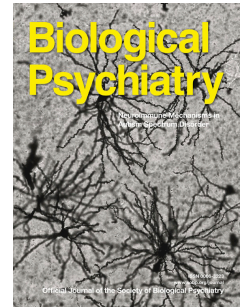# Journal Pre-proof

Defining Individual-Specific Functional Neuroanatomy for Precision Psychiatry

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Title: Defining Individual-Specific Functional Neuroanatomy for Precision Psychiatry

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Abstract:

Studies comparing diverse groups have shown that many psychiatric diseases involve disruptions across distributed large-scale networks of the brain. There is hope that fMRI functional connectivity techniques will shed light on these disruptions, providing prognostic and diagnostic biomarkers as well as targets for therapeutic interventions. However, to date, progress on clinical translation of fMRI methods has been limited. Here, we argue that this limited translation is driven by a combination of inter-subject heterogeneity and the relatively low reliability of standard fMRI techniques at the individual level. We review a potential solution to these limitations: the use of new "precision" fMRI approaches that shift the focus of analysis from groups to single individuals through the use of extended data acquisition strategies. We begin by discussing the potential advantages of fMRI functional connectivity methods for improving our understanding of functional neuroanatomy and disruptions in psychiatric disorders. We then discuss the budding field of precision fMRI and findings garnered from this work. We demonstrate that precision fMRI can improve the reliability of functional connectivity measures, while showing high stability and sensitivity to individual differences. We close by discussing the application of these approaches to clinical settings.

There is an enormous need to improve diagnosis and treatment of neuropsychiatric disorders given their personal and societal burden (1-3). A substantial body of neuroimaging work has documented variations in brain function that accompany psychiatric disorders with the hope of developing biomarkers and novel treatments. These studies generally observe that psychiatric disorders are associated not with focal brain pathology, but with widespread dysfunction of distributed brain networks (4-6). However, to date, few of these findings have been translated to clinical settings. At least two factors may contribute to this lack of translation. First, group comparisons do not capture the heterogeneity of phenomenological characteristics present across any given disorder. For example, individuals with schizophrenia can present with variable symptoms including delusions, hallucinations, disorganized behavior, and/or anhedonia. Individuals with depression may exhibit symptoms from anxiety to diminished reward sensitivity (7). Children with Tourette syndrome (TS) exhibit varied motor and vocal tics and frequently demonstrate comorbidity with ADHD and OCD (8). It is not surprising that findings from group studies do not adequately account for any individual's unique characteristics. Second, many neuroimaging techniques are noisy and exhibit low reliability in single individuals, limiting the ability to capture neural characteristics related to individual heterogeneity. Thus, new approaches are needed to measure brain function reliably in individuals.

In this review, we highlight insights that neuroimaging methods can provide about systems-level brain function in health and disease. We then review recent efforts from our laboratories and others to develop individualized ("precision") applications of fMRI using extended data acquisition strategies that can provide reliable and stable individual measures of brain organization. We close by discussing the practical application of precision fMRI in translational settings.

Measuring functional neuroanatomy with fMRI correlations
Human brain function is organized at many spatial scales, from local circuits to cortical columns, brain areas, and large-scale systems (9). The systems (10-14) and areal (15, 16) organization of human brains can be characterized noninvasively using functional connectivity MRI. Functional connectivity (FC) refers to temporal correlations in fMRI activity between different regions, which can be measured during experimental tasks or as spontaneous activity patterns during the *resting-state* (in the absence of task instructions). Resting-state methods have the advantage of not requiring patients to complete a task, which may prove challenging for patients and provide added burdens in administration for clinical centers. Despite the lack of experimental constraint, resting-state correlations demonstrate rich systematic patterns, with functionally-related regions showing high correlations to each other ("within system"), and lower correlations to regions in other systems. Indeed, resting-state fMRI has been used to define systems throughout the brain (11, 13, 17-20). These patterns are robust, with independent studies converging on similar descriptions of group-averaged system organization of the human brain (11, 13) (**Figure 1A**). Moreover, validation of FC patterns has been established through convergent evidence from other neural measures (21), lesion approaches (22, 23), and behavior (24). At a finer scale, FC can also be used to parcellate the brain into regions that approximate functional areas and map onto differences in task function (15, 16, 25).

FC approaches can be used to measure differences in brain systems between neurotypical controls and diverse neuropsychiatric populations, such as in schizophrenia (5, 26), depression (27), or TS (28, 29), and to identify commonalities across diagnostic boundaries (e.g.,(30-32)). Additionally, functional network mapping provides context for interpreting brain activity during tasks. Task results are often described using large, poorly-defined anatomical locations (e.g., "lateral prefrontal cortex"). With coincident FC, task results can instead be ascribed to specific

functional systems (e.g., frontoparietal or cingulooperculary), refining our understanding of task mechanisms in healthy individuals (17, 33, 34) and youths with diverse psychiatric symptoms (35). Furthermore, FC facilitates complex systems approaches to understanding brain function (36), which can be used to identify brain hubs (37-40) that support task function (41-45) and are vulnerable to damage (46-48). Network approaches hold promise for providing concise descriptions of how complex systems like the brain change across the lifespan (49-51) and are disrupted in psychiatric disorders (52), and may help develop mechanistic theories for these alterations (52-54).

Towards clinical utility of functional connectivity
Thus, FC has strong potential for clinical applications (55), including in the use of network mapping to enhance neurosurgical planning (56-60), providing systems-level biomarkers to identify at-risk individuals (61-63), sub-typing patients with diverse etiologies (32, 64), and identifying targets for treatment (e.g., with TMS) (55, 65, 66). However, despite a 20+ year history, FC techniques have yet to become widely used clinically. This observation raises the question of why clinical implementation has stalled.

For a measure to be clinically useful, it should be both *reliable*, such that repeated measurements produce the same result, and *stable across contexts*, such that it primarily reflects trait- rather than state-dependent effects. Additionally, it should show *sensitivity* to idiosyncratic features that may be clinically relevant. We suggest that new approaches are needed to reach clinically-relevant reliability, stability, and sensitivity of FC at the individual-level.

Achieving single-subject reliability is not trivial. While group descriptions of functional networks are robust, most studies collect insufficient data (5-10 min.) to obtain reliable FC estimates in single individuals (67-71). Recent estimates suggest that at least 40 min. of low-motion fMRI data are needed to achieve high reliability (test-retest r>0.9) across the full connectome (69, 70) (**Figure 2A**). While some networks may achieve reliability more quickly (e.g., the default-mode), most single connections show poor-to-fair reliability with < 40 min. of data (67, 71) (see **Supplemental Discussion**). Derived FC measures require even more data (e.g., areal parcellations require >50 min. (72); measures of lag structure require >200 min. (73, 74)). Moreover, reliability of fMRI data usually is worse in non-cortical regions that are implicated in many psychiatric disorders (75-77). Current estimates suggest that 90 min. of data are needed to achieve high reliability of cerebellar FC (78) and >100 min. are needed for the basal ganglia and thalamus (79). Notably, it may be possible to identify an individual within a large group – so-called "fingerprinting" approaches (80, 81)– using substantially less data (81). However, subject identification is not the same as individual-specific characterization of brain-based disease processes, which requires substantially more data and is the ultimate target for clinical utility.

A precision fMRI approach
The findings above motivate an alternative strategy for data acquisition. The core feature of this approach is to collect larger quantities of fMRI data in single individuals as opposed to smaller quantities of data averaged over groups. For convenience, we call this acquisition strategy "precision" fMRI (pfMRI), though other terms, including "deep" or "high-sampling" have also been used. PfMRI data are frequently coupled with extensive phenotypic and behavioral measurements to aid in establishing validity. Moreover, pfMRI benefits from being combined with advanced analysis including dataset denoising, alignment, and network definition.

The MyConnectome dataset is one of the original demonstrations of the utility of pfMRI for functional network mapping[*]. For this dataset, Russ Poldrack scanned himself twice weekly for a year, and collected additional phenotypic variables regarding health, affect, genotype, gene expression, and metabolomics (90). This work established that even in a single person, classic network patterns are evident, but clear deviations from typical "group" organization are also observed (70). Importantly, despite modest day-to-day variability (perhaps associated with caffeine or arousal levels (70)), these network patterns were fundamentally stable over the course of the year (70, 91).

The MyConnectome study inspired several related pfMRI projects (for examples see **Table 1, Supp. Table 1**). Among these, the "Midnight Scan Club" (MSC) dataset collected >20 hrs. of fMRI data in each of 10 people (**Figure 1B**), including large amounts of task and resting-state data. Initial reports from this dataset established that extended data acquisitions can be used to generate reliable individual descriptions of functional brain organization (69). Robust individual differences in FC were observed and these network variations corresponded to brain activations during tasks (69).

Additional pfMRI datasets have made important contributions to our understanding of functional systems. For example, Braga and Buckner (92) used a four person pfMRI dataset to describe substructure within several networks that is too individually variable to easily delineate in group data. Noble et al. (71) identified brain regions that are more or less reliable with a given quantity of data, which is critical for designing studies focused on specific regions. Given the public availability of many of these datasets (**Table 1**), their contribution to the field will likely increase in future years.

Precision approaches quantify stability and variability in functional brain networks
In addition to reliability, clinical utility requires that measurements show stability across contexts. That is, a diagnostic measurement would ideally be influenced only by the conditions of interest (e.g., long-term disease status, individual traits) rather than by day-to-day variation, ongoing states, or thoughts (e.g., whether the patient ate breakfast, if they were cold in the scanner room, if a technician was calm or abrupt, etc.). Thus, the stability of FC across different time-scales and contexts is important for its utility in psychiatric care.

The pfMRI design of the MSC is well-suited to examining this issue, as it contains data from multiple tasks spanning different cognitive domains collected in multiple individuals across multiple days (69). We used these data to identify cortical network patterns that were consistent across all measurements (static "group" effects) or that varied across individuals, days, or tasks

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[*] *While pfMRI has only recently been employed in the field of large-scale functional network mapping, the practice of extended data collection in single individuals has a long history in both behavioral psychophysics and visual field mapping with fMRI (82-84). Recently these methods have been extended to measuring responses to complex naturalistic stimuli (85-87). PfMRI also mirrors the tradition of monkey electrophysiology studies that typically collect large amounts of data from small samples of monkeys (often 1-3). While these samples are not large enough for statistical testing, their logic is that they serve as study replicates across samples: i.e., an effect can be more meaningful when seen within each individual in a small group than if it is only observable on average across a large population sample (88, 89). We argue that a similar logic applies to studies of brain network organization, especially in clinical settings where treatment is applied to individuals.*

(93). Our findings demonstrated that functional networks are largely stable, with shared group patterns as well as network features that were specific to individual subjects (**Figure 2B**).

Variations in FC from day-to-day and task-to-task were also observed, but these effects were relatively small in magnitude. Interestingly, task effects on FC were largely individually-specific, rather than common across the group (93) (**Figure 2B**), consistent with previous studies showing subtle group-average task modulations of FC (45, 94) and added task-by-individual interactions (95, 96). The individual-specificity nature of task influences on brain networks suggests that their study may especially benefit from the use of pfMRI. In addition to characterizing task and daily variation, we also used pfMRI to show that FC is stable over shorter time-scales (i.e. minutes). In this work, apparent *within-session* variability in FC was primarily driven by sampling error, acquisition artifacts (such as motion), and subject arousal during scans (97).

The dominance of stable factors on FC was relatively consistent across spatial scales, from the full connectome, to single networks, regions, and even single connections (93). Subsequent work observed similar effects in subcortical and cerebellar regions (78, 79) with hints of increased individual variability (78) - an intriguing finding given evidence of variation within non-cortical structures in psychiatric disorders (75-77, 98-101).

Thus, FC techniques are well suited to measuring stable aspects of brain organization, including aberrant features that may underlie psychopathology. Moreover, these findings indicate a high sensitivity to individual differences in brain networks (see next section). Jointly, the strong reliability, stability over states, and sensitivity to individual differences seen with pfMRI methods make them strong candidates for clinical applications.

An emergent question is how FC varies across months and years. The MyConnectome dataset suggests that many aspects of FC are stable over a year (70, 91) (also seen for some networks over 3.5 years in the Kirby Weekly dataset (102)). However, new studies are needed to determine to what extent these patterns persist throughout the lifespan, from early infancy into aging, and whether they can be altered with prolonged or profound life experiences.

Characteristics of individual variation in brain networks
Individual FC differences (69, 80, 81, 103-106) have been identified at multiple scales, ranging from differences in brain-wide network organization (e.g., network "efficiency" (69)) to punctate regions that vary across individuals (70, 91, 103, 104). One open question is whether these disparate spatial scales measure related aspects of individual variation (e.g., variation in FC of a single region may cause apparent variation in brain-wide efficiency). Interestingly, in the MSC dataset different individuals are highlighted as 'atypical' depending on the scale of analysis: e.g., Gordon (69) found that brain-wide efficiency was significantly lower for subjects MSC02 and MSC06 relative to the group, but Seitzman (91) found that MSC02 and MSC06 sorted into different sub-groups based on regional variations, and Gratton (93) found that MSC01 was most different from the group in task and rest FC. An important question for future work is whether individual differences in FC reflect differences in the spatial organization of networks/areas or differences in the magnitude of functional correlations within a static spatial structure (e.g., (107, 108)).

Recent reports have observed that individuals demonstrate localized regions of distinct FC relative to the group (70, 91). We term these "network variants" (**Figure 3**). Network variants occur most frequently in association cortex (e.g., parts of the frontoparietal, default mode, and cinguloopercular systems) and appear in two general forms: border shifts between networks

(e.g., the default network enlarges, encroaching on classically frontoparietal regions) and ectopic intrusions (e.g., an isolated area in the frontoparietal network shows altered FC, such that it connects to the default network). Despite their low correspondence to the "average" architecture, network variants are common. Indeed, in preliminary investigations (70, 91) across datasets (109), we found network variants in every individual. These findings suggest that the average brain is not a veridical representation of any individual person.

Network variants have a number of systematic trait-like properties (91) that suggest they may be good candidate clinical targets. They are stable across scans (reaching r>0.8 with >40 min. of data). Moreover, like other phenotypic traits such as eye-color, blood type, or personality, individuals can be grouped based on their characteristic patterns of network variants. Two sub-groups were identified across multiple datasets: one with variants more associated with the default-mode network and another with variants more associated with goal-directed control and sensorimotor processing systems (81). These findings suggest that network variants may relate to individual differences in complex goal-directed functions subserved by these networks (17, 110-113) - functions known to vary in the typical population (114) and implicated across a range of disorders including depression (27, 64, 115, 116), schizophrenia (103-105), and TS (28, 117).

Despite the nascent state of pfMRI studies, there is preliminary convergent evidence that validates the connection between these individual differences and differences in brain function (e.g., (80, 107, 108, 118-121)). For example, network variants re-assigned to the default-mode showed de-activations during tasks– much like canonical default-mode locations – even when found within cortical territories that are classically identified with task-activated networks (e.g. frontoparietal) (91). Thus, network variants may represent locations with shifted functions, leading to altered network correlations. Other findings have also suggested that individual-specific FC – defined at rest – overlaps well with task-related brain activations (118, 119, 121). Further preliminary validation of individualized FC measures comes from their successful guidance of TMS (e.g., (66, 122)) and by comparison with structural brain measures (e.g., overlap between FC variations and variations in myelin density in (69)).

Moreover, individual differences in network organization also appear to relate to behavioral variation (80, 107, 108). In the sub-groups described above, differences in network variants were associated with small differences in quality of life and drug use (91). Similarly, Smith (120) suggests that FC differences link to a "positive-negative mode" of behavioral variation. One important question to address in future research will be which variations in brain system organization have critical consequences on behavior and which reflect degenerate solutions to carrying out the same behavioral function.

Looking forward: pfMRI and psychiatry
Thus far, pfMRI approaches have primarily examined small, homogenous cohorts (**Table 1**). These datasets have highlighted the reliability of FC measurements, in the spirit of recent movements in psychology and psychiatry to increase reproducibility in research (123-125). This work has already provided important preliminary results regarding sources of variance and stability of FC techniques. Critically, the large amounts of data per subject in pfMRI approaches allow for observations to be verified reliably at the level of *individuals* (even in clinical samples (126)), which is the level most pertinent for clinical applications. It is this feature that makes pfMRI a compelling platform to address outstanding challenges in psychiatry.

One such challenge has been in understanding differences between the 'normal' and pathologic brain, which have so far been obscured in group format studies. Group studies typically find modest differences in FC across a range of comparisons: between tasks (45, 94), across states

of consciousness (127), over development (128), and across major neurological and psychiatric disorders (30, 129, 130). One question is whether pfMRI approaches that take advantage of both group commonalities and individually specific features may be more sensitive to detecting heterogeneous differences, especially those relevant to clinical work. Early reports support this conjecture, as pfMRI approaches have demonstrated enhanced sensitivity not only to individual differences, but also to task-state effects (93), and clinical symptoms (126).

A second, related, challenge in psychiatry is to create tools for accurate diagnosis and prognosis of clinical features at the individual level. While pfMRI has yet to be used widely in clinical populations, initial accounts have suggested that high-data approaches can increase the association between fMRI measures and behavior in the neurotypical population (80, 107, 108, 120). We are aware of only one study to date to apply pfMRI to a clinical population (126). In that study, ~3.5 hrs. of MRI data were collected from 26 veterans with varying history of TBI and PTSD. Interestingly, FC mediated observed associations between TBI and PTSD symptoms. However, this relationship was only evident with large amounts of data; analyses using only 10 min. of data per subject were non-significant. Two other recent papers further highlight advantages of individualized analysis techniques in psychiatric datasets (although with lower amounts of per-subject data (131, 132)). In Wang (131), fMRI data were gathered from 158 participants diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder. FC derived from individually-specific regions significantly predicted symptom levels, while models using group regions performed consistently worse. Similarly, in participants with OCD, Brennan (132) found that brain networks modeled using individually-defined regions outperformed group-defined regions in predicting symptoms, and that individualized FC changes predicted treatment-based improvements. These findings highlight the added utility of individualized approaches to FC in psychiatry. Beyond post-hoc diagnosis, it is worth investigating whether pfMRI approaches will prove sensitive to risk factors for psychiatric disorders and disease progression, which would greatly enhance the utility of imaging in clinical management.

A third area of psychiatry that pfMRI can help to address are interventions that rely on subject-specific targeting of pathology. The spatially localized nature of many individual differences in FC (91, 103, 107, 108) means they may serve as patient-specific targets for stimulation-based interventions with TMS or DBS. While stimulation-based interventions can be effective, they suffer from variable patient responses (e.g. (133, 134)), which have been attributed to stimulation targeting procedures that do not respect individual variations in structural (135, 136) or functional (65, 137) neuroanatomy. Indeed, individual variability in FC of dorsolateral prefrontal cortex has been related to variation of TMS treatment efficacy in depression (66). Moreover, a recent pfMRI study of the sub-cortex showed that regions with consistent FC across individuals overlap with DBS stimulation sites that have shown more consistent treatment response, while DBS sites with known variability in response overlap with regions that exhibit variable FC (79). Use of pfMRI to identify individual-specific targets for brain stimulation thus has significant potential for improving treatment response rates (138).

A fourth challenge is to improve tracking of treatment efficacy and long-term remission. The multi-session nature of pfMRI allows researchers to determine how FC measurements vary over different time-scales. Thus far, evidence suggests that FC is stable across multiple sessions and even year-long periods, as long as sufficient data are collected per measurement to achieve high reliability (93). As such, pfMRI may be more sensitive to trait-like features that predict disease status or risk (e.g., whether a person has or will develop depression) than those that are associated with fluctuating behavior (e.g., current sad mood). However, pfMRI may also prove a more reliable baseline from which to expose rapid or profound changes in FC linked to

treatment response to a pharmacologic or behavioral therapy. For example, lower-data but individualized FC approaches can predict changing OCD symptoms after intervention (132).

Feasibility of pfMRI in Clinical Samples

While pfMRI has many useful properties, the feasibility and cost of collecting extended datasets in patients are commonly cited as barriers to its use. Moreover, psychopathology is prevalent across the lifespan, and collecting pfMRI data from children and elderly adults may compound feasibility concerns. Such concerns can be addressed in a number of ways.

First, initial pfMRI studies have established that 30-45 minutes of low-artifact data may be sufficient to achieve good reliability for many cortical FC measures. In our initial investigations, we find that patient, pediatric, and elderly populations retain ~50-80% of data after motion denoising (29, 126, 129); thus, 45-90 min. of data collection would be needed to reach high reliability. While this is substantially more resting-state than is typically collected, this is not an unreasonable amount of scanning to ask of participants in general, as routine neurology assessments collect 2 hrs. of structural MRI. Clinicians may adjudicate whether the severity of psychiatric cases calls for similar scan investment (e.g., compare a relatively healthy patient with ADHD vs. a severely depressed patient with high suicide risk). Future methodological improvements may reduce the data needed to achieve reliable FC, though these may come at the cost of increased reliance on priors and decreased ability to observe divergent individual patterns (see *Supplemental Discussion*).

Second, since patient, pediatric, and elderly samples often exhibit increased head motion, additional strategies have been proposed to minimize motion and improve data quality (139). Our findings on FC stability suggest that data collection can effectively be split into several shorter runs within or across sessions to increase patient compliance. Indeed, breaking up data collection may even increase reliability levels (71), likely because of the autocorrelation structure of fMRI timeseries. Some have proposed combining task and rest to increase data quantities for FC (67), which could open up many current datasets for analysis. Care should be taken when mixing task and rest datasets, especially when effects of interest are small, but this may be an acceptable qualification for prediction/diagnosis (see *Supplemental Discussion*). Finally, data acquisition strategies such as movement feedback (140), on-line head motion estimates (141), and head cases to minimize motion (142) provide promising strategies to improve data quality during collection, rather than through post-hoc denoising.

Thus, while pfMRI studies require additional data per participant, for many applications the benefits of this investment (dramatically increased reliability and sensitivity to individual features) may be well worth the cost. Two or three hours of scanning may be of relatively small concern to patients considering having a DBS device implanted, suicidal individuals suffering from treatment-resistant depression, or parents seeking improved treatment for their child. We contend that it is not enormously useful to spend money on cheaper measures that do not replicate well within or across individuals – either for clinical practice or to forward research knowledge. Rather, direct translational application of neuroimaging results may be better afforded by pfMRI.

Disclosures:

Tables

Dataset name	Location of Dataset	Participants	Sessions & Collection Window	Resting-state data per session	Scan Parameters	Additional data collected
Anderson (68)	http://fcon_1000.projects.nitrc.org/indi/CoRR/html/utah_2.html	1 M (age 39)	5 sessions over 3 weeks	50 min.	• Scanner: Siemens Magnetom Trio 3T, 12 channel coil • TR: 2000 ms • Voxel Size: 3.4 x 3.4 x 3 mm • Multiband/accelerated: GRAPPA2	• Structural MRI: T1 • Task fMRI: video clips (250 min.) • Physiological Measures: Respiration, heart rate • 36 additional participants have 8 min. of resting state
IPCAS – 3 Day [IPCAS 6] Zuo (143)	http://fcon_1000.projects.nitrc.org/indi/CoRR/html/ipcas_6.html	2 (1 F, ages 21 and 25)	15 sessions over 3 days	30 min.	• Scanner: Siemens Magnetom Trio 3T, 8 channel coil • TR: 2500 ms • Voxel Size: 3.5 x 3.5 x 3.5 mm • Multiband/accelerated: none	• Structural MRI: T1, T2
MyConnectome Poldrack (90)	https://openneuro.org/datasets/ds000031/versions/00001	1 M (age 45, author)	89 sessions over 72 weeks	10 min.	• Scanner: Siemens Skyra 3T, 32 channel coil • TR: 1160 ms • Voxel Size: 2.4 x 2.4 x 2 mm • Multiband/accelerated: MB4	• Structural MRI: T1, T2, DWI • Task fMRI: ~7 hours, 7 tasks (n-back, stop signal, WM localizers, retinotopic mapping, breath holding) • Behavioral Measures: affect, sleep, health • Blood draws: RNA, genotyping, metabolomics • 11 additional fMRI sessions during a pilot phase; additional fMRI data also collected at alternate site
Kirby Weekly Dataset Choe (102)	https://www.nitrc.org/projects/kirbyweekly	1 M (age 40)	158 sessions over 185 weeks	7 min.	• Scanner: Philips Achieva 3T, 16 channel coil • TR: 2000 ms • Voxel Size: 3 x 3 x 3 mm • Multiband/accelerated: SENSE2	• Structural MRI: T1 • 21 additional participants have 7 min. of resting-state
Midnight Scan Club (MSC) Gordon (69)	https://openneuro.org/datasets/ds000224/versions/00001	10 (5 F, ages 24-34)	10 sessions within 7 weeks	30 min.	• Scanner: Siemens Trio 3T • TR: 2200 ms • Voxel Size: 4 x 4 x 4 mm • Multiband/accelerated: none	• Structural MRI: T1, T2, MRA, MRV • Task fMRI: 6 hours, 4 tasks (semantic, dot coherence, motor, categorization/implicit memory) • Behavioral Measures: neuropsychological assessment, IQ, personality
Buckner Lab Dataset Braga and Buckner (92)	-	4 (4 F, ages 21-26)	24 sessions over ~16 weeks	7 min.	• Scanner: Siemens Prisma 3T, 64 channel coil • TR: 1000 ms • Voxel Size: 2.4 x 2.4 x 2.4 mm • Multiband/accelerated: MB5	• Structural MRI: T1 • Other scans: ASL, task fMRI • Physiological Measures: Eye-tracking, respiration, heart rate, galvanic skin response • Behavioral Measures: sleep, smartphone monitoring, behavioral

Dataset	Access	Participants	Sessions	Scan length	Acquisition	Other Data
						testing
Day2Day Dataset Filevich (144)	e-mail authors	8 (6 F, ages 24-32; N=6 with > 120 min.)	11-50 sessions over 8-56 weeks	5 min.	• Scanner: Siemens Magnetom Trio 3T, 12 channel coil • TR: 2000 ms • Voxel Size: 3 x 3 x 3 mm • Multiband/accelerated: GRAPPA2	• Structural MRI: T1, T2 (hippocampus), DTI, MRS • Behavioral Measures: weather, health, sleep, affect, activity, hormones
Healthy Brain Network Dataset (HBN-SSI) O'Connor (145)	http://fcon_1000.projects.nitrc.org/indi/hbn_ssi/	13 (8 F, ages 21-42)	13 sessions over 4-8 weeks	10 min.	• Scanner: Siemens Avanto 1.5T, 32 channel coil • TR: 1460 ms • Voxel Size: 2.46 x 2.46 x 2.5 mm • Multiband/accelerated: MB3	• Structural MRI: T1, T2, DKI, FLAIR, magnetization transfer • Task fMRI: 6 hours, 3 tasks (inscape, movie, flanker) • Behavioral Measures: internal state, affect, health, activity/sleep, ADHD, voice samples
Yale Test-Retest Dataset Noble (71)	http://fcon_1000.projects.nitrc.org/indi/retro/yale_trt.html	12 (6 F, ages 27-56)	4 sessions over ~1 week	36 min.	• Scanner: Siemens Magnetom Trios 3T (2 separate matched), 32 channel coil • TR: 1000 ms • Voxel Size: 2 x 2 x 2 mm Multiband/accelerated: MB5	• Structural MRI: T1 - MPRAGE, T1-FLASH, T2 - SPACE
Meszlénvi Dataset Meszlenyi (146)	-	1 F (age 28)	10 sessions over 5 days	20 min.	• Scanner: Siemens Magnetom Prisma 3T • TR: 1770 ms • Voxel Size: 3 x 3 x 3 mm • Multiband/accelerated: MB2	• Structural MRI: T1
Gordon TBI Dataset Gordon (126)	-	26 (5 F, ages 37 +/- 11.8; 21 with TBI; N=24 with > 120 min.)	2-5 sessions over less than 12 weeks	5-44 min.	• Scanner: Philips Achieva 3T • TR: 3000 ms • Voxel Size: 3 x 3 x 3 mm • Multiband/accelerated: SENSE1.5	• Structural MRI: T1, DTI • Behavioral Measures: TBI, PTSD, combat exposure
SIMON Dataset Duchesne (147)	http://fcon_1000.projects.nitrc.org/indi/retro/SIMON.html	1 M (age 29)	15 sessions over 468 weeks	10-11 min.	• Scanner: Philips Achieva 3T, 8 channel coil • TR: 2500 ms • Voxel Size: 3.5 x 3.5 x 3 mm • Multiband/accelerated: SENSE2	• Structural MRI: T1, T2, DWI, FLAIR • Functional MRI: ASL • 58 other scans also available across 32 other scanners
Donnelly-Kehoe Dataset Donnelly-Kehoe (148)	-	1 F (age 29)	50 sessions over 26 weeks	5 min.	• Scanner: Siemens Magnetom Trio 3T, 12 channel coil • TR: 2000 ms • Voxel Size: 3 x 3 x 3 mm • Multiband/accelerated: GRAPPA2	• Structural MRI: T1, DWI • An additional 50 Participants with only 1 session

Table 1: A collection of precision fMRI datasets with resting-state data. 'Precision' datasets are defined here as datasets with >120 min. of resting state per individual collected in 2 or more sessions on the same scanner, and whole-brain data acquisition. These parameters allow for reliability and non-cortical analyses; additional "high-data" fMRI projects with 40-120 min. are listed in **Supp. Table 1**. Datasets were in part identified through Kong (149).

Figure Legends

Figure 1: Group and individual functional brain networks. (A) Robust group-average functional networks (*different colors*) are observed across multiple studies using different methods. This group-average map was created by averaging data from the MSC subjects at rest. (B) Functional networks in individuals exhibit similarities to the group-average, but also pronounced individual differences. For example, note variations in the network organization of the dorsolateral prefrontal cortex (*colors are matched to group-average labeling in A*). *A and B are based on data from (69).*

Figure 2: Reliability and stability of functional brain networks. (A) Recent studies using precision fMRI methods have demonstrated that more than 40 min. of high-quality fMRI data are necessary to achieve high test-retest reliability of functional networks in the cortex (top: functional networks from a single individual across two split-halves of the data; bottom: similarity of individual functional network measures across the connectome with increasing amounts of data). Even larger amounts of data may be needed to achieve high-reliability in non-cortical regions (78, 79). (B) Analysis of precision fMRI datasets allows for a decomposition of the sources of variance in functional networks. This work has shown that functional networks are dominated by stable factors, including common structure across groups and stable patterns of individual differences. Task-state makes modest contributions to FC that are largely individually specific, and daily variation is small with sufficient data. This is shown by examining how similar functional networks are from datasets that share group, individual, task, or session factors (or a combination). *A is from (70), B is adapted from (93).*

Figure 3: Network variants. Comparison of (A) group networks and (B) an individual from the MSC (MSC06, colors match Fig. 1). (C) Some locations exhibit low similarity to the group (a few examples are circled), which can be identified through vertex-wise spatial correlation; (D) we call these low-similarity locations network variants. (E) Variants may represent shifts of network borders (left) or isolated ectopic intrusions (right). We hypothesize that network variants are caused by stable factors that reprioritize the neural functions of cortical areas, causing shifts in the boundaries of cortical networks and ectopic intrusions. These altered prioritizations lead to changes in the dominant systems-level relationships of a region (e.g., increasing FC to relevant regions in alternate networks), causing these regions to appear as network variants. Thus, network variants may be related altered brain function during tasks and behavioral responses across individuals. See (91).

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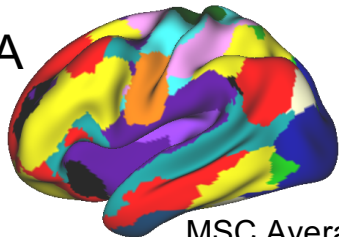
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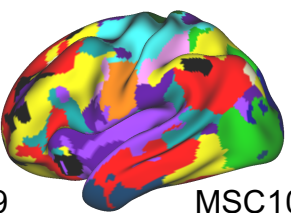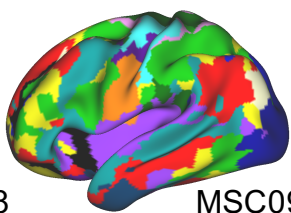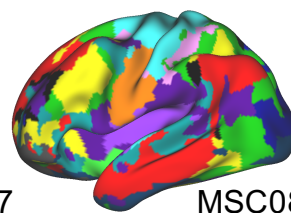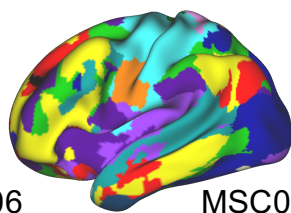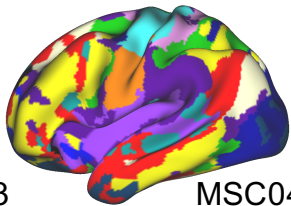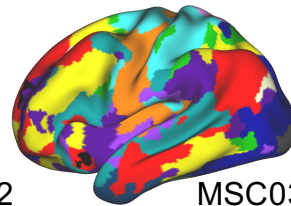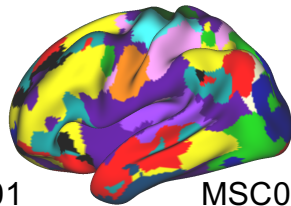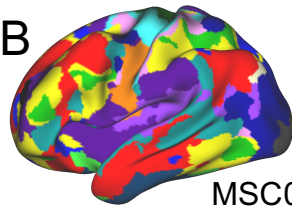
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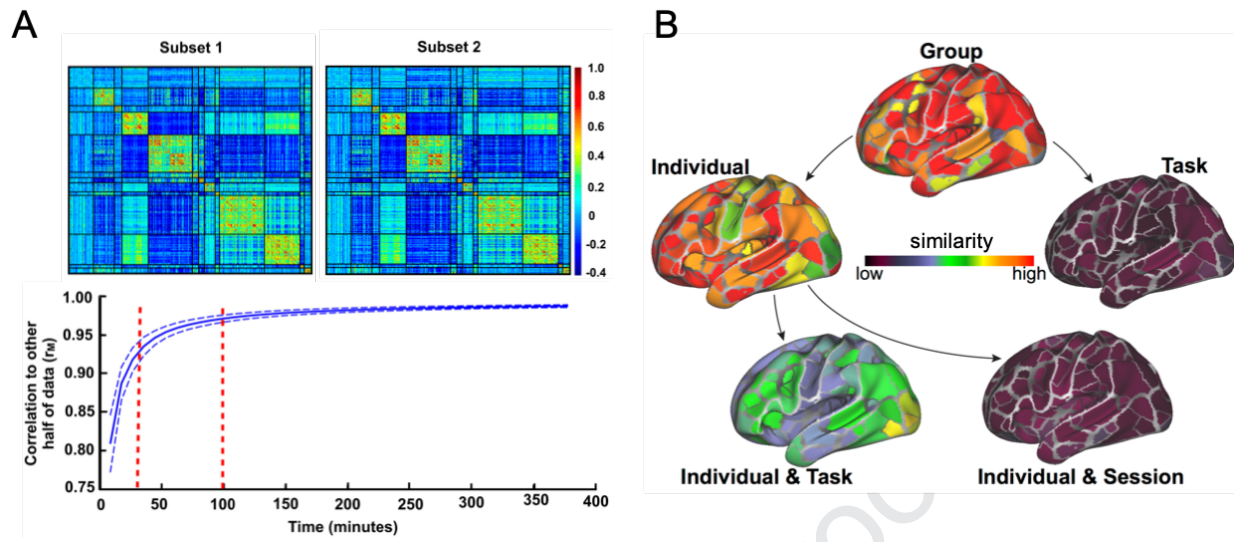
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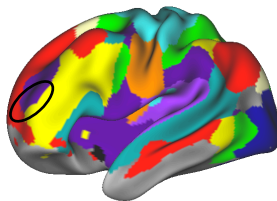
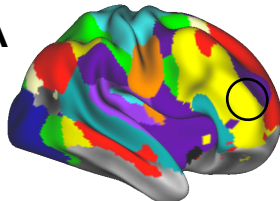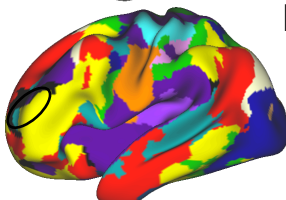149. Kong X multiBrain. https://github.com/Conxz/multiBrain.

A   MSC Average

B   MSC01   MSC02   MSC03   MSC04   MSC05

    MSC06   MSC07   MSC08   MSC09   MSC10

A

Subset 1   Subset 2

B

Group

Individual   Task

similarity
low   high
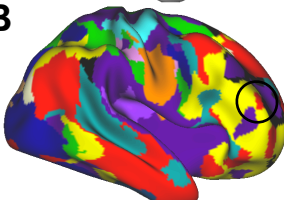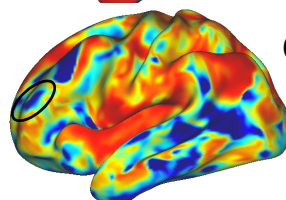
Individual & Task   Individual & Session
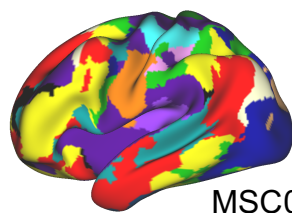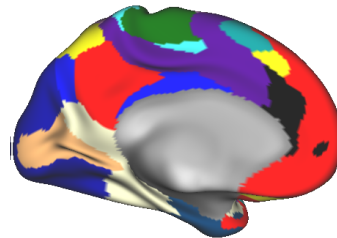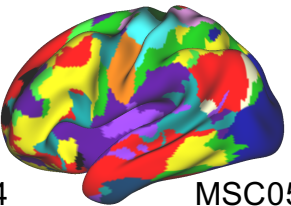
group
networks

A

MSC06
networks

B

spatial
correlation
MSC06 X group

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MSC06
variants

D
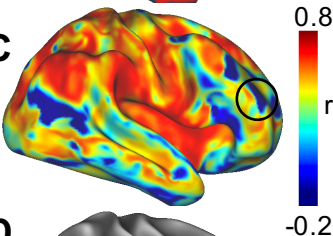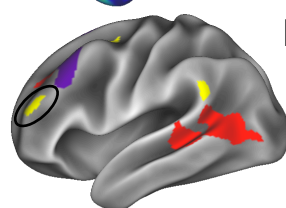
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size masked)
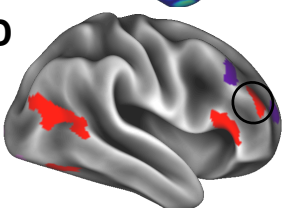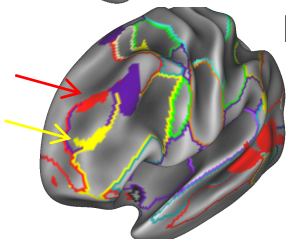
MSC06
variants
over group
networks

E

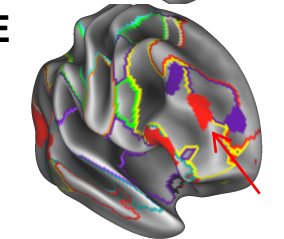*border shifts*   *ectopic intrusions*