



Review article

Self-awareness and the medial temporal lobe in neurodegenerative diseases

Chantal Chavoix^{a,*}, Ricardo Insausti^b^a Normandie Univ. UNICAEN, INSERM, COMETE, PFRS, 14000 Caen, France^b Human Neuroanatomy Laboratory, School of Medicine and CRIB, University of Castilla-La Mancha, Almansa 14, 02006, Albacete, Spain

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ABSTRACT

Accurate self-awareness is essential for adapting one's behaviour to one's actual abilities, to avoid risky behaviour. Impaired self-awareness of deficits is common in neurodegenerative diseases. Numerous studies show an involvement of midline cortical areas in impaired self-awareness. Among the other brain regions implicated stand the medial temporal lobe (MTL) structures (i.e. hippocampus, amygdala, and temporopolar, entorhinal, perirhinal and posterior parahippocampal cortices). This review aims at evaluating the role of those structures in self-awareness in neurodegenerative diseases. To this aim, we briefly review impaired self-awareness in neurodegenerative diseases, give a neuroanatomical background on the MTL structures, and report those identified in neuroimaging studies on self-awareness. The MTL shows neuropathological, and structural or functional changes in patients who overestimate their abilities in the cognitive, socio-emotional or daily life activities domains. The structures implicated differ depending on the domain considered, suggesting a modality-specific involvement. The functional significance of the findings is discussed in view of the neuroanatomical networks of the MTL and in the context of theoretical models of self-awareness.

1. Introduction

Awareness can be defined as “a reasonable or realistic perception or appraisal of one's situation, functioning or performance, or of the resulting implications, expressed explicitly or implicitly” (Clare et al., 2011). Accurate self-awareness is essential for optimal daily life activities, as it allows adapting individual behaviour to different situations according to one's actual abilities. Accurate self-awareness thus prevents from risky or withdrawal behaviour.

Impaired self-awareness may have significant adverse effects. For instance, overestimation of one's driving or postural abilities increases the risk of driving or fall accident (Morone et al., 2014; Horrey et al., 2015), and overestimation of one's cognitive abilities may negatively impact numerous daily life activities such as managing finances or shopping (Hoofien et al., 2004); likewise, inaccurate estimation of one's social skills may affect social communication. Conversely, underestimation of these same abilities may lead to a loss of autonomy and social isolation. However, overestimation is more common than underestimation of one's abilities (e.g. Michon et al., 1994; Okonkwo et al., 2008). Unawareness of deficits can be detrimental to the rehabilitation of brain damage. It also affects the patient's family and friends' quality of life, namely by increasing the caregivers' burden (Rymer et al., 2002).

Although impaired self-awareness should thus be considered as a symptom of great importance, it is often neglected, mainly because of the lack of knowledge of its pathophysiology, treatment and prevention.

Impaired self-awareness has been reported in a number of neurological and neuropsychiatric disorders (e.g. stroke, neurodegenerative diseases, traumatic brain injury, schizophrenia), and in various domains (e.g. sensori-motor, cognitive, socio-emotional, and daily life activities). This clearly demonstrates that there is no “awareness centre” in the brain, but rather suggests that self-awareness implies several areas likely organized in specific networks.

Attempts to unravel the brain networks involved in impaired self-awareness have been the focus of a number of studies. The medial prefrontal cortex is the most constantly identified region within this network. Other cortical and sub-cortical areas have been implicated. However, their role in self-awareness remains obscure (see Northoff et al., 2006 for meta-analysis). Among them, the medial temporal lobe (MTL) structures stand out, namely the hippocampus, amygdala, and surrounding cortices, i.e. the temporopolar, entorhinal, perirhinal and posterior parahippocampal cortices.

This review aims at providing an in depth analysis of the putative role of MTL in impaired self-awareness in neurodegenerative diseases,

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; bvFTD, behavioural variant of FTD; HD, Huntington's disease; MCI, mild cognitive impairment; MTL, medial temporal lobe; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis

* Corresponding author at: INSERM U1075, COMETE, PFRS, 2 rue des Rochambelles, 14032 Caen Cedex, France.

E-mail addresses: chantal.chavoix@inserm.fr (C. Chavoix), ricardo.insausti@uclm.es (R. Insausti).

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because this symptom is common in these conditions that are often associated with MTL damage albeit to varying degrees. Moreover, involvement of MTL in impaired self-awareness has never been explored specifically. Thus, we will focus on five of such neurodegenerative diseases: Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Mild cognitive impairment (MCI) has also been included in the review because many symptoms are shared and quite a few individuals will convert to AD.

2. Impaired self-awareness in neurodegenerative diseases

2.1. Methodological assessment procedures

The most frequently used method of assessing self-awareness is to compare the participant's judgments about its own abilities and behaviour with parallel ratings made by an informant (e.g. spouse and caregiver). Several validated questionnaires and standardized procedures have been developed (eg, Wilson et al., 1989; Clare et al., 2002; Starkstein et al., 2006; Bramham et al., 2009). This method, however, lacks direct measurement of performance, and a range of psychological and social factors influence ratings (Clare et al., 2011). Among the other methods employed in the assessment of self-awareness, the most appropriate is probably the comparison between subjective and objective data, i.e. performance ratings made by the participant vs. actual tests scores. This method provides a more useful indicator of awareness than the participant-informant discrepancy score (Dalla Barba et al., 1995).

2.2. Clinical data

Patients with neurodegenerative diseases tend to overestimate their functional abilities in various domains (e.g. cognition, behaviour, socio-emotion, daily life activities) (Eslinger et al., 2005; Roberts et al., 2009; Sitek et al., 2014 and Starkstein, 2014 for reviews). However, severity and domains of unawareness may vary according to the type of neurodegenerative disease considered, the severity of the disease or along the course of a given disease. Within a given neurodegenerative disease, discrepant results have often been reported, mainly because of differences in the sample characteristics, assessment methods, concept of unawareness, and aim of the studies.

2.2.1. Self-awareness in individuals with mild cognitive impairment

A recent meta-analysis found no difference in awareness between MCI and healthy subjects but highlighted that assessment technique and cognitive status influence the level of awareness (Piras et al., 2016). Vogel et al. (2014) reported that about 60% of individuals with amnesic MCI exhibit symptoms of cognitive unawareness, 12% of which show severe loss of awareness. Only 36%, mainly of the amnesic type, overestimate their abilities in daily life activities, and this was found only for relatively complex functional activities (i.e. financial management or driving abilities, Okonkwo et al., 2009). Some studies, but not all, indicate that overestimation of abilities might be a predictor of conversion from MCI to dementia (see Roberts et al., 2009 and Jacus et al., 2014 for reviews). Some individuals with MCI underestimate their cognitive performance and abilities in daily life activities (Kalbe et al., 2005; Okonkwo et al., 2008; Roberts et al., 2009). Depression, that is common in individuals with MCI, could partly account for this underestimation (Okonkwo et al., 2008; Roberts et al., 2009).

2.2.2. Self-awareness in Alzheimer's disease

Impaired self-awareness, here characterized only by overestimation of abilities, can be observed since the early stages of the disease (Amanzio et al., 2011), although the degree of impaired self-awareness varies greatly from one patient to another, even at a similar stage of the disease. Overestimation of cognitive performance in patients with AD

has been observed in most studies (e.g. Vogel et al., 2004; Kalbe et al., 2005; Salmon et al., 2006; Shany-Ur et al., 2014; Morris et al., 2016). Greater awareness of cognitive impairment has been related to better episodic memory and higher level of education (Salmon et al., 2006). Patients in the early stages of AD also overestimate their empathy, social skills and social behaviour. The following findings are more controversial: overestimation of abilities in daily life activities (e.g. Shany-Ur et al., 2014), association between impaired self-awareness and executive dysfunction, symptoms of depression, apathy and disinhibition (Michon et al., 1994; Salmon et al., 2006; Amanzio et al., 2011), and worsening of unawareness with disease progression (e.g. Michon et al., 1994; Clare et al., 2013). In most domains, patients with AD are less aware of their deficits than individuals with MCI (e.g. Zamboni et al., 2013). However, a comparable level of memory awareness was sometimes reported, especially in individuals with amnesic MCI and patients with mild AD (Vogel et al., 2004; also see Roberts et al., 2009, Jacus et al., 2014, and Starkstein, 2014 for reviews).

2.2.3. Self-awareness in frontotemporal dementia

Impaired self-awareness is a prominent feature of FTD that has been found in over three quarters of the patients (Piguet et al., 2009). Impaired self-awareness varies, however, considerably across FTD subtypes and domain of awareness. *Patients with the behavioural variant (bvFTD)* show the most severe loss of self-awareness. Although overestimation of competence in the socio-emotional domain seems to be the most prominent feature, patients with bvFTD also often exhibit early and severe overestimation of cognitive abilities (Eslinger et al., 2005; Hornberger et al., 2014; Shany-Ur et al., 2014). *Patients with progressive non-fluent aphasia* are the least affected. However, they can show unawareness of apathy (Eslinger et al., 2005) and overestimation of emotional and interpersonal functioning (Shany-Ur et al., 2014). *Patients with semantic dementia* have a relatively accurate awareness of their language and cognitive impairment, as well as level of functioning in daily life activities (Eslinger et al., 2005; Shany-Ur et al., 2014). However, they show sometimes a light unawareness of their socio-behavioural changes (Eslinger et al., 2005), especially in those with predominant right-sided atrophy (Hodges and Patterson, 2007). Patients with bvFTD appear less aware of their deficiencies than patients with AD (Eslinger et al., 2005; Hornberger et al., 2014). Minimal discrepancies were however reported between patients with language subtypes of FTD and patients with AD (Hornberger et al., 2014). Lower self-awareness was found in patients with AD or language subtypes of FTD depending of the domain considered (e.g. lower cognitive self-awareness in AD and lower self-awareness in the socio-emotion domain in FTD) (Eslinger et al., 2005).

2.2.4. Self-awareness in Parkinson's disease

Between 23.3% and 92% of the patients are unaware of levodopa-induced dyskinesias (Vitale et al., 2001; Amanzio et al., 2010; Pietracupa et al., 2013). Awareness of bradykinesia is better preserved (Amanzio et al., 2010). Discrepancy between patient and informant's rating of dyskinesias could however result from their respective perception of dyskinesias (less a handicap than bradykinesia for the patient vs. extremely unpleasant for the patient's relatives), as suggested in patients with PD with mild dyskinesias (Vitale et al., 2001). Unawareness of movement disorders is greater in "on" than in "off" state and in patients with low executive function (Amanzio et al., 2010). However, it may also occur in PD patients with normal cognition (Pietracupa et al., 2013). Overestimation of competence in daily life activities has also been reported in non-demented patients with PD (Leritz et al., 2004). The few studies in the cognitive field indicate accurate self-awareness of general cognition and memory performance (Flashman, 2002; Kudlicka et al., 2013). In case of executive dysfunction, patients with PD can, however, overestimate their executive performance (Kudlicka et al., 2013). Compared to patients with AD,

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