Resting-state fMRI: comparing default mode network connectivity between normal and low auditory working memory groups

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Abstract. The relationship between resting effective connectivity (EC) among default mode network (DMN) regions and auditory working memory (AWM) performance is still poorly understood. In this work, resting-state functional magnetic resonance imaging (rsfMRI) was used to determine the optimum connectivity model between posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) in 40 healthy male volunteers. In low and normal working memory groups of subjects. Correlation between EC with AWM performance and AWM-capacity was also studied. The participants were divided into two groups which are normal and low AWM-capacity groups based on Malay Version Auditory Verbal Learning Test. The AWM performance was assessed using a word-based backward recall task. Both assessments were conducted outside the MRI scanner. The participants were scanned using a 3-T MRI system and the data were analyzed using statistical parametric mapping (SPM12) and spectral Dynamic Causal Modelling (spDCM). Results revealed that PCC and mPFC were significantly interconnected in both groups. Group analyses showed that the connection between PCC and mPFC exhibits an anti-correlated network. The results also indicated that the AWM performance and AWM-capacity were not associated with EC. These findings suggest that EC at rest between the two regions may not significantly influence cognitive abilities important for this AWM task.
1. Introduction
Previous functional magnetic resonance imaging (fMRI) study has shown the involvement of default mode network (DMN) regions such as posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) in working memory (WM) task [1]. The PCC plays a prominent role in regulating attention [2], whereas mPFC is involved in maintenance of information [3]. Although their functional roles have been extensively studied, less is known on how the effective connectivity (EC) between these two regions influences auditory working memory (AWM) performance at rest. AWM is a cognitive system which stores and process auditory information [4]. It has been proposed that brain activity at rest may be able to predict behavioural performance [5]. A previous study has shown that resting-state connectivity between PCC and medial frontal gyrus has been associated with WM performance [6]. However, the relationship between EC (of PCC and mPFC at rest) and AWM performance has not been fully understood. Therefore, considering the crucial roles of PCC and mPFC in WM processing, there is a possibility that EC between these two DMN regions may influence AWM performance. We investigated this possibility in the present study by using resting-state functional magnetic resonance imaging (rsfMRI) to measure resting-state connectivity between PCC and mPFC. The first objective was to identify the optimum model that would best represent the EC between these two DMN regions. The second objective was to compare the EC between PCC and mPFC in both groups. Third, we examined if AWM performance is associated with EC. Finally, we investigated whether individual’s AWM-capacity is related or not related to EC. We hypothesised that strength of EC between PCC and mPFC at rest would be associated with AWM performance. Our hypotheses focus on PCC and mPFC because they are the DMN nodes commonly associated with WM network. To the best of our knowledge, there has not been any study conducted to determine the correlation between EC (of PCC and mPFC connection at rest) and AWM performance.

2. Methodology
2.1. Participants and auditory working memory screening
Forty healthy right-handed male volunteers aged between 18 to 24 years were recruited for this study. The participants were all native Malay speakers, had normal hearing sensitivity for both ears, no history of neurological or cognitive disorder, and free from any use of psychoactive medications or stimulants. Written informed-consent was obtained from each participant. This study was approved by the Institutional Ethics Committee (IEC) of the Universiti Kebangsaan Malaysia (UKM PPI/111/8/JEP-2017-117) and National Medical Research and Ethics Committee (NMRR-17-56-33800). The participants were divided equally into normal (n = 20, mean age = 21.00 ± 1.52 years, years of education = 14.00 ± 1.52) and low (n = 20, mean age = 21.75 ± 1.59 years, years of education = 15.30 ± 1.59) AWM-capacity groups based on their performance on Malay Version Auditory Verbal Learning Test (MVAVLT) [7]. Participants who scored within the upper half of the range of MVAVLT scores (scores of 38 to 75 correct) were assigned to the normal AWM-capacity group, whereas those who scored within the lower half of the range of MVAVLT scores (scores of 1 to 37 correct) were assigned to the low AWM-capacity group [8]. The AWM performance was assessed using a word-based backward recall task (BRT). In this task, participants heard a sequence of four meaningful words via headphones presented binaurally in a sound-proof room. The participants were instructed to listen, remember, and recall those words sequentially in reverse order. The words were presented for a duration of 4 seconds and participants had to immediately recall within 4 seconds. There was a total of 30 words sequences.

2.2. rsfMRI data acquisition and pre-processing
The rsfMRI images were acquired using a 3-tesla MRI system (Siemens Magnetom Verio) equipped with functional imaging capabilities at the Department of Radiology, Universiti Kebangsaan Malaysia Medical Centre. T1-weighted structural images were acquired with a multiplanar reconstruction (MPR)
spin echo pulse sequence with repetition time (TR) = 1900 ms, echo time (TE) = 2.35 ms, flip angle = 9°, voxel resolution = 1.0 × 1.0 × 1.0 mm and matrix size = 256 × 256. T2-weighted functional images were acquired with a gradient-echo EPI sequence adopted from Abbot et al. [9]. Each functional scan took 2 seconds and a total of 158 volumes were acquired. The total scan time was approximately 7 minutes. Functional MRI images were processed using MATLAB 9.3 - R2017b (MathWorks Inc., MA, USA) and Statistical Parametric Mapping (SPM12) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London, UK; www.fil.ion.ucl.ac.uk). The first four EPI scans were discarded. The remaining 154 EPI scans undergo slice-timing correction, realignment, normalisation and smoothing.

2.3. Data analysis and dynamic causal modelling
The demographic and behavioural data were analyzed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). A general linear model (GLM) containing the slice timed, realigned, normalized and smoothed images was redefined for each particular subject and a design matrix was constructed. This design matrix was then estimated and was used in extracting the time series signals from cerebrospinal fluid and white matter centered at (0, -40, -5) and (0, -24, -33) of a 6-mm radius volume of interest respectively. The extracted signals from the two regions were then used to construct a new design matrix. This new design matrix was then estimated. The design matrix was later used to extract signals from the 8-mm radius sphere of the two DMN regions; mPFC centered at (3, 54, -2) and PCC centered at (0, -52, 26). The time series signal extracted from mPFC and PCC were entered into another design matrix, together with the extracted signals from CSF, WM and six realigned parameters. The time series signals for each region were then used in specifying and constructing the causal models. Three causal models comprising of PCC and mPFC were constructed using Dynamic Causal Modelling (DCM12) [10] (Fig. 1). Model 1 has a one directional connection from PCC to mPFC. Model 2 has a one directional connection from mPFC to PCC. Model 3 has a bidirectional connection between PCC and mPFC. No input was specified as this study was motivated by resting state condition and all models are assumed to have self-connection on each region. The causal models were then estimated using spectral DCM (spDCM) [11] to obtain the coupling parameters (effective connectivity) between regions. Their endogenous fluctuation of activity was recorded and analyzed to generate complex cross spectra. The time invariant covariance of the random fluctuations between regions was then estimated to obtain the cross spectra density which was then used in estimating the EC between the DMN regions. The EC among coupled neuronal responses was then estimated using a neuronally plausible power-law model. The models were then compared by means of Bayesian Model Selection (BMS) for group studies under the FFX framework [12], to test the null hypothesis that no single model is better than any other competing models and to obtain a model that has the best balance between fit/accuracy and complexity. Upon obtaining the most optimum model, the EC values among the DMN regions were then averaged over the subjects using Bayesian Parameter Averaging (BPA). A connection is considered significant if its posterior probability value is equal or larger than 0.9.

3. Results
3.1. Behavioural data
An independent samples t-test indicated that participants in group 1 (mean MVAVLT score = 48.70, SD ± 4.73) achieved MVAVLT scores significantly higher (95% CI; 15.30, 20.40), than participants in group 2 (mean MVAVLT score = 30.85, SD ± 3.08), t(38) = 14.15, p < .001, two-tailed, d = 1.12. The independent samples t-test also revealed that participants in group 1 (mean BRT score = 21.20, SD ± 4.73) achieved BRT scores significantly higher (95% CI; 5.08, 7.02), than the those in group 2 (mean BRT score = 15.15, SD ± 1.50), t(38) = 12.59, p < .001, two-tailed, d = 2.62.

3.2. Model comparison
The values of endogenous coupling (in Hz) between PCC and mPFC were extracted for each participant and were averaged across 20 participants in each group (Figure 1). The BMS results revealed that model
3 has the highest log-evidence (relative) value, followed by model 1 and model 2 (Figure 2). This indicates that model 3 is the optimum model in both groups, demonstrating that there is a bidirectional connection between PCC to mPFC at rest.

**Figure 1.** Three causal models comprising of PCC and mPFC constructed using Dynamic Causal Modelling. Dotted arrow indicates null connection.

**Figure 2.** Bayesian model selection results showing models, relative log-evidences, and posterior probability. Bar graph indicates that model 3 is the optimum model for both groups.

### 3.3 Effective connectivity

As shown in Figure 3, the results indicated that the EC from PCC to mPFC decreases as the EC from mPFC to PCC increases (see left figure), with the normal AWM-capacity group showing a steeper decreasing trend (blue line). Similarly, the EC from mPFC to PCC decreases as the EC from mPFC to PCC increases (see right figure). However, the EC from mPFC to PCC in low AWM-capacity group shows a steeper decreasing pattern (green line).
3.4. Correlation analyses

Pearson’s correlation analysis between AWM performance and EC was not significant, indicating that AWM performance is not associated with EC between PCC and mPFC at rest for both groups. Pearson’s correlation analysis between AWM-capacity and EC was also not significant, indicating that individual’s differences in AWM-capacity is not associated with EC between PCC and mPFC.

4. Discussion

The main purpose of this study was to investigate EC between PCC and mPFC (Figure 1), and to determine the optimum model between these two regions. The results in Fig. 2 revealed that the optimum model (i.e. model 3) has a structure of interactions between PCC and mPFC. This indicates that there is a bidirectional connection between PCC to mPFC at rest [13]. Therefore, it is likely that this bidirectional connection exists because PCC and mPFC function together during rest [14]. The secondary objective was to compare EC from PCC to mPFC and from mPFC to PCC in both groups. As illustrated in Figure 3, connection between PCC and mPFC exhibits an anti-correlated network [15], where an increase in EC of one connection would result in a decrease in EC of the opposite connection. A negative EC value indicates that activity in one region inhibits activity in the other region [16]. It has been suggested that increase and decrease of EC between DMN regions is influenced by allocation of cognitive resources [17]. Referring to the functional roles of PCC and mPFC, these results may suggest that increase in level of attention would limit the amount of cognitive resources available for maintenance of information. However, future research is needed to confirm this. The third objective was to determine if AWM performance was influenced by the EC between these two ROIs. The BRT results have shown that participants in group 1 scored significantly higher (p < .001) than those in group 2. A similar finding was discovered in which individuals with normal WM-capacity achieved significantly higher behavioural scores as compared to those with low AWM-capacity [18]. Nevertheless, correlation between behavioural scores and EC was not statistically significant in both groups (p > 0.05). Therefore, although individuals with normal AWM-capacity demonstrated significantly higher BRT scores as compared those with low AWM-capacity, we are unable to provide valid evidence that AWM performance was strongly influenced by the EC between PCC and mPFC at rest. Finally, the objective of this study was to investigate the relationship between individual’s AWM-capacity and EC. The results showed non-significant correlation between mean MVAVLT scores and EC in both groups. Thus, it can
be said that individual differences in AWM-capacity was not determined by the EC between PCC and mPFC at rest. A limitation of the present study is the rsfMRI data were acquired over a short duration of time (i.e. 7 minutes), resulting in fewer available time points to be analyzed. Nevertheless, the amount of rsfMRI data acquired between 5 to 7 minutes are still reliable to show the EC [19]. Future research should explore the connection of PCC and mPFC with other brain regions related to AWM.

5. Conclusion
In summary, we have performed resting-state fMRI on individuals with normal and low WM-capacity. The results from this study revealed that the optimum model between PCC and mPFC has a bidirectional connection at rest. The results also showed that EC between PCC and mPFC at rest does not significantly influence AWM performance and individual’s AWM-capacity. Interestingly, we found significant negative correlation between EC from PCC to mPFC and EC from mPFC to PCC. In light of this finding, it has been proposed that interregional connection between PCC to mPFC at rest demonstrates an anti-correlated network and interferes with one another.

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