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Disruption of Semantic Network in Mild Alzheimer's Disease Revealed by Resting-State fMRI

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Abstract—Subtle semantic deficits can be observed in Alzheimer's disease (AD) patients even in the early stages of the illness. In this work, we tested the hypothesis that the semantic control network is deregulated in mild AD patients. We assessed the integrity of the semantic control system using resting-state functional magnetic resonance imaging in a cohort of patients with mild AD (n = 38; mean mini-mental state examination = 20.5) and in a group of age-matched healthy controls (n = 19). Voxel-wise analysis spatially constrained in the left fronto-temporal semantic control network identified two regions with altered functional connectivity (FC) in AD patients, specifically in the pars opercularis (POp, BA44) and in the posterior middle temporal gyrus (pMTG, BA21). Using whole-brain seed-based analysis, we demonstrated that these two regions have altered FC even beyond the semantic control network. In particular, the pMTG displayed a wide-distributed pattern of lower connectivity to several brain regions involved in language-semantic processing, along with a possibly compensatory higher connectivity to the Wernicke's area. We conclude that in mild AD brain regions belonging to the semantic control network are abnormally connected not only within the network, but also to other areas known to be critical for language processing.

Key words: Alzheimer's disease, semantic control network, posterior middle temporal gyrus, inferior frontal gyrus, resting-state fMRI, voxel-wise functional connectivity.

INTRODUCTION

The hallmark of Alzheimer's disease (AD) has been long recognized to be a profound deficit in episodic memory. However, language dysfunctions with a semantic basis are also observed in AD patients (Kempler, 1995) even at predementia stages (Mickes et al., 2007; Amieva et al., 2008; Taler and Phillips, 2008). The early pattern of language deterioration in AD is quite specific and characterized by a predominant semantic impairment with a relatively sparing of other language features, such as syntax or phonology (Kirshner, 2012). The most evident symptom is a word-finding difficulty which can be observed in spontaneous speech (Nicholas et al., 1985) as well as in language standardized tests (e.g., confrontation naming and verbal fluency; Henry et al., 2004). While the neural substrates underlying episodic memory impairment in AD have been extensively studied, the role of semantic memory still remains poorly investigated. PET studies indicated that frontal and lateral temporal regions are implicated in semantic deterioration in AD (Zahn et al., 2004; Teipel et al., 2006; Nelissen et al., 2007; Melrose et al., 2009), yet the question arises of which component of semantic cognition is being affected by the pathology.

Semantic cognition is theorized to include the storage of conceptual knowledge and the process by which such knowledge is manipulated in a time, context, and task appropriate fashion (Tulving, 1987). These two components (i.e., storage and control) are thought to be subserved by two distinct but interactive neuronal systems (Jefferies, 2013; Ralph et al., 2017). The conceptual

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Abbreviations: AD, Alzheimer's disease; BOLD, blood-oxygen-level-dependent; CSF, Cerebral Spinal Fluid; EPI, echo planar imaging; FC, functional connectivity; FD, framewise displacement; fMRI, functional magnetic resonance imaging; FWHM, full width at half maximum; GLM, general linear model; GM, gray matter; GMV, gray matter volume; HC, healthy controls; MMSE, mean mini-mental state examination; MNI, Montreal Neurological Institute; pMTG, posterior middle temporal gyrus; POp, pars opercularis; TMS, transcranial magnetic stimulation; wGBC, weighted Global Brain Connectivity; WM, White Matter; wRBC, weighted Regional Brain Connectivity.

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knowledge is controlled by a wide-distributed network composed of sensorimotor and verbal-related areas that store object-specific features and lexical information (Damasio et al., 2004; Martin, 2007), along with an amodal hub, located in the bilateral anterior temporal lobe, acting as a convergence zone (Patterson et al., 2007). On the contrary, the semantic control is supported by a left-lateralized fronto-temporal and possibly parietal network (Jefferies and Ralph, 2006; Noonan et al., 2010). In particular, the left inferior frontal gyrus (pars opercularis and triangularis), and the left posterior middle temporal gyrus (pMTG) are considered the most relevant regions in the semantic control network (Whitney et al., 2011a,b; Jefferies, 2013; Krieger-Redwood and Jefferies, 2014). However, other regions have been implicated in semantic control, including the dorsal angular gyrus (Noonan et al., 2013) and the posterior cingulate cortex (Binder et al., 2009), although their exact role needs to be clarified.

Neuropsychological research about the nature of semantic deficits in AD has provided conflicting results, pointing to either a degraded conceptual knowledge (Hodges et al., 1992; Garrard et al., 2005; Lin et al., 2014) or a deregulated control/access to this information (Bayles et al., 1991; Nebes and Halligan, 1996). The apparent inconsistency among neuropsychological studies could be related to disease severity (Bayles et al., 1991; Duong et al., 2006). This notion is supported by a recent study that examined how different stages of the pathology affect distinct components of semantic cognition (Corbett et al., 2012). Specifically, in the mild stage (mean mini-mental state examination, MMSE $\sim$ 20) patients showed impairments distinctive of deregulated control of semantic information, whereas in the severe stage (mean MMSE $\sim$ 10) this problem, besides getting worse, became compounded by degradation of semantic representations (Corbett et al., 2012). The pathophysiological counterpart of the reported pattern of semantic impairment in AD is expected to be a functional alteration in the semantic control system, which should be visible early in the disease progression. To the best of our knowledge, such hypothesis has not been tested yet.

Here we adopted resting-state functional magnetic resonance imaging (rsfMRI), based on the blood-oxygen-level-dependent (BOLD) signal, to examine, for the first time, the functional connectivity (FC) integrity of the semantic control network in patients with AD at mild stage. Compared to task-based fMRI, the resting-state design has the advantage of not relying on any task choice. This feature is particularly important for dementia subjects in which uncontrolled familiarity of stimulus concepts and/or task demands might represent critical, and not manageable, confounds (Bayles et al., 1991). Our main hypothesis was that mild AD patients are characterized by altered FC within the semantic control network. Secondly, we hypothesized that such alteration correlates with language impairment (verbal fluency and confrontation naming). Finally, given the continuous interplay between the semantic control and the wide-distributed representation network, we expected that affected regions in the semantic control network would present FC abnormalities in other semantic-related regions.

EXPERIMENTAL PROCEDURES

Subjects

A cohort of 38 right-handed patients with probable AD-typical were recruited for the current study. The diagnosis of probable AD was performed according to the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA, McKhann et al., 2011). To be included, patients had to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria (American Psychiatric Association, 2013) for the diagnosis of major neurocognitive disorders due to AD. An expert neurologist (M.B.) in each recruited patient reviewed carefully the clinical history, the cognitive profile and the conventional MRI scan and excluded the vascular signs and symptoms associated typically with vascular dementia. Nineteen right-handed healthy elderly individuals were also recruited and served as healthy controls (HC). All healthy subjects reported scores within the range of normality at the Mini Mental State Examination (MMSE, Italian cut-off $>$ 23.8; Folstein et al., 1975; Magni et al., 1996). Major systemic, psychiatric, vascular and other neurological illnesses were carefully investigated and excluded in all recruited subjects. The study was carried out in accordance with a protocol approved by the Ethics Committee of Santa Lucia Foundation. All recruited subjects gave written informed consent in accordance with the Declaration of Helsinki and European Union regulations.

Neuropsychological assessment

All participants underwent a neuropsychological battery covering several cognitive domains, which included: (1) verbal episodic long-term memory: 15-Word List (Immediate and 15-min Delayed recall; Carlesimo et al., 1996); Short Story Test (Immediate and 20-min Delayed recall; Carlesimo et al., 2002); (2) visuo-spatial long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall; Carlesimo et al., 2002); (3) short-term memory: Digit span and the Corsi Block Tapping task (Monaco et al., 2013); (4) executive functions: Phonological Word Fluency (Carlesimo et al., 1996) and Modified Card Sorting Test (Nocentini et al., 2002); (5) language: Naming objects subtest of the BADA (''Batteria per l'Analisi dei Deficit Afasici", Italian for ''Battery for the analysis of aphasic deficits"; Miceli, 1994); (6) reasoning: Raven's Coloured Progressive Matrices (Carlesimo et al., 1996); (7) constructional praxis: copy of simple drawings with and without landmarks (Carlesimo et al., 1996) and copy of Complex Rey's Figure (Carlesimo et al., 2002).

Data acquisition

Data were acquired on a 3 T MRI system (Magnetom Allegra, Siemens, Erlangen, Germany). All subjects underwent a resting-state fMRI scan using an echo planar imaging (EPI) sequence with the following parameters: TR = 2080 ms, TE = 30 ms, 32 axial slices parallel to AC-PC plane, matrix = 64 $\times$ 64, in