Neurosci* 2005; 25: 7134–8.
- Karussis D, Leker RR, Abramsky O. Cognitive dysfunction following thalamic stroke: a study of 16 cases and review of the literature. *J Neurol Sci* 2000; 172: 25–9.
- Kortte KB, Wegener ST, Chwalisz K. Anosognosia and denial: their relationship to coping and depression in acquired brain injury. *Rehabil Psychol* 2003; 48: 131–6.
- Kortte KB, Wegener ST. Denial of illness in medical rehabilitation populations: theory, research and definition. *Rehabil Psychol* 2004; 49: 187–99.
- Lam CS, McMahon BT, Priddy DA, Gehred-Schultz A. Deficit awareness and treatment performance among traumatic head injury adults. *Brain Inj* 1988; 2: 235–42.
- Levenson JL, Kay R, Monteferrante J, Herman MV. Denial predicts favorable outcome in unstable angina pectoris. *Psychos Med* 1984; 46: 25–32.
- Levine J, Warrenburg S, Kerns R. The role of denial in recovery from coronary heart disease. *Psychos Med* 1987; 49: 109–17.
- Levine DN, Calvanio R, Rinn WE. The pathogenesis of anosognosia for hemiplegia. *Neurology* 1991; 41: 1770–81.
- Lu LH, Barrett AM, Cibula JE, Gilmore RL, Fennell EB, Heilman KM. Dissociation of anosognosia and phantom movement during the Wada test. *J Neurol Neurosurg Psychiatry* 2000; 69: 820–3.
- Maeshima S, Dohi N, Funahashi K, Nakai T, Itakura T, Komai N. Rehabilitation of patients with anosognosia for hemiplegia due to intracerebral haemorrhage. *Brain Inj* 1997; 11: 691–7.
- Marcel A, Tegnér R, Nimmo-Smith I. Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. *Cortex* 2004; 40: 19–40.
- Mark DH. Interpreting the term selection bias in medical research. *Fam Med* 1997; 29: 132–6.
- Mathias JL, Coats JL. Emotional and cognitive sequelae to mild traumatic brain injury. *J Clin Exp Neuropsychol* 1999; 21: 200–15.
- McGlynn SM, Schacter DL. Unawareness of deficits in neuropsychological syndromes. *J Clin Exp Neuropsychol* 1989; 11: 143–205.
- Meador KJ, Loring DW, Feinberg TE, Lee GP, Nichols ME. Anosognosia and asomatognosia during intracarotid amobarbital inactivation. *Neurology* 2000; 55: 816–20.
- Nelson LD, Satz P, Mitrushina M, Van Gorp W, Cicchetti D, Lewis R. Development and validation of the Neuropsychology Behavior and Affect Profile. *J Consult Clin Psychol* 1989; 1: 266–72.
- Nimmo-Smith I, Marcel A, Tegnér R. A diagnostic test of unawareness of bilateral motor task abilities in anosognosia for hemiplegia. *J Neurol Neurosurg Psychiatry* 2005; 76: 1167–9.
- Pedersen PM, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Frequency, determinants and consequences of anosognosia in acute stroke. *J Neurol Rehabil* 1996; 10: 243–50.
- Pia L, Neppi-Modona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. *Cortex* 2004; 40: 367–77.
- Prigatano GP. Behavioural limitations TBI patients tend to underestimate: a replication and extension to patients with lateralized cerebral dysfunction. *Clin Neuropsychol* 1996; 10: 191–201.
- Prigatano GP. Principles of neuropsychological rehabilitation. New York: Oxford University Press; 1999.
- Prigatano GP. Disturbances of self awareness and rehabilitation of patients with traumatic brain injury: a 20-year perspective. *J Head Trauma Rehabil* 2005; 20: 19–29.
- Prigatano GP. Anosognosia and the process and outcome of neuro-rehabilitation. In: Stuss DT, Winocur G, Robertson IH, editors. *Cognitive neurorehabilitation: evidence and application*. 2nd edn., Cambridge: Cambridge University Press; in press.
- Prigatano GP, Fordyce DJ, Zeiner HK, Roueche JR, Pepping M, Wood BC, editors. *Neuropsychological rehabilitation after brain injury*. Baltimore: John's Hopkins University Press; 1986.
- Prigatano GP, Schacter DL, editors. *Awareness of deficit after brain injury: clinical and theoretical issues*. New York: Oxford University Press; 1991.
- Prigatano GP, Klonoff PS. A clinician's rating scale for evaluating impaired self-awareness and denial of disability after brain injury. *Clin Neuropsychology* 1998; 12: 56–67.
- Prigatano GP, Borgaro S, Baker J, Wethe J. Awareness and distress after traumatic brain injury: a relative's perspective. *J Head Trauma Rehabil* 2005; 20: 359–67.
- Ramachandran VS. Anosognosia in parietal lobe syndrome. *Conscious Cogn* 1995; 4: 22–51.
- Ramachandran VS. The evolutionary biology of self-deception, laughter, dreaming and depression: some clues for anosognosia. *Med Hypotheses* 1996; 47: 347–62.
- Ramachandran VS, Rogers-Ramachandran D. Denial of disabilities in anosognosia. *Nature* 1996; 382: 501.
- Rizzolatti G, Fadiga L, Gallese V, Fogassi L. Premotor cortex and the recognition of motor actions. *Cogn Brain Res* 1996; 3: 131–41.
- Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. *Electroencephal Clin Neurophysiol* 1998; 106: 283–96.
- Rizzolatti G, Craighero L. The mirror-neuron system. *Ann Rev Neurosci* 2004; 27: 169–92.
- Robinson RG. Poststroke depression: prevalence, diagnosis, treatment and disease progression. *Biol Psychiatry* 2003; 54: 376–87.
- Robinson RG. Anosognosia and denial of illness following stroke. In: Beitman BD, Nair J, editors. *Self awareness deficits in psychiatric patients. Neurobiology, assessment and treatment*. New York: WW Norton & Co; 2004. p. 255–79.
- Rode G, Charles N, Perenin M, Vighetto A, Trillet M, Aimard G. Partial remission of anosognosia for hemiplegia and somatopaphrenia through vestibular stimulation in a case of unilateral neglect. *Cortex* 1992; 28: 203–8.
- Rode G, Perenin MT, Honore J, Boisson D. Improvement of the motor deficit of neglect patients through vestibular stimulation: evidence for a motor neglect component. *Cortex* 1998; 94: 253–61.
- Rubens AB, Garrett MF. Anosognosia of linguistic deficits in patients with neurological deficits. In: Prigatano GP, Schacter DL, editors. *Awareness of deficit after brain injury: clinical and theoretical issues*. New York: Oxford University Press; 1991. p. 40–52.

- Rüsch N, Corrigan PW. Motivational interviewing to improve insight and treatment adherence in schizophrenia. *Psychiatric Rehabil J* 2002; 26: 23–32.
- Sackeim HA, Greenberg MS, Weiman AL, Gur RC, Hungerbuhler JP, Geschwind N. Hemispheric asymmetry in the expression of positive and negative emotions. Neurologic evidence. *Arch Neurol* 1982; 39: 210–8.
- Samsonovich AV, Nadel L. Fundamental principles and mechanism of the conscious self. *Cortex* 2005; 41: 669–89.
- Sherer M, Bergloff P, Boake C, High W, Levin E. The awareness questionnaire: factor structure and internal consistency. *Brain Inj* 1998; 12: 63–8.
- Sherer M, Hart T, Nick TG. Measurement of impaired self-awareness after traumatic brain injury: a comparison of the Patient Competency Rating Scale and the Awareness Questionnaire. *Brain Inj* 2003; 17: 25–37.
- Spalletta G, Pasini A, Costa A, De Angelis D, Ramundo N, Paolucci S, et al. Alexithymic features in stroke: effects of laterality and gender. *Psychos Med* 2001; 63: 944–50.
- Spalletta G, Ripa A, Bria P, Caltagirone C, Robinson RG. Response of emotional unawareness after stroke to antidepressant treatment. *Am J Ger Psychiatry* 2006; 14: 220–7.
- Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Anosognosia in patients with cerebrovascular lesions. A study of causative factors. *Stroke* 1992; 23: 1446–53.
- Starkstein SE, Fedoroff JP, Price TR, Robinson RG. Denial of illness scale: a reliability and validity study. *Neuropsychiatr Neuropsychol Behav Neuro* 1993; 6: 93–7.
- Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A diagnostic formulation for anosognosia in Alzheimer's Disease. *J Neurol Neurosurg Psychiatry* 2006; 77: 719–25.
- Stone SP, Halligan PW, Greenwood RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Ageing* 1993; 22: 46–52.
- Swenson WM. Sample selection bias in clinical research. *Psychosomatics* 1980; 21: 291–2.
- Turnbull OH, Evans CE, Owen V. Negative emotions and anosognosia. *Cortex* 2005; 41: 67–75.
- Vallar G, Bottini G, Sterzi R. Anosognosia for left-sided motor and sensory deficits, motor neglect and sensory hemiattention: is there a relationship? *Prog Brain Res* 2003; 142: 289–301.
- Vallar G, Ronchi R. Anosognosia for motor and sensory deficits after brain damage: a review. *Restor Neurol Neurosci* 2006; 24: 247–57.
- Vuilleumier P. Anosognosia: the neurology of beliefs and uncertainties. *Cortex* 2004; 40: 9–17.
- Weinstein EA, Kahn RL. Denial of illness. Symbolic and physiological aspects. Springfield, IL: Charles C Thomas; 1955.
- Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science* 1995; 269: 1880–2.
- Wolpert DM, Ghahramani Z, Flanagan JR. Perspectives and problems in motor learning. *Trends Cogn Sci* 2001; 5: 487–94.