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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, 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 fMRI scans of eighteen 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.

Keywords: confabulation, functional connectivity, fMRI, mild cognitive impairment, graphabulation

Highlights

- Confabulations are rare in early Alzheimer's disease and are of provoked type
- Confabulators have reduced connectivity between right inferolateral frontal cortex and right mediotemporal structures
- Increases in connectivity in midline frontal and anterior cingulate regions is also present
- Confabulations in early Alzheimer's disease result from disconnection between right frontal and mediotemporal computational hubs and are fostered by upregulation of frontal activity which causes inefficient monitoring of output 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 et al., 1990) and may also be detected at the earliest stages of Alzheimer's disease (AD) (Green, 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 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, Shanks & Venneri, 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 and colleagues (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-learned material in AD were studied by Attali et al. (2008), 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 (Fotopolou, 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. In an opposite fashion, 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 upregulation 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 generation of delusions (Turner & Coltheart, 2010). In fact, the presence of delusional (and aggression) symptoms influenced the presence of confabulations during cognitive tasks (Lee, Akanuma, Meguro, Ishii, Yamaguchi & Meguro, 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, Shanks, Macintosh, Pestell, Gemmell & Venneri, 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. Based 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 management of memory retrieval (as, for instance, suggested by Dalla Barba & 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 patients with early AD who had shown evidence of verbal and non-verbal confabulatory tendencies (these latter referred to as "graphabulations" (Roh, Lee, Chin, Kim & Na, 2012), as they are expressed in the visuospatial/graphic domain) during their neuropsychological assessment. Although being conceptually distinct from the "typical" confabulations described as distorted retrograde information (La Corte et al., 2010), the types of symptom we investigated are akin to the definition of "confabulation-like behaviour", introduced by Kern and coworkers (1992), and emerging as intrusive elements in the

performance obtained on neuropsychological tests. Two cohorts of AD patients were examined, and group differences in functional connectivity of the prefrontal cortex were studied between confabulators and "graphabulators", and age-matched patients showing absence of this trait.

2. Material and methods

A large number of datasets were explored in a retrospective way to identify the appropriate sample to be included in this study. Data for this study were extracted from two databases, both originally based on cohorts of healthy adults and patients diagnosed with AD neurodegeneration, and both inclusive of neurological and neuropsychological examinations, and resting-state brain fMRI acquisitions. The patients included in the final inferential models had been all diagnosed with AD, either at a prodromal stage (characterised by Mild Cognitive Impairment, whose AD aetiology had been confirmed by subsequent follow up clinical examinations), or at a stage of minimal-to-mild dementia. Since the purpose of the study was to investigate a specific neural signature of confabulatory tendencies shown during retrieval processes but irrespective of the encoding modality, equal weight was given to the verbal and visuospatial domains for the constitution of the sample of patients. In order to do so, the two databases were explored in search of "graphabulatory traits" and verbal confabulatory tendencies.

2.1 Database 1 – Visuospatial domain.

A qualitative inspection of the performance on the delayed (10-min) recall of the Rey-Osterrieth Complex Figure was carried out to detect proneness to generate confabulatory elements in the visuospatial context (Osterrieth, 1944; Rey, 1941). In this test patients have

to draw from memory a complicated black-and-white geometrical structure which had been copied and encoded ten minutes earlier. One hundred twenty-one patients, recruited at the IRCCS San Camillo Hospital Foundation, Venice Lido (Italy), had been administered this neuropsychological test at least once, as part of the original recruitment and follow-up procedures. Ten graphic recalls were judged as suggestive of graphic confabulatory tendencies. Nine of these patients (5 females) had a resting-state fMRI acquisition free from artefacts, and were thus suitable for inclusion. Figure 1 illustrates three examples of the graphic production which were judged by at least two independent observers to show aspects of graphabulatory retrieval. Additionally, other nine patients (5 females) of comparable diagnostic status were identified. Absence of confabulatory tendencies in this second sample was ascertained by carefully inspecting the performance shown in a series of tests of visuospatial as well as verbal declarative memory (Rey-Osterrieth Complex Figure test – delayed recall, Prose Memory test – immediate and delayed recall, and Paired Associates Learning test).

[Insert Figure 1 about here]

These two samples showed no difference in age, education levels or gender (all $p > 0.7$), or disease severity, as estimated by the Mini Mental-State Examination (MMSE) (Folstein, Folstein & McHugh, 1975; $p > 0.4$). All patients were residents in the Venetian archipelago. The MRI protocol administered to this group included two resting-state fMRI echoplanar sequences acquired with the following characteristics: pre-scan dummy-volume time: 20 s; repetition time 2 s, echo delay time 50 ms, flip angle 90°, voxel dimensions 3.28 × 3.28 × 6.00 mm, field of view 230 mm, slices per volume: 20, number of volumes per run: 120, number of runs: 2, and volume acquisition modality: gapless, contiguous, ascending. A

complementary three-dimensional anatomical T1-weighted scan was acquired with the following parameters: voxel size 1.1 × 1.1 × 0.6 mm, field of view 250 mm, matrix size 256 × 256 × 124, repetition time 7.4 ms, echo time: 3.4 ms, and flip angle 8°. This MRI protocol was acquired on a 1.5 T Philips Achieva scanner.

2.2. Database 2 – Verbal domain

Forty-six patients recruited at the Royal Hallamshire Hospital, Sheffield (United Kingdom) were considered for inclusion. Similar to participants from Database 1, all patients had completed clinical neurological and neuropsychological procedures and an MRI protocol. The performance on a number of tests measuring verbal learning and declarative memory was inspected to evaluate the potential presence of confabulatory tendencies. These were the Paired Associates Learning test (Calkins, 1894), the Prose Memory test (Morris et al., 2014), and the verbal recall of the CERAD test battery (Lamberty, Kennedy & Flashman, 1995). In the Paired Associates Learning test participants had to memorise a list of words structured in pairs, some being characterised by a semantic association, some being unrelated. Three repetitions of the pair list were administered. The Prose Memory test consisted in the memorisation of verbal material characterised by an internal contextual coherence (a short story describing an event that had occurred). An immediate and a delayed (ten minutes) retrieval was asked. Finally, the verbal recall of the CERAD was based on the learning of a list of ten words, and included three immediate and one delayed recalls. The output on these tests was reviewed to detect responses, the nature of which could have originated from a confabulatory process. Semantic paraphasias (e.g., from the CERAD list of words, the term "sand" instead of "shore"), substantial rephrasing (e.g., from the Prose Memory test, "The police felt sorry for her" instead than "The police, touched by the woman's story"), and phonological errors (e.g., during the Paired Associates Learning test, "petal" as word

associated with “flower”, while the word ”metal” was part of the learning material) were not considered. Also, task-inconsistent contents associated with the material included in a different test administered at a short distance before the verbal retrieval phases were ignored (e.g. words retrieved during the CERAD learning phase which are part of the modified Boston Naming task, normally administered immediately before the learning task). Nine patients (5 females) in total were reputed having signs of potential confabulation (see Figure 1 for some examples of the confabulatory exemplars produced by these patients). Additionally, nine patients free from any confabulatory recall were included as institution-specific control group. No difference in disease severity was detected between these two samples, as measured by the MMSE ($p > 0.7$), and, similarly, no between-sample differences in age, education levels or gender were reported (all $p > 0.4$). These eighteen patients had undergone an MRI protocol, which had been acquired using a Philips Ingenia 3.0 T. Structural three-dimensional T1-weighted scans were recorded using the following parameters: voxel size 0.94 × 0.94 × 1.0 mm, field of view 256 mm, matrix size 256 × 256 × 124, repetition time 8.2 ms, echo time: 3.8 ms, and flip angle 8°. Resting-state fMRI sequences were instead acquired with the following specifics: pre-scan dummy-volume time: 20 s; repetition time 2.6 s, echo delay time 35 ms, flip angle 90°, voxel dimensions 1.80 × 1.80 × 4.00 mm, field of view 230 mm, slices per volume: 35, number of volumes per run: 125, number of runs: 1, and volume acquisition modality: gapless, contiguous, ascending. Ethical approval for scanning had been obtained from the local Ethics Committee in both institutions for specific studies for which these patients had volunteered. Patients’ written permission for future retrospective additional analyses of their data had been obtained at the time of their initial testing, enabling, researchers to re-use their anonymised data for future retrospective research. All procedures were carried out in accordance with The Code of

Ethics of the World Medical Association (Declaration of Helsinki). Informed written consent was obtained from all participants at the time of their participation in the original studies.

2.3 Analytical procedures

The demographic descriptives of the sample included in this study are detailed in Table 1. In all 36 cases, the functional acquisition had been acquired at a short temporal distance from the cognitive assessment (mean distance in days: 21.7). Procedures of diffeomorphic Voxel-Based Morphometry were carried out on the entire set of 36 anatomical scans (Ashburner, 2007), using SPM12b software, running in a Matlab environment (version R2011b; Mathworks Inc., UK). Furthermore, native-space global volumes of grey matter, white matter and cerebrospinal fluid were quantified using the "get totals" script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m). This served for further sample characterisation of tissue class volumes and ratios (Table 2). Hippocampal volumes were extracted based on the STEPS segmentation (Cardoso et al., 2013), available as a fully-automated procedure at http://cmictig.cs.ucl.ac.uk/niftyweb/. The same preprocessing and modelling procedure was applied to the functional scans of both institutions. All runs were initially slice-timed and realigned in space. Vectors indicating linear and rotational volume-to-volume motion were plotted and inspected to rule out the possibility of artefacts due to excessive movements. On this note, no patients showed problematic acquisitions (no time-course exceeded 1.5 mm or 3 degrees motion from the first volume). Scans were then normalised in Montreal Neurological Institute space and were smoothed with a 6 mm at half maximum gaussian kernel. The entire preprocessing pipeline was carried out with SPM12b. A band-pass filter was applied to the images before the final smoothing. The software REST served this purpose (Song et al., 2011).

[Insert Tables 1-2 about here]

To extract individual maps of functional connectivity, three seed regions were created (Figure 2). The main seed of interest was obtained from the right inferior-dorsal portion of the orbitolateral prefrontal cortex, encompassing Brodmann areas 45 and 47. These areas were chosen based on evidence from brain morphometric or blood flow/metabolism imaging studies of AD patients showing confabulatory or delusional behaviours. A homologous seed was created in the contralateral region to compute a control pattern of prefrontal connectivity (anatomical control). A third seed was drawn in the calcarine cortex, bilaterally, to include primary visual areas which are largely spared in AD and, presumably, are not significantly involved in any pathological processes seen in neurodegeneration (methodological control). Two additional masks, finally, were created based on the white-matter and cerebrospinal-fluid maps. All seed regions were generated using the WFU PickAtlas toolbox (Maldjian, Laurienti, Kraft & Burdette, 2003). The MARSeille Boîte À Région d'Intérêt (MarsBaR) software (marsbar.sourceforge.net) was used to extract the seed-specific signal time-courses within the aforementioned five regions for each of the 36 datasets (Brett, Anton, Valabregue, & Poline, 2002). Subsequent subject-specific and group-level analyses were run with SPM12b. Individual maps of seed-based connectivity were computed regressing out the signal time-courses associated with the maps of white matter and cerebrospinal fluid, and the six vectors of linear and rotational in-scanner motion estimated during realignment. A conjunction analysis was run to describe the patter of functional connectivity of the three seeds. These are illustrated in Figure 3 for descriptive purposes. Group-level differences in connectivity between patients with and patients without confabulatory tendencies were then inferred by running t tests, collapsing the maps of all participants into a single model. All

comparisons were run controlling for age, MMSE score, and institution of recruitment, to correct for technical differences in acquisition specifics.

[Insert Figures 2-3 about here]

An uncorrected set-level p value equal to 0.005 was chosen as threshold of significance. This was further reduced to $p < 0.0017$ to account for the number of seeds. Only clusters surviving a cluster-level Family-Wise Error-corrected $p < 0.05$ were considered for interpretation. Peak coordinates of surviving clusters were converted into Talairach space using a non-linear transform (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m), and were interpreted using the Talairach Daemon client (http://www.talairach.org/client.html), selecting the "Nearest Gray Matter" search option (Lancaster et al., 2000).

3. Results

No differences in core demographic or neuro-structural indices were found between the sample of patients showing tendencies to confabulate and controls (Tables 1-2). Also, VBM analyses revealed no group-differences in grey matter or white matter. This held true when the analysis-specific template was constructed based on the pooled sample as well as when institution-specific templates were created. Among the cognitive indices of Database 1, graphabulators had significantly lower scores on the test performance of the Rey-Osterrieth Figure. No between-group differences in verbal-memory performance were instead found in Database 2 (Table 3). Figure 3 shows the functional connectivity of the three seeds across the entire sample. While the occipital seed showed mainly a pattern of connectivity limited

to local areas, the two orbitolateral prefrontal seeds showed a connectivity pattern with the contralateral region, the ipsilateral caudate nucleus, and ipsilateral frontal and temporo-insular regions.

Differences in prefrontal connectivity were found (Table 4, Figure 4). Patients with a confabulatory retrieval had decreased functional connectivity between the right seed and the right mediotemporal complex, including the hippocampus, amygdala, and uncus, bordering to lateral temporal regions. Moreover, a significant decrease was also found in the insula, bilaterally. At the same time, this group also showed increased seed-based connectivity within the contralateral Brodmann Area 47 and other prefrontal regions. Group-differences were also visible in the connectivity pattern of the anatomical-control seed. Patients with a confabulatory retrieval had increased seed-based connectivity in the caudate nucleus and within a midline cluster located between the posterior portion of the ventromedial prefrontal cortex and the anterior cingulate gyrus. A concurrent decrease was found in left temporal regions. No meaningful group differences were found in the functional connectivity of the methodological-control occipital seed.

[Insert Figure 3 and Tables 3-4 about here]

The presence of increased connectivity between the right seed and regions centred in the left seed was further explored. Post-hoc analyses were run to understand whether the increased connectivity between the right and the left seed seen in confabulators was the result of compensatory mechanisms. This was investigated in Database 2 only. The performance on the delayed recall of the Rey-Osterrieth Complex Figure, in fact, is usually scored 0 if the participant draws, for instance, a house (as shown in Figure 1). For this reason, memory scores collected in Database 1 were not appropriate for hypothesis testing. To test this

hypothesis the timecourse of the two seeds was extracted, and Pearson's r was calculated. Partial correlations were run controlling for the timecourse of white matter and cerebrospinal fluid signal, and in-scanner motion regressors (i.e. controlling for the same vectors as with the voxel-by-voxel seed-based connectivity maps). r scores were converted into z scores using Fischer's r-to-z transformation. A verbal memory composite was built. For sake of simplicity, the raw scores on the five memory tests were summed up to obtained a score indicative of the total number of retrieved items. An r coefficient of correlation was then modelled to test the presence of an association between z-transformed seed-to-seed connectivity and memory retrieval. To test the hypothesis of compensatory mechanism a one-tailed significance was chosen, under the assumption that a positive coefficient of correlation would support the compensatory nature of this functional connection. Surprisingly, a significant negative correlation was found ($r = -0.452$, $p = 0.030$), indicating that the stronger the connectivity, the poorer the retrieval (Figure 5).

[Insert Figure 5 about here]

4. Discussion

In this study, reduced functional connectivity between right inferolateral frontal cortex and right mediotemporal regions including hippocampus, uncus and amigdala was detected only in those patients who showed a tendency to confabulate either in the visuospatial or in the verbal domains. Insular down-regulations were also found in both hemispheres. Increased connectivity between the right seed and some of the homologous areas on the left side was detected within the inferolateral prefrontal cortex. When functional connectivity of the homologous controlateral seed was analysed, confabulators showed increased functional

connectivity between this left seed and the anterior cingulate and ventromedial prefrontal cortex, plus an involvement of the right caudate. These findings seem to suggest that confabulatory tendencies occur as the result of a multiplicity of disrupted connectivity processes associated with crucial frontotemporal regions in patients in the early stage of neurodegeneration of AD type. A crucial element for confabulatory tendency to emerge seems to be a reduction in connections between memory retrieval structures in mediotemporal regions and behaviour monitoring computational hubs in the frontal cortex. This is in line with the hypothesis of malfunctioning of the hippocampus proposed by Dalla Barba and La Corte (2013). Based on this finding, the malfunctioning would consist in a loss of communication with the prefrontal regions deputed to some sort of control.

Disruption of functional connectivity was also found between the right frontal seed and the insular region. The insula is part of the limbic system and it is richly interconnected with temporopolar and lateral orbital structures. It is the main point of cortical connection between mediotemporal structures, especially the amygdala, and orbitofrontal cortex (Mesulam & Mufson, 1982). Confabulations have been observed following damage of the insula (see Schnider, 2008). Breakdown of insular connectivity, therefore, would disrupt communication between crucial cortical hubs supporting memory retrieval and verification, facilitating the emergence of confabulatory intrusions. In addition, the evidence of increased connectivity between the right and left seed might indicate a contribution from overfiring left frontal regions, whose output cannot be promptly and thoroughly sifted through by defective mediotemporal and right inferolateral frontal regions and their associated processes. Importantly, post-hoc analyses suggested that increases in this cross-hemispheric pathway connectivity did not support a compensatory regulation. In fact, an index of connectivity calculated ad hoc was negatively associated with memory performance.

An interesting finding is also that related to the functional connectivity of the left frontal anatomical control seed. As indicated by Figure 3 illustrating the connectivity of the seeds in the entire sample, the caudate belongs to the "standard" pattern of connectivity. Group-differences found in this region can therefore be simply seen as a simple intensification of this pattern. More relevant is the increased functional connectivity found within a midline cluster located between the posterior portion of the ventromedial prefrontal cortex and the anterior cingulate gyrus. Up-regulation of frontal activity, and especially of midline and anterior cingulate regions, might be responsible for the inefficient output monitoring of confabulators. There is extensive evidence that up-regulation of brain default activity in frontal midline regions is not advantageous for cognitive efficiency in ageing (Grady, Springer, Hongwanishkul, McIntosh & Winocur, 2006; Persson, Lustig, Nelson & Reuter-Lorenz, 2007; Duverne, Motamedinia & Rugg, 2009). There is, in fact, evidence that, even in healthy older adults, inefficient suppression of default mode activity (i.e. the brain activity present when the brain is not engaged in any purpose led activity, as described by Raichle and colleagues (2001)) when engaging in cognitive tasks leads to poorer cognitive performance (Miller et al, 2008). Such inability to disengage from default-mode areas has been held accountable for increased vulnerability to distraction from irrelevant information in ageing. Such a mechanism, but exacerbated by the additional burden of neuropathology, might be at play in the inability to distinguish accurately signal from noise in memory retrieval in confabulators and to exercise early cognitive control on behaviourally salient elements such as internally generated signal errors. Additionally, it is possible that this mechanism interacts with the monitoring role of the orbitofrontal cortex proposed by Schnider (2001) based on lesion studies.

Reduced connectivity of the right seed region of interest was found with the hippocampal region on the right side only. This finding might not necessarily signify that right

hippocampal disconnection might be a crucial player in the genesis of confabulation. An equal role might also be played by its contralateral counterpart. Furthermore, the group of confabulators investigated in this report produced confabulatory responses both in the verbal and the visuospatial domain. A possible explanation for the unilateral alteration in connectivity with right mediotemporal structures might be that this finding is a statistical artefact due to the fact that by this stage of disease the left hippocampal region is already significantly more damaged than the right and any possible analysis of synchronous activity such as that at the basis of the seed based connectivity analysis used in this study would be too underpowered in that region to emerge as a significant finding. Relative more atrophy of the left hippocampus than the right is a recurrent finding in the early stages of AD (Vijayakumar & Vijayakumar, 2013). Within subject analysis of hippocampal volume in the sample included in this study confirmed the presence of hippocampal asymmetry (right hippocampus bigger than left) also in these patients. This was visible in the entire sample (paired t test to compare the two volumes, $p = 0.018$).

This study is not free from limitations. The small sample size dictated by the rarity of confabulatory tendencies in early AD begs caution on the generalisability of the findings to interpret more consolidated forms of confabulation. Furthermore, the heterogeneity of the sample including both confabulators in the verbal and in the visuospatial domain might also have been a confounding factor. Nevertheless, the approach used for the first time in this study suggests that more than dysfunction or lesion in a unique site, it is the interaction between two or more computational hubs that is important to maintain normal cognitive performance. It can be suggested that when homeostasis in the system is disrupted in regions that support crucial key computation relevant for memory performance, then confabulation may appear.

This study is by no means definite evidence but offers a possible interpretational avenue to be more exhaustively explored by future studies of patients presenting more consolidated and established confabulatory phenomena.

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Annalena Venneri, Micaela Mitolo and Matteo De Marco declare that they do not have any conflict of interest.

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Figure captions

Figure 1.

(a) Three examples of the performance in the delayed recall of the Rey-Osterrieth Figure test of patients who show graphabulatory tendencies (Database 1). Below (b), examples of confabulatory elements visible from the performance in tests of verbal memory and learning

Figure 2.

The three seeds investigated in this study. The main seed, encompassing the right Brodmann Areas 45 and 47 is indicated in blue. The anatomical-control left seed encompassing the left Brodmann Areas 45 and 47 is illustrated in red. The anatomical-control seed located in the calcarine cortex is shown in green in the last slice. The figure is in neurological visualisation. Axial slices in the MNI space are as follows: z = -24, -21, -8, -1, 10, 25, 12

Figure 3.

Pattern of seed-based connectivity across the entire sample. Each prefrontal seed was functionally connected with ipsilateral areas (prefrontal, insular, anterior temporal, and the caudate) and the contralateral homologous. The figure is in neurological visualisation. Axial slices in the MNI space are as follows: z = -15, -10, -5, 0, 15, 25

Figure 4.

Significant group differences between patients with and patients without confabulatory retrieval. The differences seen in the connectivity of the right seed are illustrated in red (non-confabulators > confabulators) and blue (confabulators > non-confabulators). In order, the MNI coordinates of these four slices are: z = -29, z = -2, z = 34, z = 22. The differences seen

in the connectivity of the left seed are illustrated in green (non-confabulators > confabulators) and light blue (confabulators > non-confabulators). In order, the MNI coordinates of these four slices are: z = 7, x = 40, x = 17, x = -3

Figure 5

Linear association between the seed-to-seed pattern of connectivity of the orbitolateral prefrontal cortex and memory-retrieval performance

Table 1. Demographic characterisation of the sample included in this study

Variable	Presence of Confabulatory Tendencies	Absence of Confabulatory Tendencies	p
Age at scan (years)	68.67 (10.56)	66.89 (11.47)	0.632
Education Levels (years)	10.69 (4.15)	10.92 (4.14)	0.873
Gender (f/m)	10/8	10/8	1.000
Mini Mental-State Examination (Max. 30)	21.50 (3.31)	22.28 (4.04)	0.532

Apart from the variable "Gender", means and standard deviations are indicated. Between group differences were computed with Independent-sample t tests. Gender-ratio differences were instead calculated with a chi-square test

Table 2. Global brain structural properties of the sample included in this study

Variable	Presence of Confabulatory Tendencies	Absence of Confabulatory Tendencies	p
Grey-Matter Volume (cm^3)	531.62 (73.31)	546.16 (66.48)	0.537
White-Matter Volume (cm^3)	406.08 (53.05)	407.32 (58.35)	0.947
Cerebrospinal-Fluid Volume (cm^3)	440.37 (115.07)	482.85 (124.11)	0.294
Grey-Matter Fraction	0.3869 (0.05)	0.3835 (0.05)	0.833
White-Matter Fraction	0.2952 (0.03)	0.2840 (0.02)	0.253
Brain Parenchymal Fraction	0.6821 (0.07)	0.6675 (0.06)	0.514
Total Intracranial Volume (cm^3)	1378.07 (124.00)	1436.34 (186.50)	0.277

Between group differences were computed with Independent-sample t tests

Table 3. Cognitive scores in the two groups of patients included in this study

Variable	Presence of Confabulatory Tendencies	Absence of Confabulatory Tendencies	p
Rey-Osterrieth Figure - Delayed Recall (Max. 36)	1.72 (2.05)	6.44 (3.75)	0.004 *
Paired Associates Test (Max. 24)	5.11 (3.89)	7.44 (6.48)	0.368
Prose Memory Test - Immediate Recall (Max. 24)	5.33 (4.03)	5.89 (3.82)	0.768
Prose Memory Test - Delayed Recall (Max. 24)	3.67 (4.58)	7.00 (5.59)	0.186
CERAD Learning Test (Max. 30)	11.33 (5.27)	10.56 (4.36)	0.737
CERAD Verbal Recall Test (Max. 10)	1.78 (2.54)	3.22 (2.28)	0.222

Database-specific statistics are reported. Specifically, the performance on the delayed recall of the Rey-Osterrieth Figure was investigated in Database 1, whereas the remaining, verbal tests were investigated in Database 2. Means and standard deviations are indicated

Table 4. Difference in functional connectivity between the two groups

Cluster-Level pFWE	Extent (voxels)	Peak-level Z Score	Brain Region	BA	Talairach Coordinates x	y	z
Right Prefrontal Seed - Non Confabulators > Confabulators							
0.028	156	4.13	Superior Temporal Gyrus	38	38	1	-15
		3.97	Uncus	20	34	-9	-26
		3.75	Hippocampus		30	-10	-23
< 0.001	612	4.64	Insula	13	44	-19	12
		4.07	Superior Temporal Gyrus	22	50	-2	2
		4.07	Insula	13	55	-38	18
< 0.001	321	4.32	Claustrum		-36	-2	-2
		4.13	Insula	13	-46	10	-2
		4.09	Superior Temporal Gyrus	38	-42	7	-10
Right Prefrontal Seed - Confabulators > Non Confabulators							
0.004	228	4.01	Inferior Frontal Gyrus	47	-28	25	-13
		3.78	Inferior Frontal Gyrus	11	-20	27	-13
		3.59	Caudate Head		-6	18	3
< 0.001	1088	4.37	Superior Frontal Gyrus	10	20	58	-8
		4.35	Superior Frontal Gyrus	10	32	51	18
		4.28	Frontal, Sub-Gyral		34	43	-2
0.008	200	4.03	Superior Frontal Gyrus	10	-16	55	17
		3.74	Medial Frontal Gyrus	9	-8	37	33
		3.49	Medial Frontal Gyrus	9	-4	44	33
Left Prefrontal Seed - Non Confabulators > Confabulators							

< 0.001	491	4.89	Superior Temporal Gyrus	22	-53	-29	7
		4.61	Superior Temporal Gyrus	41	-53	-19	3
		4.29	Superior Temporal Gyrus	22	-63	-25	7
0.001	326	4.24	Fusiform Gyrus	37	-50	-44	-18
		4.16	Middle Temporal Gyrus	20	-48	-37	-7
		4.15	Parahippocampal Gyrus	36	-36	-24	-19
0.005	230	4.23	Superior Temporal Gyrus	38	38	3	-10
		3.82	Inferior Frontal Gyrus	47	30	15	-14
		3.64	Insula		40	-10	0
Left Prefrontal Seed - Confabulators > Non Confabulators							
< 0.001	1329	4.51	Superior Frontal Gyrus	9	16	50	27
		4.48	Medial Frontal Gyrus	6	4	29	34
		4.46	Frontal Lobe, Sub-Gyral	8	-12	25	41
< 0.001	892	4.29	Insula	13	-32	26	15
		4.24	Sub-lobar, Extra-Nuclear	13	-26	19	-9
		4.15	Precentral Gyrus	44	-51	8	5
0.002	270	3.86	Caudate Body		16	16	10
		3.67	Caudate Head		16	19	-3
		3.64	Caudate Body		16	8	9

Only contrasts revealing significant group differences are reported

Figure 1

a **Examples from the delayed recall of the Rey-Osterrieth Complex Figure**

b **Examples from Paired-Associates performance**

Obey → "*Order*"
Cabbage → "*Sport*"
Baby → "*Dummy*"
Rose → "*Thorn*"
Crush → "*Mash*"
Cabbage → "*Cauliflower*"

Examples from Prose-Memory test

"*... shepherd who looked after his sheep...*" (delayed recall)
"*... a bus that came early on...*" (immediate recall)
"*It had a donkey in it which had a bucket with some fruit in it...*" (delayed recall)

Examples from CERAD verbal memory tests

"*Bucket*" (learning phase)
"*Dog*" (learning phase)
"*Somebody trying to go over a fence*" (learning phase)
"*Style*" (recall pahse)

Figure 2

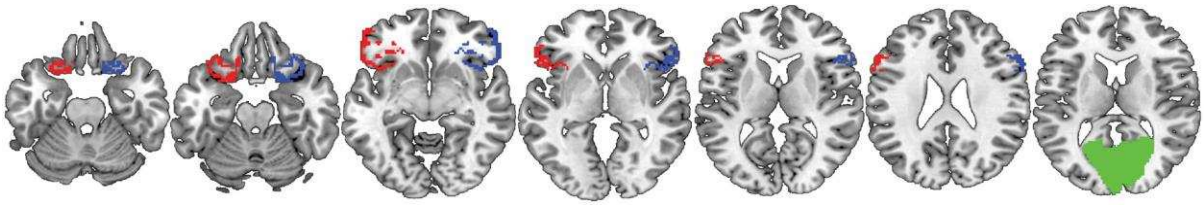


Figure 3

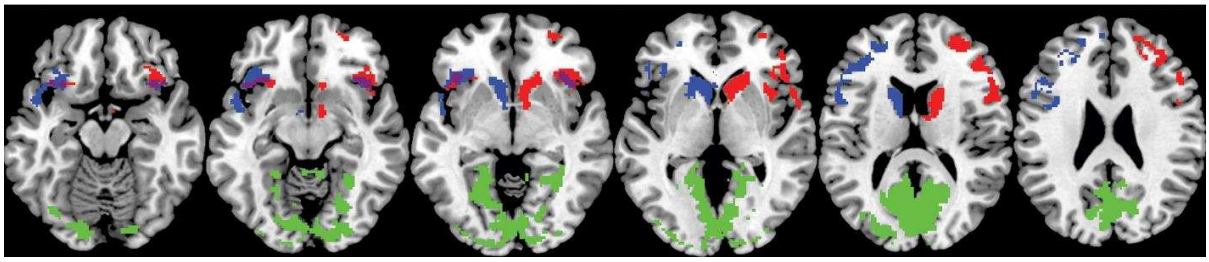


Figure 4

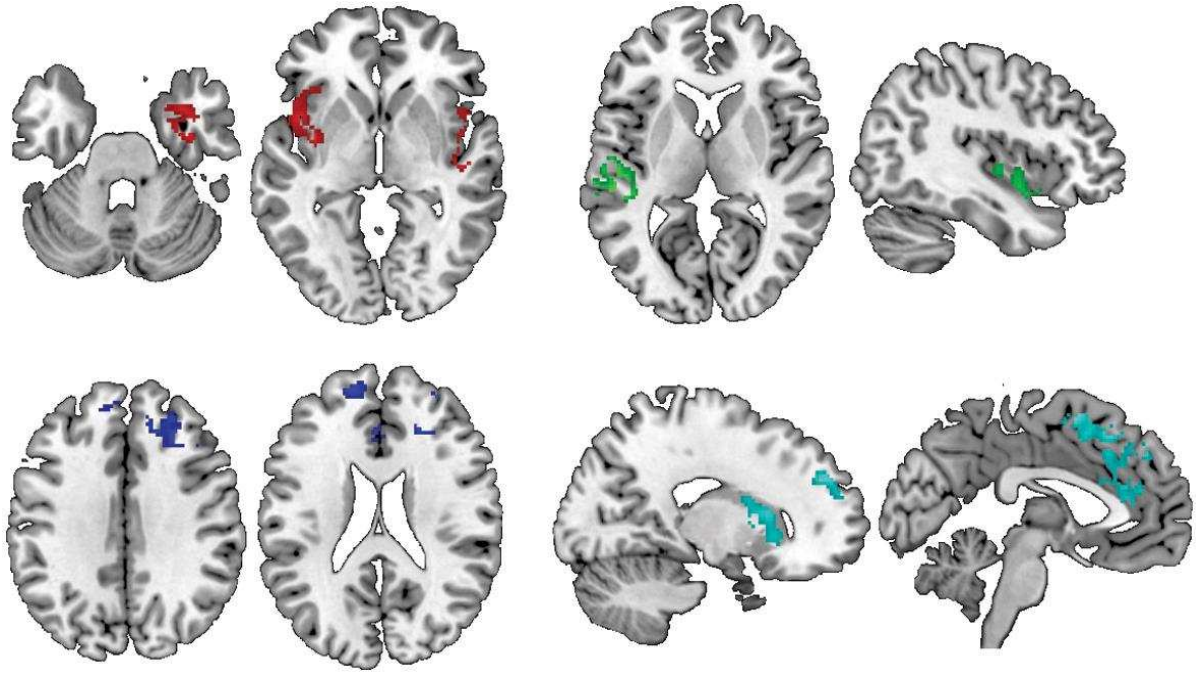
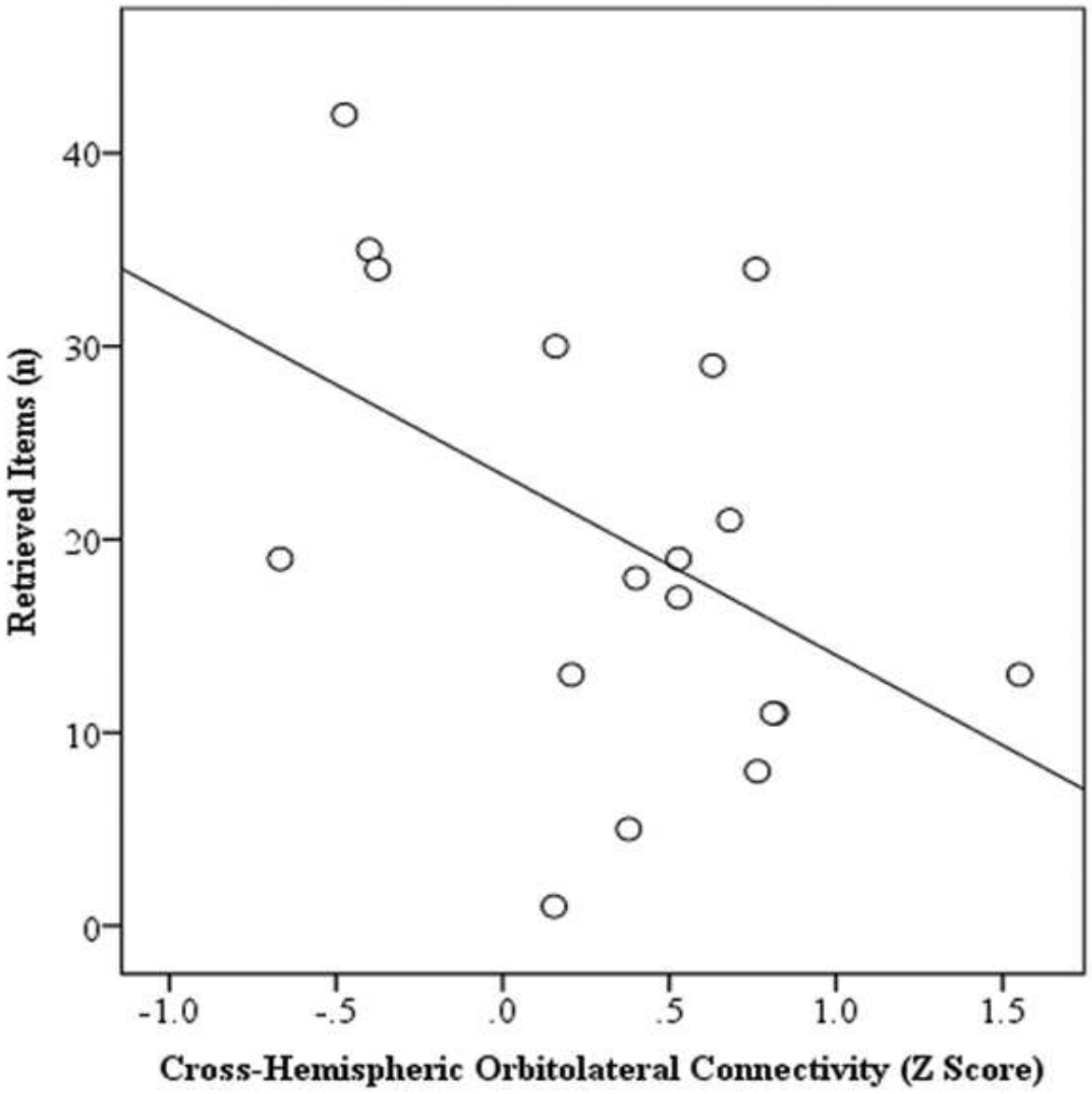


Figure 5


Retrieved Items (n)
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30
20
10
0
-1.0
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.5
1.0
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Cross-Hemispheric Orbitolateral Connectivity (Z Score)