Reduced integration and improved segregation of functional brain networks in Alzheimer’s disease

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Abstract

Objective. Emerging evidence shows that cognitive deficits in Alzheimer’s disease (AD) are associated with disruptions in brain functional connectivity. Thus, the identification of alterations in AD functional networks has become a topic of increasing interest. However, to what extent AD induces disruption of the balance of local and global information processing in the human brain remains elusive. The main objective of this study is to explore the dynamic topological changes of AD networks in terms of brain network segregation and integration.

Approach. We used electroencephalography (EEG) data recorded from 20 participants (10 AD patients and 10 healthy controls) during resting state. Functional brain networks were reconstructed using EEG source connectivity computed in different frequency bands. Graph theoretical analyses were performed assess differences between both groups.

Main results. Results revealed that AD networks, compared to networks of age-matched healthy controls, are characterized by lower global information processing (integration) and higher local information processing (segregation). Results showed also significant correlation between the alterations in the AD patients’ functional brain networks and their cognitive scores.

Significance. These findings may contribute to the development of EEG network-based test that could strengthen results obtained from currently-used neurophysiological tests in neurodegenerative diseases.

Keywords: EEG signal processing, brain networks, Alzheimer’s disease

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\footnotesize{Supplementary material for this article is available online}

(Some figures may appear in colour only in the online journal)
In this context, electroencephalography (EEG) has some major assets since it is a non-invasive, easy to use and clinically available technique. A potential framework for advanced EEG analysis is the emerging technique called ‘MEG/EEG source connectivity’ (de Pasquale et al 2010, Hipp et al 2012, Mehrkanoon et al 2014, Hassan et al 2015, Kabbara et al 2017). As shown by several recent studies (Hassan et al 2017a, 2017, Engels et al 2017), this technique could indeed respond to clinical demand, provided that appropriate information processing is performed. Previous results, using the EEG source connectivity methods, showed alterations in the functional connectivity at the theta and alpha2 bands in AD patients compared to controls (Canuet et al 2012). Relationships between the dysfunctional connections in AD patients and the cognitive decline progression were also observed (Hata et al 2016). Moreover, Vecchio et al showed, in a large group of AD patients, changes in topological brain network characteristics mainly in the clustering coefficient and the path length measures (Vecchio et al 2014).

However, to what extent the AD modifies the brain network segregation (local information processing) and integration (global information processing) remains unclear. This is the main objective of the paper. More precisely, we address two questions: (i) do the dynamic brain network segregation and integration changes in AD compared to controls? And (ii) is there a correlation between the network disruptions and the cognitive score of the AD patients? To tackle this issue, we combined the use of the EEG source connectivity with the graph theory based analysis. Resting state EEG data were recorded from 20 participants (10 AD patients and 10 age-matched controls). The functional networks were reconstructed at the cortical level from scalp EEG electrodes. The identified networks were then analyzed by graph measures that allow the characterization of these networks at different scales from high-level topology to low-level topology.

Materials and methods

The full pipeline of this study is illustrated in figure 1.

Participants

Ten healthy controls (6 males and 4 females, age 64–78 year) and ten patients diagnosed with AD (5 females and 5 males, age 66–81 year) participated in this study. All subjects provided informed consent in accordance with the local institutional review boards guidelines (CE-EDST-3-2017). Patients were recruited from the memory clinic of Dar al-Ajaza Hospital and from Mazloum Hospital, Tripoli, Lebanon. Age-matched healthy controls were recruited from Dar Al-Ajaza Hospital and the local community. For each subject medical history, a cognitive screening test and EEG recording were performed. The mini-mental state examination (MMSE) was used as an indicator of the global cognitive performance (Folstein et al 1975). This test has been widely used to characterize the overall cognitive level of AD patients and to estimate the severity and progression of cognitive impairment (Ismail et al 2010). Based on Mungas (1991), any score greater than or equal to 24 points out of 30 (MMSE ≥ 0.8) indicates normal cognitive functions. Below this score indicate cognitive impairment.

Data acquisition and preprocessing

EEG signals were recorded using a 32-channel EEG system (Twente Medical Systems International-TMSi-, Porti system) placed on the head according to the 10–20 system (Klem et al 1999). Signals were sampled at 500 Hz and band-pass filtered between 0.1–45 Hz. All subjects underwent 10 min of resting-state in which they were asked to relax and keep their eyes closed without falling asleep.

EEG signals are often contaminated by several sources of noise and artifacts. In order to clean raw signals, the pre-processing followed the same steps as described in several previous studies dealing with EEG resting state data (Onton et al 2006, Korjus et al 2015, Li et al 2015, Hassan et al 2017b, Kabbara et al 2017). Briefly, the bad channels (i.e. displaying signals that are either completely flat or are contaminated by movement artifacts) were first identified by visual inspection, complemented by the power spectral density, when needed. Then, these bad channels were recovered using an spherical interpolation procedure implemented in EEGLAB (Delorme and Makeig 2004). In addition, epochs with voltage fluctuation > +80 μV and < −80 μV were removed. Consequently, for each participant, four artifact-free epochs of 40s lengths were selected. This epoch length was largely used previously and considered as a good compromise between the needed temporal resolution and the reproducibility of the results (Kabbara et al 2017). As the recorded EEG data used here has a very high temporal resolution (~1 ms), the number of available samples is largely sufficient to compute statistically-consistent functional networks. By using a sliding window approach while calculating the functional connectivity, a high number of networks were obtained for each 40 s-epoch and for different frequency bands.

The EEGs and MRI template (ICBM152) were co-registered after identifying the anatomical landmarks (left and right pre-auricular points and nasion) using Brainstorm (Tadel et al 2011). An atlas-based segmentation approach was used to project EEGs onto an anatomical framework consisting of 68 cortical regions identified by means of Desikan-Killiany (Desikan et al 2006) atlas, see table S1 (supplementary materials (stacks.iop.org/JNE/15/026023/mmedia)) for more details about the names and abbreviations of these regions. The lead field matrix was then computed for a cortical mesh of 15 000 vertices using OpenMEEG (Gramfort et al 2010).

Brain networks construction. Brain networks were constructed using the ‘EEG source connectivity’ method (Hassan et al 2014). It includes two main steps: (1) Reconstruct the temporal dynamics of the cortical sources by solving the inverse problem, and (2) Measure the functional connectivity between the reconstructed time series. Here, we used the weighted minimum norm estimate (wMNE) algorithm
as inverse solution (Hamalainen and Ilmoniemi 1994). The reconstructed regional time series were filtered in different frequency bands (theta (4–8 Hz); alpha1 (8–10 Hz); alpha2 (10–13 Hz); beta (13–30 Hz)). The functional connectivity was computed, for each frequency band, between the regional time series using the phase locking value (PLV) measure (Lachaux et al 1999). The PLV ranges between 0 (no phase locking) and 1 (full synchronization).

Using PLV, dynamic functional connectivity matrices were computed for each epoch using a sliding window technique (Kabbara et al 2017). It consists in moving a time window of certain duration \( \delta \) along the time dimension of the epoch, and then PLV is calculated within each window. As recommended in Lachaux et al (2000), we chose the smallest window length that is equal to \( \frac{6}{\text{central frequency}} \) where 6 is the number of ‘cycles’ at the given frequency band. In theta band, as the central frequency (CF) equals to 6 Hz, \( \delta \) equals 1s. Likewise, \( \delta = 666 \text{ ms} \) in alpha1 band (CF = 9 Hz), 521 ms in alpha2 band (CF = 11.5 Hz), and 279 ms (CF = 21.5 Hz) in beta band. Functional connectivity matrices were represented as graphs (i.e. networks) composed of nodes, represented by the 68 ROIs, and edges corresponding to the functional connectivity values computed over the 68 regions, pair-wise.

Considered \( \delta \) values yield, for each epoch, to 33 networks in theta band, 66 networks in alpha1 band, 76 networks in alpha2 band and 130 networks in beta band.

**Multi-slice networks modularity.** The modularity aims at decomposing a network into different communities of high intrinsic connectivity and low extrinsic connectivity (Eickhoff et al 2005). To describe and quantify the evolution of brain networks as a function of time, we applied the multi-slice modularity (Bassett et al 2013). In this method, the nodes across network slices (time windows) are linked via a coupling parameter using a quality function given by the following formula:

\[
Q_{ml} = \frac{1}{2m} \sum_{ijl} \left\{ \left( A_{ijl} - \gamma \frac{k_{il}k_{jl}}{2m} \right) \delta_{x} + \delta_{y} C_{ijl} \right\} \delta \left( M_{il}, M_{jl} \right).
\]

Where nodes \( i \) and \( j \) are assigned to communities \( M_{il} \) and \( M_{jl} \) in slice \( l \), respectively. \( A_{ijl} \) represents the weight of the edge between \( i \) and \( j \). \( \gamma \) is the structural resolution parameter of slice \( l \). \( C_{ijl} \) is the connection strength between the node \( j \) in slice \( r \) and the node \( j \) in slice \( l \). The structural resolution parameter \( \gamma \) and the inter-slice coupling parameter are set to 1. \( k_{il} \) is the strength of the node \( i \) in slice \( l \), the \( \delta \)-function \( \delta(x, y) \) is 1 if \( x = y \) and 0 otherwise, \( m = \frac{1}{2} \sum_{ij} A_{ij} \) and \( \mu = \frac{1}{2} \sum_{j} k_{jl} \).

The multi-slice modularity algorithm was applied with diagonal and ordinal inter-slice couplings. Diagonal and ordinal coupling means that each node is only connected to itself in the adjacent slices. Here, a slice corresponds to a network at a given time period. Hence, the number of slices equals the number of windows at a given frequency band.

To deal with the ‘degeneracy’ problem, we computed a 68 \times 68 association matrix (Sales-Pardo et al 2007, Rubinov and Sporns 2011, Lancichinetti and Fortunato 2012) where the element \( A_{ij} \) represents the number of times the nodes \( i \) and \( j \) are assigned to the same module across 200 runs using Louvain algorithm (Blondel et al 2008). The association
matrix was then compared to a null-model generated from 100 random permutations of the original partitions. That is, for each of the 100 partitions, we reassign nodes uniformly at random to the modules present in the partition. This generates a null model matrix whose element $A_{ij}$ is the number of times the node $i$ and $j$ are randomly assigned to the same community. To remove randomness, we kept the significant values of the original association matrix by setting any element $A_{ij}$ whose value is less than the maximum value of the random association matrix to 0 (Bassett et al. 2013). Finally, the thresholded association matrix was re-clustered using Louvain algorithm.

Network measures

The topological properties of identified networks were characterized using the following graph measures:

Average clustering coefficient. The clustering coefficient of a node represents how close its neighbors tend to cluster together (Watts and Strogatz 1998). Accordingly, the average clustering coefficient of a network is considered as a direct measure of its segregation (i.e. the degree to which a network is organized into local specialized regions) (Bullmore et al. 2009). In brief, the clustering coefficient of a node is defined as the proportion of connections among its neighbors, divided by the number of connections that could possibly exist between them (Watts and Strogatz 1998).

Global efficiency. The global efficiency of a network is the average inverse shortest path length (Latora and Marchiori 2001). A short path length indicates that, on average, each node can reach other nodes with a path composed of only a few edges (Sporns 2010). Thus, the global efficiency is one of the most elementary indicators of network’s integration (i.e. the degree to which a network can share information between distributed regions).

Recruitment. The recruitment of a node $i$ corresponds to the average probability that the node is in the same module across runs and slices (i.e. time windows). It is calculated as follows:

\[
\text{Recruitment}_i = \frac{1}{nM} \sum_{j \in M} A_{ij}.
\]  

(2)

Where $M$ is the module of the node $i$, $nM$ denotes the number of nodes assigned to the module $M$. $A_{ij}$ represents the number of times the nodes $i$ and $j$ are assigned to the same module across slices and runs. A region with high recruitment value tends to maintain itself in the same community across time (Bassett et al. 2015).

Integration. It reflects how modules are interacting with each other. It is computed as the average number of links each node in a given module has with the nodes in the other modules across runs and slices (i.e. time windows). It is calculated as follows:

\[
\text{Integration}_i = \frac{1}{N - nM} \sum_{j \in M} A_{ij}.
\]

(3)

Where $M$ is the module of the node $i$. $N$ denotes the total nodes number, $nM$ the number of nodes assigned to the module $M$. $A_{ij}$ represents the number of times the nodes $i$ and $j$ are assigned to the same module across slices and runs. A region with high integration value tends to be present in communities other than its own across time (Bassett et al. 2015).

Hubs identification

Hubness is a key feature when exploring the brain network architecture due to the high influence of hub nodes on network dynamics and information processing (van den Heuvel and Sporns 2013). Once modules are identified, the 68 nodes were classified into three main categories (non hubs, provincial hubs and connector hubs) using combination of two measures. The first one is the within-module degree $Z$ defined as:

\[
Z_i = \frac{K_i(M_i) - K(M_i)}{\sigma_{k(M_i)}}.
\]

(4)

Where $K_i(M_i)$ is the within-module degree of the node $i$, $K(M_i)$ is the mean of within module degree of nodes assigned to the same community as node $i$, and $\sigma_{k(M_i)}$ is the standard deviation. A positive $Z$ value indicates that the node is highly connected to other members of the same community (Guimerà et al. 2005). In our study, a node is considered as hub if the corresponding within module degree is greater than 1.5.

We then focused on classifying hubs into provincial and connector based on a second metric known as participation coefficient ($P$). This metric characterizes how a node’s edges are distributed across modules:

\[
P_i = 1 - \sum_{c=1}^{C} \left( \frac{K_i(m)}{K_i} \right)^2.
\]

(5)

Where $C$ is the number of modules, $K_i(m)$ is the number of edges between node $i$ and nodes in module $M$. Based on the criteria proposed by Guimerà and Nunes Amaral (2005), a provincial hub having most of its links inside its own module has a $P_i$ value lower than 0.3; while a connector hub has a $P_i$ value greater than 0.3. These values were used in our study.

Attacks on nodes

Like any other networked system, the brain network may lose some of its effectiveness as a result of an ‘attack’. In particular, attacks on regions playing a key role will lead to significant network disruption. For this reason, we quantified the importance of each node in terms of its attack influence on the global network efficiency. This quantification is usually done using a graph measure known as ‘vulnerability’. It is defined as the reduction in global efficiency of the network when the...
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node and all its edges are removed (Goldshtein et al. 2004). Thus, critical nodes can be identified from high vulnerability values as their attack (i.e. node and associated edges removal) leads to significant drop of the whole network efficiency.

Statistical tests

To quantify the differences between healthy and AD networks in terms of RSNs connectivity, average clustering coefficient, global efficiency, integration/segmentation measures and vulnerability, statistical tests were performed. For each subject, we averaged all the metrics values obtained from the different networks among all epochs and time windows for each subject. As data were not normally distributed, we assessed the statistical difference between the two groups using the Mann Whitney U Test also known as Rank-Sum Wilcoxon test (degree of freedom = 18).

For hubs identification, each group was considered separately. First, we concatenated the metrics values (participation coefficient and within-module degree Z) from all group subjects, epochs and time windows. Based on the criteria of hubs classification (Guimera and Nunes Amaral 2005), each node was assigned to its corresponding category (i.e. provincial, connector or non-hub) for each window. Then, the brain regions that are significantly behaving as connector or/and provincial hubs during time were extracted using a chi-squared test (as described in our previous work (Kabbara et al. 2017)). To deal with the family-wise error rate, the statistical tests were corrected for multiple comparisons using Bonferroni method (pBonferroni adjusted < \frac{0.05}{N} ), with N (68) denotes the number of brain regions.

The parcellation into RSNs

Each brain region of the Desikan-Killiany atlas was associated to its corresponding RSN based on Shirer et al. (2012) in which authors identified fourteen functional networks: anterior salience network, auditory network, basal ganglia network, dorsal default mode network, higher visual network, language network, left executive control network, sensorimotor network, posterior salience network, precuneus network, primary visual network, right executive control network, ventral default mode network, and visuospatial network. Here, we focused on five RSNs: the default mode network (DMN) obtained by combining the regions of the dorsal and the ventral default mode network, the salience network (SAN) obtained by associating all the regions in anterior and posterior salience networks, the visual network (VIS) obtained by combining of the higher and primary visual networks. This same parcellation was also used in our previous study (Kabbara et al. 2017).

Results

Intrinsic connectivity of RSNs

First, we were interested in evaluating the differences among the RSNs between healthy controls and AD patients. For this reason, we associated each brain region of the Desikan-Killiany atlas to its corresponding RSN according to Kabbara et al. (2017). Results in Table 1 show significant decreases in DMN connectivity in AD compared to healthy controls in the theta (p = 0.02, U = 15, r = 0.51) and alpha2 (p = 0.031, U = 17, r = 0.47) bands. Similarly, reduced visual network
connectivity was found in beta band ($p = 0.003$, $U = 5$, $r = 0.72$). Conversely, increased SAN connectivity was observed in the theta band ($p = 0.047$, $U = 15.5$, $r = 0.5$).

**Network integration and segregation**

Here, we explored the difference of brain network dynamics between the two groups in terms of segregation using clustering coefficient and integration using the global efficiency measures. No group difference was observed in alpha1, alpha2 and beta bands. In contrast, in theta band, an increase in clustering coefficient ($p = 0.006$; $U = 9$, $r = 0.57$) associated with a decrease in global efficiency ($p = 0.03$; $U = 16$, $r = 0.49$) was found in AD networks.

To better explore the difference between the two groups, we clustered the networks into sub-networks (i.e. modules or communities) for which the integration and the segregation parameters were extracted. AD networks were characterized by a low inter-modular activity (low integration) and high intra-modular connectivity (high segregation) in theta (figure 2), alpha1 (figure S1, supplementary materials), and alpha2 (figure S2, supplementary materials) bands in contrast with results obtained in beta band (figure S3, supplementary materials).

**Hubs identification**

The cortical distributions of connector and provincial hubs identified in healthy subjects and AD patients are illustrated in figure 3. A loss in connector hubs number was observed in AD networks, while the number of provincial hubs was found to increase compared to healthy networks. Specifically, only the left middle orbito-frontal region was conserved in AD network as a connector hub, whereas the right middle orbito-frontal, the left rostral anterior cingulate, the right transverse temporal, the left posterior cingulate, the right posterior cingulate, the right isthmus cingulate and the left precuneus regions were present in healthy networks. In contrast, the left middle orbito-frontal, the right middle orbito-frontal and the right insula appeared as provincial hubs in AD networks.

We then investigated the influence of each node’s removal on the global efficiency of the networks using the vulnerability metric. Results are shown in figure 4. We realized that 11 brain regions were more vulnerable in healthy networks versus AD networks ($p < 0.05$). However, only the right middle orbito-frontal and the left lateral orbito-frontal regions have resisted the Bonferroni correction ($p_{\text{Bonferroni adjusted}} < 0.05$). While the 11 nodes are distributed across several RSNs, the majority of these regions corresponds to DMN (6/11) including mainly
the isthmus cingulate, the middle orbito-frontal and the rostral cingulate.

**Correlation between network measures and cognitive scores**

To assess the relationships between functional connectivity and the AD patient’s cognitive impairment, we have estimated the correlation between the cognitive score (MMSE) and the network measures (clustering coefficient, global efficiency and vulnerability). A negative correlation between the average clustering coefficient and MMSE score ($\rho = -0.95$; $p < 0.001$) was found, while a positive correlation between the network global efficiency and MMSE score ($\rho = 0.94$; $p < 0.001$) was obtained (figure 5). Concerning the vulnerability, we focused on the two nodes that showed statistical difference between groups. Figure 5 shows that the MMSE score correlates positively with the left lateral orbito-frontal region ($\rho = 0.84$; $p = 0.002$), and the right middle orbito-frontal region ($\rho = 0.87$; $p = 0.001$).

**Discussion**

The main objective in this study is to explore the dynamic topological properties of AD networks compared to healthy controls. Particularly, we focused on examining the shifting balance between brain network integration and segregation in Alzheimer’s disease. For this end, resting state EEG signals were recorded from 20 participants (10 AD patients and 10 controls). The cortical functional networks were reconstructed from scalp signals using the EEG source connectivity method. A sliding window approach was used to track the dynamics of networks. To examine the differences between the two groups (AD versus controls), several network measures were extracted. The measures used to quantify the integration of networks are: the network global efficiency, the inter-modular connections and the connector hubs. To quantify segregation we extracted the clustering coefficient, the intra-modular connections and the provincial hubs. The nodes resilience against attacks was also analyzed in order to identify the main brain regions potentially affected by AD. Interestingly, a general trend is that all metrics showed that AD networks tend to have improved segregation (higher local information processing) and reduced integration (lower global information processing). Results also showed a significant correlation between patients’ cognitive performance (as measured by the MMSE score) and network measures. Results are discussed in detail hereafter.

**AD networks: high segregation and low integration**

Results indicated that AD networks are characterized by lower integration (revealed by a decrease in the network global efficiency, the number of connector hubs and the integration measure), and higher segregation (revealed by an increase...
in clustering coefficient, in the number of provincial hubs and in the recruitment measure) compared to healthy control networks. One possible interpretation of the increased local connectivity is a possible compensatory mechanism that is triggered by the dysfunctional integration in the AD brain networks (Afshari and Jalili 2017). These findings are in line with studies that revealed decrease in the network global efficiency (Stam et al 2009, Lo et al 2010, Douw et al 2011, Stam

Figure 4. Difference between healthy subjects and AD patients in term of node vulnerability. (A) Distribution of vulnerability values for the 68 ROIs in healthy control networks (black color) and in AD networks (red color). A node is marked with * if it shows significant difference between groups ($p < 0.05$, uncorrected) and with ** if it shows significant difference after correction for multiple comparisons. (B) Cortical distribution of the 11 significant nodes. The node color corresponds to the matching RSN (see table 1 for ROI names and abbreviations). The nodes with larger size are those who resisted the multiple comparison adjustment.
Altered brain networks/regions in Alzheimer’s disease

On the one side, the detection of nodal changes can reveal important insights about which brain regions are severely altered by the disease. Our results show a change in hub properties for R MOF, L rACC, R TT, L/R pCC and L pCUN (see table 1 for abbreviations). We also hypothesized that the removal of an important brain region will affect the information processing in the whole network, while an attack to a less critical region will have a smaller influence on the global network efficiency. We found 13 brain regions that have more importance in healthy network than in AD networks. One can realize that some of the affected hubs (figure 3) coincide with the 13 nodes (rACC, MOF, pCUN, TT). These affected nodes were also reported in Sorg et al (2007), Bai et al (2009), Buckner et al (2009), Mormino et al (2011), De Haan et al (2012), Vemuri et al (2012) and Tijms et al (2013b). Other studies also reported that amyloid decomposition in AD coincide with hubs location (Buckner et al 2009).

On the other side, alterations in the default mode network (DMN) connectivity in AD patients were reported in several studies (Li et al 2002, Greicius et al 2004, Wang et al 2006, Sorg et al 2007, Hedden et al 2009, Sheline et al 2010, Drzezga et al 2011, Mormino et al 2011, Vemuri et al 2012). Our results showed that the majority of the affected nodes in terms of vulnerability and hub dys-functionality are associated to the DMN. The disruption of DMN was also demonstrated by its reduced intrinsic connectivity as reported in table 1. The increased connectivity of DAN and SAN shown in table 1 may be interpreted as a compensatory mechanism due to the DMN alteration (Bai et al 2011, Damoiseaux et al 2012).

Correlation between network measures and AD patient’s cognitive scores

Single-subject analyses showed significant correlation between the MMSE score (used here to provide an overall measure of cognitive impairment) and network global efficiency, average clustering coefficient and vulnerability. Although the MMSE test has received good acceptance as a diagnostic test in the clinical and research community (Nieuwenhuis-Mark 2010), it is recommended not to be used as a stand-alone single administration test (Arevalo-Rodriguez et al 2015). Previous studies have shown that age, education and socio-cultural variables affect the effectiveness of MMSE to detect cognitive impairment (Bleecker et al 1988, Brayne and Calloway 1990, Crum 1993). Hence, the demand is high for other tests that provide higher detection accuracy (Carnero-Pardo et al 2011, 2014), as well as more specific scores (semantic, memory related... etc). In addition, the use of cognitive tasks that stimulate the affected networks in the case of AD (the memory network for instance) may improve the correlations with network based metrics. It is worth noting that the MMSE is not the unique test for AD diagnosis. It is currently used within a set of other tests including clinical examination (reflexes, muscle tone, balance) and brain imaging (such MRI and CT scan) aimed to
pinpoint visible abnormalities related to conditions other than AD (stroke, trauma, etc). However, when MRI is negative (no visible anatomical damages), the screening of cognitive performance using clinical tests such as MMSE (or other specific cognitive scores) is mandatory. The proposed network-based metrics provides additional quantitative indications potentially useful for neurologists to complement diagnosis based on neuropsychological tests.

**Limitations**

First, one of the main limitations of this study is the relatively low number of patients. Our intent was to show the difference between two groups: totally normal (control group) and AD patients with ‘severe’ cognitive impairment. Nevertheless, we are aware that the AD is very heterogeneous and may have different stages including patients with moderate or mild cognitive impairment. Detecting these ‘early’ cognitive deficits is on the major challenges in AD and will certainly be the subject of future investigation. These investigations should be performed on larger cohorts of patients in different AD stages, using other experimental paradigms and additional cognitive scores, in order to be able to generalize the conclusions of the reported analysis.

Second, the EEG source connectivity was applied here to 32 scalp EEG channels. This method has previously proved its robustness in exploring resting-state topology using dense-EEG (>128 electrodes) (Kabbara et al 2016, 2017, Hassan et al 2017b). As reported in Hassan et al (2014), the use of a smaller number of electrodes (in the context of cognitive task) will result in a reduction in the accuracy of the obtained results. Nevertheless, several studies showed the possible extraction of useful information using low number of electrodes (19, 32, 64) (Canuet et al 2012, Vecchio et al 2014, 2017, Hata et al 2016). This can be explained by the facts that these studies (as the presented study) focus on the investigation of ‘large-scale’ networks to compare two groups with the same conditions. In addition, we conjecture that a compromise between the number of channels and the number of ROIs should be necessarily respected. Our very recent findings showed that a high number of electrodes (>32) is mandatory in the case of applications that require higher ‘granularity’, i.e.
spatial precision and accurate characterization of the network local properties, such as the identification of epileptogenic networks (unpublished data).

Third, it is important to keep in mind that measuring the functional connectivity is generally corrupted by the volume conduction problem (Schoffelen and Gross 2009). While the effects of this problem are reduced by the analysis of connectivity at source level, some ‘mixing effects’ remain (Brookes et al 2014). At the source level, few strategies have been suggested (Brookes et al 2012, Colclough et al 2015). The proposed approaches are all based on ignoring zero-lag interactions among signals, by supposing that their contributions are only due to the source leakage. Although these approaches have some advantages, they may also remove true communications that occur at zero lag (Finger et al 2016). In our study, we used the phase locking value measure. In a previous study, we showed that the metrics extracted from the networks constructed using PLV (including the within-module degree, clustering coefficient, betweenness centrality and the participation coefficient) were not affected by the spurious short connections (Kabbara et al 2017). Nevertheless, we believe that further methodological efforts are needed to completely solve the spatial leakage problem.

Fourth, a proportional threshold of 10% was used to remove the spurious connections from the connectivity matrices. Here, we preferred using a proportional threshold to absolute threshold to ensure equal density between groups, as recommended by van den Heuvel et al (2017). Moreover, Garrison et al (2015) showed that network measures are stable across proportional thresholds, in contrast to absolute thresholds. A variety of thresholding methods are available, but no method is free of bias. It is then recommended to perform studies across different values of thresholds (in addition to the use of alternative strategies) to ensure that the obtained findings are robust to this methodological factor.

Fifth, the choice of the inverse solution/connectivity combination was supported by two comparative studies using simulated data from a biophysical/physiological model (Hassan et al 2017a) and real data recorded during a cognitive task (Hassan et al 2014). In both analyses, the combination that showed the highest similarity between reference (ground truth) and estimated networks was the wMNE/PLV, used in the present paper. Nevertheless, other combinations or strategies that showed accurate construction of cortical networks from sensor level recordings could be also investigated and compared such as the use of beamforming combined with amplitude correlation between band-limited power envelopes as reported in several studies (Brookes et al 2011, Brookes et al 2012, Colclough et al 2015, 2016, O’Neill et al 2016).

Conclusions

We reported a study using EEG connectivity at the source level in AD patients and healthy controls. We showed that AD networks are characterized by a reduction in their global performance (integration) associated with an enhancement in their local performance (segregation). We also showed that these network topologies are correlated with the patient’s cognitive scores. We speculate that our findings, when validated on larger cohort, could contribute to the development of EEG-based tests that could consolidate results of currently-used neurophysiological tests.

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References

Afshari S and Jalili M 2017 Directed functional networks in Alzheimer’s disease: disruption of global and local connectivity measures IEEE J. Biomed. Health Inform. 21 949–55

Arevalo-Rodriguez I et al 2015 Mini-mental state examination (MMSE) for the detection of Alzheimer’s disease and other dementias in people with mild cognitive impairment (MCI) Cochrane Database Syst. Rev. 21 CD010783

Axmacher N et al 2006 Memory formation by neuronal synchronization Brain Res. Rev. 52 170–82

Bai F et al 2009 Abnormal resting-state functional connectivity of posterior cingulate cortex in amnestic type mild cognitive impairment Brain Res. 1302 167–74

Bai F et al 2011 Specifically progressive deficits of brain functional marker in amnestic type mild cognitive impairment PLoS One 6 e24271

Bassett D S et al 2013 Robust detection of dynamic community structure in networks Chaos 23 (https://doi.org/10.1063/1.4790830)

Bassett D S et al 2015 Learning-induced autonomy of sensorimotor systems Nat. Neurosci. 18 744–51

Bennys K, Rondouin G, Vergnes C and Touchon J 2001 Diagnostic value of quantitative EEG in Alzheimer’s disease Neurophysiol. Clin./Clin. Neurophysiol. 31 153–60

Benz N, Hatz F, Bousleiman H, Ehrenspeger M M, Gschwandtner U, Hardmeier M, Ruegg S, Schindler C, Zimmermann R and Monsch A U 2014 Slowing of EEG background activity in Parkinson’s and Alzheimer’s disease with early cognitive dysfunction Front. Aging Neurosci. 6 314

Bleecker M L et al 1988 Age-specific norms for the mini-mental state exam Neurology 38 1565–8

Blondel V D et al 2008 Fast unfolding of communities in large networks J. Stat. Mech.: Theory Exp. 2008 P10008

Bosboom J L W et al 2009 MEG resting state functional connectivity in Parkinson’s disease related dementia J. Neural Trans. 116 193–202

Brayne C and Calloway P 1990 The association of education and socioeconomic status with the mini mental state examination

A Kabbara
and the clinical diagnosis of dementia in elderly people Age Ageing 19 91–6
Brookes M J et al 2011 Measuring functional connectivity using MEG: methodology and comparison with fcMRI NeuroImage 56 1082–104
Brookes M J, Woolrich M W and Barnes G R 2012 Measuring functional connectivity in MEG: a multivariate approach insensitive to linear source leakage NeuroImage 63 910–20
Brookes M J, Woolrich M W and Price D 2014 An introduction to MEG connectivity measurements Magnetoencephalography, ed Supek S and Aine C (Berlin: Springer) pp 321–58
Buckner R L et al 2009 Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer’s disease J. Neurosci. 29 1860–73
Bullmore E et al 2009 Complex brain networks: graph theoretical analysis of structural and functional systems Nat. Rev. Neurosci. 10 186–98
Buzsáki G and Draguhn A 2004 Neuronal oscillations in cortical networks Science 304 1926–9
Canolty R T and Knight R T 2010 The functional role of cross-frequency coupling Trends Cogn. Sci. 14 506–15
Canuet L et al 2012 Resting-state network disruption and APOE genotype in Alzheimer’s disease: a lagged functional connectivity study PLoS One 7
Carnero-Pardo C et al 2011 Diagnostic accuracy, effectiveness and cost for cognitive impairment and dementia screening of three short cognitive tests applicable to illiterates PLoS One 6
Carnero-Pardo C et al 2014 A systematic review and meta-analysis of the diagnostic accuracy of the Phototest for cognitive impairment and dementia Dement. Neuropsychol. 8 141–7
Colclough G L et al 2015 A symmetric multivariate leakage correction for MEG connectomes NeuroImage 117 439–48
Colclough G L et al 2016 How reliable are MEG resting-state connectivity metrics? NeuroImage 138 284–93
Crum R M 1993 Population-based norms for the mini-mental state examination by age and educational level J. Am. Med. Assoc. 269 2386–91
Damoiseaux J S et al 2012 Functional connectivity tracks clinical deterioration in Alzheimer’s disease Neurobiol. Aging 33
De Haan W et al 2012 Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer’s disease NeuroImage 59 3085–93
de Pasquale F et al 2010 Temporal dynamics of spontaneous MEG activity in brain networks Proc. Natl Acad. Sci. USA 107 6040–5
Delbeuck X et al 2003 Alzheimer’s disease as a disconnection syndrome? Neuropsychol. Rev. 13 70–92
Delorme A and Makeig S 2004 EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis J. Neurosci. Methods 134 9–21
Desikan R S et al 2006 An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest NeuroImage 31 968–80
Douw L et al 2011 Cognition is related to resting-state small-world network topology: an magnetoencephalographic study Neuroscience 175 169–77
Drzezga A et al 2011 Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden Brain 134 1635–46
Eickhoff S B et al 2005 A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data NeuroImage 25 1325–35
Engels M M A et al 2017 ‘Alzheimer’s disease’: the state of the art in resting-state magnetoencephalography Clin. Neurophysiol. 128 1426–37
Finger H et al 2016 Modeling of large-scale functional brain networks based on structural connectivity from DTI: comparison with EEG derived phase coupling networks and evaluation of alternative methods along the modeling path PLoS Comput. Biol. 12
Folstein M F, Folstein S E and McHugh P R 1975 ‘Mini-mental state’. A practical method for grading the cognitive state of patients for the clinician J. Psychiatric Res. 12 189–98
Garrison K A et al 2015 The (in)stability of functional brain network measures across thresholds NeuroImage 118 651–61
Gol’dshtein V, Koganov G A and Surdutovich G I 2004 Vulnerability and hierarchy of complex networks Physics (arXiv:cond-mat/0409298)
Gramfort A et al 2010 OpenMEEG: opensource software for quasistatic bioelectromagnetics Biomed. Eng. Online 9 45
Greicius M D et al 2004 Default-mode network activity distinguishes Alzheimer’s disease from healthy aging: evidence from functional MRI Proc. Natl Acad. Sci. USA 101 4467–42
Guimerà R and dome Amaral L A 2005 Functional cartography of complex metabolic networks Nature 433 895–900
Hamalainen M S and Ilmoniemi R J 1994 Interpreting magnetic fields of the brain: minimum norm estimates Med. Biol. Eng. Comput. 32 35–42
Hassan M et al 2014 EEG source connectivity analysis: from dense array recordings to brain networks PLoS One 9 (https://doi.org/10.1371/journal.pone.0105041)
Hassan M et al 2015 Dynamic reorganization of functional brain networks during picture naming Cortex 73 276–88
Hassan M et al 2017a Identification of interictal epileptic networks from dense-EEG Brain Topogr. 30 60–76
Hassan M et al 2017b Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson’s disease NeuroImage 14 591–601
Hata M et al 2016 Functional connectivity assessed by resting state EEG correlates with cognitive decline of Alzheimer’s disease—an eLORETA study Clin. Neurophysiol. 127 1269–78
Hedden T et al 2009 Disruption of functional connectivity in clinically normal older adults harboring amyloid burden J. Neurosci. 29 12686–94
Hipp J F et al 2012 Large-scale cortical correlation structure of spontaneous oscillatory activity Nat. Neurosci. 15 884–90
Ismael Z, Rajji T K and Shulman K I 2010 Brief cognitive screening tools for cognitive impairment and dementia screening of three cost for cognitive impairment and dementia screening of three
J. Neurosci. 9
Kabbara A et al 2016 Graph analysis of spontaneous brain network using EEG source connectivity Int. Conf. on Bio-engineering for Smart Technologies (BioSMART) (Dubai, UAE, 4–7 December 2016) (arXiv:1607.00952)
Kabbara A et al 2017 The dynamic functional core network of the human brain at rest Scientific Reports 7 2936
Klem G H, Lüders H O, Jasper H H and Elger C 1999 The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology Electroencephalogr. Clin. Neurophysiol. Suppl. 52 3–6
Klimesch W 1999 EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis Brain Res. Rev. 29 169–95
Korjus K et al 2015 Personality cannot be predicted from the power of resting state EEG Front. Human Neurosci. 9
Lachaux J P et al 1999 Measuring phase synchrony in brain signals Human Brain Mapp. 4 194–208
Lachaux J P et al 2000 Studying single-trials of phase synchronous activity in the brain Int. J. Bifurcation Chaos 10 2429
Lanchinetti A and Fortunato S 2012 Consensus clustering in complex networks Sci. Rep. 2 336
Latora V and Marchiori M 2001 Efficient behavior of small world networks Phys. Rev. Lett. 87 1998701
Li F et al 2015 Relationships between the resting-state network and the P3: evidence from a scalp EEG study Sci. Rep. 5 15129
Li S-J et al 2002 Alzheimer disease: evaluation of a functional MR imaging index as a marker Radiology 225 253–9
Lo C et al 2010 Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer’s disease J. Neurosci. 30 16876–85
Mehrkanoon S et al 2014 Intrinsic coupling modes in source-reconstructed electroencephalography Brain Connect. 4 812–25
Montez T et al 2009 Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease Proc. Natl Acad. Sci. 106 1614–9
Morabito F C et al 2015 A longitudinal EEG study of Alzheimer’s disease’s progression based on a complex network approach Int. J. Neural Syst. 25 1550005
Mormino E C et al 2011 Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging Cerebral Cortex 21 2399–407
Mungas D 1991 In-office mental status testing: a practical guide Geriatrics 46 54–8, 63, 66
Nieuwenhuis-Mark R E 2010 The death knoll for the MMSE: has it outlived its purpose? J. Geriatr. Psychiatry Neurol. 23 151–7
O’Neill G C et al 2016 Measurement of dynamic task related functional networks using MEG NeuroImage accepted (https://doi.org/10.1016/j.neuroimage.2016.08.061) (Elsevier)
Onton J et al 2006 Imaging human EEG dynamics using independent component analysis Neurosci. Biobehav. Rev. 30 808–22
Pievani M et al 2011 Functional network disruption in the degenerative dementias Lancet Neurol. 10 829–43
Rubinov M and Sporns O 2011 Weight-conserving characterization of complex functional brain networks NeuroImage 56 2068–79
Sales-Pardo M et al 2007 Correction for Sales-Pardo et al extracting the hierarchical organization of complex systems Proc. Natl Acad. Sci. USA 104 18874
Santinello M et al 1998 Synchronization between prefrontal and posterior association cortex during human working memory Proc. Natl Acad. Sci. USA 95 7092–6
Sauseng P et al 2010 Control mechanisms in working memory: a possible function of EEG theta oscillations Neurosci. Biobehav. Rev. 34 1015–22
Schoffelen J M and Gross J 2009 Source connectivity analysis with MEG and EEG Hum. Brain Mapp. 30 1857–65
Schroeder C E and Lakatos P 2009 Low-frequency neuronal oscillations as instruments of sensory selection Trends Neurosci. 32 9–18
Sheline Y I et al 2010 Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly Biol. Psychiatry 67 584–7
Shirer W R et al 2012 Decoding subject-driven cognitive states with whole-brain connectivity patterns Cerebral Cortex 22 158–65
Siegel M, Donner T H and Engel A K 2012 Spectral fingerprints of large-scale neuronal interactions Nat. Rev. Neurosci. 13 20–5
Sorg C et al 2007 Selective changes of resting-state networks in individuals at risk for Alzheimer’s disease Proc. Natl Acad. Sci. USA 104 18760–5
Sporns O 2010 Networks of the Brain (Cambridge, MA: The MIT Press)
Stam C J 2000 Brain dynamics in theta and alpha frequency bands and working memory performance in humans Neurosci. Lett. 286 115–8
Stam C J and Van Dijk B W 2002 Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets Physica D 163 236–51
Stam C J and van Straaten E C W 2012 The organization of physiological brain networks Clin. Neurophysiol. 123 1067–87
Stam C J et al 2009 Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer’s disease Brain 132 213–24
Supekar K et al 2008 Network analysis of intrinsic functional brain connectivity in Alzheimer’s disease PLoS Comput. Biol. 4
Tadel F et al 2011 Brainstorm: a user-friendly application for MEG/EEG analysis Comput. Intell. Neurosci. 2011 (https://doi.org/10.1155/2011/879716)
Tijms B M et al 2013a ‘Alzheimer’s disease: connecting findings from graph theoretical studies of brain networks Neurobiol. Aging 34 2023–36
Tijms B M et al 2013b Single-subject grey matter graphs in Alzheimer’s disease PLoS One 8 (https://doi.org/10.1371/journal.pone.0058921)
Uutaniemi S et al 2016 Graph theory network function in parkinson’s disease assessed with electroencephalography Clin. Neurophysiol. 127 2228–36
van Dellen E et al 2015 Loss of EEG network efficiency is related to cognitive impairment in dementia with Lewy bodies Mov. Disorder. 30 1785–93
van den Heuvel MP and Sporns O 2013 Network hubs in the human brain Trends Cogn. Sci. 17 683–96
van den Heuvel MP et al 2017 Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: issues and recommendations NeuroImage 152 437–49
Vecchio F et al 2014 Human brain networks in cognitive decline: a graph theoretical analysis of cortical connectivity from EEG data J. Alzheimer’s Dis. 41 113–27
Vecchio F et al 2017 ‘Small World’ architecture in brain connectivity and hippocampal volume in Alzheimer’s disease: a study via graph theory from EEG data Brain Imaging Behav. 11 473–85
Vemuri P, Jones D T and Jack C R Jr 2012 Resting state functional MRI in Alzheimer’s disease Alzheimers Res. Ther. 4 2
Von Stein A and Sантинэль J 2000 Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization Int. J. Psychophysiol. 38 301–13
Wang L et al 2006 Changes in hippocampal connectivity in the early stages of Alzheimer’s disease: evidence from resting state fMRI NeuroImage 31 496–504
Watts D J and Strogatz S H 1998 Collective dynamics of ‘small-world’ networks Nature 393 440–2
World Health Organization 2012 Dementia: a public health priority Dementia (Geneva, Switzerland: World Health Organization) p 112
Zhao X et al 2012 Disrupted small-world brain networks in moderate Alzheimer’s disease: a resting-state fMRI study PLoS One 7
Zhou J et al 2010 Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer’s disease Brain 133 1352–67