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Functional correlates of preserved naming performance in amnestic Mild Cognitive Impairment

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ABSTRACT

Naming abilities are typically preserved in amnestic Mild Cognitive Impairment (aMCI), a condition associated with increased risk of progression to Alzheimer's disease (AD). We compared the functional correlates of covert picture naming and word reading between a group of aMCI subjects and matched controls. Unimpaired picture naming performance was associated with more extensive activations, in particular involving the parietal lobes, in the aMCI group. In addition, in the condition associated with higher processing demands (blocks of categorically homogeneous items, living items), increased activity was observed in the aMCI group, in particular in the left fusiform gyrus. Graph analysis provided further evidence of increased modularity and reduced integration for the homogenous sets in the aMCI group. The functional modifications associated with preserved performance may reflect, in the case of more demanding tasks, compensatory mechanisms for the subclinical involvement of semantic processing areas by AD pathology.

1. Introduction

The neural basis of semantic processing has been addressed by many functional neuroimaging studies in healthy subjects. Recent meta-analyses have underlined the role of a distributed network involving several regions, i.e., the posterior inferior parietal lobule (angular gyrus and portions of supramarginal gyrus), middle temporal gyrus, fusiform and parahippocampal gyri, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial prefrontal cortex, and posterior cingulate gyrus (Binder et al., 2009), and the specific contribution of the anterior temporal lobe (ATL) as a crucial hub for semantic processing (Visser et al., 2010).

Studies of patients with neurodegenerative conditions provide considerable additional evidence on the neural substrate of semantic memory. In particular, patients suffering from Alzheimer's disease (AD) show semantic memory deficits (Chertkow and Bub, 1990; Hodges, 2006), characterized by a greater impairment of subordinate than superordinate knowledge (Chertkow and Bub, 1990; Alathari et al., 2004; Duarte et al., 2009; Garrard et al., 2005; Giffard et al., 2001, 2002), and of biological more than non-biological entities (Fung et al., 2001; Gonnerman et al., 1997; Whatmough et al., 2003; Catricalà et al., 2014). Naming abilities are impaired from the early stages of the disease, with errors consisting of anomias and semantic paraphasias or superordinate responses. These disorders are generally attributed to an underlying semantic memory deficit, due to loss (Chertkow and Bub, 1990; Hodges et al., 1992; Martin and Fedio, 1983; Lin et al., 2014), or defective access to semantic information (Nebes et al., 1989; Nebes 1992; Ober and Shenaut, 1988). The possible contribution of lexical impairment is also discussed, at least for the early phases of disease (Funnell and Hodges, 1991). Consistent with the hypothesis of a underlying lexical-semantic deficit for the naming impairment in AD, PET and structural MRI studies have found that naming deficits are predominantly associated with abnormalities in the temporal cortex (Teipel et al., 2006; Hirono et al., 2001; Melrose et al., 2009; Domoto-Reilly et al., 2012), including left fusiform gyrus (Teipel et al., 2006; Melrose et al., 2009) and the left ATL (Domoto-Reilly et al., 2012; Frings et al., 2011; Melrose et al., 2009), and extending to frontal and parieto-occipital cortex (Apostolova et al., 2008).

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Zahn et al. (2004) have shown that metabolism in left anterior temporal, posterior inferior temporal, inferior parietal and medial occipital areas (Brodmann areas: 21/38, 37, 40 and 19) correlated with both verbal and nonverbal semantic performance in AD. Similarly, Libon et al. (2013) found that gray matter atrophy affecting the left posterolateral temporal–parietal regions (including fusiform, parahippocampal, superior temporal and inferior parietal (BA 40) gyri) predicted the AD performance on a semantic categorization task.

Changes in brain activation and in functional connectivity may precede structural changes and behavioral manifestations (Wierenga and Bondi, 2007; Bokde et al., 2006). In this view, functional magnetic resonance imaging (fMRI) activation studies may represent a possible preclinical biomarker of AD, as they are able to detect early abnormalities in brain function and to highlight the defective integration of different regions into a neural network for successful completion of a task that could reflect initial stages of AD neuropathology.

AD is often preceded by a phase characterized by an isolated episodic memory impairment, defined as amnestic Mild Cognitive Impairment (aMCI) (Petersen, 2004). While the majority of structural imaging has focused on the involvement of the medial temporal lobe structures (Varon et al., 2014), functional PET imaging has shown more widespread changes in aMCI, including an involvement of the distributed semantic network, i.e., in the inferior parietal and posterior cingulate cortex and in the left parahippocampal gyrus (Anchisi et al., 2005). An MR study reported that atrophy of the middle and inferior temporal gyrus and the fusiform gyrus (in addition to anterior medial temporal regions) had predictive value for progression to AD in Mild Cognitive Impairment subjects (Convit et al., 2000).

As an episodic memory deficit is the hallmark and the major symptom of AD, the majority of the functional activation studies on patients in the prodromal stage of AD focused on memory tasks (Sugarman et al., 2012; Wierenga and Bondi, 2007). The results, however, are discordant (showing both hypoactivity and hyperactivity), and difficult to interpret, given the associated defective performance (Sperling et al., 2010; Wierenga and Bondi, 2007). An additional problem is that episodic memory decline is also present in normal aging (Nilsson, 2003), and thus does not necessarily reflect AD neuropathology. The findings may thus simply reflect defective performance, rather than disease-specific functional changes (Woodard et al., 2009). The use of tasks that patients can perform accurately may be useful to prevent ambiguities in results interpretation due to defective performance (Price and Friston, 1999; Wierenga and Bondi, 2007), allowing valid inferences on the pathogenesis of cognitive alterations and on the contribution of specific brain regions to cognitive processes.

Unlike episodic memory skills, semantic memory abilities remain relatively intact both in normal aging (Nilsson, 2003) and in aMCI, at least when assessed with clinical tests (Joubert et al., 2008). Naming deficits are not prominent in aMCI, who may have mild, subclinical naming disorders. Deficits in naming objects are in fact an uncommon finding (Balthazar et al., 2008; Clague et al., 2011; Adlam et al., 2006; Choi et al., 2013; Gardini et al., 2013; but see Joubert et al., 2010 and Ahmed et al., 2008), while naming pictures of unique entities including famous people, famous buildings and famous public events seems to be more consistently affected (Joubert et al., 2010; Gardini et al., 2013; Ahmed et al., 2008; Estévez-González et al., 2004; Clague et al., 2011). On the other hand, disease progression is associated with semantic memory dysfunction, and there is some evidence that subtle semantic deficits (semantic fluency) are a predictor of progression towards dementia (Gainotti et al., 2014).

All the outlined clinical evidence indicates semantic processing as a possible subclinical marker of AD pathology, leading us to assess in the present context if alterations of the neural underpinnings of semantic processing at the neural level are already present in aMCI subjects showing a normal performance on picture naming task. Our prediction is that functional changes can be already observed in these subjects in regions subserving or contributing to semantic processing. An hyperactivation of the specific "semantic" circuits, and/or an involvement of additional regions not normally engaged in healthy individuals (compensatory "recruitment") may represent the mechanisms supporting the preserved naming performance. As a control condition, we used a task of reading regular words. This is a performance with limited requirements for semantic processing (Woollams et al., 2007), which has been shown, accordingly, to be spared until the late stages of AD (Colombo et al., 2000).

To further increase the sensitivity of the task for subtle semantic dysfunction, we used a naming paradigm taking into account the influence of the semantic context. Behavioral studies in healthy subjects documented greater latencies in naming objects blocks belonging to the same semantic category (homogeneous condition) when compared to blocks including different categories (heterogeneous condition) (Damian et al., 2001; Levelt et al., 1999; Kroll and Stewart, 1994). An fMRI study in healthy subjects revealed increased perfusion fMRI signal bilaterally in the hippocampus and in the left middle to posterior superior temporal cortex for the homogeneous condition (Hocking et al., 2009).

In addition, we looked for the possible influence of the semantic category, which has been shown to affect naming performance in AD. An inferior performance for living than non-living entities has been repeatedly reported in AD (Fung et al., 2001; Gonnerman et al., 1997; Whatmough et al., 2003). We thus hypothesized that living things may be particularly sensitive to early subclinical dysfunction. In the homogeneous condition, we created different blocks for living and non-living things. The two classes of entities were balanced for a large number of intrinsic variables that could account for dissociations, in order to exclude that differences in brain activity could be ascribed to different stimulus processing demands. For example, the activations in the premotor cortex generally reported for tools appear to be due to the manipulability of the objects, as they are found when tools are compared with animals but not with vegetables (Devlin et al., 2002; Gerlach et al., 2002). In order to avoid spurious activation differences between living and non-living items, the two categories were balanced also for volumetric manipulability (i.e., how an object is associated to gestures used to pick up the object).

2. Methods

2.1. Subjects

We screened a large population of subjects with a clinical diagnosis of aMCI (Petersen et al., 2001) and we enrolled patients who fulfilled the following criteria: 1) no evidence of other causes of memory impairment as demonstrated by neuroimaging (standard brain MR scan) and laboratory tests (blood tests for hepatic and kidney functions, electrolytes, glucose, thyroid functions, lipids, syphilis infection, B12 vitamin and folic acid deficits) 2) a selective and isolated deficit of episodic memory as investigated with the Rey Auditory Verbal Learning Test (Rey AVLT) (Table 1); 3) semantic memory integrity, as revealed by a detailed semantic memory battery, including two naming tasks, one with colored pictures and the other in response to an oral description, a word-picture matching task, a picture sorting task and a sentence verification task (Catricalà et al., 2013). Eight patients were thus enrolled in the study (5 males; age range: 59–77, mean=71.62; education range: 5–18).

Sixteen controls (8 males) matched for education (education