Moving beyond the mean: Subgroups and dimensions of brain activity and cognitive performance across domains

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A B S T R A C T

Human neuroimaging during cognitive tasks has provided unique and important insights into the neurobiology of cognition. However, the vast majority of research relies on group aggregate or average statistical maps of activity, which do not fully capture the rich intersubject variability in brain function. In order to fully understand the neurobiology of cognitive processes, it is necessary to explore the range of variability in activation patterns across individuals. To better characterize individual variability, hierarchical clustering was performed separately on six fMRI tasks in 822 participants from the Human Connectome Project. Across all tasks, clusters ranged from a predominantly ‘deactivating’ pattern towards a more ‘activating’ pattern of brain activity, with significant differences in out-of-scanner cognitive test scores between clusters. Cluster stability was assessed via a resampling approach; a cluster probability matrix was generated, as the probability of any pair of participants clustering together when both were present in a random subsample. Rather than forming distinct clusters, participants fell along a spectrum or into pseudo-clusters without clear boundaries. A principal components analysis of the cluster probability matrix revealed three components explaining over 90% of the variance in clustering. Plotting participants in this lower-dimensional ‘similarity space’ revealed manifolds of variations along an S ‘snake’ shaped spectrum or a folded circle or ‘tortilla’ shape. The ‘snake’ shape was present in tasks where individual variability related to activity along covarying networks, while the ‘tortilla’ shape represented multiple networks which varied independently.

Introduction

Functional magnetic resonance imaging (fMRI) has resulted in a dramatic improvement in our understanding of human brain function and cognition over the past 25 years. The great majority of these studies have made conclusions about groups of individuals (based on a disorder, age-range, or lack of a disorder, i.e. a healthy group). These findings can give the impression that any ‘group’ is homogeneous, i.e. brain activation representing a group-average might represent that of an individual. However, a growing body of work is bringing to light the tremendous variability among individuals in brain function. For example, typical patterns of connectivity observed at the group level are not well represented at the individual level (Gordon et al., 2017), and individual variability is greater in heteromodal cortices such as the fronto-parietal network (Mueller et al., 2013). The extent and distribution of different patterns of activity among individuals during cognitive tasks is not optimally captured by group statistical maps (Hawco et al., 2019; Miller et al., 2009; Miller and Van Horn, 2007). Further, there is evidence to support that people may use different cognitive strategies during task performance (Guimond et al., 2017; Kirchhoff and Buckner, 2006; Miller et al., 2012). For example, strategy training in individuals with normal memory abilities can develop patterns of activity that resemble exceptional ‘memory athletes’ (Dresler et al., 2017). Additionally, individuals with greater differences in cognitive styles have concomitant differences in brain activity (Miller et al., 2012), demonstrating a relationship between cognitive strategies during task performance and patterns of brain activity.

Much progress has also been made in the identification of individual brain systems, which vary according to dimensions such as cognitive abilities. Regression approaches often used in these investigations are predominantly sensitive to variation, which linearly maps onto a common spatial pattern of brain-behavior relationships across all individuals. However, such approaches are not designed to capture unique brain-behavior relationships among sub-groups of participants (Easson et al., 2018). There are also important statistical considerations whereby linear regressions may overestimate brain-behavior relationships (Vul et al., 2009), and issues regarding reliability at lower sample sizes have been well-documented (Button et al., 2013; Zuo et al., 2019). Due to the challenges of interpreting single subject data related to the high dimensionality and complexity of brain imaging data, few fMRI studies have focused on mapping differences in brain function among subgroups, and even fewer among individuals (Braga and Buckner, 2017; Gordon et al., 2017; Miller et al., 2012; Miller et al., 2009).

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One intermediate approach between group level analyses and visualizing data at the individual level is to perform clustering on participants, grouping together those with similar neurobiological characteristics (Clémentz et al., 2016; Drysdale et al., 2017; Fecko et al., 2018; Hawco et al., 2019; Stefanik et al., 2018). In a recent investigation including individuals with and without psychiatric disorders, we identified and replicated three sub-groups (clusters) demonstrating distinctly different patterns of brain activity during emotional face processing. These sub-groups were comprised of a generally ‘deactivating’ group, a typical/expected group (i.e. representative of the group average), and a ‘hyperactivating’ group (Hawco et al., 2019). These sub-groups were not related to diagnostic status (e.g. with or without psychiatric diagnosis), but did show differences in cognitive performance. There has been a growing interest in the application of clustering approaches to brain imaging data, particularly in psychiatry. This is related to the idea of biotyping; existing diagnostic categories are not specifically related to the underlying biological disorder involved in specific expressions of mental illness, and replacing these diagnostic groups with biologically defined ‘biotypes’ will enhance treatment development and response (Voinoskos et al., 2020). However, the pattern of brain activity observed in the clustering derived from task fMRI described above (Hawco et al., 2019) fell along a spectrum (deactivating/negative, intermediate, strongly activating). A careful examination of raw data underlying clusters in other recent clustering papers in psychiatry (Clémentz et al., 2016; Drysdale et al., 2017) suggests that the clusters may not fall into distinct sub-groups, but instead clustering is separating individuals along underlying continuous dimensions. It remains unknown whether a) our previously observed pattern from ‘most deactivating’ to ‘most activating’ is present across most fMRI tasks, and b) if such variability would be optimally represented as discrete sub-groups or along a continuum of individuals.

The primary purpose of this study was to examine how clustering could be used to identify the range of different patterns of human brain activity during task processing. We leveraged the large sample available in the Human Connectome Project (HCP), which includes fMRI tasks covering multiple cognitive domains (Barch et al., 2013). Clustering was used as a novel way to examine individual variability. In previous work applying hierarchical clustering across a small sample of repeatedly scanned individuals, we demonstrated that in the presence of separable data (in this case, participants scanned repeated across different MRIs), clustering largely grouped repeated scans by participant (Hawco et al., 2018). This validates the use of hierarchical clustering in high dimensional MRI data to identify sub-groups of related scans. Out-of-scanner cognitive performance was used as a validation of the behavioral relevance of clustering-related variance in brain activity. Given the prominence of clustering for identifying clinical ‘biotypes’, a second goal of this study was to consider if task activation patterns across participants fell into discrete sub groups, pseudo-clusters, or along a continuum.

Methods

Participants

Data were obtained from the HCP 900 release (Barch et al., 2013; Glasser et al., 2016; Van Essen et al., 2013), ranging in age from 22 to 35. Of the 899 participants with fMRI data available, only those who completed all six fMRI cognitive tasks were included, leaving a sample of 822.

Subject-level activation maps

Task activation maps from specific contrasts across six cognitive paradigms in HCP were used, including (selected contrast in parentheses): Emotional (Faces-Shapes), Gambling (Reward-Punish), Language (Story-Math), Relational (Related-Match), Social (TOM-Random), and N-Back Working Memory (2Back-0Back). Individual subject statistical analyses provided as part of the HCP S900 release (Barch et al., 2013; Glasser et al., 2013) were used for all further analysis. To facilitate group-wise comparisons, data were selected from the surface smoothed (8mm FWHM) using the HCP minimal preprocessing pipeline (Glasser et al., 2013). This pipeline includes motion correction, distortion correction, registration to standard space, and generation of a grayordinate (cortical surface) time-series for each task run. For each task, the HCP collected two runs which differed with respect to the MRI phase encoding direction (left to right, or right to left). Statistical analyses were performed in FSL. Fixed-effects (“first-level”) analysis was performed on each run separately, including the smoothing stage (performed on the cortical surface), and then the two runs for each task were combined via a second fixed-effects analysis. These second fixed-effect t-maps from task for each participant were used for further analysis. We used t-maps as opposed to Beta estimates for cluster analysis as the t-values are deweighted in noisy voxels due to the higher variance; within the t-maps the sample variance across time (df= number of data points) is taken into account.

Initial cluster analysis

All clustering analyses were completed in MATLAB (R2017b). Hierarchical clustering with Euclidean distance and Ward’s linkage was used (Hawco et al., 2019; Hawco et al., 2018). In order to perform the clustering, a ‘spatial’ matrix was created by extracting the t-statistics across the cortex for each participant as a vector and stacking participants (producing a matrix of spatial activation across subjects, size 822 participants by 58,997 cortical vertices). Clustering was then run on each task separately; in order to examine a range of potentially informative clustering solutions, clustering was calculated from k=2 to k=10 clusters. An additional analysis was run using K-means, with k=4, for visual comparisons with the results from hierarchical clustering.

Group analysis by cluster

In order to visualize patterns of activity within each cluster, group-level maps were created for each separate cluster. Second-level (group) one-sample t-tests were performed using SPM12, using the contrast maps provided by HCP for the contrast of interest. The statistical threshold for the group/cluster map is dependent upon sample size. That is, a smaller sample requires a larger t-value to establish significance. In order to allow for a clearer visual comparison between groups, a minimum t-value was set of t~5, which approaches or exceeds p<0.05 FWE at the single vertex level for most clusters (if n >>100). By comparison, p<0.001 uncorrected t-values ranges from about 2.8 to 3.2 for most cluster sizes. Thus, this t-value avoids individual thresholding for each cluster solution (which may make direct visual comparisons across maps challenging) but is a stringent correction for multiple comparisons (Eklund et al., 2016).

Comparisons of clustering across tasks

Previous work has suggested task activity is built on an architecture of functional connectivity (Cole et al., 2014; Cole et al., 2016; Tavor et al., 2016), indicating that participants with similar functional connectivity may show similar task activation patterns. In order to assess if participants clustered similarly across the six tasks, we used the Adjusted Rand Index (ARI). The ARI indicates similarity between two cluster solutions while adjusting for random chance (i.e. ARI = 1 indicates perfect overlap in cluster membership, while ARI ~ 0 indicates no relationship, random chance). ARI was calculated for each pair of tasks (e.g. Emotional-Gambling, Emotional-Language, etc.) for each value of k.
Cognitive data

Cognitive data consisted of 12 measures available within the HCP protocol. From the NIH toolbox, the provided age-adjusted scores were taken from the Picture Sequence test (memory), List Sort test (working memory), Dimensional Card Sort test (executive function, cognitive flexibility), Flanker task (inhibition), the Pattern Completion test (processing speed), Reading in English test, and the Picture Vocabulary test. Additional cognitive measures included were the Short Penn Continuous Performance task true positives (sustained attention), Penn Word Memory Test (verbal episodic memory), the Variable Short Penn Line Orientation test median correct reaction time (spatial orientation), Raven’s Progressive Matrices correct responses (fluid intelligence), and the Penn State Emotional Recognition test reaction time (emotional processing).

All cognitive scores were Z-transformed (within the sample) to a mean of zero and standard deviation of one to allow direct comparison across tests. Initially, a PCA was run on all 12 test scores for data reduction purposes; however, the first three components only accounted for 25%, 15%, and 9% of the variance, respectively. Therefore, all 12 scores were used in subsequent analyses. For each cognitive test, each cluster, and each value of k, a one-way ANOVA was performed to examine differences in cognitive test scores across members of the different clusters. That is, differences in cognitive scores between clusters were examined across all six tasks for cluster solutions (k=2 to k=10) for all 12 cognitive scores (e.g. examining differences across k=4 groups derived from the Working Memory task on performance on Raven’s Matrices; a total of 648 one-way ANOVAs were performed). Significance was defined as p < 0.05. FDR corrected across all 648 tests performed. Selected relevant within-scanner fMRI task performance variables were also extracted for each of the six fMRI tasks (24 scores total), and Z-transformed to a mean of 0 and standard deviation of 1, and relationships across clusters and task performance as considered separately.

Signal characteristics and noise

In order to determine if clustering was driven by signal characteristics or noise such as motion, metrics were pulled and related to clustering. Signal characteristics of temporal signal to noise ratio (tSNR) and global signal variance were extracted from the preprocessed time series data. As each of tSNR and variance is calculated for each cortical vertex, a summary score was created for each participant by taking the mean across all vertices. However, mean variance and mean tSNR were found to be highly negatively correlated (Rho > -0.95), so we retained tSNR and did not further consider variance. Motion was examined by taking the mean framewise displacement (the average motion across all TRs). tSNR and mean FD were calculated separately for each participant for each task. Mean tSNR and mean FD were also correlated (Rho > 0.5 for all tasks), but both were retained as they explained some unique variance. Differences between clusters in tSNR and mean FD were examined via one-way ANCOVAs, similar to what was done for the cognitive scores, though given that tSNR and mean FD were correlated we covared each analysis for the other measure. Furthermore, tSNR has a spatial pattern across the cortex, making it possible to examine the relationship of the spatial pattern of tSNR to the spatial pattern of brain activity. For each participant across all six tasks, Spearman’s Rho was calculated between tSNR maps and task related brain activity (single subject t-maps).

Cluster resampling analysis

A key goal of the present study was to better understand if participants fall more along a continuum or into relatively discrete groups (i.e. clusters). In order to interrogate the underlying structure of the cluster solutions, a resampling without replacement approach was employed. Resampling was run for each of the six tasks and each cluster size from k=2 to k=10, running 1000 bootstraps without replacement using a randomly selected 75% of the sample. For each combination of task and k value (e.g. Working Memory task, k=4), a ‘clustering probability’ matrix was calculated to capture the probability of each pair of participants clustering together. This was quantified as the probability (from 0 to 1) of a pair of participants being in the same cluster when they were both in a permutation. This resulted in an NxN matrix of clustering probabilities (referred to as a ‘cluster probability matrix’). For visualization purposes, an optimal ordering function (MATLAB’s optimaledgefor.m) was run using hierarchical clustering with Euclidean distance and average linkage to sort these cluster probability matrices in such a way as to maximize the sum of the similarity between adjacent participants. This approach ‘declustered’ the data relative to the initial whole sample cluster solution, but resulted in visually more informative data by placing similar participants together and allowing patterns within the cluster probability matrices to emerge unconstrained by the whole sample solution.

Resampling components analysis

Examination of the cluster resampling matrices indicated that the data did not necessarily fall into distinct clusters, but a large proportion of variance was represented by the position on the diagonal of the matrix. However, the matrices also suggested there may be more than a single dimension to the data (i.e. off-diagonal ‘bulges’). In order to better understand the factors driving clustering results, a Principal Component Analysis (PCA) was run in MATLAB on the probability matrices to extract the top three components. Note that these components were not taken from the t-maps, but from the cluster probability matrices. The components are therefore representations of the lower-dimensional factors which cause participants to cluster together or not. Data were visualized by plotting participants into 3D space using the component scores for each participant.

To assess behavioral relevance, a Spearman’s correlation was conducted between the component scores and 12 cognitive scores (the components did not follow a normal distribution, see Supplemental Fig. 15). The top three component scores for k=4 for each task were compared to each of the 12 cognitive scores (3 scores x 12 tests x 6 tasks = 216 total correlations); significance was determined by FDR correction applied to the full set of 216 correlations.

Regressing PCA scores to recover associated patterns of brain activity

In order to visualize the spatial patterns related to the components, we used a regression approach in SPM12. The component scores were regressed against the amount of task-evoked activity (i.e. the task beta weights) at each vertex across the sample (similar to the approach used in many brain-behavior regressions). This identified vertices in which participants with higher or lower component scores showed corresponding higher or lower brain activity, thus identifying the spatial pattern of activity associated with each component score.

Pseudo-simulations reproducing the component score plots

In order to identify the characteristics of variations in functional activity driving the shapes in the cluster probability component plots, a pseudo-simulation approach was undertaken. The fMRI t-maps which were used in the resampling analysis were used, but modified to explore different hypotheses; 1) cluster probability may be related to mean brain activity across the cortex; 2) cluster probability may be related to activity in independent systems; or 3) cluster probability may be an element of random similarities between scans. Pseudo-simulations were conducted by performing specific operations on the input data matrix (participant’s t-statistics cortical vertices; t-maps), rerunning the cluster bootstrap across 1000 iterations at k=4 for each task, calculating the
first three principal components of the pseudo-simulated cluster probability matrix, and plotting each participant in 3D component space. Modifying the actual t-maps allowed us to consider the effects of different aspects of the data which may underlie the observed cluster shapes on simulated data with similar characteristics/distribution to the original data. In the first simulation, t-maps from each participant were demeaned; this leaves relative differences across brain networks while removing any potential effects of overall activity across the brain. In the second simulation, the spatial order of vertices for each participant were randomized, removing any coherent spatial organization of activity between participants, but the mean was maintained. This examined the effects of mean differences in brain activity between participants when no network structure was commonly present between participants. In the third simulation, t-maps were spatially shuffled and demeaned; this examined the effects of removing spatial relationships across individuals, while maintaining a realistic distribution of t-statistics within individuals. Finally, for the fourth simulation t-maps were demeaned and shuffled, but three simulated networks were added to the data, each independently modulated by creating network weights; ranging from −1 to 1 (for a network ranging from negative to positive), from 0.0012 (1/822; multiplying network by zero would produce unrealistic results) to 1 (for a positive weighted network) and −0.0012 to −1 (for a negative weighted network). Each network had 822 unique weights (1 per individual), which were randomly assigned to participants, randomly across networks. As such, each network was independently modulated across participants (e.g. it was possible to have high positive and low negative network modulation, or both low, both high, or one intermediate and the other high or low, etc.). This pseudo-simulation tested the effects of independent networks which could be more or less engaged across participants, causing both localized differences as well as a distribution of mean activity.

Hemodynamic response related to the first component in Working Memory

Given the bimodal/anti-normal shape of the distribution for component 1 of the clustering probability matrix in working memory, we took 100 participants from each end of the distribution (i.e. the 100 participants with the highest and 100 participants with the lowest component score). The ‘Low’ group were those who showed less positive, more negative activity in the 2Back > 0Back contrast. Time-series regions of interest (ROIs) were extracted from ROIs from the Glasser HCP parcellation (Glasser et al., 2016) from the preprocessed but unsmoothed time-series (dsseries) MRI files. For a selected group of ROIs, we extracted the time-series and created an average of 0Back and 2Back blocks (e.g. the volumes corresponding to the task blocks), including two volumes before task onset and lasting 30 s (the task block duration). Mean time-series were created for each group (averaging participants and task blocks) to visualize group mean hemodynamic changes during 2Back and 0Back N-back performance. Mean time-series were baseline corrected to a baseline mean of zero using the first 5 volumes (2 before and 3 after task onset). No statistical tests were performed on this output; this is a qualitative visualization of the difference in hemodynamic responses between groups who have already been demonstrated to show statistical differences in brain activity.

Code accessibility

Code and processed data is made available via github (https://github.com/colinhawco/HCP_cluster_analysis).

Results

Clustering revealed a gradient of activity across individuals for each task

The aim of this study was to visualize the range of activity across sub-groups of participants rather than identify specific ‘best’ cluster solutions. For the initial cluster solution, results from k=4 are presented in Fig. 1, as a representative visualization of the result. Results from all other values of k are presented in Supplemental Figs. 1-8, as well as being available online (see code and data availability in methods). A similar pattern was observed at other values of k (i.e. a range of activity from most deactivating to most activating). Participants separated along a gradient from predominantly negative activation (or deactivation) towards predominantly positive activation. While the center/intermediate clusters tended to partially resemble the full sample group average, the more ‘deactivating’ and ‘hyper-activating’ clusters (shown on the top and bottom in Fig. 1, respectively) showed distinct patterns from each other and the total sample group maps. Exemplifying this were groups with strong positive and strong negative activation in the Gambling and Relational tasks. These findings demonstrate substantial variations in patterns of brain activity across groups, which were not captured by a standard analysis using the full sample. In order to confirm that these group patterns ranging from deactivation to activation were not specific to hierarchical clustering, clustering was repeated using the K-means approach (k=4), which produced similar patterns of activation across clusters (Supplemental Fig. 9). To explore that the observed variation from positive to negative was not driven by differences in the variance term of the t-statistic, we repeated the analysis using the contrast beta coefficients; results for the Working memory task are shown in Supplemental Fig. 10.

Clustering of participants is not similar across tasks

Across all pairs of tasks at all levels of k, the ARI was very close to zero (all ARIs < 0.03), demonstrating there was no relationship between how participants clustered across tasks.

Clusters show differences in cognitive abilities

In order to demonstrate that clustering was identifying cognitively relevant sub-groups, we performed one-way ANOVAs examining differences across cluster groups using 12 cognitive test scores included within the HCP battery (Fig. 2; the full set of p-values after FDR correction is listed in Supplementary Table 1). The p-values were FDR corrected (648 total tests; FDR corrected threshold was p < 0.0188) across all ANOVAs performed. All tasks showed at least some significant differences in cognitive scores among clusters. In some cases, the p-values for cluster differences were quite small (e.g. p < 1 × 10^{-10}), though effect sizes were small (largest effect size, eta^2 = 0.112).

The Language, Relational and Working Memory tasks showed the most significant differences in cognitive test scores across clusters; these three tasks might be considered the ‘most cognitive’ of the HCP task battery (Gambling taps reward circuits while the Emotional and Social tasks relate to socio-cognitive processing). The greatest differences in performance across clusters for these three tasks were present in the Picture Vocabulary and Reading tests from the NIH toolbox, associated with Crystallized intelligence, and the progressive matrices (PMAT) proposed to approximate a test for overall fluid intelligence (Gray and Thompson, 2004). That is, clustering the task data separates participants along a domain of general measures of crystallized or fluid intelligence, as opposed to more domain specific tests. As an additional check, the ANOVAs were rerun, but cluster labels were randomly reassigned prior to the ANOVA; no ANOVAs were significant following FDR correction when labels were randomized.

As a summary visualization, cluster differences in performance for tasks showing significant cluster differences in PMAT are plotted in Supplemental Fig. 11. While in our previous work the ‘deactivating’ cluster showed the strongest cognitive capabilities (Hawco et al., 2019), here it was observed that the pattern of activity associated with the highest PMAT score varied by task; the most deactivating groups showed the lowest PMAT score in Emotional and Relational, while the least activating clusters in Language and Working Memory showed the lowest
PMAT scores. A similar analysis was done using behavioral scores (e.g., accuracy or reaction time) taken from performance on the fMRI tasks, representing performance more closely related to the tasks themselves (Supplemental Fig. 12). For all tasks except Gambling, group differences were found between clusters in behavioral performance on the fMRI task.

Clusters also show differences in motion

Global signal variance and tSNR were highly correlated in all tasks (Rho < -0.95), and tSNR and mean FD were moderately correlated (Rho < -0.5 for all tasks). Differences were observed across clusters in tSNR and motion (Supplemental Table 2). The effect sizes of motion differences across clusters were small (eta2 < 0.1). When examining tSNR and motion differences across clusters at k=4 (Supplemental Fig. 13), motion was largely overlapping between clusters and higher motion was not related to any specific pattern of brain activity (e.g., most activating or deactivating groups), though the clusters in language and WM showing highest motion also showed the least overall task related activity. When we examined how the spatial pattern of tSNR was related to the spatial pattern of brain activity (Supplemental Fig. 14), median Rho for all tasks was between -0.12 and 0.12, suggesting that the spatial pattern of tSNR generally explained only a small amount of variance in the spatial patterns of task-evoked brain activity. In order to confirm the observed patterns of clustering were not driven by high motion participants, the clustering analysis was repeated using only participants with mean framewise displacement of less than 0.2 mm. Similar patterns were found as in the full sample (i.e. a gradient from predominantly negative activation towards predominantly positive activation; Supplemental Fig. 15).

Resampling stability assessments suggest ‘pseudo-groups’, which fall along a continuum

For each combination of task and k value (e.g., Working Memory task, k=4), the proportion of times that any given pair of participants clustered together whenever they were both present in a given resampling solution was calculated (i.e. showing the probability of any two participants clustering together across bootstraps). This was then organized as an N x N (822 x 822) ‘cluster probability’ matrix (Fig. 3). In the case of highly stable clustering, we would expect a “box-like” pattern within these matrices, whereas if the range of patterns of brain activity were best represented by a pure spectrum, we would expect a wide diagonal blob shape with no bulges. Instead, patterns emerged between these two outcomes; a spectrum across the middle with varying degrees of off-diagonal bulges. This suggests that participants do not fall into distinct sub-groups, or the borders between groups are not easily distinguishable, while the off-diagonal bulges suggest some localized clustering representing sub-groups along the continuum, to varying degrees across tasks.

Component scores of the clustering probability matrices reveal a new manifold space of participant similarity

The cluster probability matrices (Fig. 3) suggest some discrete clustering in cases (e.g. off diagonal bulges in the graph), but there was an apparent dimensional component in all cluster solutions. In order to
Fig. 2. Results of one-way ANOVAs comparing differences between clusters on cognitive test scores. For each fMRI task a one-way ANOVA was run for each cluster solution ($k=2$ to $k=10$; columns) for each cognitive test (rows; test names are shown on both sides for readability). $P$-values from each ANOVA are presented as a colored box. ANOVAs were run for the clustering solutions using hierarchical clustering. Any $p$-values which were not significant (FDR corrected across all tests, $p<0.05$) are shown as white.

Fig. 3. Cluster probability matrices for each task modality, $k=2$ to $k=10$. The matrices are each an $N\times N$ ($N$ being participants, 822 total), showing the percentage of times that any pair of participants clustered together if both were present in the resampling. Each matrix was individually reordered to maximize the sum of the similarity between adjacent participants (MATLAB's optimal leaf order function). If participants formed discrete clusters we would expect to see ‘boxes’ within the matrix.
further explore these results, a principal component analysis (PCA) was performed on each cluster probability matrix to identify underlying patterns observed across tasks, such as in Fig. 4A. A scree plot confirmed the use of the top three components (i.e. an elbow was present between components 3 and 4). The result was plotted and examined for all solutions. The \( k=4 \) data were further analyzed as a representation of all patterns as it maximized the shared variance across the three components (i.e. it maximized the relative contributions of components 2 and 3, and the top three components accounted for 90% or more of the total variance in each task; Fig. 4B).

Component scores were visualized by plotting the location of each participant on a 3D scatterplot based on participants’ scores from the first three components (Fig. 5A; results for all values of \( k \) are shown in Supplemental Fig. 16). Two specific shapes emerged: either a ‘snake’ shape, with two curves (for Gambling, Relational, and Social), or a folded circular shape (a ‘tortilla’ chip’ shape; for Emotional, Language, and Working Memory), in which all participants fall on or near the surface of the ‘tortilla’ shape and most participants fall along the edges. At higher values of \( k \), the scatterplots for the Relational and Social tasks transition from a ‘snake’ to a ‘tortilla’ shape (Supplemental Fig. 16),
suggested that the commonality between the two shapes may suggest a common underlying derivation. While the plots show the multi-dimensional complexity underlying similarity across participants, the ‘snake’ shape suggests that some tasks may fall along a lower-dimensional continuum. In order to further explore this, component scores were plotted color-coded by mean activity during the task, defined as the mean of all t-statistics within the cortex for each participant for the contrast map used in the clustering analysis. Position within both ‘snake’ and ‘tortilla’ shapes were related to mean activity; in ‘snake’ shapes, mean activity related to order along the ‘snake’, while for ‘tortilla’ shapes, participants varied in mean activity in a continuum along the circular edge (Supplemental Fig. 17). The space captured within these 3D plots may represent a manifold of similarity in patterns of brain activity, which underlie individual variability across the sample.

In order to consider whether the use of component scores was an appropriate means of data reduction of the cluster probability matrix, multi-dimensional scaling was applied to the cluster probability matrix to calculate 3 dimensions. These multiscale dimensions correlated with component scores from 0.89 to 0.99, and the ‘snake’ or ‘tortilla’ shapes were recreated (Supplemental Fig. 18), suggesting the ‘snake’ or ‘tortilla’ shapes were not merely a function of using PCA. We also performed a PCA on the Euclidean distance matrix calculated as part of the clustering solution (i.e. without the resampling); this separated clusters but the data fell into a less-differentiated ‘cloud’ shape (Supplemental Fig. 19).

**Patterns of brain activity linked to clustering probability components**

A regression approach identified the spatial pattern of regions related to the cluster probability components (i.e. regions in which participants with a higher component score had greater activity, or vice versa). Results of the group whole brain regression analysis using k=4 for each task are shown in Fig. 5B. For all six task modalities, the first component was mapped onto global activity with the strongest relationships in regions showing positive activity in the whole sample group maps (whole sample group maps are shown in Fig 5C). Components 2 and 3 varied by task and were driven by specific variations in activity in task-relevant networks.

In order to further quantify the regions showing the strongest relationships with component 1 (i.e, determine if specific brain systems had stronger loading onto this component), we extracted the mean t-value for component 1 from six networks from the Yeo 7 network cortical parcellation (Yeo et al., 2011) (default mode, fronto-parietal, dorsal attention, salience/ventral attention, visual, and sensory-motor networks; the ‘limbic’ network was excluded due to poor signal quality in those regions), for the whole brain regression analysis of principal component 1 of the cluster probability matrix (as shown in Fig. 6). The dorsal attention network showed the largest effect sizes in the regression of brain activity with component 1 for the Emotional, Gambling, Relational, and Social tasks. In contrast, the salience network in Language and fronto-parietal network in Working Memory had the highest mean t-values, although the dorsal attention network was still prominent. The default mode network had the lowest t-values across all six tasks. This shows that while component 1 reflects a pattern of global brain activity, it is nevertheless weighted towards the ‘task-positive’ networks (Cole and Schneider, 2007; Fox et al., 2005).

**Cognition is linked to clustering probability components**

We performed Spearman’s correlations between the three components and out-of-scanner cognitive scores (Fig. 7). No significant correlations were observed in the Social task, but were present for the other five tasks. The significant correlations between out-of-scanner tests and components 1-3 varied by fMRI task. The first component had the highest correlation with cognitive tests for the Emotional, Gambling, and Relational tasks, while the highest correlations were observed in component 3 for Language and component 2 for Working Memory. We additionally

**Fig. 6.** Network loadings of the regression analysis of component 1 on task activity. The left panel shows the regression t-statistics for each task thresholded at t>10 to better show regions with the most significant relationships. Outlines on the brain surfaces represent the six networks from the Yeo 7 network cortical parcellation (Yeo et al., 2011). The radar plots (right) show the relative contribution of each of the six networks, expressed as the average t-statistics within all vertices across that network (higher values on the outside). Mean t-stats were demeaned across networks to emphasize relative differences (Vis=Visual, SM=sensory-motor, SN=salience/ventral attention, DA=dorsal attention, FPN=fronto-parietal network, DMN=default mode network, L=left, R=right).
examined correlations with in-scanner performance on the fMRI tasks and the task components (Supplemental Fig. 20). There was a general tendency for the strongest correlations between components and performance from the same task, particularly for the Emotional, Language, Relational, and Working Memory tasks. Several correlations were also present across tasks (e.g. Relational component 1 had correlations with Working Memory task performance), which may be explained by correlations across in-scanner task performance or common activity of task positive networks captured by the first component.

**Pseudo-simulations demonstrate the factors underlying the component score plots**

In order to demonstrate that the shape of the component plots were not driven by random noise, a pseudo-simulation approach was used, modifying the input data (t-maps for each participant), and reperforming the resampling approach and component plots (Fig. 8). First, to consider the effects of global activity on the cluster probability matrices, t-maps for each participant were demeaned, preserving network structure but removing the global component. This resulted in ‘tortilla’ shapes. Second, we randomly shuffled the spatial organization of the t-maps from each participant, removing any cohesive spatial patterns or network structure, while maintaining the mean activity per participant. This transformed ‘tortilla’ shapes into ‘snake’ shapes; these results are consistent with the finding above that the ‘snake’ pattern was associated with differences in mean brain activity. When t-maps were both demeaned and spatially shuffled, the plots collapsed into single points with a small number of random outliers, showing neither a ‘snake’ nor ‘tortilla’ shape emerge from randomized inputs. Finally, the t-maps were randomly shuffled and demeaned, but three simulated ‘networks’ were added, each consisting of approximately 10% of random vertices. Each network was set to a random range of values per participant (i.e. each network could be weakly or strongly ‘activated’ independent of others); one was set to positive, one negative, and the third ranged from negative to positive. Resampling the simulated networks produced ‘tortilla’ shapes, suggesting that the observed ‘tortilla’ patterns arise when multiple brain systems are modulated in a relatively independent way.

**The first component in the working memory task does not relate to an abnormal hemodynamic response function (HRF)**

Given the global nature of component 1, one possible driving factor is abnormal hemodynamic coupling or a poor fit between the HRF models and individual HRFs. We therefore examined the hemodynamic response function in the Working Memory task. Given the bimodal/antinormal shape of the histogram for component 1, we took the 100 participants with the highest and 100 participants with the lowest component 1 score. The ‘low’ group were those who showed less positive/more negative activity in the 2Back > 0Back contrast. Mean time-series were created for each group (averaging participants and task blocks) to visualize group mean hemodynamic changes during 2Back and 0Back blocks (Fig. 9). The morphology of the hemodynamic response was similar between groups. Consistent with the finding of less task-evoked activity in the 2Back > 0Back contrast, the low group showed a reduced response to 2Back and an increased response to 0Back. This suggests that differences in the activity pattern across component 1 represents differences in task-evoked activity, as opposed to abnormal hemodynamic responses.

**Discussion**

Standard task fMRI analyses rely on group means to uncover patterns of task-induced neural activity. Our findings show that there is no single ‘group-based’ pattern of activity. The initial clustering solutions found sub-groups of participants along an apparent continuum from ‘de-activators’ to ‘strong/hyper activators’, emphasizing that whole-sample group analyses fail to capture the full range of task-evoked activity (Miller et al., 2012; Poldrack, 2006). Characterizing the range of variability across participants may lead to a more complete understanding of cognitive processing in the brain. However, it is a truism that clustering approaches will produce clusters; we therefore further examined the data to understand if these clusters in fact represented a continuum. The resampling approach allowed a closer examination of the consistency and reliability of the clustering results, while extracting the first three components provided a new approach to quantify the range of variability across individuals. The resultant ‘tortilla’ and ‘snake’ plots represent a lower-dimensional participant similarity space, not only characterizing the range of observed activity but also providing information on the patterns of activity driving this variability. Based on the simulations, the ‘snake’ shape implies a more singular system varying along a continuum, while the ‘tortilla’ shape implies multiple systems which can vary independently. Importantly, both the initial clustering solutions and cluster probability components related to out-of-scanner cognitive performance, demonstrating the behavioral relevance of these components.

Plotting participants in component space quantified the variability in brain activity across fMRI tasks. While some of the patterns of variability were explained by the positive to negative axis, other important dimensions of variability were also observed, embodied in the ‘tortilla’ and ‘snake’ shapes in the 3D plots of the components; individual variability was represented within a lower multi-dimensional space. This new space might be thought of as a lower-dimensional participant similarity space. While we made use of clustering to define this new lower-dimensional space, the results of this analysis are more in keeping with viewing pat-
terns of activity along continua. The cluster resampling approach can be considered an unsupervised feature selection step; across resamples participants are clustered according to the most salient features within the data (patterns of brain activity) which define differences and similarities across individuals. It is notable that all tasks fell along one of two spaces: an S-shaped ‘snake’ shape, in which the majority of participants fell along the line with greatest divergence at the curves; and a folded circle ‘tortilla’ shape, in which the majority of participants fell along the circle edge and most/all participants were on the ‘surface’. Simulations demonstrated that the ‘snake’ pattern was related to some variance of mean activity, driven by specific task relevant networks, while the ‘tortilla’ shape appears to be a result of multiple systems which can independently vary. The specific shapes of ‘snake’ or ‘tortilla’ may be related to the fact that we are plotting 3 orthogonal components; similar to when fitting a regression with multiple components the shape is constrained to have a number of curves equal to one less than the number of components. So while it may not be particularly important that the ‘snake’ shape shows 2 curves, the fact that a given task falls along a ‘snake’ or ‘tortilla’ shape is informative. It is also worth noting that this method may be biased toward detecting wide-spread sources of variability, missing more localized or discrete regions which vary across participants. This new participant similarity space represents a manifold demonstrating the range of patterns of activity during a cognitive task, which may have important behavioral or clinical implications for mapping brain-behavior relationships.

Consistent with the initial cluster solution, we found relatively global patterns of activity related to component 1, suggesting a positive to negative ‘axis’ of activity across participants. Prior work focused on task connectivity has suggested an increase in global integration during task performance (Cohen and D’Esposito, 2016; Shine et al., 2016) which may in part explain why such a wide range of brain regions were related to component 1. While variability across fMRI task activity patterns have been highlighted by previous studies (Miller et al., 2012; Miller et al., 2009), to our knowledge this pattern of activity ranging from positive to negative across participants has only been suggested in our previous single-task study (Hawco et al., 2019). At a network level, the first component consistently had high loading on the dorsal attention network, which is related to task-oriented top down attentional processing (Corbetta et al., 2008; Corbetta and Shulman, 2002), and serves a more domain-general rather than task-specific role in cognitive processing (Cole and Schneider, 2007; Fedorenko et al., 2013; Nagahvi and Nyberg, 2005; Ptak et al., 2017). Although this could indicate that clustering is driven by attention, reductions or variance in attention would be expected to have behavioral consequences in task performance, and the first component was not strongly related to in-scanner task performance in most cases (Supplemental Fig. 16). This argues against attention as the primary factor underlying the first component, although attention likely represents some of the observed variance.

We favor a behavioral explanation as the primary driver of cross-task variability: the pattern observed in a given participant is strongly influenced by the specific cognitive process or strategy they are using during the task. Previous work has shown how different cognitive strategies can modulate brain activity (Guimond et al., 2017; Hawco et al., 2013; Kirchhoff and Buckner, 2006; Kirchhoff et al., 2014; Miller et al., 2013; 2002; 2019)

Fig. 9. Mean hemodynamic responses to 2Back and 0Back blocks in the Working Memory task for two groups of 100 participants with the highest or lowest scores for the first component of the PCA of the cluster resampling matrix for Working Memory (k=4). The ‘low’ group are those with less positive activity in their individual activation maps. ROIs were selected from the Glasser atlas based on the group regression map (left panel).

Fig. 8. Pseudo-simulations examining the underlying structure of the component space. Cluster resampling was rerun on the originally input t-map matrices after transforms were applied. First, participant t-maps were demeaned prior to clustering, producing ‘tortilla’ shapes (top), then t-maps for each participant was shuffled into a random order but the mean was preserved, creating ‘snakes’ (second row). Data was then both shuffled and demeaned, creating essentially random input, resulting in no shapes (third row). Lastly, data was shuffled and demeaned, and three independent simulated networks were introduced; one positive, one negative, and one ranging from positive to negative, recreating the ‘tortilla’ pattern.
and that training participants to make use of alternate strategies can change observed patterns of activity (Dresler et al., 2017; Guimond et al., 2018). This was supported by the lack of overlap we found between clustering solutions across tasks. Cognitive tasks can be performed via different operational cognitive procedures (cognitive strategies), which can modify brain activity (Kirchhoff and Buckner, 2006; Kirchhoff et al., 2014; Savage et al., 2001). For example, one strategy during the N-Back might be first updating the memory set to include the current and past two items and then matching the first and last items in the set, while an alternative strategy might recall the previous two items as part of an encoded set, then matching the current item and updating the memory set. Participants with fewer cognitive resources might instead utilize a less cognitively intensive approach to matching (if an item feels familiar/recent mark it as a match) (Morrison et al., 2016), which may not require specifically maintaining and updating the memory set. Presumably this latter strategy would be less efficient in terms of accuracy, but is a viable approach that would make use of alternate brain systems. We hypothesize that this strategy would produce less activity regions associated with working memory (e.g. the fronto-parietal network) and poor task performance, such as was seen in the non-activating Working Memory subgroup. However, caution is required when making inferences on the underlying cognitive strategy based on group maps (Poldrack, 2006). Varying cognitive strategies could also explain why component scores were not correlated across tasks: specific cognitive approaches may not transfer across tasks (Morrison et al., 2016). Effort may also play a role in behavioral variability, related to the importance of the dorsal attention network in the first component.

An alternative explanation for the observed clustering is grounded in the underlying biology of participants; the pattern of activity across tasks is mainly related to the functional strength of those brain systems within those participants. Information flow across regions during task performance has been shown to follow underlying resting state network architecture (Cole et al., 2016) which is stable across cognitive tasks (Gratton et al., 2018) and resting state networks have been used to predict patterns of task induced activity (Kannarpatti et al., 2012; Tavor et al., 2016). This would suggest that the underlying network function plays a role in task activity, which in turn might indicate that participants with similar network structure might show similar activity patterns across tasks. While we did not find common clustering across tasks, network function likely plays a role in task activation patterns and could explain some of the individual variability seen in patterns of task activity. For example, Gratton et al. (2018) examined repeated tasks within a small highly sampled set of individuals and found that group network architecture and inter-subject variability explained important variance in network connectivity. A task by individual interaction explained some variance in connectivity profiles, while task alone explained little variance (Gratton et al., 2018). This suggests that the manner in which participants individually modulated their functional networks during tasks was more relevant than the task itself. The individual variability is more likely to represent a trait effect, while the individual-by-task variability is more likely to reflect individualized state changes related to task demands. This highlights the importance of both the underlying network structure (a biological factor) and individually specific patterns (potentially related to different cognitive task approaches) in task connectivity.

Our current approach, and task analyses in general, do not consider changing neural dynamics during task performance (Cohen and D’Esposito, 2016; Shine et al., 2016; Shine and Poldrack, 2018). Our analysis reveals variation in brain activity among individuals, but does not account for variability across trials within an individual. Thus, variation in brain activity may reflect the portion of time occupying different and fluctuating brain states during the course of a task (Shine et al., 2016). Future work may incorporate more dynamic information to better understand how fluctuating neural states may relate to individual patterns of activity across the whole task. Different analytical frame-works may also provide complimentary information. For example, one approach to validating clustering is to perform the analysis on a portion of the data, and measuring how well these patterns generalize to a held-out sample using a predictive modelling approach (Viviano et al., 2018). There are also considerations around cognitive tasks such as those employed as part of the HCP protocol. These tasks were designed as ‘localizer’ tasks (Barch et al., 2013) of short duration. There are questions over the reliability of voxel/vertex wise patterns of task-evoked activity (Elliott et al., 2020), and cognitive tasks do not always map well onto ‘real world’ behaviors (Elliott et al., 2020). It would be interesting to extend these results into more naturalistic and longer duration paradigms. Motion and tSNR also played a role in clustering. While the effect sizes were small (which was also true for the relationship with cognition), it is well established that motion can impact fMRI signal. The role of tSNR is less well understood; this work suggests that at least some variance in the spatial pattern at the individual level can be related to local signal characteristics. In addition to considering mean FD as a covariate in group analysis or when examining differences between groups, tSNR may be an also be a relevant variable of interest. However, as the effect sizes were generally quite small, these signal characteristics do not appear to play a driving role in differences across clusters.

These findings highlight the importance of individual variability when considering patterns of task-related brain activity related to cognitive processes. While group maps may be informative, they fail to capture the range of variability present across the population. While our results do not support the existence of highly discrete cognitive subgroups, the use of clustering approaches was beneficial to identify patterns of variability which do not emerge from more traditional analysis approaches. Individuals along the more extreme ends of the spectrum in terms of brain activity are still performing the cognitive functions being measured in a given fMRI task, though their individual brain pattern may diverge very substantially from the average map. Understanding the range of this variability can help us better understand the complex neurobiology underlying cognitive processing, with implications for both understanding cognitive systems as well as for clinical research comparing activity across groups.

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Code Accessibility

Code and processed data is made available via github (https://github.com/colinhawco/HCP_cluster_analysis). All data was provided by the publically available human Connectome Project.

Author Credit Taxonomy

CH gathered data, performed primary analysis, and drafted manuscript. ED provided methodological advice and support as well as conceptual contributions and guidance on using the HCP dataset and tools. JD and AV provided mentorship and scientific advice. GJ reviewed data. All authors discussed results and reviewed and contributed to the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117823.
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