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Resting-state functional brain connectivity predicts cognitive performance: an exploratory study on a time-based Prospective Memory task

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Abstract

Resting-state functional brain connectivity (rsFC) is in wide use for the investigation of a variety of cognitive neuroscience phenomena. In the first phase of this study we explored the changes in EEG-reconstructed rsFC in young vs. older adults, in the both the open-eyes (OE) and the closed-eyes (CE) conditions. The results showed significant differences in several rsFC network metrics in the two age groups, confirming and detailing established knowledge that aging modulates brain functional organisation. In the study's second phase we investigated the role of rsFC architecture on cognitive performance through a time-based Prospective Memory task involving participants who monitored the passage of time to perform a specific action at an appropriate time in the future. Regression models revealed that the monitoring strategy (i.e. the number of clock checks) can be predicted by rsFC graph metric, specifically, eccentricity and betweenness in the OE condition, and assortativity in the CE condition. These results show for the first time how metrics qualifying functional brain connectivity at rest can account for the differences in the way individuals strategically handle cognitive loads in the Prospective Memory domain.

Keywords

Resting-state functional connectivity; EEG; Prospective memory; Aging; segregation.

1. Introduction

Resting-state functional connectivity (rsFC) is a crucial factor for the investigation of brain activity, especially in relation to cognition [1]. Although the most common approach for the investigation of the link between brain FC and cognition is through fMRI [2,3], also electroencephalography (EEG) is currently used for this purpose [4–8]. EEG resting-state data provide insight into brain FC architecture by analysing the patterns of brain wave oscillations. For instance, by exploring the level of co-activation among different brain regions during waking rest, networks can be obtained which display explicitly the brain’s functional organisation [6]. A main challenge in this field is thus relating such EEG measures to cognition [9]. Our aim in this work was then investigating the link between brain rsFC and cognitive performance, especially in relation to healthy aging, a topic scarcely studied so far [10]. This would also help understanding inter-individual variability in behaviour and cognition [11,12].

For the above purposes, in the present study we concentrated on the EEG investigation of rsFC as derived from data on alpha oscillations (approx. 8–12 Hz). The alpha rhythm is a central feature of human brain activity, associated with a wide range of cognitive abilities, including top-down cognitive control [13], attention [14], and Prospective Memory [15]. The multi-modal nature of alpha oscillations has been highlighted for instance by Clayton et al. [16], who indicate that alpha waves exhibit at least five distinct ‘characters’: inhibition, perception, prediction, communication, and stabilisation. Here we thus derived rsFC metrics from alpha frequency EEG data, determining the associated weighted graphs in both the closed- (CE) and open-eyes (OE) conditions. We used the network backbone extraction technique by Serrano and colleagues [17], and characterised quantitatively the obtained graphs by computing a set of network features. For this we have utilised a set of metrics which are standard in brain-connectivity studies [18, for reviews on graph-analysis approach see 19–21]. Specifically, we computed both graph metrics on nodes (i.e., channels; strength, closeness, betweenness, transitivity, eccentricity, eigenvalue centrality) and metrics that reflect properties of the graph as a whole (e.g., assortativity, modularity, characteristic path length, and small-worldness; see Table 1 and *Connectivity analysis* paragraph for a description of the graph metrics).

These well-established graph-theoretical measures have already been demonstrated to reliably predict cognitive performance in pathological conditions such as Alzheimer’s Disease [22] and Schizophrenia [23], as well as in healthy controls in several domains including attention [1,24] and

working memory [25]. In particular, research on brain FC has revealed that a main dimension for the interpretation of such metrics is their role in indicating functional brain *segregation vs. integration* [26]. Functional segregation refers to the existence of ‘communities’ of functionally connected regions in which members are highly connected to each other, thus creating a modular organisation in which each module shows relative independence from the others. On the other hand, functional integration indicates the network’s ability to coordinate spatially-distributed information. The interplay between such properties of brain networks’ connectivity contributes to explain and characterize age-related cognitive decline [2], with aging being characterized by less segregated networks [2,3], and helps highlighting at the same time the role of individual differences in cognitive performance [27]. This also relates to the *dedifferentiation hypothesis* in aging, according to which neural representations lose their specialization and become common to different cognitive functions [28,29]. Within the above framework, the two-fold aim of our study is firstly to investigate the age-related differences based on alpha-related EEG-rsFC quantitative measures, and then to explore how such measures are linked to cognition.

In our context, we assess cognitive performance in relation to Prospective Memory (PM), measured by a time-based PM (TBPM) task. A similar approach has been recently applied to attentional monitoring, suggesting a key role of the Default Mode Network regions in the prediction of response inhibition failure [30] and as a potential biomarker of behavioural engagement [31]. Conversely, the cognitive processes underpinning TBPM have not yet been linked to specific rsFC patterns. TBPM is the ability to remember to carry out a specific action at the appropriate time in the future [32]. This ability is important for successful functioning in everyday life, helping us to maintain our independence and autonomy (e.g., remembering to take a medication at 5 o’clock) and safety (e.g., remembering to switch off the stove when the cake is ready). In TBPM tasks, individuals accomplish the intended action at a given time or after a time interval (e.g., taking a medication at 11 am or every six hours). A central topic in TBPM tasks is the extent to which successful performance depends on monitoring to detect the appropriate moment to implement a PM intention, or so-called target checking. This measure is considered to represent monitoring’s transient component and could be operationalised as the number of clock checks [33]. In the literature, several studies have associated the number of clock checks with successful TBPM performance, in both older adults [34] and children [35]. Thus, among the different measures of TBPM (i.e. accuracy, reaction times) analysed in previous work [15], we chose to focus on target checking, operationalised as clock checks.

The present work is divided in two Phases. In Phase 1 we investigate the differences in EEG-rsFC metrics in young vs. old adults. In Phase 2, we test the same rsFC metrics as possible predictors of

cognitive performance, taking into account the participants' age as covariate. In particular, we ask whether time monitoring in a TBPM task, as reflected by the number of clock checks, may be predicted by measures of brain FC at rest. We correspondingly seek to identify which set of rsFC metrics better explain the observed monitoring behaviour.

2. Materials and methods

The experimental session consisted of two phases. All participants first underwent EEG resting-state recording (Phase 1). After the EEG registration, the participants were asked to perform a computerised cognitive task (Phase 2) consisting of a TBPM. The event-related potentials elicited in this task have been measured and investigated in a previous work [15].

2.1 Phase 1

2.1.1 Participants

Forty-six participants (23 older and 23 young adults) underwent EEG resting-state measurements. Young adults had a mean age of 24 years (range: 21–28 years, 18 women), whereas older adults had a mean age of 67.5 years (range: 60–76 years, 14 women). All elderly participants had a Mini Mental State Examination (MMSE) > 27. All participants underwent two randomised resting-state EEG conditions: open-eyes (OE) and closed-eyes (CE), lasting 3 minutes each. The study was approved by the ethical committee of the School of Psychology of the University of Padua and was conducted according to the principles expressed in the Declaration of Helsinki. All participants were informed about the general experimental procedure and signed a written consent form.

2.1.2 Resting-state EEG recordings

The EEG data were collected while participants kept their eyes closed (CE) or open (OE) in a relaxed state, without moving or talking for 3 minutes under each condition. EEG was recorded (EEG equipment by System Plus) from an array of 30 Ag/Ag Cl scalp electrodes (Fp1, F7, F3, Fc3, Ft7, T3, T5, Tp7, C3, P3, Cp3, o1, Fp2, F4, F8, Fc4, Ft8, T4, T6, Tp8, C4, Cp4, P4, o2, Fz, Cz, Pz, Fcz, Cpz, Fpz) mounted on an elastic cap (ElectroCap by International) and positioned on the basis of the 10–20 International System. The EEG signal was digitised at a 512 Hz sampling rate. Electrode impedance was always kept below 5 k Ω .

2.1.3 EEG data pre-processing

Overall, 92 resting-state data sets were analysed. Brain potential activity has wide variability, and for this reason we studied the signal in the frequency domain. Data filtering and the detection of brain from non-brain sources were first performed. We filtered the data in the alpha-band (8–12 Hz) best characterising brain activity in the resting-state condition, using a zero-phase filter (FIR filter) which does not distort the phase of signals.

To separate and thus distinguish the different source activities, we implemented an independent component analysis (ICA) based on the signals' temporal independence [36], and we applied the complete automatic algorithm ADJUST [37] to remove artefacts from the signals. The MATLAB toolbox EEGLAB was used to clean the signals and implement the time-frequency analysis [38].

2.1.4 EEG brain-network determination

We built a weighted graph with nodes given by the EEG electrodes, and weights quantified by the functional statistical dependence between the nodes' activity, as measured through the synchronisation between different brain regions given by phase coherence [38]. The use of such a FC measure in the frequency domain is suitable for extracting graphs from EEG data because it does not require modelling assumptions but only the stationarity or local stationarity of signals. The short-time Fourier transform spectral decomposition allows the signal to be considered as piecewise linear, enabling the analysis of nonlinear signals such as brain signals [39]. The fact that the resting-state condition is usually characterised by long signals ensures that the investigated neural process occurs several times and can be sufficiently represented.

A 30-by-30 phase-coherence matrix was created based on the signals of each pair of electrodes for every data set (i.e., participant). Trials of 5 s were extracted, so that each data set (120 s out of 180 s after removing initial and final 30s) was split into 24 trials, which were subsequently averaged. A matrix was created for each pair of signals, and the time average followed by the average on the frequency band were found on each matrix, resulting in a scalar value between 0 and 1 quantifying the “coupling” between two signals. Repeating the algorithm for each signal pair produced a connectivity matrix and thus the weighted graph of the data set (two for each individual, pertaining respectively to the CE and OE conditions; see Figure 1 for mean matrices and graphs). To eliminate spurious links, instead of simple thresholding we used a disparity filter (or backbone extraction) technique to prune the number of connections at multiple interaction scales [17]. In our analysis we used a filter significance level of 0.36, which allowed us to keep between 1/3 and 2/3 of the original connections.

2.1.5 Connectivity analysis

EEG rsFC analysis was conducted on individual phase coherence matrices. First, we obtained individual rsFC matrices by computing phase coherence for each pair of channels in young and old participants both in OE and CE conditions, thus resulting in a set of 30-by-30 matrices (where 30 is the number of electrodes). Then, we averaged individual rsFC maps for each group (Figure 1, left and central column), separately for OE (Figure 1, upper section) and CE (Figure 1, bottom section) conditions. The difference in rsFC between the two groups was assessed through a series of t-tests, correcting for multiple comparisons by means of False Discovery Rate (FDR; [40]). Figure 1 shows also mean connectivity graphs for each group and for their difference (edges whose difference was significant between young and old participants).

Furthermore, the global properties of the EEG resting-state brain networks were quantitatively characterised by means of a set of standard graph-theoretical metrics, previously considered in investigations of brain functional connectivity [18, for reviews on graph-analysis approach see 19–21]. In detail, the metrics computed for our brain network analysis were as follows: *strength*, which represents the sum of the associations between a given node and all other nodes in the network; *closeness*, which classifies each node based on its ‘proximity’ to all other nodes; *betweenness*, which represents the fraction of all the shortest paths that pass through a given node; *transitivity*, which is a measure of the clustering near each node in the network; *eccentricity*, which represents the maximal shortest path length between a node and any other node; *eigenvalue-centrality*, which ranks the nodes so that a node receives a high ranking if it has strong connections with many other nodes characterised by a central position within that network; *assortativity*, defined as the correlation coefficient between the degrees of all connected nodes in the network; *characteristic path length*, which measures the length of the shortest paths between all pairs of nodes; *small-worldness*, which measures the connectivity between nodes located far from each other; and *modularity*, which quantifies the degree to which the network can be divided into well-delineated groups. These metrics provided us with the desired quantitative network features that evolve with age (Phase 1). Thus, for each metric, we checked whether the difference between the young and elderly groups within the same condition (OE or CE) was significant by means of a t-test. Then, (Phase 2) we explored the links between brain graph properties and cognitive behavioural performance. All statistical analysis were performed by means of the R software [41]; graph metrics were computed from individual rsFC matrices by means of the R library *iGraph* [42].

2.2 Phase 2

2.2.1 Participants

Twenty-two participants of Phase 1 decided to participate in Phase 2 of this study (13 young and nine elderly; mean age young = 24.3 years, range 22–28 years; mean age old = 69.15 years, range 62–76 years).

2.2.2 Cognitive Task

The cognitive TBPM task in Phase 2 comprised the ability to remember to execute a pre-defined intention at the correct time in the future while being engaged in another, ongoing task (for details on the experimental set-up and ERPs, and on the related EEG and behavioural results, see [15]).

Two blocks of tasks were administered. In the first block, participants were instructed to perform only the ongoing task (baseline block). The ongoing task, composed of 40 trials, consisted of white strings of five letters that occurred pseudo-randomly on the centre of the computer screen. The letters in the 1st, 3rd, and 5th positions were identical, whereas the letters in the 2nd and 4th positions could be either the same (e.g., DFDFD) or different (e.g., DFDGD). The participants were asked to press a key on a response box with their index finger if these target letters were the same and to press another key with their middle finger if they were different. All responses were given through the right hand, and the response mapping was counterbalanced across participants. In the second block, the participants were required to perform, together with this ongoing task, a PM task (PM block). This block included 350 ongoing trials. Together with the ongoing task, the participants were asked to remember to press a third key with their left index finger every 5 min from the beginning of the task, and to try to be as accurate as possible in the estimation. As soon as they pressed the PM key, a digital clock was presented on the centre of the screen, displaying the exact time. A PM estimation was considered correct if it was done within 15 seconds before or after the target time (e.g., for the 5.00 min PM time, a response was accurate if performed within 4.45 and 5.15 min). The PM block lasted about 27 min. This duration enabled up to five PM responses to be executed (i.e., at 5:00, 10:00, 15:00, 20:00, and 25:00 min). The monitoring processes was assessed by counting the number of clock checks throughout the PM block [15]. For the aim of the present study, the participants could check the passage of time by pressing another key with their left middle finger. This key was recognisable by a clock icon on the response box. Participants were instructed to check the clock when they needed, as often as they wanted. When they pressed the clock key to check the time, the digital clock appeared at the centre of the screen.

2.2.3 Statistical analysis

Since we were mainly interested in global properties of the brain as a network, local connectivity measures extracted in Phase 1 were averaged across electrodes to provide an overall quantification of each metric at the individual level. This approach has been adopted in previous studies (e.g., for clustering coefficient see [22,43,44]), and it is useful to investigate the relation between individual differences in brain global graph properties and cognitive performance. To this end, a linear regression model was built separately for CE and OE conditions to investigate the effects of demographic variables (age and education) and brain-connectivity measures listed earlier on the number of clock checks in the administered TBPM task. A full model (i.e., including all of the considered variables) was built separately for each condition and then subjected to a stepwise procedure based on the Akaike information criterion (AIC; [45]) to highlight the best model. Only the significant effects (t statistics) resulting from the best model (i.e., the model with the best combination of variables) will be discussed. Model building and comparison and related statistical analyses were performed by means of in-house R scripts [41].

3 Results

3.1 Phase 1

In CE condition the young vs. old comparison of rsFC matrices showed decreased homotopic connectivity in frontal regions (i.e., decreased inter-hemispheric correlation between frontal electrodes) in older adults (Figure 1, bottom-right plot). Moreover, the comparison across graph metrics showed that younger adults' rsFC were characterised by higher levels of strength, transitivity, and assortativity as compared to older adults (all p s < .01).

On the other hand, the pattern of findings in the OE condition showed that the differences in transitivity remained stable. However, in this condition, younger adults' rsFC was characterised by higher levels of closeness and modularity but decreased strength. Furthermore, consistently with previous findings [46], older participants showed a significantly increased connectivity in fronto-parietal midline electrodes (Figure 1, top-right plot).

----- Table 1 approximately here -----

----- Figure 1 approximately here -----

3.2 Phase 2

Behavioral results of the TBPM task showed a significant difference between older and younger participants only in reaction times ($t(19.6)=4.07$, $p<.001$), while no differences emerged for accuracy ($p=.43$) and number of clock checks ($p=.33$). Then, we focused in the prediction of individual differences in the number of clock checks from brain network graph-properties.

For the CE condition, the best model ($p = .043$; $R^2 = .21$; $AIC = 102.02$; see Table 2 for the model parameters) resulting from the stepwise procedure included age and assortativity as predictors. Younger adults showed a significantly higher number of clock checks than older adults ($t = -2.59$; $p = .018$; partial eta-squared = .26). The effect of assortativity on clock checking was also significant ($t = -2.44$; $p = .025$; partial eta-squared = .24), a higher number of clock checks being associated with lower assortativity (see Figure 2A).

----- Table 2 approximately here -----

----- Figure 2 approximately here -----

When focusing on the OE condition, the best model ($p = .039$; $R^2 = .21$; $AIC = 101.86$; see Table 2 for model parameters) included betweenness and eccentricity as predictors. As reported in Figure 2B, the effects of these two metrics on the number of clock checks showed opposite directions. Specifically, an increased number of clock checks was associated with higher betweenness ($t = 2.77$; $p = .012$; partial eta-squared = .29) but lower eccentricity ($t = -2.09$; $p = .049$; partial eta-squared = .19).

For both models, we checked whether linear regression assumptions were met. Collinearity across the predictors was checked by means of variance inflation factors, which were always lower than 10, thus indicating no potentially harmful collinearity [47].

The application of the Durbin–Watson test (OE: D-W statistic = 2.71, $p = .08$; CE: D-W statistic = 1.77, $p = .66$) confirmed that the assumption of independence of errors was met. Finally, the normality of the residuals was checked by means of a Shapiro–Wilk test (OE: $W = .95$, $p = .28$; CE: $W = .93$, $p = .13$), and homoscedasticity was confirmed through the Breusch–Pagan test (OE: $BP[2] = 1.41$, $p =$

.49; CE: BP[2] = 2.08, $p = .35$). The Cook distance for all observations resulted <1 for both regression models, ruling out the presence of influential outliers [48].

4. Discussion

The first aim of the present study was to delineate changes in rsFC metrics with advancing age. We found that older adults are characterised by a functional architecture with a reduced modularity, closeness, and transitivity in the OE condition, and reduced assortativity and transitivity in the CE condition (Table 1). We also observed the strength to be lower in older adults in the CE condition, but higher in the OE condition.

These results are broadly consistent with previous fMRI and EEG studies on age effects on rsFC [49,50]. Indeed, the observed reduction in transitivity [5] is consistent with the idea that aging is associated with changes in the segregation/integration balance, in the direction of a decreasing segregation [2,3,51]. Accordingly, the investigation of connectivity patterns across the adult lifespan has shown that aging is associated to lower within- and higher between-systems connectivity [2,3,52]. This is also consistent with the decreased frontal homotopic connectivity observed in older participants, and could be at least partially explained by the age-related degeneration of the anterior corpus callosum [53,54]. Indeed, the surgical section of the corpus callosum has been related to a reduction of inter-hemispheric connectivity, with a stronger effect in frontal regions compared to sensorimotor or visual areas [55].

Furthermore, assortativity (i.e., the tendency of nodes to be connected to similar nodes in a complex network [56]) is considered an index of resilience [18,57], as networks with higher assortativity are shown to have a resilient core of inter-connected high-degree hubs, while networks with lower assortativity have more widely distributed and thus more vulnerable high-degree hubs. Based on this, our observations suggest that older adults appear to have less resilient brain networks. This is also consistent with recent findings suggesting possible graph-metrics-based biomarkers for age-related pathological conditions such as subjective cognitive decline [58]. Yet more, we interpret the age-related reduction in modularity in the OE condition (i.e. with individuals at rest but engaged in sensory/perceptual processes) as supporting the dedifferentiation hypothesis in aging [28,59]. Older adults would indeed activate unspecific neural regions, losing the distinctiveness of younger adults' neural representations in cerebral areas that code for specific information [60], which are also involved in OE resting-state networks. Accordingly, in the OE condition we found an increased fronto-parietal midline connectivity in older participants, which is consistent with previous research

[46] and suggests a compensatory effect for a decline in bottom-up sensory input processing [46,61]. Taken together, our findings support the shared idea that aging leads to less distinct [49] and more random [62] brain networks. In addition, differences between young and older adults in CE vs. OE condition could reflect age-related changes in alpha reactivity as previously suggested [63].

The second aim of the present study was exploring the relation of different rsFC metrics to cognitive performance, assessed by a TBPM task. Our results show that a better ability to monitor time while doing another ongoing activity is associated with a brain functional architecture characterised by high betweenness (i.e., more nodes that bridge other nodes), lower eccentricity (i.e., nodes are functionally closer to each other), and lower assortativity. Such a pattern, indicating less segregated systems [3] suggests that a better PM performance is associated with a functional connectivity characterised by more efficient network integration. Our results support and extend the findings of Gonneaud et al. [64] suggesting that task-related difficulties with recruiting the brain networks specifically involved in strategic monitoring in PM might be due to more random brain networks [62] emerging not only during task execution, but also in the resting state. This points to a role of relatively stable individual brain FC features. While recent research on rsFC has shown system segregation at rest to be directly related to cognitive abilities [2], e.g., to long-term episodic memory [3], our findings give a first demonstration of a link to PM.

We notice that, as suggested by Cohen and D'Esposito [27], the optimal balance between segregation and integration may in general change as a function of the type of cognitive task. Based on this, we speculate that a higher degree of network integration presently found, might be useful in dual-task performance. Indeed, PM tasks involve multiple processes to be accomplished, and are peculiar because they are carried out simultaneously with other ongoing activities [65]. Moreover, our findings are in line with other studies reporting a relationship between higher network efficiency (indicated by lower eccentricity [66] and cognitive functioning, especially studies showing that efficiency predicted levels of non-verbal intelligence and that higher intelligence is related to shorter path lengths [67,68]).

A further aspect of our results relates to the role of age on the link between rsFC and cognition. Since age showed a significant influence on rsFC metrics in Phase 1, in Phase 2 age was considered as a covariate. Interestingly, in this Phase the effect of age was significant in the CE but not in OE condition. Compared to CE, the OE condition is closer to a task setting, with the CE to OE transition corresponding to the activation of a 'task mode' characterized by higher responsiveness to environmental stimuli [69,70], in which age-related rsFC differences are greatly reduced [69,71]. In this perspective, it is plausible that in the OE condition the influence of age is reduced. The different

role of aging in modulating EEG signal in CE and OE conditions might also be related to impaired alpha reactivity between these conditions, which seems to be mediated by cortical cholinergic activity (Wan et al., 2019). Alpha reactivity has been related to cognitive performance in healthy aging (Babiloni et al., 2010), and its reduction has been suggested as a possible marker of Alzheimer's disease (McBride et al., 2014). Our results, downplaying the effect of aging in the OE condition, highlight the importance of individual rsFC differences on cognitive performance. This is in agreement with recent findings [72] highlighting the role of inter-subject differences in network measures, in particular assortative and disassortative community structure, on cognitive performance. Individual differences have been proposed as a main source of variability in functional connectivity, with smaller contributions by task-state and day-to-day variability [73]. Accordingly, individual differences have been shown to shape FC in a stable and reliable ways, which can be considered as ‘signatures’ or neural ‘fingerprints’ [24,73–76]. Also Friedman and Miyake (2017) emphasised the role of individual differences in FC, highlighting them as a key point to consider for interpreting the observed patterns in different executive functions.

5. Conclusions

Research on brain connectivity at rest in relation to behaviour is relatively new, and many questions remain open in the investigation of the predictive value of rsFC features on cognition. Despite some important limitations of our study, mainly represented by the small sample size, our exploration does emphasise that EEG-derived rsFC individual graph metrics provide insights into the link between the brain’s functional organization and cognition. Indeed, our results show that resting state connectivity metrics at the individual level predict subsequent time-monitoring performance. This establishes for the first time a relation between connectivity at rest and cognition in TBPM-related processes.

While Phase 1 largely confirmed the known differences occurring in rsFC with age, in Phase 2 we also found that when rsFC is recorded in the OE conditions (i.e. closer to a ready-to-action state), individual differences in rsFC metrics emerge as essential factors for cognitive performance prediction. This relates our results to the growing literature concerning the role of individual differences in cognition.

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