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Functional connectivity in resting state as a phonemic fluency ability measure

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ABSTRACT

There is some evidence that functional connectivity (FC) measures obtained at rest may reflect individual differences in cognitive capabilities. We tested this possibility by using the FAS test as a measure of phonemic fluency. Seed regions of the main brain areas involved in this task were extracted from meta-analysis results (Wagner et al., 2014) and used for pairwise resting-state FC analysis. Ninety-three undergraduates completed the FAS test outside the scanner. A correlation analysis was conducted between the F-A-S scores (behavioral testing) and the pairwise FC pattern of verbal fluency regions of interest. Results showed that the higher FC between the thalamus and the cerebellum, and the lower FCs between the left inferior frontal gyrus and the right insula and between the supplementary motor area and the right insula were associated with better performance on the FAS test. Regression analyses revealed that the first two FCs contributed independently to this better phonemic fluency, reflecting a more general attentional factor (FC between thalamus and cerebellum) and a more specific fluency factor (FC between the left inferior frontal gyrus and the right insula). The results support the Spontaneous Trait Reactivation hypothesis, which explains how resting-state derived measures may reflect individual differences in cognitive abilities.

1. Introduction

In neuroimaging research, for years the existence of brain activity without performing any cognitive task (i.e., intrinsic or spontaneous brain activity) was considered a very low frequency random noise and, therefore, excluded. Recent studies have shown that this activity is not random, but rather well-structured and organized (Biswal et al., 1995; De Luca et al., 2005). This "resting-state" activity has a similar amplitude to what appears during task performance, and it covers the entire brain cortex (Nir et al., 2006). A further step in research on this spontaneous activity is to give a "cognitive value" to this information.

Some studies have found significant correlations between individual differences in spontaneous connectivity patterns and differences in individual task performance. Harmelech and Malach (2013) tried to unify the quantity of resting-state data under a single principle. They proposed the "spontaneous trait reactivation" hypothesis (STR), which basically states that spontaneous fluctuations could teach us about individual personality traits, abilities, and even diseases. They tested their hypothesis by reviewing a number of studies using different measures. One of these measures was individual differences in cognition. Our study aims to contribute more empirical evidence to the STR hypothesis by using a resting-state FC data analysis approach to investigate the possible individual differences when performing a verbal phonemic fluency task.

Previous results of resting-state studies agree with this proposal of using functional connectivity (FC) measures. Resting-state FC provides information about the profile of each person's neuronal connectivity biases and focuses on connectivity assessed across individual BOLD time points during resting conditions (Friston, 2009). For example, Ventura-Campos et al. (2013) showed a method for studying the brain's capacity to learn by determining FC during resting-state-fMRI (rs-fMRI) between task-related brain areas. The authors concluded that spontaneous brain activity predicts the ability to learn foreign sounds. Their work used the methodology from a study by Baldassarre et al. (2012), where a correlation between individual differences in perfor-

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mance on a perceptual task and dissimilarities in resting-state functional connectivity (rs-FC) were demonstrated. Another study showed the predictive properties of resting state fluctuations in individual performance after learning (Lewis et al., 2009). In addition, measures of the intrinsic brain activity synchronization within a region (i.e., regional homogeneity) during resting-state have predicted individual differences on a variety of cognitive tasks (Barttfeld et al., 2013; Coste et al., 2011; Martin et al., 2012; Mennes et al., 2010; Wang et al., 2013; Zou et al., 2013).

Verbal fluency is an executive function that neuropsychological language production tests easily evaluate. These tests evaluate the capacity to generate words in a fixed time, usually one minute. Generally, participants have to say as many words as possible from a specific category. Categories can be semantic (produce names such as animals or fruits) or phonemic (generate words beginning with a specific letter). Those kinds of tasks require subjects to retrieve words stored in the long-term memory, and they involve frontal processes. Successful retrieval requires executive control over cognitive processes such as selective attention, working memory, language production, mental set shifting, internal response generation, and inhibition of inappropriate responses (Lezak, 1995; Patterson, 2011; Ruff et al., 1997).

Several investigations have studied the neural basis of verbal fluency (Gauthier et al., 2009; Heim et al., 2008; Weiss et al., 2004; Weiss, 2003). In a meta-analysis, Wagner et al. (2014) included twenty-eight individual studies with a total of 499 healthy volunteers to separately study the brain areas involved during the performance of phonemic and semantic verbal fluency tasks. The authors found eight regions with significant activation during phonemic verbal fluency tasks, and seven regions with significant activation during semantic verbal fluency tasks. In the case of phonemic fluency, the area most involved was the left inferior frontal gyrus (LIFG), a brain area implicated in word production and speech processing on different tasks, especially phonemic fluency (Broca, 1861; Bookheimer, 2002; Demonet et al., 1996; Hirshorn and Thompson-Schill, 2006; Indefrey and Levelt, n.d.; Price, 2000, 2010). Neuropsychological studies have revealed that patients with lesions in the left frontal lobe were more impaired in phonemic fluency than those with right frontal lesions (Robinson et al., 2012). Although right inferior frontal activation has been related with semantic tasks (sentence comprehension) (Price, 2010), it is also relevant because has been associated with attentional switching and response inhibition (Hampshire et al., 2010). The left insula was also strongly involved in phonemic processing and during the performance of the verbal fluency task (Brown et al., 2009; Gauthier et al., 2009; Price, 2010; Saur et al., 2008). Some studies have also related the insula to vocal production (Ackermann and Riecker, 2004; Riecker et al., 2000). Other brain structures associated with phonemic fluency were the thalamus, the cerebellum and the supplementary motor area (SMA). On the one hand, activations of the thalamus have been associated with processing stages during verbal fluency tasks (Llano, 2013) and activations in the cerebellum have been related to speech production (Price, 2010), selecting correct responses and attention (Senhorini et al., 2011). On the other, the SMA has been related to the cognitive effort linked to word selection processes, in addition to its role during the encoding of word form information and overt language articulation (Alario et al., 2006; Price, 2010).

The present study was designed to verify whether resting-state activity serves as a good verbal fluency ability measure. We will compare the resting-state FC of brain areas with significant activation on a phonemic fluency task to the performance on a phonemic fluency task. In agreement with the STR hypothesis and bearing in mind the results of previous investigations where resting-state FC has been able to describe individual differences in the performance on cognitive tasks, our main hypothesis was that FC patterns would be able to describe individual differences on the phonemic fluency task at the brain level. We hypothesized that participants with more coherent FC patterns will perform better on the phonemic fluency task.

2. Materials and methods

2.1. Participants

Ninety-three right-handed, healthy undergraduates (37 male) with ages ranging between 18 and 30 years (mean age=20.65; SD=2.697) participated in this study. They were native Spanish speakers, and none of them had a previous psychiatric or neurologic diagnosis. Informed consent was obtained from each subject before participation, and they received monetary compensation for their time and effort. The Ethical Committee of Universitat Jaume I approved the research project.

2.2. Behavioral task

The Spanish version of the FAS test (Spreen and Benton, 1977) was completed by all participants a day before the resting-state fMRI session. During the phonemic fluency tasks, participants were asked to orally produce as many words as possible beginning with a requested letter (F, A or S) within a prescribed time frame (a minute).

2.3. Neuroimaging data acquisition

Functional MRI sessions consisted of a resting-state scan where participants were instructed to simply rest with their eyes closed and try not to sleep or think about anything in particular. Images were acquired on a 1.5 T scanner (Siemens Avanto). Participants were placed in a supine position in the MRI scanner, and their heads were immobilized with cushions to reduce motion artifacts. For the rs-fMRI, a total of 270 volumes were recorded over 9 min, using a gradient-echo T2*- weighted echo-planar imaging sequence (TR=2000 ms; TE=48 ms; matrix, 64×64; voxel size=3.5×3.5 mm; flip angle=90°; slice thickness=4 mm; slice gap=.8 mm). We acquired 24 interleaved axial slices parallel to the anterior–posterior commissure plane covering the entire brain. Before the functional magnetic resonance sequences, a high-resolution structural T1-weighted MPRAGE sequence was acquired (TR=2200 ms; TE=3.8 ms; matrix=256×256×160; voxel size=1×1×1 mm).

2.4. Behavioral data analyses

Descriptive analyses were conducted with SPSS (v.21, Armonk, New York, USA). The mean F-A-S score was calculated for each participant and subsequently used in resting-state FC correlation analyses. In addition, the data sample distribution was studied, along with the mean and the standard deviation.

2.5. Resting-state functional connectivity analyses

2.5.1. Preprocessing

Rs-fMRI datasets were processed using a toolkit of the Data Processing Assistant for Resting-State fMRI (DPARSFA; http://rfmri.org/DPARSF) (Yang and Zang, 2010), based on some Statistical Parametric Mapping functions (SPM v.8 Wellcome Trust Centre for Neuroimaging, London, UK) to preprocess the rs-fMRI data and REST software (http://www.restfmri.net) for the connectivity analysis. Prior to preprocessing, we applied artifact correction (automatic detection and reparation of bad slices) with the ArtRepair toolbox for SPM (Mazaika et al., 2007). The rs-fMRI preprocessing included the slice-timing correction for interleaved acquisitions using sinc-interpolation and resampling with the middle slice (24th) in time as the reference point. Head motion correction was performed, where the functional images were realigned and resliced to the mean functional image. Afterwards, the anatomical image (T1-weighted) was co-registered to the mean functional image, and the transformed anatomical image was