VIEWPOINT

ANOSOGNOSIA: THE NEUROLOGY OF BELIEFS AND UNCERTAINTIES

Patrik Vuilleumier

(Laboratory for Behavioural Neurology and Imaging of Cognition, Departments of Clinical Neurosciences and Physiology, University Medical Center, Geneva)

ABSTRACT

Anosognosia is a common, fascinating, and ill-understood disorder following brain damage, where patients who suffer severe deficits such as hemiplegia may remain unaware of and deny their handicap. Many studies including recent work published in this journal have attempted to determine the neurological, cognitive, and motivational bases of anosognosia. These studies have typically focused on descriptive correlations between anosognosia and various clinical factors, but did not identify a consistent pattern of brain lesion or dysfunction. Rather, the results have emphasized the complex and multifacet nature of anosognosia. This review discusses the implications of existing results, and proposes a general "ABC" framework for anosognosia where various problems in Appreciation, Belief, and Check operations may contribute to abnormal cognitive and affective appraisal of a deficit. New experimental approaches and new therapeutic tools are needed to better understand the neurocognitive mechanisms responsible for our awareness of normal functioning and failures.

Key words: Anosognosia, denial, awareness, neglect, motivation, belief

Anosognosia is a perplexing condition. It can affect patients with various neurological impairments who appear unable to notice and acknowledge the existence of their deficits, often despite blatant evidence for their handicap. Typical examples are hemiplegic patients who may assert that their paralyzed limbs are still functioning normally. Other patients with bilateral cortical blindness may claim that their vision is intact, or amnesics may contend that their memory is excellent (for detailed review see Prigatano and Schacter, 1991; Vuilleumier, 2000). In fact, patients may be anosognosic for virtually any neurological deficit following brain injury, including aphasia (Lebrun, 1987), prosopagnosia (Young et al., 1990), or apraxia (Berti et al., 1996).

Anosognosia for hemiplegia (AHP) is thought to be relatively common, encountered in at least 20-30% of hemiplegics after an acute stroke (Cutting, 1978; Stone et al., 1993). However, we still have a very poor understanding of anosognosia. This is perhaps not too surprising given the heterogeneity of this phenomenon. But more surprisingly, only few systematic studies have been carried out in these patients with the aim of better characterizing the crucial clinical features and their possible underlying cognitive mechanisms. Most existing studies have been descriptive (e.g., examining the correlation with different lesion types, severity of neurological impairment, etc.), whereas experimental investigations have been rare or performed only in a few single cases (for review see Vuilleumier, 2000).

In this issue of Cortex, a paper by Marcel and colleagues provides us with a complex set of new data that revisit many important questions about anosognosia for hemiplegia. Marcel et al. (2004, this issue) rightly considered that we have no secure grip on the characteristics of what has to be accounted for in anosognosia, neither on how to account for it, and therefore wished to remedy this poor knowledge by a systematic investigation in a group of 64 hemiplegic stroke patients. A valuable aspect of this investigation was to employ a number of original experiments that were designed to test specific hypotheses (e.g., general performance monitoring abilities, mental flexibility, first vs third person perspective). Marcel et al. (2004, this issue) point to many interesting tracks that need further explorations. However, this new study also clearly shows that much work remains to be done. The reported results underscore the complex cognitive picture of anosognosic disorders, and raise many new questions in addition to offering tentative answers to some interrogations that have recurrently been debated over the last century. I will review a few of these questions here, and discuss whether existing data can now allow us to incriminate any particular neurological, cognitive, or motivational factors in anosognosia.

What is the Role of Concomitant Neurological Deficits?

A question posed ever since Babinski (1914, 1918, 1924) first described anosognosia for hemiplegia concerns the role of sensory deafferentation, especially proprioceptive loss. An early and reasonable belief based on clinical impression was that a lack of sensory inputs might deprive the patients of direct feedback about their affected limbs' state and impair the conscious representation of their half-body, resulting in "asomatognosia". However, many subsequent

studies (Bisiach et al., 1986; Starkstein et al., 1992) as well as the new report by Marcel et al. (2004, this issue) have shown that anosognosia does not correlate with severity of primary sensory loss. A fascinating case study by Garcin et al. (1938) also showed long ago that a patient's inability to recognize his left hand as his own could resolve without any improvement in proprioceptive sensation, in sharp contrast with a deficit in intentional motor use that appeared much more determinant for the lack of self-hand recognition. Yet, informal clinical impression would still compel many neurologists to believe that prototypical anosognosic patients present with an impaired sensory experience of their affected limbs. This is why Marcel et al. (2004, this issue) and other investigators (Starkstein et al., 1992; Stone et al., 1993; Small and Ellis, 1996) have repeatedly set out to re-examine this issue. However, a question may still remain unsatisfactorily addressed in these studies, namely, what is the type of "sensory loss" that most matters in anosognosia. Obviously, anosognosia is usually not associated with complete sensory deafferentation due to peripheral lesions, although it can occur after brachial plexus damage (Laplane and Degos, 1984) or pedonculopontine stroke (Bakchine et al., 1998) when there is a concomitant confusion or dementia. Perhaps, a more specific sensory deficit or a combination of deficits might play a critical role. For example, allesthesia and tactile extinction appear more often correlated with AHP than true perceptual loss (Vuilleumier, 2000), suggesting a problem in integrating sensory inputs with spatial or bodily representations at a higher-level of processing. Global measures collapsing all sensory functions into a single number on a three-point scale, as employed by Marcel et al. (2004, this issue) and other group studies (Bisiach et al., 1986; Starkstein et al., 1992; Stone et al., 1993; Small and Ellis, 1996) are certainly too crude to provide an appropriate characterization of deficits associated with AHP.

Likewise, a majority of studies including the work by Marcel et al. (2004, this issue) have demonstrated a lack of reliable correlation between the severity of motor loss and the presence of AHP (Cutting, 1978; Starkstein et al., 1992; Small and Ellis, 1996). Here again, however, the most relevant type of motor dysfunction might concern higher-level processes, related to the subjective correlates of action planning and motor intention (Heilman, 1991; Daprati et al., 2000; Frith et al., 2000), rather than just the degree of weakness. In line with earlier observations by Garcin et al. (1938), Heilman and colleagues (Heilman, 1991; Gold et al., 1994; Adair et al., 1997) have suggested that abnormal motor intention might disrupt some "feedforward" signals conveying a subjective sensation of volitional effort, and thus prevent the patient from detecting a mismatch between the required and performed motor action. By analogy, a deficit in initiating and monitoring active memory searches might also contribute to anosognosia for amnesia in some patients (Vuilleumier, 2000). However, EMG measures in patients with AHP suggest that covert planning of actions may still take place (e.g., during mental imagery of bimanual actions) even though patients are unable to execute such actions voluntarily (Hildebrandt and Zieger, 1995). Altogether, these findings suggest that any abnormalities in motor control associated with AHP are likely to implicate a complex representation of intended actions as made available in conscious awareness, rather than just a weaker motor command that can easily be scored on the MRC scale. Indirect measures of motor intention as used by Heilman and colleagues (Heilman, 1991; Gold et al., 1994; Adair et al., 1997) or measures of motor planning in bimanual tasks as proposed by Marcel et al. (2004) and others (Hildebrandt and Zieger, 1995; Ramachandran, 1995) might be more revealing, although tricky to design and interpret. Marcel et al. (2004, this issue) reported that patients with right brain damage and AHP tended to overestimate their bimanual abilities during a structured questionnaire, but since data for unimanual abilities were not reported, it is unclear whether there is anything special to this "bimanual" condition as compared with the basic propensity of patients with AHP to overestimate usage of their contralesional hand alone. It would be interesting to know whether anosognosia for left hand function is exacerbated by imagining or planning concurrent right hand actions.

In this respect, contralesional spatial neglect is a notable suspect in anosognosia. Neglect is a condition where perceptual experience can be suppressed despite well-preserved sensory inputs, and willed action compromised despite well-preserved motor strength. Therefore, contralesional sensory and motor extinction associated with neglect might be more important than elementary sensory or motor loss in excluding information about current states of the limb from the patient's awareness. The results from Marcel et al. confirm several previous studies indicating a consistent correlation between neglect and AHP (for review: Feinberg, 1997; Vuilleumier, 2000; see also Cocchini et al., 2002). However, dissociations have been reported. A few patients with AHP have been observed who showed no signs of personal or extrapersonal neglect (Bisiach et al., 1986; House and Hodges, 1988; Small and Ellis, 1996; Dauriac-Le Masson et al., 2002), and AHP during the Wada test is not consistently accompanied by neglect (Adair et al., 1995). It has been argued that neglect and AHP are two dissociable conditions (Bisiach et al., 1986; Feinberg, 1997; Dauriac-Le Masson et al., 2002). But here too, the measures and criteria used to diagnose neglect vary among the studies, and are probably often insufficient given the large

heterogeneity of neglect-related disorders. First, many tests were too insensitive (e.g., Albert test) or based on a single trial (e.g., Bisiach et al., 1986). Second, traditional tests could potentially be inadequate for assessing those components of neglect that may turn out to be more specifically implicated in anosognosia. It is noteworthy that measures of anosognosia have been found to correlate more strongly with signs of spatial neglect in everyday life than with neglect as measured in conventional test batteries (Azouvi et al., 1996; 2002). Thus far, what seems to have been established is that the severity of spatial neglect revealed on usual tests cannot be sufficient by itself to account for anosognosia (Dauriac-Le Masson et al., 2002); and that a distinction between neglect for personal vs. extrapersonal space (Bisiach et al., 1986) does not help delineate a specific mechanism for AHP (Adair et al., 1995).

One of the conclusions drawn by Marcel et al. (2004) may therefore still be premature. These authors argue that their new findings refute the "discovery theory" of anosognosia proposed by Levine and colleagues (Levine, 1990; Levine et al., 1991). According to this theory, a loss of function does not produce any immediate experience of loss but must be "discovered" by observation or inferred by indirect means, so that an impaired bodily sensation combined with some additional cognitive deficits might eventually lead to persistent unawareness and denial of disease. However, the "discovery theory" did not imply that impaired bodily experience could only result from a complete proprioceptive deafferentation or complete motor paralysis, with concomitant mental confusion or dementia being responsible for anosognosia (although this was assumed to be a common cause, see Levine et al., 1991). The "discovery theory" had a broader scope by suggesting that no single deficit is likely to be responsible for all types of anosognosia, but instead that any neurological dysfunction susceptible to alter the phenomenal experience of a defect might provide the ground out of which anosognosia can develop when permissive cognitive factors are also present (Levine, 1990). A weakness of this broad version of the "discovery theory" is that the determinant conditions for the causal sensory and cognitive disturbances remain under-specified. But in fact, this view agrees with the proposal by Marcel et al. (2004, this issue) that anosognosia may not be an unitary disorder, and perhaps involves different kinds of deficits in different patients.

What is the Role of Concomitant Cognitive Disturbances?

Babinski (1914, 1918) and his students (Barré et al., 1923; Joltrain, 1924; Barkman, 1925) emphasized that anosognosia was not related to global mental confusion or other major intellectual disturbance. Consistent with their clinical assessment, more recent but still crude psychometric tests such as the Mini-Mental State Examination have typically failed to show greater impairment in anosognosic than non-anosognosic patients (Starkstein et al., 1992; 1993; Small and Ellis, 1996; Marcel et al., 2004, this issue). Reasoning tasks based on verbal material may also be preserved (Cocchini et al., 2002). Therefore, it is commonly thought that cognitive disturbances are not a prerequisite of anosognosia (McGlynn and Schacter, 1989; Bisiach and Geminiani, 1991). However, some investigators reported that disorientation (Nathanson et al., 1952; Cutting, 1978), motor impersistence (Hier et al., 1983; Starkstein et al., 1993), and more specific frontal lobe-related deficits in set shifting and flexibility (Levine et al., 1991; Starkstein et al., 1992), might be more frequent in anosognosic patients. Such problems might contribute to the lack of "discovery" of the defect and to denial (Levine, 1990). But it is not clear whether such associations simply reflect a statistical co-occurrence due to the size or site of lesion, rather than truly causal factors.

In this respect, the study by Marcel et al. (2004, this issue) provide interesting data not only because they directly tested the hypothesis of deficient mental flexibility in traditional tests of frontal-lobe function (category sorting task, verbal fluency), but also examined more specifically the ability of patients to flexibly evaluate their own performance, based on expectations and observed outcome, for both sensorimotor and cognitive tasks. No association was found between signs of anosognosia and scores in frontal-lobe tests. However, an interesting pattern emerged from self-evaluation measures. Patients were asked to estimate how many words they thought they could produce in a one-minute fluency task, and how many digits they thought they could repeat back in correct order in a short-term memory task, before they had actually performed these tests. A first finding was that, although AHP was more frequent in patients with right-brain damage (RBD) than those with left-brain damage (LBD), the latter showed a greater overestimation of their performance on these tasks (compared with their actual performance) when they made an estimation prior to being tested. This discrepancy is of course consistent with their performance on such verbal tasks being more likely to be impaired by left hemisphere damage, but more importantly, this also points to the fact that knowledge about one's performance is not directly available to the subject before experiencing its actual execution. A second finding was that the proportion of patients overestimating their performance was higher among those who showed the most severe impairment in digit span, leading Marcel et al.

(2004) to suggest that "overestimation of ability is associated with more severe deficit". As the authors acknowledge, this could result from trivial statistical reasons, because lower performance allows a greater chance of discrepancy with actual ability, especially if people were providing relatively "constant" ratings for their estimated ability. But this also suggests that the patients' estimation may primarily rely on their premorbid expectations and beliefs, much more than on their current state. Finally, a third interesting finding comes from the clever idea of Marcel et al. (2004, this issue) to ask patients to estimate their performance again after having completed these tasks. Now LBD patients showed a significant adjustment of their estimates (i.e., they predicted lower performance), whereas RBD patients showed less flexibility in re-calibrating their judgments based on experience with the task – even though this primarily concerned their verbal capabilities. Moreover, only RBD patients overestimated their motor performance during neurological testing, as well as their ability to execute bimanual tasks (both before and after being asked to attempt some of them). Unfortunately, Marcel et al. (2004, this issue) did not report whether there was any correlation between measures of anosognosia and the failure to learn from experience in the verbal fluency and digit span tasks, in individuals with RBD.

Altogether, these results suggest that anosognosia is not associated with a general lack of mental flexibility or a general tendency to overestimate any deficient abilities. In fact, some patients may deny a deficit such as plegia but still complain of their other neurological problems (Roth, 1949; Bisiach and Geminiani, 1991; Berti et al., 1996). Moreover, self-monitoring of a function is not necessarily compromised by a loss of the function, as also exemplified by amnesics with hippocampal damage who can give accurate self-ratings and "feeling-of-knowing" judgments about their poor memory performance, unlike amnesics with Korsakoff syndrome who deny their memory problem and often confabulate (Shimamura and Squire, 1986; Parkin et al., 1988; Janowsky et al., 1989). Accurate awareness of a deficit seems to require some calibration based on a direct personal experience with the deficit, plus a special type of mental flexibility that is needed to adjust behaviour based on such personal experience. More abstract and cognitive domains of flexibility and reasoning might not necessarily be implicated.

A problem in self-relevant adjustment is revealed by another intriguing finding of Marcel et al. (2004) (see also House and Hodges, 1988), that patients with AHP gave worse estimates of bimanual abilities (on a scale from 0 to 10) when questioned in first-person forms (i.e., "How well would you be able to do this task in your present state?") than when questioned in third-person forms (i.e., "How well would the examiner be able to do this task if he was in your state?"). One interpretation of this dissociation could be that patients with AHP have a more specific deficit in adjusting beliefs about their own personal states than about other people's states, although a lack of concern for consistency (Marcel et al., 2004, this issue) or psychodynamic motivational defence (Weinstein and Kahn, 1953) might potentially also be responsible. In fact, several authors previously emphasized that anosognosia involves "more than a mere ignorance of the paralysis... (but also) an obstinate determination not to accept it" (Barré et al., 1923), often characterized by an "apparent resistance or reluctance" to recognize and acknowledge the deficit (Critchley, 1953; Ullman et al., 1960). The origin of such resistance has still to be elucidated.

What is the Role of Motivational and Emotional Factors?

Following Babinski (1914) who described anosognosia and anosodiaphoria as related disorders on a continuum ranging from a complete lack of acknowledgement to a lack of concern for the deficits, many authors have discussed whether affective factors might be more important than cognitive factors in determining awareness of disease. Such affective components might reflect premorbid personality traits (Weinstein and Kahn, 1953), brain damage (Frederiks, 1985), or a combination of both (Ullman et al., 1960). In particular, Weinstein and colleagues (Kahn 1950, 1953, 1955) put forward the view that anosognosia might result from a motivated defence reaction, including strong needs for self-esteem and inability to cope with failure. According to this view, patients with AHP may know they are paralyzed but refuse to admit this.

Interestingly, a number of findings reported by Marcel et al. (2004, this issue) could be taken to suggest some degree of motivated denial, although the authors carefully avoided making such a claim. First, as mentioned above, patients with RBD showed greater overestimation of their abilities when asked in the first-person rather than third-person form. Second, overestimation of the ability to drive a car was significantly more common in men than women, consistent with cars being socially more important for men than women. Unfortunately, it was not reported whether such overestimation was specifically exaggerated in patients with AHP as compared with those without AHP. Third, patients with AHP (but not others) often gave bizarre answers to justify their failure on motor tasks, with their answers sometimes suggesting implicit knowledge of the deficit (e.g., "I should use a robot", or "My arm has a cold"). Likewise, one of Babinski's patient put the blame on a phlebitis. These observations are reminiscent

of other patients who may deny their left paresis but complain of weakness or paresthesia on their intact right side (Roth, 1949; Gilliatt and Pratt, 1952; Tei, 2000). In fact, such effects seem to imply some degree of residual sensory processing that fails to be correctly integrated within conscious experience of one's own body and own intention. These phenomena may indeed correspond to a form of "clouded awareness" of the deficit, first described by Anton (1899), and resemble the bizarre verbal rationalization sometimes provided by split-brain patients in response to material presented to their right hemisphere (Assal, 1983; Gazzaniga, 1992). Bisiach and colleagues (Bisiach and Geminiani, 1991; Bisiach and Berti, 1995) also remarked that most patients who verbally deny their hemiplegia usually seem to implicitly accept the deficit by staying in a bed or wheelchair.

As Marcel et al. (2004, this issue) suggested, such dissociations and contradictions in the patients' behaviour do not necessarily support the role of psychological defence mechanisms. Inconsistencies between different measures of awareness of the deficit would be problematic only if we had to assume a strict singularity of consciousness – which is an assumption already proven false by numerous neuropsychological observations (Galin, 1992; Gazzaniga, 1992; Marcel, 1993). In fact, similar observations have led several authors to distinguish between different types or degrees of anosognosia, beyond the original distinction with anosodiaphor, e.g., "complete" vs. "incomplete" (Gerstmann, 1942), "obstinate" vs. "appreciative " (Critchley, 1953), "systematic" vs. "partial" denial (Willanger et al., 1981), "verbal" vs. "behavioural" anosognosia (Frederiks, 1985), etc. (for review see Vuilleumier, 2000). In keeping with this, Marcel et al. (2004, this issue) also suggested that different forms of anosognosia might exist, possibly reflecting multiple separate mechanisms. They further suggested that right brain damage may alter emotional and attitudinal processes implicated in self-concern and self-attribution of perceptual experiences, although their study did not include any test specifically designed to probe such emotional processes.

Future studies need to better tackle the role of emotional attitudes of patients in relation to their subjective evaluation and adjustment to the deficit. Contrary to the earlier view of Weinstein and Kahn (1950, 1953, 1955), it is now commonly considered that motivational factors alone cannot account for several aspects of anosognosia, particularly in the sense of unconscious motives to suppress unpleasant thoughts about the deficit (see also Bisiach and Geminiani, 1991; Berti et al., 1996; Vuilleumier, 2000). For instance, a greater frequency after central vs. peripheral paralysis suggests that an inability to cope with emotional consequences of a severe neurological loss is not sufficient, since many peripheral disorders are very invalidating but practically never associated with true denial. Some particular brain states seem required to permit anosognosia. Similarly, a greater frequency in acute vs. post-acute stages also suggests that sustaining more diffuse brain dysfunction may be more critical than having a longer time to realize the severity and persistence of the deficit (although in the longer-term during chronic stages, time may also allow progressive psycho-affective adjustment and better acceptance of illness). Other problems for accounts based on motivated repression or avoidance include the fact that anosognosia can dissociate between different deficits or between different limbs within the same patient (see Bisiach and Geminiani, 1991; Berti et al., 1996). This would require relatively *post-hoc* interpretations to be explained solely in terms of self-esteem protection. In addition, a transient disappearance of anosognosic disturbances during vestibular stimulation (e.g., Cappa et al., 1987; Rode et al., 1992) would suggest that this specific manipulation (known to influence spatial and bodily representations) can also have effects on the motivational needs and tolerance of patients. Finally, several studies using systematic questionnaires have failed to reveal distinctive personality traits in patients with AHP (Levine et al., 1991; Starkstein et al., 1992; Small and Ellis, 1996).

However, affective factors might have been too quickly discarded and remain insufficiently investigated, by contrast with more cognitive factors. Clearly, psychological motivation can induce denial for severe medical illnesses (such as heart disease, cancer, AIDS, etc.) in patients without brain damage (Lewis, 1991; Moyer and Levine, 1998). Normal people also show a "natural bias" to express a positive level of subjective well-being, more than to report negative states (Diener and Diener, 1996), often associated with a tendency to minimize one's own health concerns and risks (Doyle and Youn, 2000). Such tendencies might be unveiled or exaggerated following some brain lesions or some cognitive states (Gagne and Lydon, 2001). Moreover, patients with AHP have been found to rate themselves as less able to admit illness than other patients (Small and Ellis, 1996), and severity of denial of memory disturbances and confabulation in senile dementia may also vary depending on social cultural background (Gainotti, 1975). It is conceivable that distinct patterns of affective and social responses could result from complex interactions between individual predispositions and brain dysfunction (Prigatano, 1992). Emotional disturbances are frequently reported in patients with anosognosia although they are variable, including not only inappropriate cheerfulness and jocularity (Gainotti, 1972) but also apathy (Cutting, 1978; Levine et al., 1991) and depression (Starkstein et al., 1990; 1992). Interestingly, anosognosic patients may report less

frequent experience of fear (Ghika-Schmid et al., 1999) and show an impaired recognition of emotional expressions in faces and voices (Starkstein et al., 1993).

Therefore, rather than an abnormal affective drive to deny a perceived deficit, anosognosia might involve a deficient affective drive to respond to uncertainties about current bodily states or current cognitive abilities (Vuilleumier, 2000). Affective signals can exert substantial influences on cognitive processing and reasoning, and such signals might be necessary to activate some appraisal operations that allow a flexible adjustment of behaviour and beliefs according to novel contingencies (Tiedens and Linton, 2001). Reduced emotional impact of perceived or supposed failure might also contribute to impede "discovery" of the deficit, besides any concomitant failure to monitor and cognitively reason about sensorimotor performance. Clinical impression suggests that many anosognosic patients might exhibit an altered experience of complex affective states akin to surprise, astonishment, or doubt. Damage to specific right hemisphere processes involved in affective evaluation and novelty detection might play a critical role in such problems (Bear, 1982; Ramachandran and Rogers-Ramachandran, 1996) and perhaps explain the greater frequency of anosognosia after right brain lesions. However, since anosognosia can also occur with aphasia following left hemisphere lesions, it remains to determine whether similar mechanisms are implicated in unawareness of speech errors vs unawareness of hemiplegia or unawareness of amnesia. It is also possible that damage to subcortical circuits (e.g. basal ganglia) that are involved both in motivation and in detection of "errors" might lead to an inability to engage self-monitoring processes (Berns et al., 1997; Carr, 2000; Schultz et al., 2000) and to modify belief formation based on novel perceptual experience (Cummings, 1985; Vuilleumier, 2000). Anosognosia would thus appear as the counterpart of a striato-frontal dysfunction associated with obsessive-compulsive disorders, where there is an increased need for repetitive checking of objects or situations that are perceived as uncertain (Pitman, 1989; Lopatka and Rachman, 1995). Instead, patients with anosognosia may placidly accept only partial knowledge about their current states and fail to engage in verification procedures that one would normally carry out when faced with novel or threatening challenges. It would be interesting to learn whether these patients show abnormal responses during error processing conditions that are known to be affected by impaired action-monitoring and basal ganglia dysfunction (Gehring et al., 2000; Falkenstein et al., 2001).

What Do We Need to Know Better?

The study of Marcel et al. (2004, this issue) adds to a wealth of data providing compelling evidence that AHP (and other forms of anosognosia) cannot be explained by a single defective neurological mechanism such a severe deprivation of proprioceptive inputs, loss of motor control, hemispatial or hemipersonal neglect, general lack of mental flexibility, etc. Neither is it easily explained by a unique combination of such deficits, at least as assessed by usual neuropsychological tools (see Cocchini et al., 2002). New directions need to be explored. Many persisting beliefs and uncertainties about the behavioural features of anosognosia will probably not be clarified just by accumulating more data on the prevalence of sensory loss and/or spatial neglect. New approaches using less conventional experimental tests and an improved analysis of pertinent behavioural features may be required to make significant advances. A valuable aspect of the work of Marcel et al. (2004, this issue) is precisely to have begun to employ original tests – and doing so, to complicate further the picture.

Their results point out that some part of the difficulty in understanding "anosognosia" may be due to the difficulty in defining more exactly what is denoted by this term. As they put it themselves: "in so far as anosognosia is taken to be 'unawareness', it is crucial to address the issue of what it is one is aware of (under what description) and the mode or channel of access of such awareness". Thus, different measures (e.g., explicit-verbal vs. implicit-nonverbal) or different questions (e.g., in first vs. third person forms) may yield distinct estimates of anosognosia. Different behavioural manifestations might or might not share a common neuropsychological substrate, as illustrated by the unresolved question of a continuum between "negative" and "positive" symptoms of abnormal awareness of a deficit (Bisiach and Geminiani, 1991), which can range from a lack of complaint, lack of concern, or apparent forgetfulness in some patients, through minimization, rationalization, and frank denial, to delusional somatoparaphrenia in others. This diversity of behaviours raises the question of what really counts as anosognosia, and what is the threshold for accrediting "normal" nosognosia. Over the past century, denial, unawareness, unconcern, and anosognosia all have been used and become interchangeable, yet these different terms might well pinpoint distinct facets of behaviour. An important goal for future research is therefore to refine our definition of the relevant dimensions of anosognosia, and operationalize such definition in terms that can be experimentally tested. A related goal is also to go beyond purely observational and correlative studies, since even a strong correlation between anosognosia and the presence of some neurological variable (e.g., neglect) would not prove any significant causation.

Accordingly, new empirical approaches appear needed. Impaired awareness of deficits after brain

injury might be related to neuropsychological changes not measured by current standard tests (Prigatano and Altman, 1990). Systematic and standardized questionnaires have often been used (Cutting, 1978; Bisiach et al., 1986; Vuilleumier, 2000), allowing an easier assessment and comparison of large groups of patients, but they provide only a crude measure that typically involves a single trial methodology and reduces a complex phenomenology into a single score along a single dimension (e.g., on a 3-point scale). Instead, we may need to break down anosognosia into a multidimensional construct, with more precise cognitive and affective components that are tractable to experimental investigations. To this aim, specific hypotheses should be drawn and tested, concerning the possible neuropsychological mechanisms involved in normal awareness of performance and of failure. Distinct mental capacities contributing to judgments about current states of the self should be teased out and specifically tested in the patients. The fact that a myriad of explanations have already been invoked in anosognosia is perhaps a hint that multiple mechanisms are likely to play a role (Vuilleumier, 2000).

The ABC rudiments of judgments about the self that need to be considered in anosognosia might be tentatively delineated as a basic set of Appreciation, Belief, and Check operations. Different changes in the functioning of these operations might then determine Denial or Doubt for a given state of affairs. Alternatively, patients may fail to appreciate a deficit, or maintain inadequate beliefs, or fail to check the consequences of a deficit, but not deny it when directly confronted with it. This framework would potentially allow for different subtypes of anosognosia. Defect in Appreciation might involve various disorders that can alter the subjective experience of a patient with a specific function (e.g., moving, seeing, remembering), including perceptual deafferentation, neglect, completion, phantom sensation, etc., all of which may concur to prevent a direct first-person knowledge about the deficit (Levine, 1990). Such defects would not necessarily produce anosognosia if Belief and Check operations are engaged in opposition to the abnormalities in appreciation. Conversely, aberrant Belief or deficient Check processes might promote different reactions to a particular experience, eventually triggering either doubt, denial, or even delusion (Halligan and Marshall, 1996). Thus, when confronted with degraded perception or unexplained signals about their performance, patients may be forced to base their judgments on beliefs and expectations, or forced to use indirect verification procedures and flexibly check the validity of available information. Belief and Check operations are especially important when subjects deal with uncertainties about current states, since they must then rely on general heuristics or previous knowledge unrelated to their direct experience. Detecting and responding to uncertainties might implicate specific "metacognitive" processes whose function is precisely to trigger adaptive strategies to cope with the situation (e.g., Check, Doubt), either as a reaction to unexpected feedback cues or in preparation to predicted difficulties in a feedforward manner. A capacity for uncertainty monitoring has been studied in a variety of animals placed in difficult perceptual tasks (Smith et al., 1997) and could be influenced by motivational and reward signals (Shields et al., 1997). New experimental approaches to anosognosia might usefully borrow from such paradigms developed to study uncertainty responses in animals and humans. Other new approaches might exploit knowledge gained in other fields of psychology that deal with the formation of beliefs and attitudes (Ajzen, 2000). Changes in beliefs and attitudes are known to reflect specific cognitive operations that depend on processing of cognitive dissonance and conflicting information, but are also sensitive to a variety of affective factors, as well as personality and social factors (Petty et al., 1997). It is conceivable that an impairment in whatever cognitive operations underlying beliefs and attitudes in normal people might also contribute to Doubt or Denial in patients with brain damage. Furthermore, such constructs are potentially amenable to specific experimental tests and comparison with control data from normal subjects (unlike many other tasks used in anosognosic patients that would be too trivial in normals; see Marcel et al., 2004, this issue).

A final benefit from developing new testable concepts in anosognosia would be the possibility to design experiments directly aiming at influencing the degree of awareness, beliefs, or attitudes in the patient towards their deficit. Initial attempts of this have been made by only a few previous investigators (Vallar et al., 1990; Adair et al., 1997), and by Marcel et al. (2004, this issue) who examined how subjective evaluation of performance changed before and after actual execution of manual tasks. Such approaches are important because they may open the way to new therapeutic strategies for the rehabilitation of patients. Anosognosia has major implications for prognosis and functional recovery, but very few structured principles have been proposed for therapeutic interventions (Prigatano, 1986; Vuilleumier, 2000).

Conclusion

Many speculations and theories have been proposed to account for anosognosia over the last hundred years, yet none of them appear entirely satisfying. Various beliefs and uncertainties about the role of critical neuropsychological features are still unsettled, although there is a rich body of

literature that has delineated a range of phenomena in need of explanations. Marcel et al. (2004, this issue) have now added a few more pieces to this puzzle. Still other speculations and conjectures are hoped for, but these should generate new experiments and new treatments.

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References

ADAIR JC, NA DL, SCHWARTZ RL, FENNELL EM, GILMORE RL and HEILMAN KM. Anosognosia for hemiplegia: Test of the personal neglect hypothesis. *Neurology, 45:* 2195-2199, 1995.

ADAIR JC, SCHWARTZ RL, NA DL, FENNEL E, GILMORE RL and HEILMAN KM. Anosognosia: Examining the disconnection hypothesis. *Journal of Neurology, Neurosurgery and Psychiatry, 63:* 798-800, 1997.

AJZEN I. Nature and operation of attitudes. *Annual Review of Psychology, 52:* 27-58, 2000.

ANTON G. Ueber die Selbstwahrnehmung der Herderkrankungen des Gehirns durch den Kranken bei Rindenbleiheit und Rindentaubheit. *Archiven für Psychiatrie und Nervenkrankenheiten, 32:* 86-127, 1899.

ASSAL G. Non, je ne suis pas paralysée, c'est la main de mon mari. *Schweizer Archiv für Neurologie, Neurochirurgie, und Psychiatrie, 133:* 151-157, 1983.

AZOUVI P, MARCHAL F, SAMUEL C, MORIN L, RENARD C, LOUIS-DREYFUS A, JOKIC C, WIART L, PRADAT-DIEHL P, DELOCHE L and BERGECO C. Functional consequences and awareness of unilateral neglect: Study of an evaluation scale. *Neuropsychological Rehabilitation, 6:* 133-150, 1996.

AZOUVI P, SAMUEL C, LOUIS-DREYFUS A, BERNATI T, BARTOLOMEO P, BEIS JM, CHOKRON S, LECLERCQ M, MARCHAL F, MARTIN Y, DE MONTETY G, OLIVIER S, PERENNOU D, PRADAT-DIEHL P, PRAIRIAL C, RODE G, SIEROFF E, WIART L, ROUSSEAUX M and FRENCH COLLABORATIVE STUDY GROUP ON ASSESSMENT OF UNILATERAL N. Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *Journal of Neurology, Neurosurgery and Psychiatry, 73:* 160-186, 2002.

BABINSKI J. Contribution a l'étude des troubles mentaux dans l'hémiplégie organique (anosognosie). *Revue Neurologique, 27:* 845-848, 1914.

BABINSKI J. Anosognosie. *Revue Neurologique, 31:* 365-367, 1918.

BABINSKI J. Un nouveau cas d'anosognosie. *Revue Neurologique, 40:* 235-254, 1924.

BAKCHINE S, CRASSARD I and SEILHAN D. Anosognosia for hemiplegia after a brainstem haematoma: A pathological case. *Journal of Neurology, Neurosurgery and Psychiatry, 63:* 686-687, 1998.

BARKMAN A. De l'anosognosie dans l'hémiplégie cérébrale: Contribution clinique à l'étude de ce symptome. *Acta Med Scand, 62:* 235-254, 1925.

BARRÉ JA, MORIN L and KAISER J. Etude clinique d'un nouveau cas d'anosognosie de Babinski. *Revue Neurologique, 39:* 500-503, 1923.

BEAR DM. Hemispheric specialization and the neurology of emotion. *Archives of Neurology, 40:* 195-202, 1982.

BERNS GS, COHEN JD and MINTUN MA. Brain regions responsive to novelty in the absence of awareness. *Science, 276:* 1272-1275, 1997.

BERTI A, LADAVAS E and DELLA CM. Anosognosia for hemiplegia, neglect dyslexia, and drawing neglect: Clinical findings and theoretical considerations. *Journal of the International Neuropsychological Society, 2:* 426-440, 1996.

BISIACH E and BERTI A. Consciousness in dyschiria. In Gazzaniga M, *The Cognitive Neurosciences*, Cambridge, MA: MIT Press, 1995, pp. 1331-1340.

BISIACH E and GEMINIANI G. Anosognosia related to hemiplegia and hemianopia. In Prigatano GP and Schacter DL, *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues*, New York: Oxford University Press, 1991, pp. 17-39

BISIACH E, VALLAR G, PERANI D, PAPAGNO C and BERTI A. Unawareness of disease following lesions of the right hemisphere: Anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia, 24:* 471-482, 1986.

CAPPA S, STERZI R, VALLAR G and BISIACH E. Remission of hemineglect and anosognosia during vestibular stimulation. *Neuropsychologia, 25:* 775-782, 1987.

CARR C. Locating an error correction signal for adult birdsong. *Nature Neurosciences, 3:* 419-421., 2000.

COCCHINI G, BESCHIN N and DELLA SALA S. Chronic anosognosia: A case report and theoretical account. *Neuropsychologia, 40:* 2030–2038, 2002.

CRITCHLEY M. *The Parietal Lobes*, New York: Hafner, 1953.

CUMMINGS JL. Organic delusions: Phenomenology, anatomical correlations, and review. *British Journal of Psychiatry, 146:* 184-197, 1985.

CUTTING J. Study of anosognosia. *Journal of Neurology, Neurosurgery and Psychiatry, 41:* 548-555, 1978.

DAPRATI E, SIRIGU A, PRADAT-DIEHL P, FRANCK N and JEANNEROD M. Recognition of self-produced movement in a case of severe neglect. *Neurocase, 6:* 477-486, 2000.

DAURIAC-LE MASSON V, MAILHAN L, LOUIS-DREYFUS A, DE MONTETY G, DENYS P, BUSSEL B and AZOUVI P. Double dissociation between unilateral neglect and anosognosia. *Revue Neurologique, 158:* 427-430, 2002.

DIENER E and DIENER C. Most people are happy. *Psychological Science, 7:* 181-185.

DOYLE KO and YOUN S. Exploring the traits of happy people. *Social Indicators Research, 52:* 195-209, 2000.

FALKENSTEIN M, HIELSCHER H, DZIOBEK I, SCHWARZENAU P, HOORMANN J, SUNDERMAN B and HOHNSBEIN J. Action monitoring, error detection, and the basal ganglia: An ERP study. *Neuroreport, 12:* 157-161, 2001.

FEINBERG TE. Anosognosia and confabulation. In Feinberg TE and Farah MJ, *Behavioral Neurology and Neuropsychology*, New York: McGraw-Hill, 1997, pp. 369-390.

FREDERIKS JAM. Disorders of the body schema. In Frederiks JAM, *Hanbook of Clinical Neurology*, vol. 45, Amsterdam: Elsevier, 1985, pp. 373-404.

FRITH CD, BLAKEMORE SJ and WOLPERT DM. Abnormalities in the awareness and control of action. *Philosophical Transactions of the Royal Society of London, Series B, Biological Science, 355:* 1771-1788, 2000.

GAGNE FM and LYDON JE. Mind-set and close relationships: When bias leads to (In)accurate predictions. *Journal of Personality and Social Psychology ,81:* 85-96, 2001.

GAINOTTI G. Emotional behavior and hemispheric side of the lesion. *Cortex, 8:* 41-55, 1972.

GAINOTTI G. Confabulation of denial in senile dementia. An experimental study. *Psichiatria Clinica, 8:* 99-108, 1975.

GALIN D. Theoretical reflections on awareness, monitoring, and self in relation to anosognosia. *Consciousness and Cognition, 1:* 152-162, 1992.

GARCIN R, VARAY A and DIMO H. Document pour servir à l'étude des troubles du schéma corporel. *Revue Neurologique, 69:* 498-510, 1938.

GAZZANIGA MS. Brain modules and belief formation. In Kessel FS, Cole PM and Johnson DL, *Self and consciousness: multiple perspectives*, Hillsdale: Lawrence Erlbaum Associates, 1992, pp. 88-102.

GEHRING WJ, HIMLE J and NISENSON LG. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science, 11:* 1-6, 2000.

GERSTMANN J. Problems of imperception of disease and of impaired body territories with organic lesions: Relation to body scheme and its disorders. *Archives of Neurology and Psychiatry, 48:* 890-913, 1942.

GHIKA-SCHMID F, VAN MELLE G, GUEX P and BOGOUSSLAVSKY J. Subjective experience and behavior in acute stroke: The Lausanne Emotion in Acute Stroke Study. *Neurology, 52:* 22-28, 1999.

GILLIATT RW and PRATT RTC. Disorders of perception and performance in a case of right-sided cerebral thrombosis. *Journal of Neurology, Neurosurgery and Psychiatry, 15:* 264-271, 1952.

GOLD M, ADAIR JC, JACOBS DH and HEILMAN KM. Anosognosia for hemiplegia: An electrophysiologic investigation of the feed-forward hypothesis. *Neurology, 44:* 1804-1808, 1994.

HALLIGAN PW and MARSHALL JC. The wise prophet makes sure of the event first: Hallucinations, amnesia, and delusions. In Halligan PW and Marshall JC, *Method in Madness: Cases studies in Cognitive Neuropsychiatry*, Hove (UK): Psychology Press, 1996, pp. 237-266.

HEILMAN KM. Anosognosia: Possible neuropsychological mechanisms. In Prigatano GP and Schacter DL, *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues.* New York: Oxford University Press, 1991, pp. 53-62.

HIER DB, MONDLOCK J and CAPLAN LR. I. Behavioral abnormalities after right hemisphere stroke; II. Recovery of

behavioral abnormalities after right hemisphere stroke. *Neurology, 33:* 337-344; 345-350, 1983.

HILDEBRANDT H and ZIEGER A. Unconscious activation of motor responses in a hemiplegic patient with anosognosia and neglect. *European Archives of Psychiatry and Clinical Neuroscience, 246:* 53-59, 1995.

HOUSE A and HODGES J. Persistent denial of handicap after infarction of the right basal ganglia: A case study. *Journal of Neurology, Neurosurger, and Psychiatry, 51:* 112-115, 1988.

JANOWSKY JS, SHIMAMURA AP and SQUIRE LR. Memory and metamemory: Comparisons between patients with frontal lobe lesions and amnesic patients. *Psychobiology, 17:* 3-11, 1989.

JOLTRAIN E. Un nouveau cas d'anosognosie. *Revue Neurologique, 31:* 638-640, 1924.

LAPLANE D and DEGOS JD. Troubles inhabituels du schéma corporel par désafférentation périphérique. *Revue Neurologique, 140:* 45-48, 1984.

LEBRUN Y. Anosognosia in aphasics. *Cortex, 23:* 251-263, 1987.

LEVINE DN. Unawaremess of visual and sensorimotor defects: A hypothesis. *Brain and Cognition, 13:* 233-281, 1990.

LEVINE DN, CALVANIO R and RINN WE. The pathogenesis of anosognosia for hemiplegia. *Neurology, 41:* 1770-1781, 1991.

LEWIS L. Role of psychological factors in disordered awareness. In PRIGATANO GP and SCHACTER DL, *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues*, New York: Oxford University Press, 1991, pp. 223-239.

LOPATKA C and RACHMAN S. Perceived responsability and compulsive checking: An experimental analysis. *Behaviour Research and Therapy, 33:* 673-684, 1995.

MARCEL AJ. Slippage in the unity of consciousness. *Ciba Foundation Symposium, 174:* 168-180, 1993.

MARCEL AJ, TEGNÉR R and NIMMO-SMITH I. Anosognosia for plegia: Specificity, extension, partiality and disunity of unawareness. *Cortex, 40:* 17-38, 2004.

MCGLYNN SM and SCHACTER DL. Unawareness of deficits in neuropsychological syndromes. *Journal of Clinical and Experimental Neuropsychology, 11:* 143-205, 1989.

MOYER A and LEVINE EG. Clarification of the conceptualization and measurement of denial in psychosocial oncology research. *Annals of Behavioral Medicine, 20:* 149-160, 1998.

NATHANSON M, BERGMAN PS and GORDON CG. Denial of illness: Its occurence in one hundred consecutive cases of hemiplegia. *Archives of Neurology and Psychiatry, 68:* 380-387, 1952.

PARKIN AJ, BELL WP and LENG NRC. Metamemory in amnesic and normal subjects. *Cortex, 24:* 141-147, 1988.

PETTY RE, WEGENER DT and FABRIGAR LR. Attitudes and attitude change. *Annual Review of Psychology, 48:* 609-647, 1997.

PITMAN RK. Animal models of compulsive behavior. *Biological Psychiatry, 26:* 189-198, 1989.

PRIGATANO GP. *Neuropsychological rehabilitation after brain injury*, Baltimore: Johns Hopkins University Press, 1986.

PRIGATANO GP. Personality disturbances associated with traumatic brain injury. *J Consult Clin Psychol, 60:* 360-368, 1992.

PRIGATANO GP and ALTMAN IM. Impaired awareness of behavioral limitations after traumatic brain onjury. *Archives of Physical Medicine and Rehabilitation, 71:* 1058-1067.1990.

PRIGATANO GP and SCHACTER DL. *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues*, New York: Oxford University Press, 1991.

RAMACHANDRAN VS. Anosognosia in parietal lobe syndrome. *Consciousness and Cognition, 4:* 22-51, 1995.

RAMACHANDRAN VS and ROGERS-RAMACHANDRAN D. Denial of disabilities in anosognosia. *Nature, 382:* 501, 1996.

RODE G, CHARLES N, PERENIN MT, VIGHETTO A, TRILLET M and AIMARD G. Partial remission of hemiplegia and somatoparaphrenia through vestibular stimulation in a case of unilateral neglect. *Cortex, 28:* 203-208, 1992.

ROTH M. Disorders of the body image caused by lesions of the right parietal lobe. *Brain, 72:* 89-111, 1949.

SCHULTZ W, TREMBLAY L and HOLLERMAN JR. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cerebral Cortex, 10:* 272-284., 2000.

SHIELDS WE, SMITH JD and WASHBURN DA. Uncertain responses by humans and rhesus monkeys (Macaca mulatta) in a psychophysical same-different task. *Journal of Experimwental Psychology-General, 126:* 147-164, 1997.

SHIMAMURA AP and SQUIRE LR. Memory and metamemory: A study of the feeling-of-knowing phenomenon in amnesic patients. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 12:* 452-460, 1986.

SMALL M and ELLIS S. Denial of hemiplegia: An investigation into the theories of causation. *European Neurology, 36:* 353-363, 1996.

SMITH JD, SHIELDS WE, SCHULL J and WASHBURN DA. The uncertain response in humans and animals. *Cognition, 62:* 75-97, 1997.

STARKSTEIN SE, BERTHIER ML, FEDOROFF P, PRICE TR and ROBINSON RG. Anosognosia and major depression in 2 patients with cerebrovascular lesions [see comments]. *Neurology, 40:* 1380-1382, 1990.

STARKSTEIN SE, FEDOROFF JP, PRICE TR, LEIGUARDA R and OTHERS A. Neuropsychological deficits in patients with anosognosia. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 6:* 43-48, 1993.

STARKSTEIN SE, FEDOROFF JP, PRICE TR, LEIGUARDA R and ROBINSON RG. A. Neuropsychological deficits in patients with anosognosia. *Neuropsychiatry, Neuropsychology and Behavioral neurology, 6:* 43-48, 1993.

STONE SP, HALLIGAN PW and GREENWOOD RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age and Ageing, 22:* 46-52, 1993.

TEI H. Right ipsilateral hypersensation in a case of anosognosia for hemiplegia and personal neglect with the patient's subjective experience. *Journal of Neurology, Neurosurgery and Psychiatry, 69:* 274-279, 2000.

TIEDENS LZ and LINTON S. Judgment under emotional certainty and uncertainty: The effects of specific emotions on information processing. *Journal of Personality and Social Psychology, 81:* 973-988, 2001.

ULLMAN M, ASHENHURST EM, HURWITZ LJ and GRUEN A. Motivational and structural factors in the denial of hemiplegia. *Archives Neurology, 3:* 306-318, 1960.

VALLAR G, STERZI R, BOTTINI G, CAPPA S and RUSCONI ML. Temporary remission of left hemianesthesia after vestibular stimulation: A sensory neglect phenomenon. *Cortex, 26:* 123-131, 1990.

VUILLEUMIER P. Anosognosia. In Bogousslavsky J and Cummings JL, *Behavior and Mood Disorders in Focal Brain Lesions*, Cambridge, UK: Cambrige University Press, 2000, pp. 465-519.

WEINSTEIN EA and KAHN RL. The syndrome of anosognosia. *Archives of Neurology and Psychiatry. 64:* 772-791, 1950.

WEINSTEIN EA and KAHN RL. Personality factors in denial of illness. *Archives of Psychiatry and Neurology, 69:* 355-367, 1953.

WEINSTEIN EA and KAHN RL. *Denial of Illness: Symbolic and Physiological Aspects*, Springfield: Charles C Thomas, 1955.

WILLANGER R, DANIELSEN UT and ANKERGUS J. I. Denial and neglect of hemiparesis in right-sided apoplectic lesions; II. Visual neglect in right-sided apoplectic lesions. *Acta Neurologica Scandinavica, 64:* 310-326; 327-336, 1981.

YOUNG AW, DE HAAN EHF and NEWCOMBE F. Unawareness of impaired face recognition. *Brain and Cognition, 14:* 1-18, 1990.

Patrik Vuilleumier, Laboratory for Neurology and Imaging of Cognition, Departments of Clinical Neurosciences and Physiology, CMU, 1 rue Michel-Servet, 1211 GENEVA 4, Switzerland. E-mail: patrik.vuilleumier@medecine.unige.ch