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Neuroanatomical correlates of awareness of illness in patients with amnestic mild cognitive impairment who will or will not convert to Alzheimer's disease

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ABSTRACT

Background: Awareness of cognitive deficits may be reduced in mild cognitive impairment (MCI). This may have a detrimental effect on illness course and may be a predictor of subsequent conversion to AD. Although neuropsychological correlates have been widely investigated, no evidence of a neuroanatomical basis of the phenomenon has been reported yet. This study was aimed at investigating the neuroanatomical correlates of deficit awareness in amnestic MCI to determine whether they constitute risk factors for conversion to AD.

Method: A sample of 36 first-diagnosis amnestic MCI patients were followed for five years. At the first diagnostic visit they were administered an extensive diagnostic and clinical procedure and the Memory Insight Questionnaire (MIQ), measuring a total index and four sub-indices, to investigate awareness of deficits in dementia; they also underwent a high resolution T1-weighted Magnetic Resonance Imaging (MRI) investigation. Grey matter brain volumes were analysed on a voxel-by-voxel basis using Statistical Parametric Mapping 8. Data of 10 converter patients (CONV) and those of 26 non converter patients (NOCONV) were analysed using multiple regression models.

Results: At baseline, self-awareness of memory deficits was poorer in CONV compared to NOCONV. Furthermore, reduced awareness of cognitive deficits in CONV correlated with reduced grey matter volume of the anterior cingulate (memory deficit awareness), right pars triangularis of the inferior frontal cortex (memory deficit awareness) and cerebellar vermis (total awareness), whereas in NOCONV it correlated with reduced grey matter volume of left superior (total awareness) and middle (language deficit awareness) temporal areas. Further, at baseline self-awareness of memory deficits were poorer in CONV than in NOCONV.

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Conclusions: Defective awareness of cognitive deficits is underpinned by different mechanisms in CONV and NOCONV amnestic MCI patients. Our data support the hypothesis that poor awareness of cognitive deficit is a predictor of subsequent conversion to AD.

1. Introduction

Self-awareness is a high-order cognitive function which allows individuals to have a reasonable perception or appraisal of the self, and plays a crucial role in the development of identity implying physical, cognitive and affective aspects (Zeman, 2006). Self-awareness is underpinned by the complex interaction of different cognitive and metacognitive components, such as autobiographical memory, semantic memory, metamemory and cognitive control (Agnew & Morris, 1998; Morris & Mograbi, 2013). In Alzheimer's Disease (AD) the disruption of self-awareness is dramatic and relentless, rising even in the very early stages of illness as a decreased ability in monitoring one's own cognitive performances, thus failing to correctly appraise cognitive deficits, behavioural changes and limitations in activities of everyday living (Gil et al., 2001; Reed, Jagust, & Coulter, 1993). Then in the later stages, this progressive erosion of autonoetic knowledge (Kalenzaga & Clarys, 2013) determines a progressive loss of pieces of self-experience and difficulties in updating one's self-image, giving place to a sort of unchanging petrified self (Mograbi, Brown, & Morris, 2009). This phenomenon is termed anosognosia (Morris & Mograbi, 2013; Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2008). Anosognosia may lead to an increased risk for self-harming behaviours, increased costs for the public health system, jeopardize patients' quality of life and contribute to caregivers' stress (Ready, Ott, & Grace, 2006; Smyth et al., 2002; Starkstein, Jorge, Mizzahi, Adrian, & Robinson, 2007).

Increasing recognition of the need to identify subjects at risk of developing dementia, and to detect predictors of conversion to AD (Gainotti, Quaranta, Vita, & Marra, 2014; Pozueta, Rodriguez-Rodriguez, Vazquez-Higuera, Mateo, Sanchez-Juan, et al., 2011; Risacher et al., 2009), also highlighted by the recent nosological and diagnostic proposals (Cummings, Dubois, Molinuevo, & Scheltens, 2013; Dubois, Feldman, Jacova, Cummings, Dekosky, et al., 2010), stimulated the investigation of awareness of cognitive failures, in pre-clinical stages of the illness, namely, in the mild cognitive impairment (MCI) stage (Albert et al., 2011; Petersen, 2004). In fact, today it is well known that defects in awareness of illness, although much less severe than in AD, may occur also in MCI (Clement, Belleville, & Gauthier, 2008; Orfei et al., 2010; Rieset al., 2007; Vogel et al., 2004). Indeed, decreased self-appraisal ability in MCI may have a deleterious impact as it leads to underestimation of limitations in the activities of daily living, failure to use compensatory strategies, a tendency to adopt dangerous behaviours and delayed requests for medical care and well-timed interventions (Marková, Berrios, & Hodges, 2004; Starkstein et al., 2007). Previous investigations of poor self-appraisal in MCI were mainly focused on clinical and neuropsychological correlates. The most frequent results showed a relationship between lower self-awareness and increased global cognitive impairment (Albert et al., 1999; Kalbe et al., 2005; Ready et al., 2006; Vogel et al., 2004) or reduced verbal memory performance (Bruce et al., 2008; Chung & Man, 2009; Orfei et al., 2010; Tremont & Alosco, 2011). A still largely unexplored issue concerns the neural correlates of defective awareness of cognitive deficits in MCI. In fact, a number of studies have investigated the neuroanatomical underpinnings of anosognosia in AD, mostly stressing a relationship with hypometabolism or hypoperfusion in orbital, lateral and medial frontal cortex (Derousné et al., 1999; Hanyu et al., 2008; Harwood et al., 2005; Reed et al., 1993; Salmon et al., 2006; Sedaghat et al., 2010), and temporal cortical regions (Ott, Noto, & Fogel, 1996; Salmon et al., 2006; Sedaghat et al., 2010). On the contrary, very few data are available for MCI. The sparse results on this topic tend to confirm the role of frontal, prefrontal and temporal areas (Ries et al., 2007; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005; Zamboni et al., 2013), whose deterioration in MCI subjects is frequently described as characteristic of a subsequent conversion to AD. Unfortunately, some of the cited studies did not focus only on MCI patients, but included other diagnostic groups. Moreover, since the etiopathogenic course of AD is clearly characterized by severe structural alterations, due to atrophic processes, it is reasonable to investigate also the structural correlates of deficit awareness, as in studies on awareness of illness carried out in other neuropsychiatric conditions, such as stroke and psychosis (Aleman, Agrawal, Morgan, & David, 2006; Orfei et al., 2008; Shad, Tamminga, Cullum, Haas, & Keshavan, 2006), in order to integrate functional information. Finally, all the above mentioned studies of symptom awareness in MCI provided cross-sectional data, but in an at-risk prevention perspective, aimed at identifying the early signs of dementia in pre-clinical populations, the use of designs focused on clinical outcomes is required. Notably, to our knowledge only one study compared MCI patients who would subsequently convert to AD to those who would not and suggested that defective self-appraisal is predictive of a future diagnosis of AD (Tabert et al., 2002). However, this study only analysed awareness of functional deficits and did not make a more detailed investigation of MCI patients' appraisal of cognitive and behavioural deficits.

Notably, failures in self-appraisal represent a complex and multidimensional function, involving several metacognitive components (Ansell & Bucks, 2006; Morris & Mograbi, 2013). The present study focused on alterations of the global level of metacognition, which refers to the ability to update beliefs concerning one's cognitive capacities and sense of self-efficacy (Gallo, Cramer, Wong, & Bennett, 2012). Further, the