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Characterizing individual differences in functional connectivity using dual-regression and seed-based approaches

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ABSTRACT

A central challenge for neuroscience lies in relating inter-individual variability to the functional properties of specific brain regions. Yet, considerable variability exists in the connectivity patterns between different brain areas, potentially producing reliable group differences. Using sex differences as a motivating example, we examined two separate resting-state datasets comprising a total of 188 human participants. Both datasets were decomposed into resting-state networks (RSNs) using a probabilistic spatial independent component analysis (ICA). We estimated voxel-wise functional connectivity with these networks using a dual-regression analysis, which characterizes the participant-level spatiotemporal dynamics of each network while controlling for (via multiple regression) the influence of other networks and sources of variability. We found that males and females exhibit distinct patterns of connectivity with multiple RSNs, including both visual and auditory networks and the right frontal–parietal network. These results replicated across both datasets and were not explained by differences in head motion, data quality, brain volume, cortisol levels, or testosterone levels. Importantly, we also demonstrate that dual-regression functional connectivity is better at detecting inter-individual variability than traditional seed-based functional connectivity approaches. Our findings characterize robust—yet frequently ignored—neural differences between males and females, pointing to the necessity of controlling for sex in neuroscience studies of individual differences. Moreover, our results highlight the importance of employing network-based models to study variability in functional connectivity.

Introduction

Individuals are remarkably diverse, exhibiting variation across a host of behaviors and phenotypes. Psychologists have long recognized the importance of including individual variability in cognitive models (Underwood, 1975), and neuroscientists have begun to identify underlying structural and functional variability in specific brain regions (Braver et al., 2010; Hariri, 2009) and how that variability relates to individual differences in a range of domains: motivation (Clithero et al., 2011; Mobbs et al., 2009; Strauman et al., 2013), reward sensitivity (Beaver et al., 2006; Carter et al., 2009), trait anxiety (Bishop, 2009; Etkin et al., 2004), and working memory capacity (Osaka et al., 2003; Todd and Marois, 2005).

Yet, many computations are distributed across networks of regions rather than being restricted to a specific region (Friston, 2009). Accordingly, studies of functional connectivity of the brain at rest have converged on the idea that the brain is organized into multiple, overlapping resting-state networks (RSNs) (Beckmann et al., 2005; Smith et al., 2009). Some of these networks, including the default-mode network (Buckner et al., 2008; Raichle et al., 2001), are observed in multiple species (Hayden et al., 2009; Lu et al., 2012; Vincent et al., 2007), which highlights the fundamental nature of their role in neural organization. Although RSNs represent a primary target of recent work on individual differences, even relatively straightforward questions regarding sex differences have led to equivocal results (Biswal et al., 2010; Filippi et al., 2012; L. Wang et al., 2012; Weissman-Fogel et al., 2010). The lack of consensus across these studies could be due to a number of factors, including small sample sizes (Yarkoni, 2009) and the inability of traditional analysis approaches to accurately represent the distributed computations that occur across RSNs (Cole et al., 2010).

Characterizing the neural bases of sex differences could provide a crucial first step toward understanding the mechanisms of psychopathologies that are linked to sex (Rutter et al., 2003). We therefore investigated whether sex differences are expressed in patterns of functional connectivity during the resting state. We recruited a large sample of participants (N = 188), which we partitioned into split samples for an

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internal replication. For each dataset, we computed a spatial independent component analysis (ICA) that parceled the functional data into a set of independent spatial maps (Fig. 1), some reflecting artifactual spatial structures and others reflecting well-characterized RSNs (Smith et al., 2009). We then employed a dual-regression functional connectivity analysis, which quantifies connectivity with an entire RSN—rather than a representative node of the RSN, a limitation of traditional seed-based approaches (Cole et al., 2010)—while controlling for the influence of other RSNs (Filippini et al., 2009; Leech et al., 2011, 2012). Our analyses revealed two key results. First, functional connectivity patterns between distinct brain regions and multiple RSNs reliably predicted sex differences. Second, functional connectivity estimates derived from dual-regression analysis were better at classifying males and females than similar estimates obtained from a seed-based analysis, suggesting that dual-regression analysis provides a superior representation of the distributed computations that occur within RSNs.

Materials and methods

Participants

A total of 209 participants completed a resting-state scan that was included as the last scan of a larger study containing three decision-making tasks. Although the results from those tasks are not described here, we note that we did not observe sex differences in response times on any task (Table 1). Furthermore, all participants completed the same tasks, in the same order, prior to the resting-state scan. These observations are important in light of recent work highlighting the plastic nature of RSNs, where prior tasks can influence resting-state results (Lewis et al., 2009; Z. Wang et al., 2012).

During the resting-state scan, participants were told that they should maintain visual fixation on a central cross, with no other explicit instructions. All participants reported no prior psychiatric or neurological illness, via pre-screening for the study. Twenty-one participants were excluded prior to statistical analysis because their data failed to meet quality criteria for inclusion (see FMRI preprocessing section), leaving a final sample of 188 participants. We split the sample into two randomly-determined datasets so that we could explicitly test all findings for replication, internally [Dataset 1: $N_1 = 94$ (57 females), mean age = 21.8 years; Dataset 2: $N_2 = 94$ (46 females), mean age = 21.9 years]. The relative proportion of males and females in each sample was not significantly different from chance (binomial test for Dataset 1: $p = 0.15$; binomial test for Dataset 2: $p = 0.15$), and we additionally account for numerical imbalances between males and females with non-parametric permutation-based testing (Nichols and Holmes, 2002). All participants gave written informed consent as part of a protocol approved by the Institutional Review Board of Duke University Medical Center.

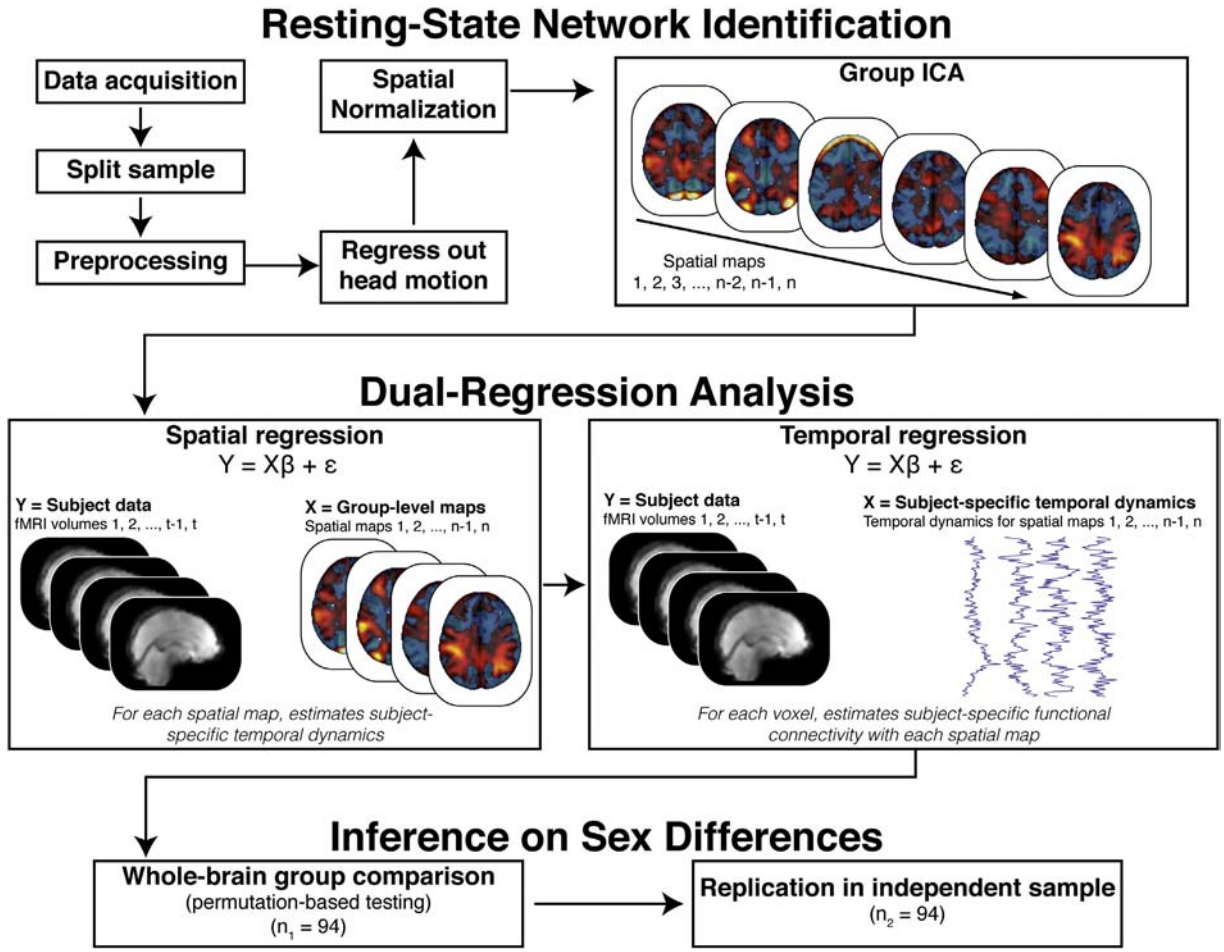

Fig. 1. High-level schematic of analytical approach. Our analyses proceeded in several steps. After splitting our sample into two independent datasets ($n_1 = 94$; $n_2 = 94$), the data were preprocessed and motion-related variance was removed from the time series via multiple regression. Group independent component analyses were performed on each dataset, with resulting spatial maps being entered into separate dual regression analyses. Importantly, the dual regression analysis allowed us to quantify, within each subject, each voxel's functional connectivity with each spatial map while controlling for the influence of other, potentially confounding, maps. The resulting functional connectivity measures were then subjected to permutation-based statistical testing to test for sex differences. Finally, we supplemented all of our results by testing for replication in the independent sample of data.