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Finer parcellation reveals detailed correlational structure of resting-state fMRI signals

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HIGHLIGHTS

- We study correlational structure of an 'average brain' at O(1 cm^3) resolution.
- We describe a simple method for finer functional parcellation (758 clusters).
- Quality of functional clustering remained comparable at all resolutions.
- Mutual information of correlations increased in proportion to resolution.
- Correlations and connectivity of an 'average brain' are reproducible at O(1 cm^3).

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ABSTRACT

Background: Even in resting state, the human brain generates functional signals (fMRI) with complex correlational structure. To simplify this structure, it is common to parcellate a standard brain into coarse chunks. Finer parcellations are considered less reproducible and informative, due to anatomical and functional variability of individual brains.
New methods: Grouping signals with similar *local* correlation profiles, restricted to each anatomical region (Tzourio-Mazoyer et al., 2002), we divide a standard brain into 758 'functional clusters' averaging 1.7 cm^3 gray matter volume ('MD758' parcellation). We compare 758 'spatial clusters' of similar size ('S758').
Results: 'Functional clusters' are spatially contiguous and cluster quality (integration and segregation of temporal variance) is far superior to 'spatial clusters', comparable to multi-modal parcellations of half the resolution (Craddock et al., 2012; Glasser et al., 2016). Moreover, 'functional clusters' capture many *long-range* functional correlations, with $O(10^5)$ reproducibly correlated cluster pairs in different anatomical regions. The pattern of functional correlations closely mirrors *long-range anatomical connectivity* established by fibre tracking.
Comparison to existing methods: MD758 is comparable to coarser parcellations (Craddock et al., 2012; Glasser et al., 2016) in terms of cluster quality, correlational structure (54% relative mutual entropy *vs* 60% and 61%), and sparseness (35% significant pairwise correlations *vs* 36% and 44%).
Conclusion: We describe and evaluate a simple path to finer functional parcellations of the human brain. Detailed correlational structure is surprisingly consistent between individuals, opening new possibilities for comparing functional correlations between cognitive conditions, states of health, or pharmacological interventions.

1. Introduction

Spontaneous fluctuations of brain activity at rest (Biswal et al., 1995; Nir et al., 2006) episodically express distinct correlation patterns ("resting state networks") (Fox and Raichle, 2007; Florin et al., 2015; Raichle, 2015), which are thought to delineate large functional networks in the brain ("functional connectomics") (Power et al., 2011; Smith et al., 2013). While the full significance of resting-state activity has yet to become clear, its complexity continues to stimulate the development of innovative methods of analysis (Deco et al., 2015; Mitra and Raichle, 2016; Cabral et al., 2017).

To better characterize and interpret the correlational structure of resting-state activity, it may be helpful and indeed necessary

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to reduce the high dimensionality of functional magnetic resonance signals (typically $O(10^5)$ voxels). This may be achieved by parcellating the brain into distinct chunks (typically with $O(10^3)$ voxels each) and by averaging signals spatially over the voxels of each chunk. Ideally, a parcellation will combine signals with similar time-courses, and distinguish signals with dissimilar time-courses, such as to reduce dimensionality without compromising dynamical information (Eickhoff and Grefkes, 2011; de Reus and van den Heuvel, 2013; Thirion et al., 2014). If such an 'information-preserving' reduction of dimensionality could be attained, this would greatly simplify subsequent network analyses of resting-state activity (Sporns, 2012).

Resting-state activity has been analyzed with many different brain parcellations, some based on anatomical criteria, some on functional criteria, and some on both. Some widely used parcellations distinguish brain regions with the help of anatomical landmarks (e.g., cortical sulci and gyri), such as 'automated anatomical labeling' (Tzourio-Mazoyer et al., 2002; 90 regions) or 'Harvard-Oxford' parcellation (Desikan et al., 2006; 68 regions), while others rely on post-mortem cyto- and myelo-architectonic criteria (Eickhoff et al., 2005, 62 regions; Lancaster et al., 1997, 160 regions).

Alternatively, brain regions may be defined on the basis of correlations of temporal variance ("functional connectivity", Biswal and Hyde, 1997). When adjoining voxels are compared in terms their respective correlations to a given set of reference voxels, the two 'correlation profiles' are often similar, but sometimes sharply dissimilar (Zang et al., 2004; Cohen et al., 2008). Such discontinuities may indicate putative region boundaries and supply the rationale for "functional parcellations" (de Reus and van den Heuvel, 2013; Eickhoff et al., 2015). For example, Craddock et al. (2012) combined homogeneity of functional connectivity and spatial contiguity to divide the human brain into 200 or 400 parcels ('CC200', 'CC400'). Recently, Glasser et al. (2016) combined several complementary types of information – functional connectivity, cortical architecture, task-related activity, and spatial contiguity – to establish a 'multi-modal parcellation' into 360 parcels ('HCP360').

Here we reexamine the reproducibility and informativeness of finer parcellations with cluster volumes of $O(1\,cm^3)$. Due to the anatomical and functional variability of individual brains, functional parcellations are expected to be less reproducible at higher resolutions (Craddock et al., 2012). Moreover, functional parcellations appear to be no more informative than spatial parcellations (Craddock et al., 2012), which are far easier to obtain. We decided to revisit these findings, encouraged in part by the quality of functional brain imaging signals at our site.

Specifically, we sought to compare purely functional and purely spatial parcellations of higher resolution with widely used anatomical and multi-modal parcellations of lower resolution. Two levels of comparison seemed pertinent. To what extent are clusters of a given parcellation functionally homogeneous in terms of *local* voxel-to-voxel correlations within the surrounding anatomical region and, further, to what extent does a parcellation capture consistent *long-range* cluster-to-cluster correlations between distant anatomical regions? In this way, we hoped to determine whether or not the computational effort of finer functional parcellations is worthwhile.

To address these questions, we started from a coarse parcellation with few, large parcels, specifically, the 'AAL90' parcellation (Tzourio-Mazoyer et al., 2002), with 90 anatomically identified regions averaging 14 cm^3 grey matter volume. Using either exclusively functional or exclusively spatial criteria, we separately subdivided each anatomical region into smaller parcels of a chosen size. For example, we obtained two novel, finer parcellations, with 758 'functional clusters' or 'spatial clusters', averaging 1.7 cm^3 grey matter volume, termed 'MD758' and 'S758', respectively.

Our results showed that finer parcellations can be both reproducible and informative. Firstly, the functional homogeneity of clusters increased with decreasing size, at least down to 0.8 cm^3 grey matter volume, consistent with previous results (Craddock et al., 2012). Secondly, the quality of small 'functional clusters', in terms of integrating similar and segregating dissimilar sources of temporal variance within a *local* anatomical region, was comparable to larger clusters of sophisticated, multi-modal parcellations (Craddock et al., 2012; Glasser et al., 2016) and far exceeded the quality of 'spatial clusters' of the same size. Thirdly, 'functional clusters ' in distant anatomical regions revealed a reproducible, *long-range* correlation structure. Of the 282,566 unique pairs of 'functional clusters' in different anatomical regions, approximately 34% proved to be consistently and significantly correlated. The pattern of *long-range* functional correlations closely mirrored the anatomical connectivity of 'functional clusters', established by means of fibre tracking and diffusion-tensor imaging (DTI). Fourthly, both the relative number of correlated cluster pairs and the relative mutual information encoded by correlations approached the values of sophisticated, multi-modal parcellations with larger clusters (Craddock et al., 2012; Glasser et al., 2016). In other words, the correlational information captured by MD758 remained nearly proportional to its resolution.

In conclusion, we report a simple but effective way to capture functional correlations in the human brain at $O(1\,cm^3)$ resolution. This offers new possibilities for comparing functional correlations between, for example, different cognitive conditions, different states of health, or different pharmacological interventions.

2. Methods

2.1. Participants

Eight selected subjects participated in the study (age 28.5 ± 4.5 years, four females, one left-handed). All subjects were healthy, experienced with MRI, and known to produce strong functional signals. Subjects gave written consent according to the guidelines of the Centre for Neuroscientific Innovation and Technology, Magdeburg.

2.2. Magnetic-resonance imaging

All magnetic-resonance imaging was performed on a 3-T Siemens Magnetom Prisma scanner for all imaging. Functional images were acquired with a T2* weighted single-shot gradient EPI sequence with ramp sampling ($TE = 30$ ms, $TR = 2$ s, 90° flip angle, isotropic resolution 3 mm × 3 mm × 3 mm, slice thickness 3 mm with a gap of 0.6 mm or 20%; 36 transverse slices oriented ac/pc; matrix size 72 × 72). During functional runs, observers rested in the scanner with closed eyes for 5.5 min (165 TR). Four such runs were acquired on two successive days (two runs each). From each run, the first 15 TR were discarded and the remaining $N_t = 150$ TR were retained. Repeated observations were separated by approximately 15 min.

To correct for magnetic field distortions, we obtained a field map with a gradient dual echo sequence (echo 1: $TE = 4.92$ ms, echo 2: $TE = 7.38$ ms, $TR = 720$ ms, spatial resolution 1.594 mm × 1.594 mm × 2 mm, 72 transverse slices oriented ac/pc; matrix size of 138 × 138; scan time 3 min 20 s).

Anatomical images were collected using a T1-weighted, 3D-modified, driven equilibrium FTP sequence ($TE = 2.82$ ms; $TR = 2500$ ms; 192 phase encoding steps; isotropic resolution of 1 mm × 1 mm × 1 mm; sagittal orientation; matrix size of 256 × 256; scan time of 5 min 18 s).

To trace fibre bundles in the white matter, Diffusion Weighted Imaging (DWI) was acquired with 128 optimal nonlinear diffu-