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The network substrate of confabulatory tendencies in Alzheimer's disease

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ABSTRACT

Confabulatory phenomena are rare in the early stage of Alzheimer's disease (AD), are often provoked and are triggered by questions or in response to neuropsychological testing. In this retrospective study functional connectivity alterations were investigated for the first time in a group of patients with early AD who had shown evidence of verbal and non-verbal confabulatory tendencies. Resting-state functional magnetic resonance imaging (fMRI) scans of 18 confabulating patients were compared with those of 18 non confabulators. The finding showed that confabulators had decreased connectivity between a seed region in the right inferolateral frontal cortex and right mediotemporal and insular regions, and increased connectivity with frontal areas and a homologous region on the left. The seed control region in the left inferolateral frontal cortex showed increased connectivity with midline frontal and anterior cingulate regions, while a decrease was found in temporal areas. Confabulatory tendencies appear in early AD as a result of disconnection between crucial computational hubs in frontal and mediotemporal regions. This disconnection is coupled with the presence of up-regulation of frontal activity, and especially of midline and anterior cingulate regions, which might disrupt efficient output monitoring in confabulators.

1. Introduction

Confabulations, defined as memory distortions consisting of production of statements incongruous to the subject's history and background (Dalla Barba, 1993), have been observed in various conditions affecting the nervous systems, e.g., Korsakoff's disease, encephalitis, or head injury (Baddeley & Wilson, 1986; Dalla Barba, Cipolotti, & Denes, 1990) and may also be detected at the earliest stages of Alzheimer's disease (AD) (Greene, Hodges, & Baddeley, 1995). Severe confabulatory phenomena are, however, not very frequent in early AD, and often only confabulatory tendencies or confabulatory instances elicited in response to testing procedures or specific contextual circumstances are observed in the earliest stage of this disease (Cooper, Shanks, & Venneri, 2006).

In an attempt to disentangle the neural causes behind the presence of this particular symptom in AD, a useful classification is that proposed by Kopelman (1987), who distinguished 'spontaneous' from 'provoked' confabulations, with the

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former reflecting the production of an 'incoherent and context-free retrieval of memories and associations', whereas the latter refer to simple memory fabrications, typically elicited by questions (Kopelman, 1987). The peculiar features normally observed in these two types of confabulation should reflect different underlying brain dysfunctions. Provoked confabulation might be more frequent in the initial symptomatic stages of AD, because in some patients these may be the outcome of breakdown of cognitive processes linked to neurodegeneration mainly in mediotemporal and frontal regions (Dalla Barba, Nedjam, & Dubois, 1999). Progression of neurodegeneration more globally within the brain would lead to production of more elaborate confabulations in patients who are at more severe stages of the disease, and spontaneous confabulatory behaviours or even delusions would then be more frequent (Cooper et al., 2006). The presence of confabulatory tendencies in AD, therefore, reflects the disruption of cognitive modules which are crucially susceptible to neurodegenerative processes very early on in the natural history of AD. Although a considerable proportion of AD patients already shows deficits in declarative memory at the early stages of the disease (during the mild cognitive impairment and mild dementia phases), only part of this group, however, generates confabulatory material during memory retrieval. Although the AD-related taxonomy of confabulations proposed by La Corte, Serra, Attali, Boissé, and Dalla Barba (2010) focuses on retrograde memory as a major domain affected by confabulatory retrieval, typically neuropsychological assessment for patients with neurodegenerative conditions includes predominantly tests of anterograde memory. Provoked confabulations in the context of newly-learnt material in AD were studied by Attali, De Anna, Dubois, and Dalla Barba (2009), who highlighted the role of poor encoding skills in the genesis of this symptomatic trait. A number of additional theories centred on cognitive frameworks have been put forward to account for the presence of confabulations. These highlight the role of the interplay among memory, consciousness and temporality (Dalla Barba, 2000), motivational factors (Fotopoulou, Solms, & Turnbull, 2004), and preconscious computational processes (Schnider, Bonvallat, Emond, & Leemann, 2005). Most of these, however, are suitable frameworks to explain confabulatory phenomena in retrograde memory, but would not be valuable interpretational avenues for confabulatory tendencies in anterograde memory. Studies carried out on other, non-AD populations may be helpful in the attempt to clarify the neural and cognitive mechanisms which foster the genesis of confabulatory recalls. Based on investigations carried out on brain-damaged patients, a hypothesis of disruption of frontal/executive processes at retrieval has been proposed. On this note, being executive processes paramount for the supervision of information retrieval, confabulations might originate from defective monitoring functions (Burgess & Shallice, 1996; Moscovitch & Melo, 1997). On a similar note, in a review authored by Gilboa and Moscovitch (2002) it was reported that 81% of confabulators had damage to the prefrontal cortex, supporting the idea that dysregulation of cognitive control might underlie the presence of this symptom. These authors also reported that the most common lesional sites were the orbitofrontal and ventromedial aspects of the frontal lobe. On the other hand, a second review highlighted instead the absence of a specific region responsible for this class of symptoms, as lesions triggering confabulations may also occur in multiple non-prefrontal areas (Schnider, 2001). The study of brain injuries is typically in line with a localisation-based approach, in which it is the single area which sustains a psychological process. The more recent, hierarchically superior, connectivity-based approach theorises instead that it is the interaction between two or more computational hubs that supports normal cognitive functioning. The diverse lesional locations documented by previous research would have, in fact, a common denominator in the anatomical connections with orbitofrontal territory (Schnider, 2001). On this note, the presence of confabulations during retrieval might originate from a dysfunctional signal pathway affecting prefrontal regions, or regions located on important computational pathways of communication between the prefrontal cortex and other key areas (hence the absence of a "signature" lesional site). It is also possible that confabulatory evidence in early AD might emerge because of disconnection between crucial computational hubs, or even because of up-regulation of signal in crucial areas which then interferes with signal-to-noise distinction and performance monitoring in this population of patients who are cognitively inefficient. These latter hypotheses seem to be a more realistic reflection of the kind of brain function disruption that might be expected in early AD. The mechanisms of confabulation share important theoretical commonalities with the processes behind the manifestation of delusions (Turner & Coltheart, 2010). In fact, the presence of delusional (and aggression) symptoms influenced the presence of confabulations during cognitive tasks (Lee et al., 2007). Evidence emerging from a set of studies investigating structural as well as functional neuroimaging associations indicates that the presence of delusional thoughts in AD is associated with morphometric changes or with dysfunction in a major computational region located in the right prefrontal cortex, particularly the orbitolateral portion (Bruen, McGeown, Shanks, & Venneri, 2008; Nakano, Yamashita, Matsuda, Kodama, & Yamada, 2005; Staff et al., 1999; Venneri, Shanks, Staff, & Della Sala, 2000). These studies, however, due to the static snapshot state of their analyses, have not clarified the nature and the role of this association. Rooted on a connectivity-based hierarchy and on common associational grounds as in the study of delusions, it can be suggested that in AD confabulatory tendencies might occur because of dysfunctional connectivity of the right orbitolateral prefrontal cortex and, potentially, regions which are crucial in the management of memory retrieval [as, for instance, proposed by Dalla Barba and La Corte (2013)]. It can be suggested that patients prone to confabulate would have reduced connectivity between these right prefrontal areas and regions involved in declarative memory (i.e., as measured by the task where confabulations emerge). Although confabulation has been studied primarily in the verbal domain, it is likely that non-verbal confabulation may be just as common, although of more difficult detection because confabulatory retrieval of non-verbal material has to be associated with a very large degree of salience in order to be clinically perceived as result of confabulations.

In this retrospective study functional connectivity alterations were investigated for the first time in a group of