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Task-residual Functional Connectivity of Language and Attention Networks

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Abstract

Functional connectivity using task-residual data capitalizes on remaining variance after mean taskrelated signal is removed from a time series. The degree of network specificity in language and attention domains featured by task-residual and resting-state data types were compared. Functional connectivity based on task-residual data evidenced stronger laterality of the language and attention connections and thus greater network specificity compared to resting-state functional connectivity of the same connections. Covariance between network nodes of task-residuals may thus reflect the degree to which two regions are coordinated in their specific activity, rather than a general shared co-activation. Task-residual functional connectivity provides complementary data to that of resting-state, emphasizing network relationships during task engagement.

Keywords

functional connectivity; language; attention; resting-state; task-residual

1. Introduction

The purpose of this study was to compare the sensitivity of task-residual and resting-state functional connectivity in addressing domain-specific and domain-general connectivity related to language production, using a simple, transparent method.

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1.1. Task-Residual and Resting-State fMRI for Determining Functional Connectivity

Resting-state functional connectivity (rsFC) MRI is the dominant methodology used to capture functional connectivity networks (Greicius et al., 2009; Biswal et al., 2010). Taskresidual functional connectivity (trFC) is an alternative approach that may offer additional information about coherence of brain systems. In trFC analysis, the effects of an active block or event-related task are regressed out of the fMRI time series and the resulting residual time series is used to define a covariance matrix (Fair et al., 2007; Andrews-Hanna et al., 2007; Zhang & Li, 2010; Fornito et al., 2012). Residuals are typically considered error variance when calculating the mean task-evoked signal. However, areas that are functionally related still show covariation and are related to behavioral differences (Al-Aidroos et al., 2012; Davies-Thompson & Andrews, 2012).

Task-residual functional connectivity may provide more specific information about networks in cognitive states than resting-state functional connectivity (Rogers & Gore, 2008; Fair et al., 2007; Norman-Haignere et al., 2011). When the mean effects of the task are regressed out, block-by-block (or trial-by-trial) variability relevant to the task remains in the residual signal (Fair et al., 2007). Block-by-block variability may encompass coordinated activity not consistently represented in modeling techniques of the hemodynamic response function that assume time invariance. As items differ in their neural demands (e.g., variation in task difficulty between individual items or blocks), functional network components that cooperate to meet those demands may show covarying fluctuations. Thus, in analysis techniques assuming time invariance, the activity associated with individual items and/or blocks is not captured in the task signal but may accumulate in the residuals (Fair et al., 2007). Thus, trFC may be more sensitive to functional interactions of specific, task-relevant network connections compared to rsFC.

1.2. Functional Connectivity Networks related to Language

In the present study, participants completed a resting-state scan and a covert verbal fluency task (semantic and phonemic word generation) as part of a larger project (Cognitive Connectome Project; Gess et al. 2016). To observe activity related to language function during the verbal fluency task, strength of laterality was used (left-hemisphere functional connectivity compared to functional connectivity of right-hemisphere homologues). Because language networks are known to be left-hemisphere lateralized and task-residual data may contain time-invariant effects of the language task, our central hypothesis was that languagebased task-residual data would show stronger left-hemisphere lateralization than restingstate data. We used three network relationships to demonstrate our central hypothesis.

The three network relationships used to examine functional connectivity were the following: 1) nodes within the domain-specific language network, 2) nodes that intersect language and attention networks, and 3) nodes within the domain-general intention-attention network. We hypothesized that in each of the three network relationships, task-residual data would show stronger left-lateralized functional connectivity than resting-state data. The first network (language) nodes were comprised of cortex in Broca's area of the inferior frontal gyrus (IFG) and the posterior perisylvian region (PPS) (Zlatar et al., 2013; Binder et al., 2009), based on their involvement in verbal fluency tasks. Given the positive correlation between

these two regions (Tomasi & Volkow, 2012), we expected functional connectivity between the IFG and PPS to show stronger left-lateralized functional connectivity in task-residual data compared to resting-state data.

The second network relationship investigated was the intersection between anterior language and posterior attention nodes. Portions of PPS, such as the angular gyrus, are involved in both the task-positive language network and task-negative default mode network (DMN) (Wirth et al., 2011; Davey et al. 2015; Humphreys & Lambon Ralph, 2015). Posterolateral DMN regions included the angular gyrus are believed to be involved in self-referential attention and internal processes (Wirth et al., 2011) and show deactivation during effortful language tasks (Seghier et al., 2010; Meinzer et al., 2012). In resting-state functional connectivity studies, goal-directed regions, such as the IFG, and DMN attention regions typically show an inverse functional relationship, also referred to as an anticorrelation (Fox et al., 2006a). We thus expected the left IFG (task-positive) and areas of the left PPS converging with DMN functions (task-negative) to be anti-correlated. We expected this anticorrelation to have stronger left-lateralized functional connectivity in task-residual data compared to resting-state data.

The third network relationship of investigation comprised nodes of the domain-general executive attention, or intention-attention network. The pre-supplementary motor area (pre-SMA) was used for its involvement in task-positive activity and intentional response selection relevant to verbal fluency (Lau et al., 2004; Nachev et al., 2007). The posterior cingulate/precuneus (PC/Pc) region is associated with the DMN and involved in various forms of attention, (Cavanna & Trimble, 2005; Vanhaudenhuyse et al., 2011; Cato, et al. 2004; Nadeau et al., 1997). These two anterior and posterior regions are consistently found to be anti-correlated in resting-state functional connectivity literature, such that as dorsal anterior goal-directed regions (e.g., pre-SMA) are invoked (Fox et al., 2006a), activity in the posterior attentional regions is suppressed (Fox et al., 2005). Thus, we expected an anticorrelation between these two network nodes that would have stronger left-lateralized functional connectivity in task-residual data compared to resting-state data.

2. Method

2.1. Participants

A subset of 21 participants were selected from participants recruited for a parent study, the Cognitive Connectome Project at the University of Arkansas for Medical Sciences (UAMS) (Gess et al., 2014). The parent study consisted of healthy adults between the ages of 18–50. Study procedures were approved by the UAMS Institutional Review Board in accordance with the Declaration of Helsinki. Informed consent was obtained for all participants in the study. Inclusion criteria for this study were healthy right-handed, native English speakers with at least an eighth-grade reading and writing proficiency. We restricted the age range (18–30) of our adult sample because age-related functional alterations are evident at midlife (McGregor et al., 2013). Other exclusion criteria and recruitment procedures are described in a previous study (Gess et al., 2014). Demographic information for the sample is presented in Table 1.

2.2. Verbal Fluency Task and Resting-state Scans

During the MRI session, participants were asked to silently generate as many words as possible that began with a specific category or letter prompt. Covert word generation has shown to reliably recruit language regions while minimizing motion artifact (La et al., 2016). The task consisted of one run containing 15-second blocks of alternating letter and semantic category prompts separated by 15 seconds of rest. The letter or cue word was presented for the entire 15 seconds of word generation. A total of five letters (i.e., R, P, W, S, J) and five categories (i.e., plants & flowers, clothing, foods, states, jobs) were presented. During rest (non-task) blocks, participants were shown a screen-centered fixation cross, and instructed to cease word generation until the next trial. For the resting-state scan, participants were instructed to relax, rest, and keep their eyes focused on the fixation cross in the center of the screen for the 7-minute acquisition.

2.3. Scanning Procedures

Imaging data were acquired using a Philips 3T Achieva X-series MRI scanner. Anatomic images were acquired with a MPRAGE sequence with the following parameters: matrix $=$ 256×256 ; 22 sagittal slices; TR = shortest; TE = shortest; FA = 8°; resolution = 0.94 \times 0.94 \times 1 mm³. Functional images for the early participants (1–50) were acquired using an 8channel head coil with an echo planar imaging (EPI) sequence and the following parameters: TR = 2000 msec; TE = 30 msec; FA = 90°; FOV = 240 \times 240 mm²; matrix = 80 \times 80, 37 oblique slices parallel to orbitofrontal cortex; "Philips interleaved" for participants 1–28 and interleaved for participants 29–49; resolution = $3.0 \times 3.0 \times 4.0$ mm³. Functional images for the remaining participants (51–79) were acquired using a 32-channel head coil with the following parameters: $TR = 2000$ msec; $TE = 30$ msec; $FA = 90^{\circ}$; $FOV = 240 \times 240$ mm; matrix $= 80 \times 80$, 37 oblique axial slices parallel to orbitofrontal cortex; sequential ascending acquisition; slice thickness = 2.5 mm with a 0.5 mm gap, resolution = $3.0 \times 3.0 \times$ 3.0 mm³ . Three image volumes (6s) at the beginning of each functional run were discarded to allow the spin lattice magnetization to stabilize.

2.5. Imaging Data Analysis

2.5.1. Data Preprocessing—Functional images were pre-preprocessed using Analysis of Functional NeuroImages Software (AFNI;<http://afni.nimh.nih.gov>; Cox, 1996) and fMRI Software Library (FSL) (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>; Smith et al., 2004; Jenkinson et al., 2012). Skull stripping was performed on anatomic data using FSL's Brain Extraction Tool (BET) (Smith, 2002). Functional data underwent motion correction, slice timing correction, and Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) (Smith et al., 2004) for denoising motion artifacts. Figure 1 outlines the processing steps.

2.5.2. Denoising—All the following processing steps were performed in native space. Within MELODIC, independent component analysis (ICA) was used to decompose each participant's functional time series into different spatial and temporal components. FSL's FMRIB's ICA-based Xnoiseifier (FIX) was used to identify motion-related noise components using classifiers provided by the software authors (Salimi-Khorshidi et al.,

2014; Griffianti et al., 2014). All components labeled as noise were visually inspected via their IC spatial maps, IC time courses, and power spectral density profiles to confirm that no probable signal was removed. Probable signal was defined as components in which suprathreshold focal activity was present in regions of interest, with an absence of patterns indicative of noise. Examples include heavily clustered activity at the frontal pole, ring pattern around edges of brain and "saw-tooth" pattern time courses. These criteria were based on Kelly and colleagues' (2010) descriptions of common non-signal related patterns in MELODIC output.

The first and last two TRs were removed from each functional run to eliminate artifacts introduced by slice timing correction. For task data, the block basis function was used to model the mean time series using BLOCK5. Data were run through 3dREMLfit after 3dDeconvolve to correct for temporal correlations and to prepare for local white matter regression. Local white matter was regressed using ANATICOR to reduce bias in correlations contained within gray matter (Jo, et al., 2010). The resultant residual time series, after extraction of effects of non-interest and time-invariant task-related hemodynamic response estimates, were then promoted for further analysis.

2.5.3. Region of Interest Selection—Regions of interest (ROIs) were based on the Harvard-Oxford cortical brain atlas appropriate to the goals in this study. Each ROI was back-transformed from standard space into each participant's native EPI space using FSL's Non-linear Image Registration Tool (FNIRT).

2.5.4. Time Series Extraction—Within each ROI, the top two percent of voxels active in response to the language task were selected to extract the residual time series. This was performed to compensate for structural and functional anatomic heterogeneity, thus ensuring that each ROI was task-relevant and subject-specific (e.g., Amunts et al., 2004). This procedure comprised the following steps: The F-statistic was obtained for each voxel within each ROI and sorted by variance explained by the task. A threshold was applied such that the top two percent of voxels were retained to generate a binarized relevant-voxel ROI mask for each region. This absolute statistical threshold was used as an objective means to equate for differences in sensitivity across subjects. The PPS was divided into two separate masks of task-positive and task-negative voxels, to distinguish portions of the PPS associated with language and the DMN, respectively. The spatially distinct task-positive and task-negative masks underwent the same thresholding procedure as the other ROIs.

For each participant, the relevant-voxel ROI masks were then registered to rest EPI space. For both task-residual and resting-state analyses, the time series was extracted from the active-voxel ROI masks in each participant's native task and rest EPI space. The time series of each voxel in each mask was averaged and correlated between ROI pairs. Fisher's r-to-z transformation was used to yield normalized functional connectivity values for each ROI pair.

2.5.5. Comparison of Task-Residual and Resting-State Data—We hypothesized that left-hemisphere lateralization of language and attention connections derived from taskresidual data would be stronger than those derived from resting-state data. We compared

task-residual and resting-state functional connectivity by calculating a "laterality difference index" (LDI) for each subject in IBM SPSS Statistics for Windows version 21.0. The LDI was calculated by the difference between z-normalized functional connectivity of lefthemisphere ROIs and their right-hemisphere homologues. Thus, the index represents the magnitude of difference between FC of the two hemispheres. For ROI pairs with a positive correlation, higher values indicate stronger left-hemisphere connectivity and values closer to or less than zero indicate weaker left-hemisphere connectivity, or stronger right-hemisphere connectivity, respectively. Conversely, for ROI pairs with a negative correlation, more negative values indicated stronger left-hemisphere connectivity.

Paired-samples tests were conducted to compare the LDI of resting-state and task-residual data. Although the LDI comparison provides an omnibus indication of whether a laterality difference exists, the relative contribution of each hemisphere is unknown. Hence, to better understand the contribution of the two hemispheres to the laterality comparison, both pairedand one-sample follow up tests were performed. The follow up analyses were performed to explain the magnitude and direction of connectivity contributing to the LDI results. These follow up analyses included 1) paired samples t-tests to compare FC between left- and righthemisphere ROI pairs in both data types and 2) one-sample tests to characterize the nature of the laterality findings, by determining whether each intra-hemispheric ROI pair was significantly correlated.

3. Results

3.1. Comparison of Task-Residual and Resting-State Data

3.1.1. Network 1: Laterality of Language Connectivity—Based on normality test results from the Shapiro-Wilk test, a paired sample t-test was appropriate to compare resting-state and task-residual data. The task-residual time series between language ROIs (left IFG and left PPS task positive nodes) were positively correlated, consistent with their participation in the language network. Our laterality hypothesis was partially supported by the data. Results showed that in language ROIs, task-residual data demonstrated a trend toward stronger left-hemisphere laterality compared to resting-state data, as indicated by a higher positive LDI in task-residual data, $p = 0.05$ (Table 2; Fig. 3).

Follow up tests were conducted to clarify the contribution of the two hemispheres to the laterality findings. Paired samples t-tests revealed that in task-residual data, left-hemisphere language regions were significantly more correlated ($M = 0.65$, $SD = 0.34$) than their righthemisphere homologues ($M = 0.44$, $SD = 0.36$), $t(20) = 2.51$, $p = 0.02$. Contrastingly, in resting-state data, no significant difference was found in functional connectivity between left-hemisphere language regions ($M = 0.41$, $SD = 0.29$) and their right-hemisphere homologues ($M = 0.33$, $SD = 0.28$), $t(20) = 1.24$ $p = 0.23$.

One sample t-tests, conducted to examine whether intra-hemispheric normalized correlations were significantly different than zero (Fig. 3), revealed that all intra-hemispheric correlations were significant: left-hemisphere task-residual data ($M = 0.65$, $SD = 0.34$), $t(20) = 8.78$, p $=$.000; right-hemisphere task-residual data ($M = 0.44$, $SD = 0.36$), $t(20) = 5.55$, $p = .000$; left-hemisphere resting-state data ($M = 0.41$, $SD = 0.29$), $t(20) = 6.56$, $p = .000$; right-

hemisphere resting-state data ($M = 0.33$, $SD = 0.28$), $t(20) = 5.39$, $p = .000$. To summarize the follow up analyses, results show that although functional connectivity exists between language regions and their homologues in both task-residual and resting-state data, there is stronger connectivity in the left hemisphere in task-residual data but not resting-state data.

3.1.2. Network 2: Laterality of Language-Attention Connectivity—In addition to having language eloquent functions, areas of PPS are also associated with the DMN. This analysis examined the intersection between anterior language regions (IFG) and posterior language regions associated with the DMN (areas characterized by negative BOLD response of the PPS). Task-residual time series for these regions were anticorrelated, consistent with their involvement in task-positive vs. task-negative networks. Results supported our laterality hypothesis, in which task-residual data demonstrated stronger laterality than resting-state data as indicated by greater absolute value of the LDI in task-residual data, $p =$ 0.003 (Table 2; Fig. 4).

Follow up paired samples *t*-tests revealed that in task-residual data, left-hemisphere regions were more negatively correlated ($M = -0.26$, $SD = 0.33$) than their right-hemisphere homologues ($M = 0.03$, $SD = 0.33$), $t(20) = -3.80$, $p = .001$. In resting-state data, no significant difference was found in the functional connectivity between left- $(M = 0.15, SD$ $= 0.21$) and right-hemisphere (M = 0.22, $SD = 0.27$) regions, $t(20) = -1.06$, $p = 0.30$. One sample t-tests conducted to examine whether intra-hemispheric normalized correlations were significantly different than zero (Fig. 4) revealed that the correlation between lefthemisphere task data was significant ($M = -0.26$, $SD = 0.33$), $t(20) = -3.70$, $p = .001$, but the correlation between right-hemisphere task data was not significant ($M=0.03$, $SD=$ 0.33), $t(20) = 0.36$, $p = .72$. In resting-state data, both left and right intra-hemispheric correlations were positive and significant: left $(M = 0.15, SD = 0.21)$, $(20) = 3.18, p = .005$; right ($M = 0.22$, $SD = 0.27$), $t(20) = 3.74$, $p = .001$.

3.1.3. Network 3: Laterality of Intention-Attention Connectivity—Task-residual time series for pre-SMA and PC/Pc were anti-correlated, consistent with their involvement in task-positive vs. task-negative networks. Consistent with our laterality hypothesis, a paired samples *t*-test showed that task-residual data demonstrated stronger left-hemisphere laterality than resting-state data, $p = 0.04$ (Table 2; Fig. 5). The intention-attention connections were more left-lateralized in task-residual data than in resting-state data, as indicated by greater absolute value of the LDI in task-residual data.

In spite of the significantly stronger LDIs for task-residual than resting-state data, follow up paired samples *t*-tests revealed that in task data, no significant difference was found in functional connectivity between left- $(M = -0.21, SD = 0.30)$ and right-hemisphere $(M =$ -0.13 , $SD = 0.33$) intention-attention regions, $t(20) = -1.26$ $p = 0.22$. Similarly, in restingstate data, no significant difference was found in the functional connectivity between left (M) $= 0.08$, $SD = 0.18$) and right ($M = 0.07$, $SD = 0.23$) hemisphere intention-attention regions, $t(20) = 0.17$ $p = 0.87$. One sample *t*-tests (Fig. 5) revealed that in task-residual data, lefthemisphere correlations were significant $(M = -0.21, SD = 0.30)$, $(20) = -3.26, p = .004$, but right-hemisphere correlations were not $(M = -0.13, SD = 0.33)$, $t(20) = -1.74$, $p = .097$. In resting-state data, there were no significant differences from zero in the left-hemisphere

correlations ($M = 0.08$, $SD = 0.24$), $\ell(20) = 1.96$, $p = .064$, or the right-hemisphere correlations ($M = 0.07$, $SD = 0.24$), $t(20) = 1.33$, $p = .199$. These results show that the greater laterality in task-residual data compared to resting-state data may be driven by the magnitude of the task-residual connectivity between the left pre-SMA and PC/Pc.

4. Discussion

Using transparent methods, we compared task-residual and resting-state approaches to characterize the FC of three network relationships. Task-residuals accentuated leftlateralized communication between intra-hemispheric nodes in both domain-specific and domain-general systems, suggesting that FC is altered during task engagement. The implications of these findings are discussed below.

4.1 Task-Residual Versus Resting-state Data

Our hypothesis that connectivity from task-residual data would be more lateralized (leftdominant) than resting-state data was partially supported. Nodes in the intention-attention network and language-attention network were more left-dominant in task-residual data compared to resting state data. However, language nodes showed a trend in the hypothesized direction.

Follow-up testing of language network laterality demonstrated that left-hemisphere regions were more strongly correlated than the right-hemisphere in task-residual data but not restingstate data. Despite significant right-hemisphere connectivity in both data types, lefthemisphere regions were still more tightly coupled than right in task-residual data. Although resting-state data showed significant FC in both hemispheres, it lacked the degree of network specificity that task-residual data afforded. Hence, laterality, one of the hallmarks of neural systems for language, is captured by task-residual comparisons but not by resting-state analyses. Overall, the data suggest that task-residuals highlight network specificity to a greater degree than in resting-state data, consistent with other context-dependent functional connectivity studies (Al-Aidroos et al., 2012).

The correlation between the anterior language region (IFG) and the posterior language region converging with DMN functions (characterized by negative activity in the posterior perisylvian region) had stronger laterality in task-residual data than resting-state data. In the follow-up comparisons, left-hemisphere correlations were significantly stronger than right in task-residuals but not resting-state data, implicating an upregulation of left-hemisphere functional connectivity and downregulation of irrelevant right-hemisphere connectivity. Again, task-residual data were more sensitive to lateralized relationship of frontal language cortices to lateral portions of the DMN than resting-state data. A possible explanation for this cross-network interaction is suppression of attentional mechanisms in the DMN so that subjects can focus on the demands of word generation in verbal fluency.

Task-based residual activity appears sensitive to functional interactions between taskrelevant regions and may deemphasize functional interactions between task-irrelevant regions (Al-Aidroos et al., 2012; Davis-Thompson & Andrews, 2012; Norman-Haignere et al., 2012). One study involving face processing and visual attention (Al-Aidroos et al., 2012)

reported that attending to faces strengthened the connectivity between occipital areas and the fusiform face area (FFA) but not between occipital areas and the parahippocampal place area (PPA), whereas attending to scenes strengthened the connectivity between occipital areas and the PPA but not between the occipital areas and the FFA. This pattern was observed despite robust responses from task-irrelevant areas. Task-residuals are sensitive to the functional interactions between task-relevant regions as opposed to regions that are evoked in response to a stimulus but do not interact.

Our study extends this line of research by exploring language and intention-attention networks. Although our study examined different networks, these investigations converge on the finding that task-based residuals can be used to feature interdependence between domain-specific regions. Additionally, the functional interdependence in task-residuals reflect synchronized activity in the context of a task even when time-invariant stimulusevoked responses have been accounted for.

4.3 Study Limitations

It is possible that the trend detected in the language system did not reach significance due to a lack of statistical power. However, that the observed trend was in the hypothesized direction offers an empirical warrant for further investigation. Additionally, the use of both semantic and phonemic stimuli may have biased the selection of voxels in language cortices toward those more highly activated in both semantic and phonological processing than those activated more highly for one of these processes versus the other (Devlin et al., 2003). Thus, when averaging the response of active voxels in each ROI, the spatial distribution of activity reflected more heterogeneity than a single stimulus class would have, potentially reducing the coherence of correlations. Considering this possibility, however, the robustness of taskresidual data in demonstrating the laterality expected in language processing is impressive.

4.4 Conclusion

The present findings indicate that task-residual data can be used to characterize specificity of network coherence. The degree to which domain-general and domain-specific regions share variance above and beyond the mean hemodynamic response during a task highlights context-relevant functional connectivity that is not present in resting-state data. Thus, taskresidual data can offer complementary information to resting-state functional connectivity data. Future studies should continue to explore the sensitivity of this approach in detecting early age- or disease-related network alterations.

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Highlights

- **•** Task-residual functional connectivity captures synchrony between regions recruited for a task after removing task-evoked signal.
- **•** Task-residual data revealed greater network specificity than resting-state as measured by functional connectivity of left-hemisphere language regions and right-hemisphere homologs.
- **•** Reduced functional connectivity in domain-general attention regions is associated with reduced opposing coherence between task-positive and tasknegative regions.

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Fig. 3.

(LEFT) Laterality of functional connectivity between language nodes, IFG and PPS, in taskresidual and resting-state data. There was a trend that task-residual showed a greater LDI than resting-state data, $p=0.05$. (RIGHT) Functional connectivity of language nodes in each hemisphere based on task-residual and resting-state data. (*Significant at $p < 0.05$).

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Fig 4.

(LEFT) Laterality of functional connectivity between language-attention nodes, IFG and negative PPS, in task-residual and resting-state data. (RIGHT) Functional connectivity of language-attention nodes in each hemisphere based on task-residual and resting-state data. (*Significant at $p < 0.05$).

Fig. 5.

(LEFT) Laterality of functional connectivity between intention-attention nodes, preSMA and PC/Pc, in task-residual and resting-state data. (RIGHT) Functional connectivity of intentionattention nodes in each hemisphere based on task-residual and resting-state data. (*Significant at $p < 0.05$).

Table 1

Demographic characteristics

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Comparison of task-residual and resting-state laterality difference indices Comparison of task-residual and resting-state laterality difference indices

