Cognition-centric brain activity across diverse imaging tasks constrains the representation of mental health in task-evoked brain function

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Abstract

Identifying individual differences in brain activity that reflect variation in domains of mental health – including those in the Research Domain Criteria (RDoC) framework – remains a core challenge in neuropsychiatry. Here, we cross-analyzed mental health and brain function profiles in hundreds of individuals using factor analysis of 87 neurocognitive/psychiatric assessments and tensor independent component analysis of functional magnetic resonance imaging (fMRI) data acquired during task and movie-watching paradigms with putative mental health relevance. Across 77 brain network variants evoked across five paradigms, univariate and multivariate network activity differences predominantly reflected and predicted cognition, weakly indexing other mental health domains despite their similar reliability and interindividual variability. Normative mental health variation was not reflected in comparatively homogeneous evoked brain activity, and clustering subjects by brain function versus mental health produced discordant subtypes. Brain activity evoked by common fMRI paradigms may contain insufficient non-cognitive information to differentiate mental health in the general population.

Introduction

Our experiences of and responses to cognitive challenges, positive and negative emotions, reward and loss, and social interactions are core determinants and reflections of mental health. In 2009, the Research Domain Criteria (RDoC) framework[1] was introduced to reconceptualize mental health in terms of individual variation in these and other core domains of neurobehavioral functioning, moving away from symptom-based diagnostic categories that increasingly demonstrated questionable neurobiological validity[1,2]. Ultimately, the RDoC framework aims to facilitate more biologically-grounded research and treatment efforts in the field of mental health[1]. As such, a major goal of recent work has been to identify the neurobiological features whose variability between individuals maps to and predicts interindividual variability in behavioural and self-report measures of mental health within RDoC functional domains – both within and beyond normative ranges of functioning. These domains include cognitive systems (CS) like memory, positive valence systems (PVS) like reward responsiveness, negative valence systems (NVS) like threat processing, and social processes (SP) like understanding others' mental states[3].

Among the neuroimaging modalities and imaging derived phenotypes (IDPs) available to quantify structural and functional features of the brain, many studies,[4-7] though not all[8,9], find that functional magnetic resonance imaging (fMRI)-derived metrics display the strongest relationships with behavioural and neuropsychiatric phenotypes. To date, studies using fMRI have identified links of moderate strength between individual differences in brain activity and individual differences in cognition[10-15]. However, though group-level fMRI research has robustly mapped neural substrates for behavioural and self-report measures of PVS[16], NVS[17], and SP[18], links between individual differences in these units of analysis within the PVS, NVS and SP domains remain largely elusive and well-short of clinical applicability[7,19-21]. Even as many studies achieve statistically significant brain function-mental health associations or predictions, findings are generally of small to modest effect size[7,22,23], and are frequently not reproducible[24,25].

Emerging recognition of these weak associations has motivated several tracks of recent work to improve the effect size and replicability of brain function-mental health associations. These have included application of more rigorous fMRI signal denoising methods[26], development of more sophisticated analytic[27,28] and modelling validation techniques[24,29], the use of larger sample-sizes, and deeply sampled data[30]. These advances have yielded unmistakeable, though still largely marginal, gains in brain-behaviour effect sizes and replicability within individual-differences research. An additional avenue of work has sought to identify whether brain activity evoked under certain conditions might better convey mental health information than others. Indeed, recent work has identified that brain activity recorded during active task and movie-watching conditions has stronger links to individual differences in traits and behaviour than that recorded during resting-state conditions[10,31,32].

As such, task-based and movie-watching fMRI data collected in large-scale neuroimaging cohorts – best powered for individual differences analyses – have held promise for identifying robust brain function-mental health links. While there are dozens of different fMRI tasks, most large-scale neuroimaging studies draw from a similar set of block-design tasks. These include the

emotional face-matching task (UK Biobank, Human Connectome Project (HCP)-Young Adult, HCP-Development, HCP-Anxious Misery, HCP-Disordered Emotional States, Transdiagnostic Connectome Project), incentive salience/gambling (HCP-Young Adult, HCP-Anxious Misery, HCP-Disordered Emotional States), n-back working memory task (Adolescent Brain Cognitive Development (ABCD), HCP-Young Adult), and social cognition task (HCP-YA). Several datasets also use naturalistic movie-watching (HCP-YA, Healthy Brain Network, Naturalistic Neuroimaging Database). Yet, even in large-scale cohorts, across resting-state[4,7,23,31,33-36], task-based[4,7,23,37], and movie-watching[31] fMRI paradigms, links between brain activity and non-cognitive mental health domains (e.g., positive and negative emotional reactivity) remain comparatively weak relative to links with cognitive measures (i.e., CS). Even brain activity during tasks like the emotional face matching task – widely thought to index interindividual variability in the NVS – has recently been found to instead predominantly reflect the CS[37-39]. As such, it remains unclear which – if any - fMRI paradigms evoke brain activity in a way that meaningfully reflects non-cognitive domains of mental health.

An oft-posited[4,31] contributor to this discrepancy is a difference in reliability between behavioural measures of the CS – which tend to be performance-based and relatively stable over time – versus behavioural measures of the PVS and NVS – which tend to be based on self-report or subjective evaluation and can be more variable over time. As a result, the former tend to have higher measurement reliability than the latter[40], and recent work has found that the measurement reliability of target behavioral phenotypes is an important moderator of brain-behavior relationship strengths[41]. One way to increase reliability is to aggregate data across many individual assessments, via techniques such as hierarchical factor analysis (hFA)[42], which can produce composite scores with high reliability even from individual assessment scores with lower reliability[43,44].

A final consideration is the scale of brain activity to be examined. Prior work has demonstrated that properties of brain activity at the level of large-scale distributed networks yield higher subject discriminability[12] and stronger reproducibility[45] than properties of brain activity at the level of individual connections. Moreover, functions spanning CS, PVS, NVS, and SP domains are now understood to be subserved more so by large-scale distributed networks than by individual brain regions or connections[46-49]. In the context of task and movie-watching fMRI, where stimuli presentation is standardized across subjects in time, tensor independent components analysis (tICA) offers a robust, data-driven method to identify and quantify the simultaneous activity of all large-scale brain networks activated by a given task[38,50].

In the present study, we leveraged the above considerations and disaggregated brain activity across both tasks and large-scale brain networks to allow for nuanced probing of where (i.e., in the brain) and when (i.e., during what task) individual differences in brain activity optimally reflect individual differences in key RDoC mental health domains. In split-half samples of a large-scale cohort (HCP-YA; n=1200), we first applied Schottner and colleague's hFA[42] to 87 behavioral and neuropsychiatric assessments to generate high reliability mental health factor scores in five latent domains: cognition (CS), positive affect/well-being (PVS), negative affect/internalizing (NVS), processing speed, and substance use. Next, we applied tICA[45] to fMRI data collected across paradigms with putative relevance to these RDoC domains (i.e., emotional face-matching, incentive salience/gambling, social cognition task, n-back working

memory, and movie-watching of socioemotional content) to identify and quantify evoked brain network activity. The subject-level mental health and brain function profiles generated from this integrated multivariate approach were then cross-analyzed and compared in several ways to identify mental health-brain function correspondences. In their absence, we sought to determine the contributing factors to and consequences of their misalignment.

Results

Task-Evoked Brain Networks

tICA identified 77 evoked large-scale network variants across the five fMRI paradigms (**Fig. 1**) in the discovery sample (Group 1). Individual network maps have been made viewable and accessible in a "Task-Evoked Network Atlas" (https://identifiers.org/neurovault.collection:20820). Hierarchical clustering based on the network spatial maps resolved them into a set of nine Network Families (**Figs. 1-2**). Data are consistent with the notion of a circumscribed set of canonical large-scale networks that manifest in context-dependent spatial variants[51] and undergo network-network coupling reconfigurations[52] to meet particular task demands.

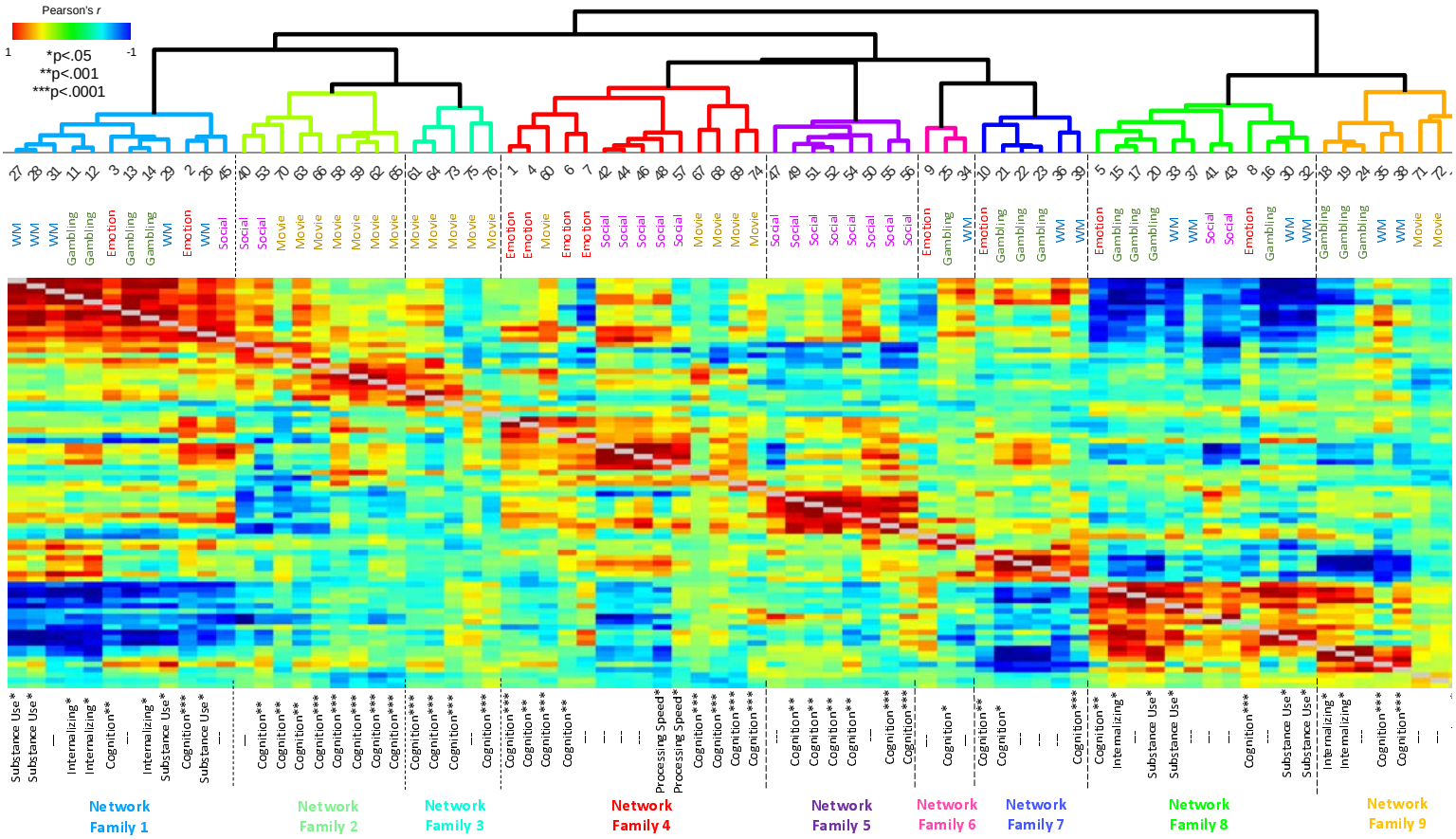

Figure 1. *Hierarchical clustering of task-evoked network spatial maps.* Heat map depicts the correlation matrix of unthresholded network spatial maps, with red indicating correlated spatial maps and blue indicating inversely

correlated spatial maps. Also depicted is the task each network was evoked by (i.e., Emotion, Gambling, Working Memory, Social Cognition, or Movie-Watching) and whether variability in a network's activation across subjects correlated with variability in one of the five mental health domains: Cognition, Internalizing/negative affect, Well-being/ positive affect, Processing Speed, and Substance Use (*p<.05 uncorrected; **p<.001 uncorrected; ***p<.0001 Bonferroni corrected threshold for 385 tests: 77 networks * 5 mental health facets).

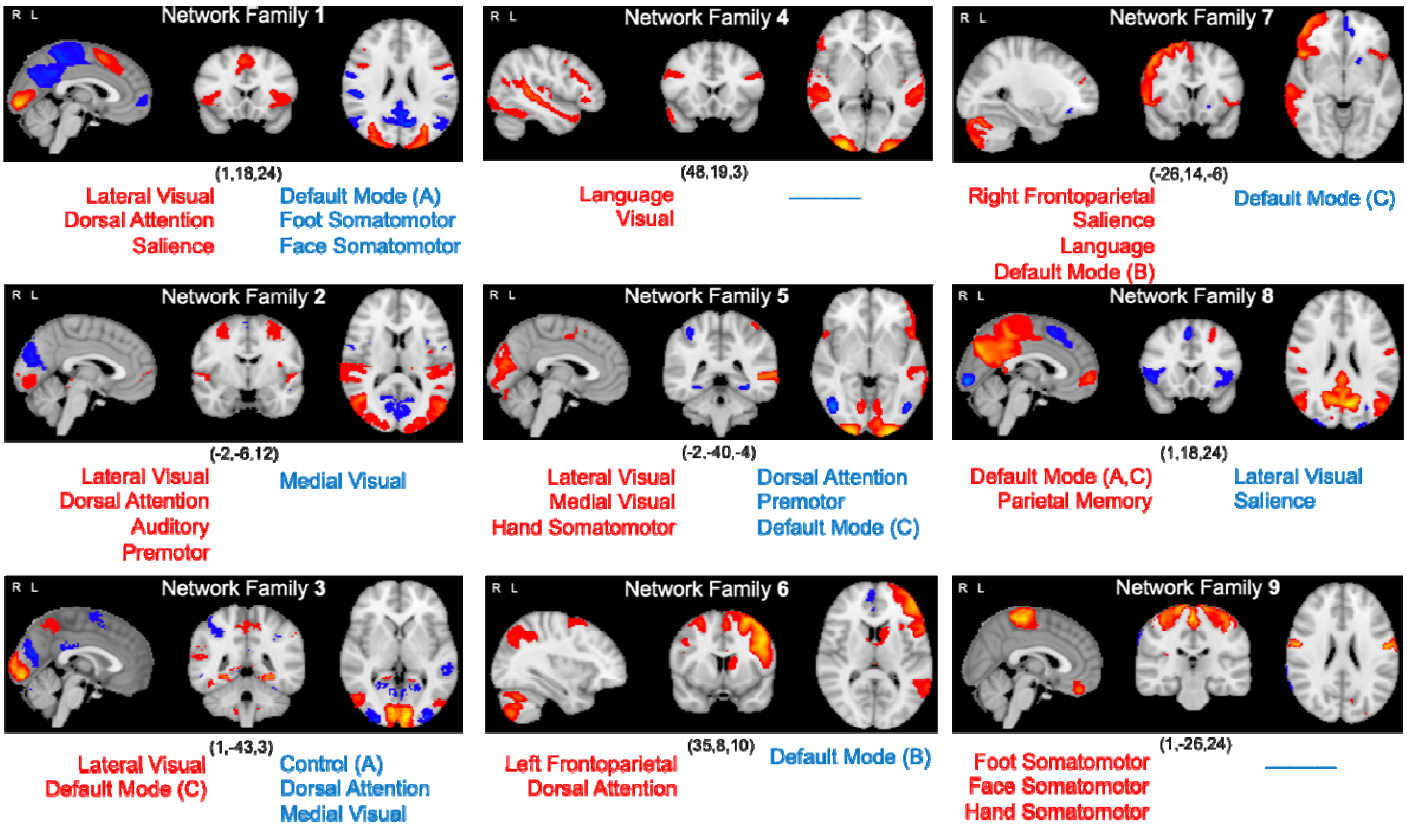

Figure 2. *Task-evoked network family spatial maps.* For each network family, the positive (red) and negative (blue) components of each network were thresholded at p=0.5 (mixture-modeling) and then averaged together to compute a mean network family spatial map. Overlap between the positive and negative components of each network family map and each of 17 canonical large-scale networks defined in the Gordon et al. parcellation[53] was computed using the network correspondence toolbox (NCT)[54]. Networks names listed in red showed significant overlap with positive task network components and networks listed in blue showed significant overlap with negative task network components

Network Activity Predominantly Reflects Cognition Across All Tasks

First, we examined the univariate links between the activity of the 77 evoked large-scale brain network variants (indexed by tICA subject loadings[50]) and factor scores on each of the five mental health domains. These analyses controlled for age and sex and corrected for covariance in family structure within the participant sample (i.e., family members with non-independent data) using permutation analysis of linear models (PALM)[55] with multi-level exchangeability blocks[56].

We applied a conservative Bonferroni significance threshold (p<0.0001) to correct for multiple comparisons (77 networks * 5 mental health domains = 385 tests). Across both Group 1 (discovery sample) and 2 (replication sample), across all tasks, and across all brain Network Families, only associations between network activity and cognition were statistically significant after correcting for multiple comparisons or replicable across groups, even at uncorrected thresholds (**Fig. 3**).

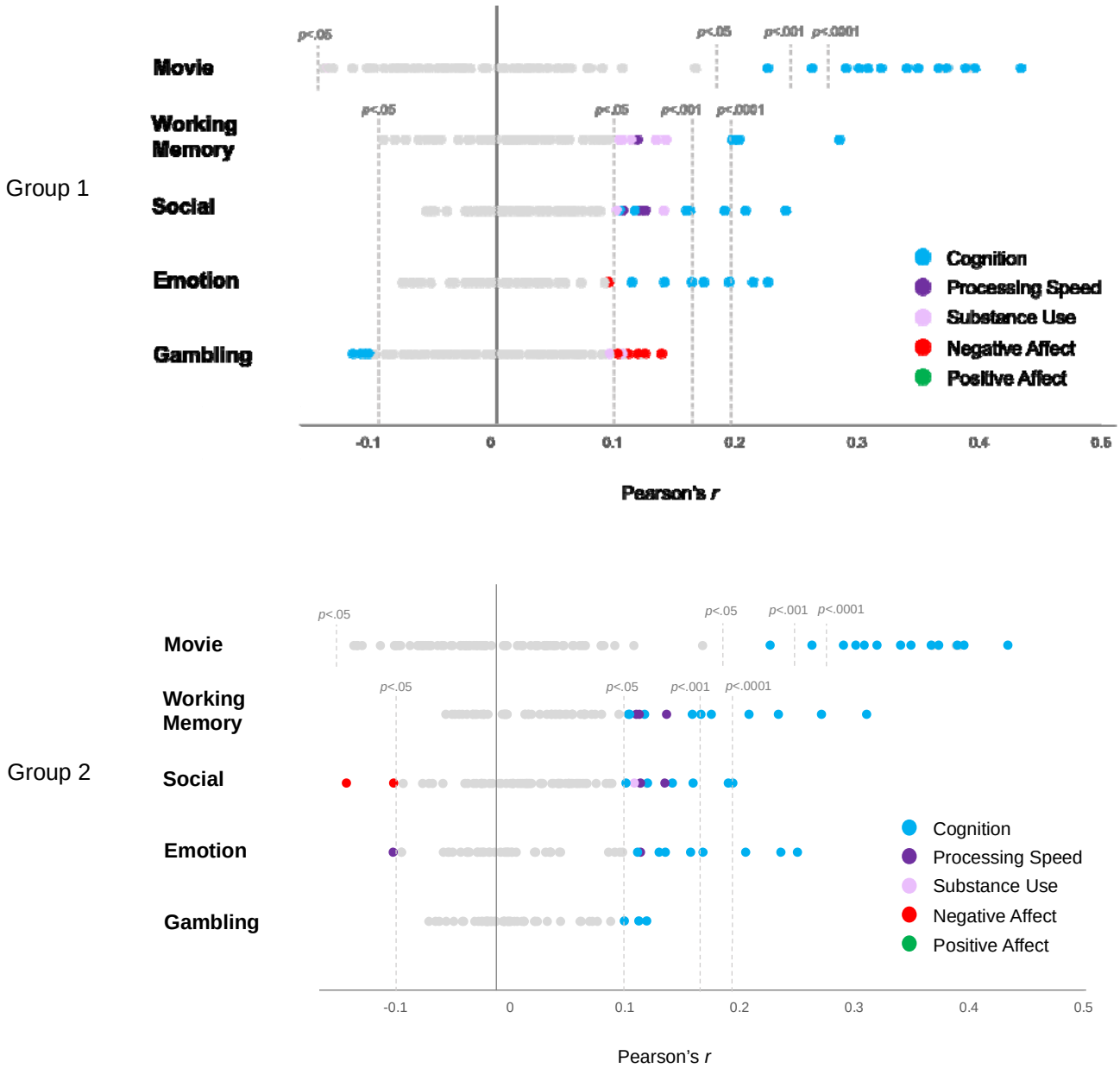

Figure 3. *Univariate links between task-evoked network activation strengths and mental health factor scores.* For each of the five tasks (rows), the Pearson's correlation between the activation strength of each network evoked by the task and each of the five mental health factor scores (dots). Significance was assessed both at the uncorrected p<.05 and p<.001 levels and Bonferroni-adjusted p<.0001 level to correct for multiple comparisons. Analyses

controlled for age, sex and education and corrected for covariance in family structure. All relationships significant at the p<.05 level or less are color-coded by mental health domain. All non-significant relationships are grayed out. Findings are presented separately for Group 1 and Group 2. Movie-watching data was obtained in only a subset of HCP-YA subject (n=184) and therefore was not split across groups. Data from this subset is visualized on both the Group 1 and Group 2 figures for benchmarking purposes.

Even when considering findings significant at the uncorrected p<.05 or p<.001 levels, activity in five of the nine Network Families (2, 3, 5, 6 and 7) exclusively reflected cognition, regardless of the task (**Fig. 1**). In Group 1, Network Families 1, 8 and 9 were the only ones whose activity reflected negative affect (NVS) or substance use at the uncorrected level. However, none of these non-cognitive relationships replicated in Group 2. Moreover, links with positive affect (PVS) were not observed even at the uncorrected level in either Group 1 or Group 2. Only relationships with cognition replicated across groups. In both Groups 1 and 2, the Movie-Watching task elicited brain activity with the strongest link to individual differences in cognition by a wide margin, followed by the Working Memory task (**Fig. 3**). Conversely, in both groups, brain activity during the Gambling task had the weakest links with individual differences in mental health. Notably, brain network activity during the Social Cognition task displayed the most consistent link to individual differences in substance use across both groups, albeit at a modest level (p<.05) and in different Network Families.

Measurement Reliability Differences Do Not Account for Predominance of Cognition

Recent work has found that an important moderator of brain-behavior relationship strengths is the measurement reliability of target behavioral phenotypes[41]. Therefore, we examined the possibility that the appreciably weaker brain function links with non-cognitive mental health domains across tasks were an artifact of comparatively lower measurement reliability relative to the cognition domain. To do so, we leveraged the HCP-YA's Test-Retest sample (n=46) to compute the intraclass correlation (ICC) of each of the five mental health facets. ICC is the predominant index of measurement reliability in the clinical neuroimaging literature[41,57,58], and quantifies the percent of total variance (i.e., between-subject, within-subject, and error variances) attributable to between-subject variance[59]. Retest subjects conducted their second set of HCP-YA assessments an average of 139.3 days (SD=69.0 days) after conducting their first set of assessments. The retest protocol included 78 of 87 behavioral and neuropsychiatric assessments included in the initial testing protocol, with all nine of the missing variables belonging to the substance abuse facet. While the factor analysis procedure we employed[42] imputes missing values, we elected not to interpret ICC values for the substance abuse facet since only two of the eleven initial substance use measurements were available in the retest data.
ICC values for the remaining four mental health facets were all very high; ($ICC_{COGNITION}$ = 0.991; $ICC_{NEGATIVE\ AFFECT}$ = 0.937; $ICC_{POSITIVE\ AFFECT}$ = 0.988; $ICC_{PROCESSING\ SPEED}$ = 0.999). These high ICC values are consistent with prior work showing that composite measures tend to have appreciably higher reliability than the individual measures that make them up[43,44]. Most importantly, they indicate that the large discrepancy in strength observed here between brain function relationships with Cognition versus with the other mental health domains cannot be explained by differences in measurement reliability.

Interindividual Variability Differences Do Not Account for Predominance of Cognition

Given that HCP-YA selects for generally healthy young adults, we also examined the possibility that narrower interindividual variability in the non-cognitive mental health domains compared to the cognitive domain accounted for the imbalance in brain function associations. However, interindividual variation, as measured by the average coefficient of variation (CV) of the assessment items in each domain, was actually lowest for cognition ($CV_{COGNITION}$=.16; $CV_{PROCESSING\ SPEED}$=0.18; $CV_{POSITIVE\ AFFECT}$=0.18; $CV_{NEGATIVE\ AFFECT}$=0.47; $CV_{SUBSTANCE\ USE}$=2.21). This shows that variability in brain function data was sensitive to variability in Cognition despite its low variability across subjects compared to the other mental health domains. Conversely, these data underscore the insensitivity of the brain function data to the non-cognitive mental health domains despite the larger variability of these domains across subjects. In all, differences in interindividual variability cannot account for the brain function data's predominant reflection of cognition.

Multivariate Brain Function Profiles Predict Cognition, Processing Speed but not Positive or Negative Affect

Next, we examined whether considering subjects' multivariate activity across all evoked networks could predict mental health scores. In order to facilitate training and testing across consistent networks in Groups 1 and 2, we restricted this analysis to the 46 Emotion, Gambling, Working Memory, and Social Cognition task networks that were identified across both groups (**Supplementary Table S1**), and to the subjects (Group 1: n=324; Group 2: n=330) who had complete data across all four tasks. Movie-watching networks were not included in this analysis given the smaller subset of subjects with this data (n=184 total). We trained a random forest machine learning regressor model on Group 1 to make individualized predictions in Group 2 of each mental health factor score based on subjects' brain function profiles. We subsequently applied SHAP (SHapely Additive exPlanations)[60] to the predictions made by each model to quantify the feature importance of each brain network for predicting scores in each mental health domain.

In the test set (Group 2), a subject's profile of brain activity across the 46 task-evoked networks significantly predicted their Cognition score (correlation between actual and predicted score: r=.15, p=.005, MSE=0.919) and Processing Speed score (r=.11, p=.041, MSE=1.184) to modest degrees. SHAP analysis revealed that the network with the highest feature importance for predicting Cognition was a variant from Network Family 9, evoked during the n-back Working Memory task, which involved left-lateralized motor cortex, rostral ventral putamen, and orbitofrontal cortex, as well as bilateral hippocampus and ventromedial prefrontal and ventral visual cortices, anticorrelated with bilateral frontoparietal control networks, the anterior and posterior dorsal midline and cerebellum (**Fig. S1a**). The network with the highest feature importance for predicting processing speed was a variant from Network Family 6, which involved bilateral frontoparietal and dorsal attention networks, anticorrelated with the default mode network (**Fig. S1b**). Multivariate brain network activity profiles could not significantly predict Positive Affect (r=.003, p=.956, MSE=1.255), Negative Affect (r=.03, p=.630, MSE=1.059) or Substance Use (r=.02, p=.681, MSE=1.226).

Brain Function Subtypes and Mental Health Subtypes Have Poor Correspondence

Next, to evaluate the extent to which the multivariate content of brain function profiles and mental health profiles reflect one another, we conducted a parallel subtyping analysis. To do so, we applied hierarchical clustering, separately, to subjects' brain function profiles and mental health profiles (**Fig. S2**). This clustered each individual into one subtype based on their brain function profile and one subtype based on their mental health profile. Then, we assessed the correspondence between these two sets of subtypes at each clustering solution level common to both the brain function and mental health subtyping sets (i.e., k=2, 5 and 10). The mental health characteristics of each subtyping solution are presented in **Supplementary Figure S3**.

Mental Health Subtype

Brain Network Subtype (*k=2*)	1	2
1	n=92 (*100.9*)	n=126 (*117.1*)
2	n=58 (*49.1*)	n=48 (*56.9*)

$X^2(1)=4.49$
$p=.034$

Mental Health Subtype

Brain Network Subtype (*k=5*)	1	2	3	4	5
1	n=25 (*23.5*)	n=6 (*9.4*)	n=11 (*12.9*)	n=12 (*14.0*)	n=17 (*11.2*)
2	n=24 (*28.4*)	n=11 (*11.4*)	n=17 (*15.7*)	n=21 (*17.0*)	n=13 (*13.5*)
3	n=20 (*20.2*)	n=6 (*8.1*)	n=13 (*11.1*)	n=8 (*12.1*)	n=14 (*9.6*)
4	n=16 (*18.8*)	n=13 (*7.6*)	n=11 (*10.4*)	n=13 (*11.3*)	n=4 (*9.0*)
5	n=22 (*16.2*)	n=7 (*6.5*)	n=7 (*8.9*)	n=10 (*9.7*)	n=3 (*7.7*)

$X^2(16)=23.81$
$p=.094$

Mental Health Subtype

Brain Network Subtype (*k=10*)	1	2	3	4	5	6	7	8	9	10
1	n=3 (*2.4*)	n=3 (*3.5*)	n=3 (*4.4*)	n=5 (*4.1*)	n=2 (*3.1*)	n=4 (*2.5*)	n=4 (*3.4*)	n=0 (*1.2*)	n=1 (*1.6*)	n=6 (*4.9*)
2	n=3 (*3.1*)	n=3 (*4.5*)	n=10 (*5.7*)	n=1 (*5.3*)	n=4 (*3.9*)	n=1 (*3.2*)	n=4 (*4.3*)	n=2 (*1.5*)	n=1 (*2.1*)	n=11 (*6.3*)
3	n=3 (*3.6*)	n=4 (*5.2*)	n=6 (*6.7*)	n=4 (*6.3*)	n=4 (*4.7*)	n=5 (*3.8*)	n=6 (*5.1*)	n=1 (*1.7*)	n=5 (*2.5*)	n=9 (*7.4*)
4	n=1 (*3.0*)	n=3 (*4.3*)	n=7 (*5.6*)	n=7 (*5.2*)	n=5 (*3.9*)	n=3 (*3.1*)	n=5 (*4.2*)	n=3 (*1.4*)	n=1 (*2.1*)	n=4 (*6.2*)
5	n=2 (*1.8*)	n=1 (*2.6*)	n=4 (*3.3*)	n=1 (*3.1*)	n=3 (*2.3*)	n=1 (*1.9*)	n=3 (*2.5*)	n=0 (*0.9*)	n=1 (*1.2*)	n=7 (*3.6*)
6	n=3 (*2.9*)	n=7 (*4.2*)	n=3 (*5.4*)	n=5 (*5.1*)	n=6 (*3.8*)	n=3 (*3.1*)	n=2 (*4.1*)	n=1 (*1.4*)	n=1 (*2.0*)	n=7 (*6.0*)
7	n=4 (*2.3*)	n=3 (*3.3*)	n=4 (*4.3*)	n=6 (*4.0*)	n=1 (*3.0*)	n=2 (*2.4*)	n=2 (*3.3*)	n=3 (*1.1*)	n=3 (*1.6*)	n=2 (*4.7*)
8	n=1 (*2.0*)	n=2 (*2.9*)	n=2 (*3.7*)	n=7 (*3.5*)	n=3 (*2.6*)	n=4 (*2.1*)	n=1 (*2.8*)	n=2 (*1.0*)	n=2 (*1.4*)	n=2 (*4.1*)
9	n=3 (*2.4*)	n=5 (*3.5*)	n=5 (*4.4*)	n=6 (*4.1*)	n=2 (*3.1*)	n=2 (*2.5*)	n=5 (*3.4*)	n=0 (*1.2*)	n=1 (*1.6*)	n=2 (*4.9*)
10	n=2 (*1.4*)	n=5 (*2.0*)	n=2 (*2.6*)	n=1 (*2.4*)	n=2 (*1.8*)	n=1 (*1.4*)	n=3 (*2.0*)	n=0 (*0.7*)	n=1 (*0.9*)	n=1 (*2.8*)

$X^2(81)=76.91$
$p=.608$

Figure 4. *Assignment of subjects into brain function subtypes and mental health subtypes.* At each clustering solution level common to both the brain function and mental health subtyping sets (k=2, 5 and 10), the total count (n) of subjects with each joint brain function subtype–mental health subtype assignment. Grayed values indicate the expected count if joint subtype assignments were random. Also presented are the results of chi-squared tests examining the difference between the expected and actual joint assignment counts.

Brain function profiles and mental health profiles generated largely dissimilar sets of subject groupings at all levels of subtyping granularity (**Fig. 4**). Correspondence was statistically significant at the k=2 clustering level, $X^2(1)=4.49$, $p=.034$, but Figure 4 illustrates the low effect size and specificity of the overlap. For instance, of 218 subjects in brain function subtype 1, 42% were in mental health subtype 1 and 58% were in mental health subtype 2. Correspondence did not differ from chance at finer clustering levels (k=5: $X^2(16)=23.81$, $p=.094$; k=10: $X^2(16)=76.91$, $p=.608$).

Subtyping Misalignment Yields Groups with Discordant Brain Function-Mental Health Associations

We next examined the consequence of this subtyping misalignment for group-level analyses of brain function-mental health associations. We found that the starting point of analysis (i.e., whether to subtype subjects by mental health data or by brain activation data) meaningfully altered conclusions about brain function-mental health group-level associations, in sometimes opposite directions (**Fig. 5**).

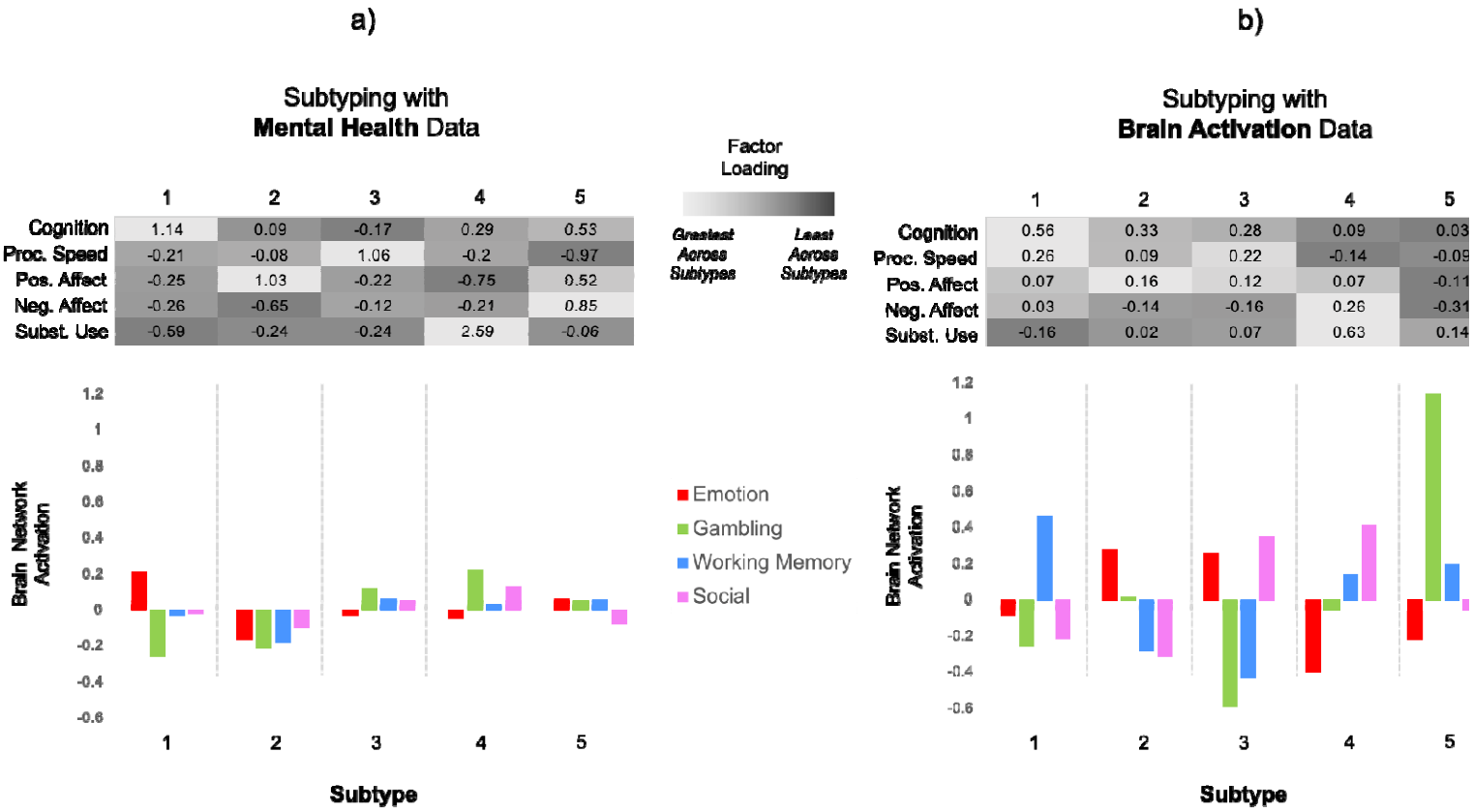

Figure 5. *Comparing brain function-mental health associations across subtyping solutions.* Average mental health profile (top panel; *Z*-scores) and average brain function profile (bottom panel; *Z*-scores) of each subtype derived from clustering of a) mental health data and b) brain function data at the k=5 clustering solution level.

For instance, in the k=5 mental health subtyping set (**Fig. 5a**), the high cognition, low substance use group (subtype 1) was characterized at the brain level by high network activation to the Emotion task and low network activation to the Gambling task, with average activation on the Working Memory and Social Cognition tasks (**Fig. 5a**). But in the k=5 brain function subtyping set (**Fig. 5b**), the analogous high cognition, low substance use group (subtype 1) was characterized at the brain level by very high network activation to the Working Memory task and average activation on the Emotion task. Similarly, in the mental health subtyping set, the high substance use group (subtype 4) was characterized at the brain level by high network activation on the Gambling task and average network activation on the Emotion task, whereas in the brain function subtype set, the high substance use group (subtype 4) was characterized at the brain

level by average network activation on the Gambling task and very low network activation on the Emotion task. Overall, due to the discordance of the mental health and brain function data, the starting point of analysis (i.e., whether to subtype subjects by mental health or brain function) meaningfully alters group-level associations between brain function and mental health.

Brain Function Subtypes Delineate Mental Health Differences Better than Mental Health Subtypes Delineate Brain Function Differences

Finally, given the observed misalignment and discordance between subtyping sets, we compared the relative ability of subtypes generated by one modality to yield groups that significantly differed in facets of the other modality. One-way ANOVAs at the k=2 clustering level demonstrated that subtypes generated using brain function data had significantly different means of cognition ($F(1,322)=10.96$, $p<.001$), processing speed ($F(1,322)=5.15$, $p=.024$), and substance use ($F(1,322)=8.15$, $p=.005$), but not of internalizing ($F(1,322)=0.46$, $p=.500$) or positive affect ($F(1,322)=1.07$, $p=.301$). On the other hand, subtypes generated using mental health data only significantly differed in brain activation on the Gambling task ($F(1,322)=8.09$, $p=.005$), and not in brain activation on the Emotion ($F(1,322)=0.65$, $p=.420$), Working Memory ($F(1,322)=1.65$, $p=.200$) or Social Cognition ($F(1,322)=2.95$, $p=.087$) tasks. Similarly, one-way ANOVAs at the k=5 clustering level demonstrated that subtypes generated using brain function data had significantly different means of cognition ($F(4,319)=3.82$, $p=.005$), internalizing ($F(4,319)=2.53$, $p=.041$), and substance use ($F(4,319)=3.36$, $p=.010$), but not of positive affect ($F(4,319)=.50$, $p=.736$) or processing speed ($F(4,319)=1.54$, $p=.190$). On the other hand, subtypes generated using mental health data only significantly differed in brain activation on the Gambling task ($F(4,319)=3.23$, $p=.013$), and not in brain activation during the Emotion ($F(4,319)=2.25$, $p=.064$), Working Memory ($F(4,319)=1.27$, $p=.281$) or Social Cognition ($F(4,319)=0.90$, $p=.466$) tasks. Overall, these findings indicate brain function data were more sensitive to mental health differences than mental health data were sensitive to brain function differences.

Comparing Interindividual Variability and Assessment Diversity in Brain Function and Mental Health Data

To investigate what may account for the above findings, we compared the brain function and mental health data in terms of interindividual variability and assessment diversity. First, within brain function data, significantly greater ($p<.05$) interindividual variation in brain activity was elicited by the Emotion task (mean coefficient of variation (CV) of 10 evoked networks=0.55) than by the Social Cognition (mean CV of 18 evoked networks=0.28), Working Memory (mean CV of 14 evoked networks=0.31), Gambling (mean CV of 15 evoked networks=0.33) or Movie-Watching (mean CV of 20 evoked networks=0.36) tasks (**Fig. S4**). Within mental health data, interindividual variation was significantly greater ($p<.05$) for measures of substance use (mean CV of 12 assessments=2.21) and negative affect (mean CV of 21 assessments=0.47) than for measures of cognition (mean CV of 27 assessments=0.16), processing speed (mean CV of 16 assessments=0.18), and well-being/positive affect (mean CV of 9 assessments=0.18). Overall, the interindividual variability of individual assessments did not differ significantly between brain function and mental health data, $t(151)=1.34$, $p=.18$.

However, the 46 reproducible brain function assessments (mean absolute assessment-assessment correlation, r=.278) were significantly more redundant with one another than the 87 mental health assessments (mean absolute assessment-assessment correlation, r=.106), t(4603)=42.73, p<.001 (**Fig. S5**). This reflects that within an individual, the activity of any given brain network on any given task moderately predicted the activity of the individual's other brain networks in the same and other tasks. Moreover, individuals exhibited almost twice as much similarity to one another in brain function (mean absolute subject-subject correlation amongst 46-network activity profiles: r=.224) as they did in mental health (mean absolute subject-subject correlation amongst 87-assessment profiles: r=.133), t(101779)=109.64, p<.001, indicating poorer overall subject discriminability in brain function data relative to mental health data.

Discussion

Hedge and colleagues describe a "reliability paradox"[61] built into many fMRI tasks, in which tasks designed to elicit robust group-level brain activations to map task-relevant brain regions must inherently have low between-subject variability in brain activity – causing low reliability for individual differences research. Yet, we demonstrate here that the magnitude of between-subject variability in task fMRI-evoked brain activity can be sufficient – with large enough sample sizes and optimized methodology – to robustly parse individual differences even in low-variability target phenotypes (i.e., Cognition). What, then, could explain why the same fMRI data does not parse individual differences in other phenotypes (i.e., PVS and NVS) with comparable measurement reliability and even larger interindividual variability? We posit that it is because the set of fMRI tasks commonly used in large-scale neuroimaging studies simply do not elicit individual differences in brain activity that are relevant to variability in non-cognitive aspects of mental health, likely because these tasks are too low-stakes and unprovocative. If this is the case, continuing advances in neuronal signal purification, modelling optimization and spatiotemporal resolution may not meaningfully strengthen our ability to extract this information. Rather, the current findings point to a need to leverage different types of tasks in future large-scale neuroimaging studies if our goal is to evoke brain activity that more holistically represents mental health.

Cardiac stress tests provide an apt analogy. Holistic assessments of cardiovascular health require not only measures of heart function at the resting or low-level activity state, but at the vigorous activity state as well. We posit that the fMRI tasks common to large-scale studies do not take the brain particularly far away from its resting-state, and that more demanding tasks that facilitate measurement of brain function during vigorous activity states will need to be more broadly implemented and incorporated into large-scale studies. fMRI tasks implemented in large-scale neuroimaging studies tend to be selected for brevity, ease of administration, and established consistency of results. This skews paradigm selection towards block designs that provide maximized signal-to-noise ratios and require less individualized analytic processing pipelines, but which often mask important nuances in brain reactivity to specific stimuli (e.g., correct versus incorrect trials) and average out significant individual differences in brain activation. While more challenging to administer consistently in a large-scale study, tasks that model subject responses and brain activity at higher detail (i.e., event-related designs) and that are more affectively provocative and high stakes (e.g., social exclusion task, cold pressor task, monetary incentive delay task) may prove more powerful in extracting individual differences in non-

cognitive mental health. Importantly, though, paradigms involving highly salient real-life consequences must be carefully considered in the context of research ethics and subject beneficence.

Many basic science investigations, clinical trials, grant proposals and large-scale study designs rely on explicit or implicit notions that particular fMRI tasks differentially probe individual differences in distinct RDoC domains. For instance, the Emotion task and related variants are commonly used as probes of NVS; the Gambling task and related variants are commonly used as probes of PVS; the Social Cognition task and related variants are commonly used as probes SP; and the Working Memory task and related variants are commonly used as probes of CS[62]. These tasks are indeed validated "functional localizers"[63] of the neural substrates relevant to distinct domains. However, as the present findings underscore, just because a task activates neural substrates underlaying a domain of function, does not necessarily mean it elicits interindividual variability in these substrates' activity that reflects variability in that domain of function. For instance, while the Emotion task robustly activated the amygdala – a structure with known roles in NVS – neither variability in networks involving the amygdala, amygdala connectivity, nor amygdala activity itself indexed interindividual variability in the composite measure of negative affect/internalizing[38]. Instead, despite these tasks' distinct names, stimuli and instructions, individual differences in brain activity evoked by the Emotion, Gambling, Working Memory, Social Cognition, and Movie-Watching paradigms all predominantly reflected variability in cognition. These tasks may all be more appropriately categorized in the CS domain of RDoC, therefore – at least when administered to generally healthy young adults. For this population, these tasks may be similarly low-stakes, unprovocative, and easily navigable with minimal recruitment of non-cognitive neural resources. Certainly, these tasks' ability to elicit brain activity reflecting cognition is valuable, given that cognitive deficits represent a core feature of numerous forms of mental illness. However, most disorders also involve a broader constellation of affective and other deficits. Eliciting and identifying brain activity that reflects these non-cognitive domains will remain a critical task of clinical neuroimaging moving forward.

It remains possible that variability in non-cognitive mental health domains may be better detected in brain activity variability modelled at other scales of brain organization than large-scale networks. However, recent work has demonstrated that region-of-interest activation and edge-level connectivity were no better than large-scale network activation in the Emotion task in representing non-cognitive mental health domains[38]. Collectively, we posit that the data implicates as the key contributing factor a fundamentally low ability of fMRI tasks currently included in most large-scale studies to elicit brain activity that reflects individual differences in non-cognitive mental health domains.

Our parallel subtyping findings point to another important set of issues. Many studies begin with mental health- or behaviour-based subject groupings (e.g., a clinical sample and a control sample) and seek to identify brain differences between the groups. Yet, we show here that groups constructed to have maximally dissimilar mental health profiles from one another nonetheless have largely similar brain function profiles. This converges with findings from the clinical realm wherein patients classified to distinct DSM diagnostic categories have minimal neurobiological differentiation from one another[64]. Our findings support the movement toward a primacy of neurobiologically-based subject classifications instead[65]. Here, subtype groups constructed to

have maximally dissimilar brain function profiles from one another were modestly successful in separating out subjects with distinct mental health profiles. For instance, brain function subtypes were able to separate out subjects with distinct levels of cognition, internalizing and substance use. Meanwhile, mental health subtypes generally were not able to parse out differences in task-evoked brain activity. These findings indicate that beginning analyses with brain-based subtypes rather than mental health/behaviour-based subtypes may provide a better means of identifying fundamentally similar individuals and may be more successful at targeting biologically-based treatment approaches to the individuals who will best respond to them.

The present study was limited in examining only generally healthy young adults. Future work aims to explore whether fMRI task batteries are more effective at eliciting brain activity reflecting non-cognitive mental health in more neuropsychiatrically diverse cohorts.

Methods

Subjects

Data used in these analyses include fMRI scans from individuals collected as part of the Human Connectome Project (HCP) 1200 subject release. A detailed description of the recruitment for the HCP is provided by others[66,67]. Briefly, individuals were excluded by the HCP if they reported a history of major psychiatric disorder, neurological disorder, or medical disorder known to influence brain function. For reproducibility assessment, we randomly separated eligible subjects into two groups (n1=607; n2=599) with non-overlapping family structures. Given the oversampling of siblings and twins in the HCP-YA cohort, consolidating subjects from the same family within the same group prevented family structure-related data leakage across the two groups. To maximize the generalizability of replication analyses, we did not rebalance the family-separated groups by other demographic variables.

Subjects had variable data availability and quality across the different fMRI tasks examined in the present study. To maximize the quantity of analyzable data for detection of task-evoked brain networks and brain function-mental health univariate relationships, we first established task-specific groups by excluding only subjects from each task group who had missing data, HCP quality assessment flags, or excessive head motion (i.e., 1 or more frames with framewise displacement > 2mm) for that task. This produced the following sample sizes for each set of task groups: Emotion (n1=413; n2=416), Gambling (n1=444; n2=444), Social Cognition (n1=406; n2=435), Working Memory (n1=404; n2=395). Then, for multi-network predictive modeling across groups, we winnowed the task-specific groups into a set of task-general groups (n1=324; n2=330) that comprised subjects with available and high-quality data across all four tasks. Separately, we also examined the subset of subjects (n=184) who had 7T movie-watching data. Given the appreciably smaller sample size of subjects with movie-watching data, we did not split this sample or include movie-watching data in multi-network predictive modeling for reproducibility analysis.

fMRI Acquisition

HCP neuroimaging data were acquired with a standard 32-channel head coil on a Siemens 3T Skyra modified to achieve a maximum gradient strength of 100 mT/m[66]. T1-weighted high resolution structural images, acquired using a 3D MPRAGE sequence with 0.7mm

isotropic resolution (FOV=224mm, matrix=320, 256 sagittal slices, TR=2400ms, TE=2.14ms, TI=1000ms, FA=8°), were used in the HCP minimal pre-processing pipelines to register functional MRI data to a standard brain space. Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired using a gradient-echo EPI sequence with the following parameters: TR = 720 ms, TE = 33.1 ms, flip angle = 52°, FOV = 280 × 180 mm, Matrix = 140 × 90, Echo spacing = 0.58 ms, BW = 2290 Hz/Px, 72 slices, 2.0 mm isotropic voxels, with a multiband acceleration factor of 8. HCP neuroimaging data were acquired in two sessions, each occurring on a different day.

HCP movie-watching fMRI data were acquired during a separate, third session on a 7T Siemens Magnetom scanner at the Center for Magnetic Resonance Research at the University of Minnesota. Data were collected using a gradient-echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 1000 ms, echo time (TE) = 22.2 ms, flip angle = 45 deg, field of view (FOV) = 208 × 208 mm, matrix = 130 × 130, spatial resolution = 1.6 mm^3, number of slices = 85, multiband factor = 5, image acceleration factor (iPAT) = 2, partial Fourier sampling = 7/8, echo spacing = 0.64 ms, bandwidth = 1924 Hz/Px. The direction of phase encoding alternated between anterior-to-posterior (AP: MOVIE1, MOVIE4) and posterior-to-anterior (PA: MOVIE2, MOVIE3).

fMRI Tasks

Detailed descriptions of the HCP-YA fMRI task paradigms can be found here[31,68]. Brief summaries of each task paradigm are provided below.

The Emotion task (i.e., emotional face-matching task) was adapted from Hariri and colleagues[69]. Subjects were presented with blocks of trials that asked them to decide either which of two faces presented on the bottom of the screen matched the face at the top of the screen, or which of two shapes presented at the bottom of the screen matched the shape at the top of the screen. The faces had either angry or fearful expressions. Each run included blocks of 6 trials of the same task (face or shape), with the stimulus presented for 2 s and a 1 s ITI. Each block was preceded by a 3 s task cue (“shape” or “face”), so that each block was 21 s including the cue. Each of the two runs included 3 face blocks and 3 shape blocks.

The Gambling task (i.e., incentive processing task) was adapted from Delgado and Fiez[70]. Subjects guessed the number on a mystery card in order to win or lose money. Card numbers ranged from 1–9, and they were told to indicate if they thought the mystery card number was more or less than 5 by pressing one of two buttons on the response box. Feedback consisted of the number on the card (generated by the program as a function of whether the trial was a reward, loss or neutral trial) and either: 1) a green up arrow with “$1” for reward trials, 2) a red down arrow next to −$0.50 for loss trials; or 3) the number 5 and a gray double headed arrow for neutral trials. The task was presented in blocks of 8 trials that were either mostly reward (6 reward trials pseudo randomly interleaved with either 1 neutral and 1 loss trial, 2 neutral trials, or 2 loss trials) or mostly loss (6 loss trials interleaved with either 1 neutral and 1 reward trial, 2 neutral trials, or 2 reward trials). All participants were provided with money for completing the task, though it was a standard amount across subjects.

The Social Cognition task (i.e., theory of mind task) was adapted from Castelli and colleagues[71] and Martin and colleagues[72]. Subjects watched short video clips (20 s) of objects (squares, circles, triangles) either interacting in some way, or moving randomly. After each video clip, subjects chose between 3 possibilities: whether the objects had a social interaction (an interaction that appeared as if the shapes were taking into account each other’s feelings and

thoughts), Not Sure, or No interaction (i.e., there was no obvious interaction between the shapes and the movement appeared random). The task included 5 video blocks (2 Mental and 3 Random in one run, 3 Mental and 2 Random in the other run) and 5 fixation blocks (15 s each).

The Working Memory task (i.e., N-back task) involved blocks of trials that consisted of pictures of faces, places, tools and body parts. Within each run, the 4 different stimulus types were presented in separate blocks within the run. Within each run, ½ of the blocks consisted of a 2-back working memory task (respond 'target' whenever the current stimulus is the same as the one two back) and ½ presented a 0-back working memory task (a target cue is presented at the start of each block, and the person must respond 'target' to any presentation of that stimulus during the block). A 2.5 s cue indicated the task type (and target for 0-back) at the start of the block. Each of the two runs contains 8 task blocks (10 trials of 2.5 s each, for 25 s) and 4 fixation blocks (15 s each). On each trial, the stimulus was presented for 2 s, followed by a 500 ms ITI. Each block contained 10 trials, of which 2 were targets, and 2–3 were non-target lures (e.g., repeated items in the wrong n-back position, either 1-back or 3-back). The inclusion of lures was critical to ensure that participants were using an active memory approach to the task and allowed one to assess conflict related activity as well as error related activity.

The Movie-Watching task involved passively viewing a series of video clips with audiovisual content. Each MOVIE run consisted of 4 or 5 clips, separated by 20 s of rest (indicated by the word "REST" in white text on a black background). The MOVIE1 run examined here contained clips from independent films (both fiction and documentary) made freely available under Creative Commons license on Vimeo, as well as a final clip comprising a montage of brief (1.5 s) videos that was identical across each of the four Movie-Watching runs (to facilitate test-retest and/or validation analyses). We focused on MOVIE1 because it was the only Movie-Watching run previously found to elicit functional brain organization predictive of both cognition and emotion[31]. Audio was delivered via Sensimetric earbuds.

fMRI Preprocessing

For the Emotion, Gambling, Social Cognition and Working Memory task fMRI data, we began with the HCP's minimally preprocessed data. The HCP minimal preprocessing pipeline for fMRI data removes spatial distortions, realigns volumes to compensate for subject motion, registers the echo planar functional data to the structural data, reduces the bias field, normalizes the 4D image to a global mean, and masks the data with a final FreeSurfer-generated brain mask[73]. We additionally applied 4mm spatial smoothing, 150 sec temporal smoothing, removal of non-steady-state frames (first 15 frames), and ICA-FIX denoising[74], which denoises residual subject motion, physiological motions, and artifacts, to the HCP minimally preprocessed task fMRI data. For movie-watching fMRI data, we used the FIX-denoised data already provided by the HCP and removed non-steady frames (i.e., the first 15 frames).

Tensor Independent Component Analysis (tICA)

tICA is a well-validated[38,50] unsupervised learning technique that detects distributed sets of brain activity whose time courses align with one or more aspects of a task stimulation time course. It can thereby identify, trace the moment-by-moment activity of, and quantify individual differences in task-evoked brain network activity. We applied tICA separately to the denoised fMRI data from each task group using MELODIC[50,75] in FSL (version 6.0). This identified task-recruited brain networks, including their voxel-wise spatial maps, their frame-wise time courses, and subject loadings (i.e., the extent to which a subject's data loads on the spatial and temporal

pattern of the group-level network) on each network, for each task in both groups. For each task, we ran tICA at varying model orders to inspect the output for the optimal model order for analysis. Because the goal was to investigate large-scale canonical brain networks, the model order of the group ICA needed to be relatively low to result in a coarse spatial scale parcellation of the brain into networks. Model orders that are too high produce finer spatial scale parcellations that reflect excessive segregation of known large-scale networks into individual or bilateral brain areas rather than networks. At the same time, model orders that are too low fail to fully disaggregate known canonical brain networks. Therefore, we tested a range of model orders from 5 to 25 to identify which decomposition parcellated the brain into canonical network patterns while effectively unmixing any noise/artifacts into separate components. For each model order, we examined the time course, power spectrum and spatial map of each component to identify those most likely to reflect task-related brain activity (e.g., components with spatial patterns resembling large-scale brain networks and with temporal courses reflecting one or more aspects of the task time course). Ultimately, we identified to d = 20 to be the optimal model order in our data that best achieved the balance between disaggregating large-scale canonical networks and not producing excessive segregation; this model order is also in line with previous reports examining the correspondence between task activation networks and canonical resting state brain networks[76,77]. Among the 20 components, those identified as noise (e.g., physiological, motion, scanner artifacts, drift) via examination of their time course, power spectrum and spatial distribution were removed from analysis, in line with best practices for identification of ICA noise components[78]. The identified network components were assessed for both spatial and temporal reproducibility across Group 1 and Group 2. For each group, before input into hierarchical clustering for subject subtyping, subject loadings were normalized by subtracting network loading means and then dividing by network loading standard deviations.

Assessing Overlap with Canonical Networks

To further characterize the spatial maps of the tICA-identified network families, we used the network correspondence toolbox (NCT)[54] to compute overlap (Dice coefficients) between the positive and negative components of each task network and each of 17 canonical large-scale networks defined in the Gordon et al. parcellation[53]. Positive and negative components were analyzed separately because we observed visually that the positive and negative parts of each component typically represented distinct networks. More generally, the tensor ICA can identify states comprised of anti-correlated network patterns that have been reported by others during both resting state and task performance (see for example Li et al. 2021[79]) as an important characteristic of brain organization. As such, the positive and negative parts were analyzed separately to determine their distinct network makeups. In order to assess statistical significance, a spin test implemented in Python was performed with 1000 permutations for each reference atlas network[54]. Significant overlap was thresholded at $p < .05$.

Hierarchical Factor Analysis (hFA)

hFA identified sets of highly correlated variables from the 87 measured by HCP assessments. These variables included behavioral measures of motor and sensory functioning, alertness, and cognition, including in-scanner task performance measures, as well as self-report measures of emotion, personality, substance use, psychiatric symptoms and general life function[42]. Full details of the procedure are outlined in Schottner et al., 2023[42]. Briefly, prior to the application of factor analysis, missing assessment values were first imputed using Multiple

Imputation by Chained Equations. Next, age and gender were regressed out by entering them as predictors in a linear regression. The residuals of this regression served as the inputs to the factor analysis. Reaction times and other error measures were inverted, and data were z-scored across subjects. We used the five-factor solution which included well-being/positive affect, internalizing/negative affect, processing speed, cognition and substance use[42].

Machine Learning Prediction of Mental Health Scores

For the machine learning regression analyses, the number of trees in the random forest was set to 1000. No maximum depth was specified for trees, the minimum number of samples required at each leaf was set to 1, the minimum number of samples required to split an internal node was set to 2, and the maximum number of features to consider when looking for the best split was set to 1. This analysis was carried out using scikit-learn[80].

Data Availability

The HCP-YA dataset is publicly available on an open access repository (https://db.humanconnectome.org/app/template/Login.vm), which can be accessed after signing a data use agreement. Individual network maps identified by tICA for the Emotion, Gambling, Working Memory, Social, and Movie-Watching paradigms have been made viewable and accessible in a "Task-Evoked Network Atlas" at https://identifiers.org/neurovault.collection:20820.

Code Availability

All code used in this paper is freely and publicly available. Code to run tensor independent component analysis (tICA) is available in Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL). Code to run the Network Correspondence Toolbox (NCT) is available here: https://github.com/rubykong/cbig_network_correspondence. Code to run factor analysis on the HCP-YA dataset to generate latent mental health factor scores is available here: https://github.com/connectomicslab/hcp-behavioral-domains. Code to run SHapely Additive exPlanations (SHAP) is available here: https://shap.readthedocs.io/en/latest/. Code to run random forest machine learning regression is available here: https://scikit-learn.org/stable/modules/generated/sklearn.ensemble.RandomForestClassifier.html.

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