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# Individualized Functional Brain System Topologies and Major Depression: Relationships Among Patch Sizes and Clinical Profiles and Behavior

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## ABSTRACT

**BACKGROUND:** Neuroimaging studies of major depression have typically been conducted using group-level approaches. However, given interindividual differences in brain systems, there is a need for individualized approaches to brain systems mapping and putative links toward diagnosis, symptoms, and behavior.

**METHODS:** We used an iterative parcellation approach to map individualized brain systems in 328 participants from a multisite, placebo-controlled clinical trial. We hypothesized that participants with depression would show abnormalities in salience, control, default, and affective systems, which would be associated with higher levels of self-reported anhedonia, anxious arousal, and worse cognitive performance. Within hypothesized brain systems, we compared patch sizes (number of vertices) between depressed and healthy control groups. Within depressed groups, abnormal patches were correlated with hypothesized clinical and behavioral measures.

**RESULTS:** Significant group differences emerged in hypothesized patches of 1) the lateral salience system (parietal operculum; $t_{326} = -3.11$, $p = .002$) and 2) the control system (left medial posterior prefrontal cortex region; $z = -3.63$, $p < .001$), with significantly smaller patches in these regions in participants with depression than in healthy control participants. Results suggest that participants with depression with significantly smaller patch sizes in the lateral salience system and control system regions experience greater anxious arousal and cognitive deficits.

**CONCLUSIONS:** The findings imply that neural features mapped at the individual level may relate meaningfully to diagnosis, symptoms, and behavior. There is strong clinical relevance in taking an individualized brain systems approach to mapping neural functional connectivity because these associated region patch sizes may help advance our understanding of neural features linked to psychopathology and foster future patient-specific clinical decision making.

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Major depressive disorder (MDD) is a debilitating mental health condition that affects millions of individuals globally and is associated with staggering costs (1,2). Despite frameworks prioritizing a push toward system-based and individualized approaches (3–6) to better address the heterogeneity of depression, there remains persistent difficulty in developing personalized treatments (7–9). Relatively few patients with depression reach remission (7–9) and many will experience relapse (10,11).

Given these substantial challenges, there is an urgent need for improved biological models of mental illness that build upon brain mapping approaches that may be able to identify underlying mechanistic processes of psychopathology (12). Spatially distributed and discrete neural regions that display highly correlated activity are referred to as brain systems, or networks, and this correlated activity is thought to reflect neural relationships within the brain (6,13–15). A variety of computational approaches have identified several relevant brain systems at an aggregated group level (16), including the affective, default, frontoparietal, and salience systems, which have been implicated in MDD (17–20). It has been proposed that abnormalities in these systems underlie psychological and behavioral features of psychopathology in MDD (17–20).

However, conclusions drawn from group-level brain system mapping may incorrectly assume that group-level neural functioning can be generalized directly to individuals. Consistent with this conundrum, a recent meta-analysis of 92 group-level neuroimaging studies of depression reported little convergence in findings (21), possibly due to imprecision of group-level quantifications for systems of interest, variability from intersystem blurring/nontarget systems for seed-based analyses, or the selected independent components. Small sample sizes are particularly susceptible to these issues, including biomarker prediction studies (22–28) that have

 

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typically included fewer than 30 participants (28,29). Given the heterogeneity of individual brain systems, taking a more person-specific approach is critical for improving the use of neuroscientific tools to aid clinical intervention (3).

Therefore, we aimed to apply an individualized brain systems functional brain mapping approach to better account for heterogeneity in neural architecture at the individual level. This approach was based on a previously described iterative optimization method (3–5,30). We aimed to develop a nuanced neuroscientific understanding of depression by identifying connections between person-specific neural functioning and symptom profiles. Such individualized approaches are rapidly gaining traction, with many studies having identified findings that are not observable using group-level approaches (4,5,30). Furthermore, individualized system patches (i.e., sets of proximal cortical vertices that belong to the same brain system) reflect person-specific functional organization and thus do not have a direct equivalent measure in group-level approaches (wherein brain system patches are assumed to be the same across individuals) (16). Here, patches refer to nodes or distinct regions of the brain that exhibit functional homogeneity and highly correlated activity (6,13,14). Patch sizes have substantial biological relevance given that the amount of brain devoted to a given function predicts functional importance or capability (31). For example, larger hippocampi predict memory performance (32), the size of functionally defined visual regions predicts reading skills (33), and auditory association cortex predicts musical ability (34). Additionally, prior studies have provided evidence that patch sizes are related to behavior and mentation. For example, Kong *et al.* recently found that patch sizes were related to behavior (e.g., reading pronunciation and delay discounting) and personality measures (the NEO Personality Inventory) (31).

Preliminary studies (17–19) using aspects of this approach have found that individualized brain systems–based functional connectivity—and notably, not traditional group-level functional connectivity—was linked to dimensional and categorical features of psychosis (30), memory impairments, and electroconvulsive therapy outcomes in individuals with severe depression (35) and dissociative symptoms in trauma-related disorders alongside individual patch size associations (36). Moreover, prior research that has used patch sizes and functional connectivity in conjunction has led to better prediction of measures of interest (e.g., behavioral tasks that probe learning or memory) than connectivity or region size alone, which suggests that patch size may supply unique information (4). Similarly, purported links between neural features and self-report and behavior that have emerged from individualized functional connectivity analyses have outperformed traditional group-level connectivity approaches (35). Collectively, these findings indicate that the relative presence and size of person-specific functional brain regions (individualized brain systems) may provide novel insights into a person-centric brain-based understanding of a highly heterogeneous disorder such as MDD. More importantly, these differences in patch sizes can only be identified using individualized approaches because there is no group equivalent given that group-based approaches use a standardized template atlas for all participants. By definition, this involves prescribing standard patch locations and sizes across participants, thus making it impossible to compare any nuanced differences in the same.

Therefore, we applied a recently developed iterative brain mapping procedure (3) coupled with a patch matching method to understand relationships among individualized patch sizes and diagnosis of MDD, symptom expression, and behavioral measures of inhibitory control by testing 1) for differences in individualized neural patch size between individuals with depression and healthy individuals; 2) putative relationships between path topology and symptom and behavior profiles; 3) geometric features of identified abnormal neural topologies; and finally, 4) quantitative decoding of identified neural regions using NeuroSynth (4,37) for additional interpretive leverage. We tested this approach in regions of interest (ROIs) implicated in MDD (17–20,38) that are core nodes of brain systems, hypothesizing that abnormal patch sizes would be present in the salience (insular and dorsomedial prefrontal cortical and amygdalar regions), control (lateral prefrontal and parietal cortical and hippocampal regions), default (medial prefrontal and parietal cortex), and affective (ventromedial, lateral cortical and striatal regions) areas (17–19,38) and subsequent relationships among identified abnormal specific brain systems regions and processes associated with those systems: anxious arousal (salience) (39), self-reported anhedonia (affective) (40), and cognitive deficits (control) (41), and overall depressive symptoms.

## METHODS AND MATERIALS

### Participants

From a total of 336 participants, we included 328 participants (66% female, 34% male) ages 18 to 65 years who had completed magnetic resonance imaging (MRI) scans and met criteria for MDD ($n$ = 288) or healthy control participants ($n$ = 40) (for further information on participant demographics, see Participant Information in the Supplement). All participants with MDD in the study were unmedicated at baseline.

### Behavioral and Symptom Measures

The Quick Inventory of Depressive Symptomatology-Self Report, Hamilton Depression Rating Scale, Snaith-Hamilton Pleasure Scale, and Mood and Anxiety Symptom Questionnaire were used to assess various symptom dimensions (e.g., anxious arousal, anhedonia, general distress, depression severity), whereas the probabilistic reward task, flanker task, and A-not-B task were used to assess reward learning, response conflict, and working memory, respectively (see Supplemental Methods; for information on data included, see Table S1).

### MRI Acquisition and Preprocessing

MRI acquisition and preprocessing were completed using common approaches (for details, see MRI Acquisition and Preprocessing in the Supplement; for information on data included, see Table S2).

### Procedures

The current study included preexisting multisite clinical trial data from the EMBARC (establishing moderators and

biosignatures of antidepressant response in clinical care) study (42). Detailed information regarding EMBARC has been published previously (42).

**Individualized Brain Systems.** An iterative parcellation approach was used (3) to map individualized brain systems. Briefly, functional mapping was initialized using a group-level functional system atlas [Yeo *et al*. (16)], which was then systematically and repeatedly adjusted by incorporating interindividual variability and signal-to-noise ratio distributions per participant to arrive at idiosyncratic person-specific brain maps (4). With each iteration, the influence from group-level information was lessened until the final system map quantitively converged on individualized neural systems mapping (3). For additional information, see Mapping Cortical Individualized Brain Systems in the Supplement. These individually derived cortical brain systems were then separated into patches using a computational neuroimaging algorithmic approach that matched patches to 116 cortical parcellated regions previously labeled in an atlas (4). That is, patches were labeled with converging regions based on overlapping vertices (≥20) and nearest-neighbors approaches based on geodesic distance of neural surfaces. If a patch overlapped with more than one ROI present within the network, then the patch was divided into multiple smaller ROIs. This patch matching and labeling approach enabled group-level analysis of individualized patches. For additional details about this approach, see Li *et al.* (4).

## Statistical Approach

**Patch Size and Diagnosis.** Patch sizes (i.e., number of vertices) within hypothesized brain systems were compared between MDD and healthy control groups. All patches were regressed against variables of noninterest including site, age, and sex, and resulting residuals were subsequently analyzed. This was primarily done to control for effects of these nuisance variables. If significant differences were identified between groups in motion (framewise displacement [FD] or percent signal change across frames), then these measures were also regressed on patch size to account for possible unintended effects of motion. In this case, all patches were regressed against FD. Prior to testing for group differences, normality of distribution was assessed for residualized data. To test for group differences in patch sizes, *t* tests were performed on normally distributed patches (e.g., parietal operculum), and Wilcoxon tests were performed for nonnormally distributed patches (e.g., left medial posterior prefrontal cortex). False discovery rate (FDR) correction was used to account for multiple comparisons within each hypothesized brain system; for example, if a brain system had 5 ROIs, then significant findings within this system were corrected across the 5 *p* values from ROIs within the system (see Figure 1 for an overview of ROIs in brain systems). We focused on systems implicated in MDD: affective, default, frontoparietal, and salience (17–20,38). Several of these may be involved in the symptoms and

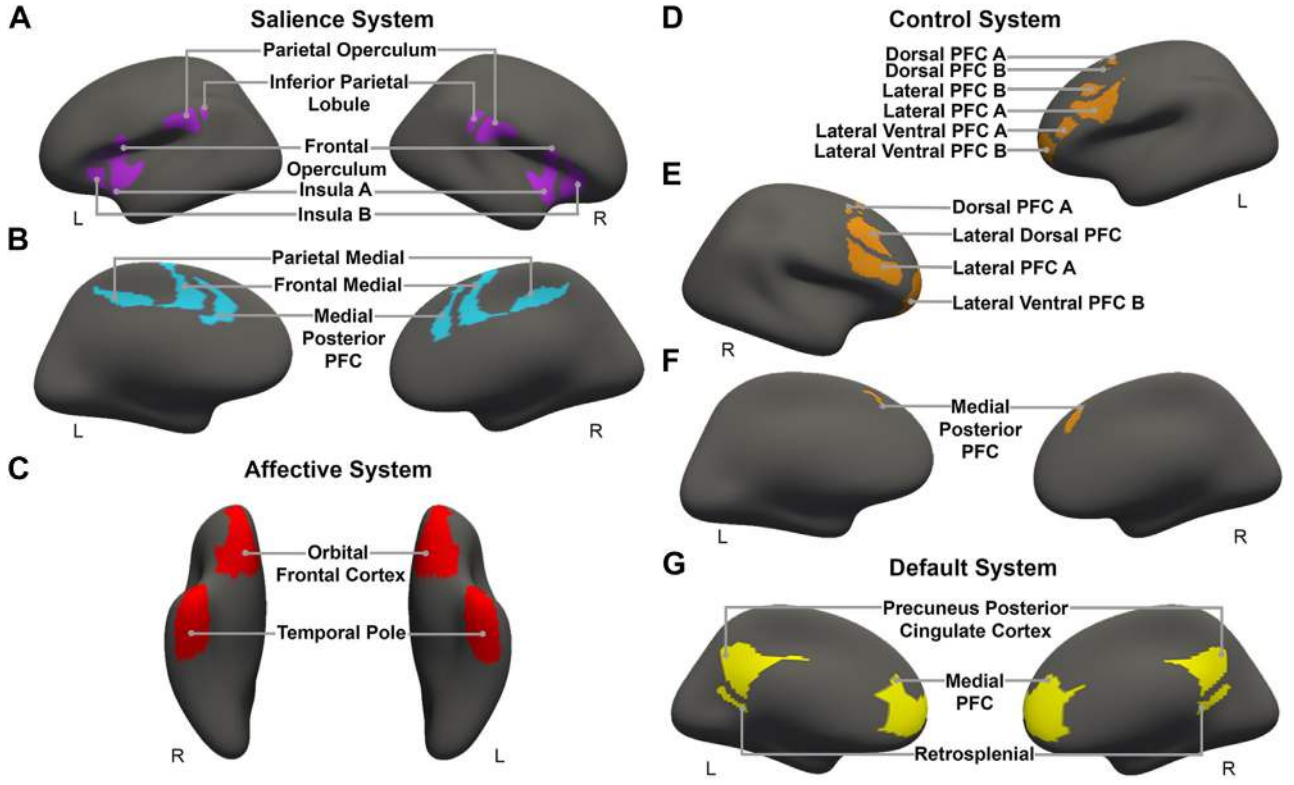


**Figure 1.** Regions of interest within each brain system: **(A)** lateral salience system; **(B)** medial salience system; **(C)** affective system; **(D–F)** control system [**(D)** left control system, **(E)** right control system, **(F)** medial control system]; and **(G)** default system. Brain regions are color-coded based on each set of false discovery rate–corrected analyses. L, left hemisphere; PFC, prefrontal cortex; R, right hemisphere.

behavior assessed here: anxiety [salience (39)], anhedonia [affective (40)], and cognitive deficits [frontoparietal (41)].

**Patch Size and Symptoms and Behavior.** Next, we further analyzed patch size significantly differing between the MDD and healthy control groups. Within the MDD group, identified patch size residuals were correlated with hypothesized clinical and behavioral measures to determine relationships among patch size and symptoms and behavior. Prior testing for group differences, normality of distribution was assessed for relevant residualized patch size data as well as behavioral variables. Pearson correlations were used if both variables were normally distributed, and Spearman correlations were used if either or both of the variables tested had a nonnormal distribution. For each brain system region that exhibited group differences, targeted analyses were conducted without correction (see Figure 1). Multiple comparison correction of statistical tests was only applied within behavioral variables that tested the same domain. In this case, multiple comparison correction was only applied to flanker and A-not-B scores.

**Coordinate Analysis.** If a patch displayed significant differences in size between MDD and healthy control groups, we further tested for differences in its center of mass coordinates following the same steps outlined above for patch sizes. That is, the coordinates were correlated against clinical and behavioral measures using the same steps outlined above for symptoms and behavior, with FDR correction applied.

**NeuroSynth.** We used the meta-analytic decoding feature of NeuroSynth (37) to identify key terms associated with patches related to MDD. NeuroSynth is a large repository of neural activation coordinates, associated key terms across prior neuroimaging findings, and meta-analytic framework (>14,000 studies, >1300 terms). NeuroSynth enabled a data-driven interpretation of brain regions rather than relying on reverse inference (43).

## RESULTS

### Movement

There was a significant difference in FD between participants with MDD ($n = 288$) and healthy control participants ($n = 40$) ($z = 3.097$, $p = .002$). Percent signal change between volumes was not significantly different in both groups ($z = 1.376$, $p = .169$). As a result, all patches were regressed against an FD-weighted average (along with other variables of noninterest) before further analyses were conducted.

### Relationships Between Patch Size and Diagnosis

Following FDR correction, significant differences between participants with depression and healthy control participants emerged in the parietal operculum region of the lateral salience system ($t_{326} = -3.11$, $p = .002$) and the left hemisphere medial posterior prefrontal cortex region from the control system ($z = -3.63$, $p < .001$) (Figures 1 and 2). For both regions, average patch sizes for participants with depression were smaller than that of control participants (Figure 2; Table 1). To strengthen our findings and control for the putative influence of different surface areas potentially occupied by a given vertex, we also ran an exploratory analysis to test for differences in surface areas between the parietal operculum and left medial posterior prefrontal cortex region. We found that our results remained unchanged and that both regions showed significantly smaller surface areas in participants with MDD than in healthy control participants (see Table S6). This underscores our confidence in the patch size methodology and our results. There were no other significant group differences in patch size of other lateral salience or control system patches. Similarly, we found no significant differences in patch sizes within the hypothesized medial salience, default, and affective systems. All results from patch size analyses between the depressed and control groups are summarized in Table 1.

### Relationships Among Patch Size and Symptoms and Behavior in the MDD Sample

Larger MDD parietal operculum patch sizes were significantly correlated with lower anxious arousal ($r = -0.13$, $p = .030$) and lower reward learning ($r = -0.14$, $p = .025$), as assessed with the Mood and Anxiety Symptom Questionnaire and the probabilistic reward task, respectively (Figure 3). The parietal operculum was not significantly correlated with any other hypothesized clinical/behavioral measure (all $|r|$s $\leq 0.12$, all $p$s $\geq .066$).

Larger left hemisphere medial posterior prefrontal cortex patch sizes within participants with MDD were significantly correlated with lower performance on a task probing working memory and reasoning (A-not-B task total correct responses $r = -0.16$, $p = .008$) and higher flanker interference effects on accuracy ($r = 0.12$, $p = .048$) (Figure 3). However, the flanker interference effects on accuracy did not survive FDR correction. This region was not significantly correlated with any other hypothesized clinical/behavioral measures (all $|r|$s $\leq 0.12$, all $p$s $\geq .064$).

Secondary correlations between MDD patch sizes and nonprimary variables of interest (e.g., additional flanker results for on-time trials and Gratton) were consistent with the primary correlational findings, see Figure S1.

### Patch Size Geometry: Coordinate Analysis

Coordinate analyses following FDR correction showed that the right hemisphere y coordinate of the parietal operculum was located more anteriorly in participants with depression than in healthy control participants ($z = 2.71$, $p = .007$). No other coordinates of the right or left parietal operculum showed significant group differences. Additionally, no coordinates of the left hemisphere medial posterior prefrontal cortex differed significantly between groups.

The right hemisphere y coordinate of the parietal operculum was significantly correlated with Mood and Anxiety Symptom Questionnaire general distress ($r = 0.15$, $p = .009$). No other clinical or behavioral measure correlations emerged (all $|r|$s $\leq 0.11$, $p$s $\geq .071$).

### NeuroSynth

As illustrated in Table S3, results indicated that the parietal operculum region of the lateral salience system was positively

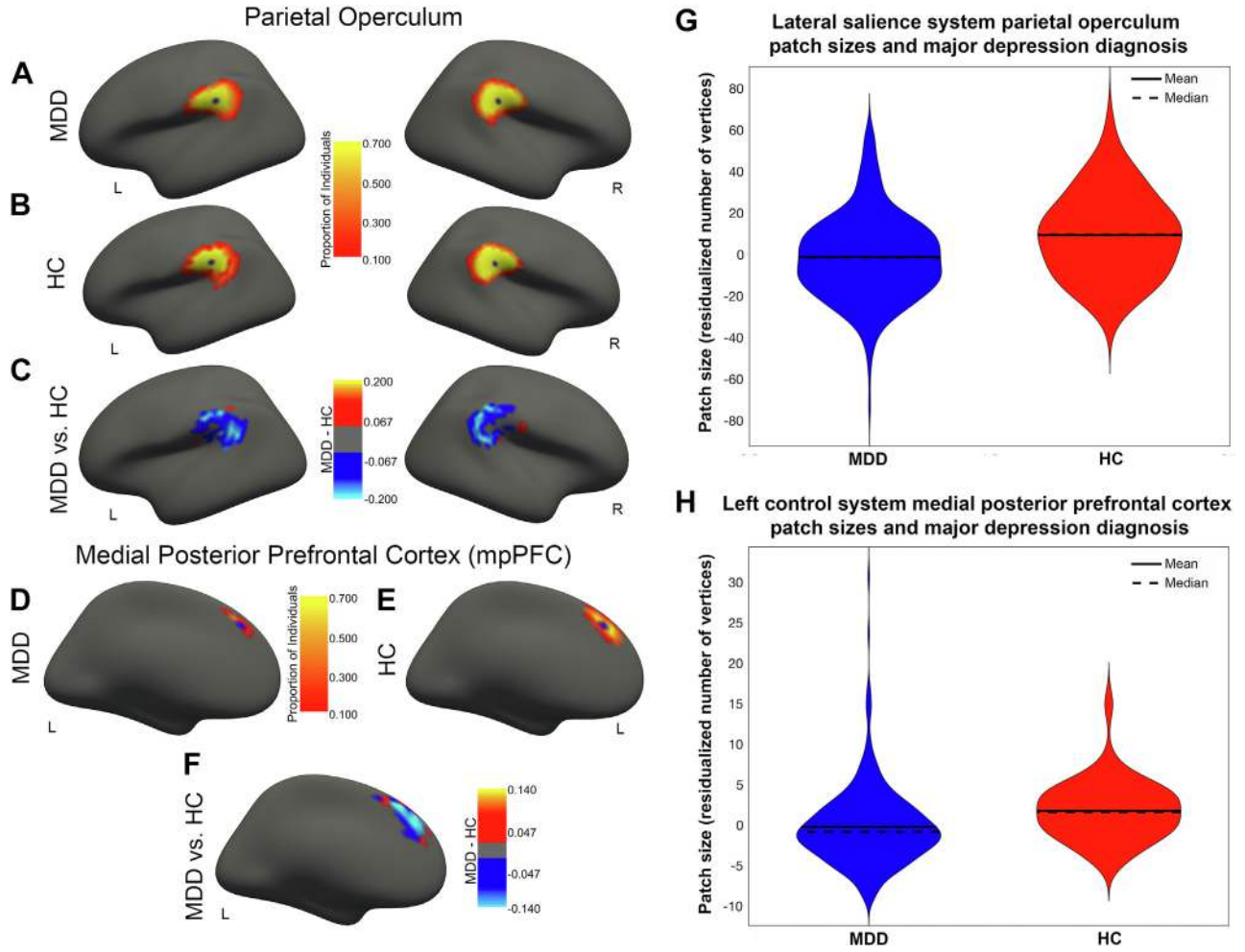


**Figure 2.** Individualized brain systems patch size differences between major depressive disorder (MDD) and healthy control participant (HC) groups. (Upper) Regions exhibiting group differences included the parietal operculum region of the lateral salience system [**(A)** MDD; **(B)** HC; **(C)** difference between MDD and HC groups] and the left hemisphere (L) medial posterior prefrontal cortex region of the control system [**(D)** MDD; **(E)** HC; **(F)** difference between MDD and HC groups]. **(G)** Patch sizes of the parietal operculum for participants with MDD and HCs. **(H)** Patch sizes of the medial posterior prefrontal cortex for participants with MDD and HCs. R, right hemisphere.

correlated with meta-analytic terms spanning somatic/somatosensory domains (e.g., somatosensory, pain, touch) and negatively correlated with terms related to memory (e.g., autobiographical, memory, episodic). Conversely, the left hemisphere medial posterior prefrontal cortex of the control system was related to meta-analytic terms that spanned cognitive domains including reasoning and decision making (e.g., reasoning, judgment, retention).

## DISCUSSION

By applying recently developed computational neuroimaging approaches to map neural functional patches that are individualized to each participant, we were able to link individualized neural architecture to diagnostic, symptom, and behavioral profiles. Analyzing abnormal patch sizes in clinical populations is a unique advantage that is only afforded by individualized approaches. In fact, there is no equivalent group-level approach because group-based approaches use a standardized template atlas for all participants, which involves fitting standardized patch locations and sizes across participants. Therefore, our findings highlight the promise of this approach and provide a foundation for continued implementation of individualized methods to relate neural activity to features of mental illness given their relationship to correlated functional activity (6,13,14). This includes symptoms, behavior, and general functioning for the individual beyond an aggregate group-level brain map.

It is well known that the amount of brain that is devoted to a given function predicts functional importance or capability (31). For example, larger hippocampi predict memory performance (32), the size of functionally defined visual regions predicts reading skills (34), and auditory association cortex predicts musical ability (34). More recent studies have provided additional evidence that patch sizes reflect the boundaries of functional units of the brain. While existing studies are informative, additional research is required to fully understand the

**Table 1. Individualized Brain System Patch Sizes by Group: Descriptive Summary of Group Patch Sizes Across Neural Regions for MDD and HC Groups**

| | MDD | | HC | | | |
|---|---|---|---|---|---|---|
| Region | Mean/Median | SD/IQR | Mean/Median | SD/IQR | *p* Value | Test Statistic |
| Lateral Salience System | | | | | | |
| Insula A[a] | −0.498 | 18.406 | 0.025 | 16.087 | .827 | 0.218 |
| Insula B[a] | −0.368 | 18.157 | 0.664 | 14.104 | .465 | −0.730 |
| Frontal operculum[a] | −1.355 | 15.855 | −0.652 | 13.561 | .642 | 0.465 |
| Parietal operculum[b] | −1.284 | 20.170 | 9.246 | 19.494 | .002[c] | −3.106 |
| Inferior parietal lobule[a] | −0.415 | 11.591 | −0.946 | 11.770 | .656 | −0.446 |
| Medial Salience System | | | | | | |
| Medial posterior prefrontal cortex[a] | −1.313 | 21.911 | −1.524 | 13.966 | .426 | 0.796 |
| Frontal medial[a] | −0.627 | 18.820 | 2.206 | 15.248 | .342 | −0.949 |
| Parietal medial[b] | −0.266 | 15.227 | 1.917 | 14.126 | .392 | −0.857 |
| Control System | | | | | | |
| L dorsal prefrontal cortex A[b] | 0.006 | 6.880 | −0.043 | 5.904 | .966 | 0.043 |
| L dorsal prefrontal cortex B[a] | −0.430 | 11.033 | −1.909 | 8.857 | .909 | 0.115 |
| L lateral prefrontal cortex B[a] | −0.525 | 9.927 | −0.575 | 7.542 | .671 | −0.424 |
| L medial posterior prefrontal cortex B[a] | −0.850 | 4.904 | 1.589 | 4.458 | <.001[d] | −3.634 |
| R medial posterior prefrontal cortex B[a] | −1.104 | 7.837 | 0.998 | 7.021 | .053 | −1.937 |
| R lateral prefrontal cortex A[a] | −0.150 | 15.907 | 2.384 | 10.915 | .691 | −0.398 |
| L lateral ventral prefrontal cortex A[a] | −0.119 | 6.277 | 0.545 | 6.908 | .244 | −1.165 |
| R lateral dorsal prefrontal cortex B[b] | −0.153 | 10.416 | 1.099 | 9.254 | .471 | −0.721 |
| R dorsal prefrontal cortex A[b] | −0.073 | 8.287 | 0.524 | 8.244 | .670 | −0.427 |
| L lateral prefrontal cortex A[b] | −0.102 | 9.035 | 0.737 | 7.021 | .573 | −0.564 |
| L lateral ventral prefrontal cortex B[b] | −0.282 | 10.235 | 2.032 | 8.109 | .171 | −1.371 |
| R lateral ventral prefrontal cortex B[a] | −0.604 | 12.886 | 0.244 | 15.059 | .752 | −0.316 |
| Default System | | | | | | |
| Precuneus posterior cingulate cortex[b] | 0.127 | 13.137 | −0.915 | 11.184 | .633 | 0.478 |
| Retrosplenial[b] | 0.366 | 12.480 | −2.636 | 13.252 | .158 | 1.415 |
| Medial prefrontal cortex[b] | −0.188 | 22.866 | 1.354 | 20.477 | .686 | −0.405 |
| Affective System | | | | | | |
| Orbital frontal cortex [b] | −0.067 | 31.361 | 0.486 | 24.949 | .915 | −0.107 |
| Temporal pole[b] | 1.058 | 39.979 | −7.621 | 35.660 | .194 | 1.303 |

Data are residuals. A and B refer to designations used in the Yeo *et al*. atlas (16). Within this atlas some systems, such as the control system and the ventral attention system (salience system), are further split into A and B systems. For instance, in this context, "L dorsal prefrontal cortex B" indicates that the ROI left dorsal prefrontal cortex lies in the control B system; similarly, "insula A" indicates that this ROI lies in the ventral attention A system.

HC, healthy control participant; L, left hemisphere; MDD, major depressive disorder; R, right hemisphere.

[a]Data were nonnormally distributed, and Wilcoxon rank-sum tests were used for statistical assessment with medians and IQRs reported. Statistical significance indicated following false discovery rate correction:

[b]Data were normally distributed, and *t* tests were used for statistical assessment, with means and SDs reported.

[c]$p < .01$.

[d]$p < .001$.

biology of patches and their pathophysiology in mental illness, and we hope this investigation provides evidence to support the use of individualized approaches.

Following FDR correction, hypothesized neural patches of 1) the lateral salience system (parietal operculum) and 2) the control system (left medial posterior prefrontal cortex region) were significantly smaller in participants with depression than in healthy control participants. NeuroSynth findings suggested that the former was associated with somatic and somatosensory domains and the latter with cognition, reasoning, and decision making. However, no differences were identified in the affective and default systems, which contrasts with prior findings of group-level clinical differences in such regions (24,27). These differences may be accounted for by the methods used to assess differences given that we probed the functional topography of individualized regions. Future work could evaluate whether individual differences in affective and default system patches differ from more prototypical group-averaged affective and default system activation.

Consistent with the group comparison (MDD < healthy control), smaller patch sizes of the parietal operculum region were further associated with higher self-reported levels of anxious arousal. However, contrary to expectation, larger patch sizes of the parietal operculum were also associated with reduced reward learning (i.e., reduced ability to modulate behavior as a function of rewards). Furthermore, larger patch sizes in the prefrontal cortex region were associated with

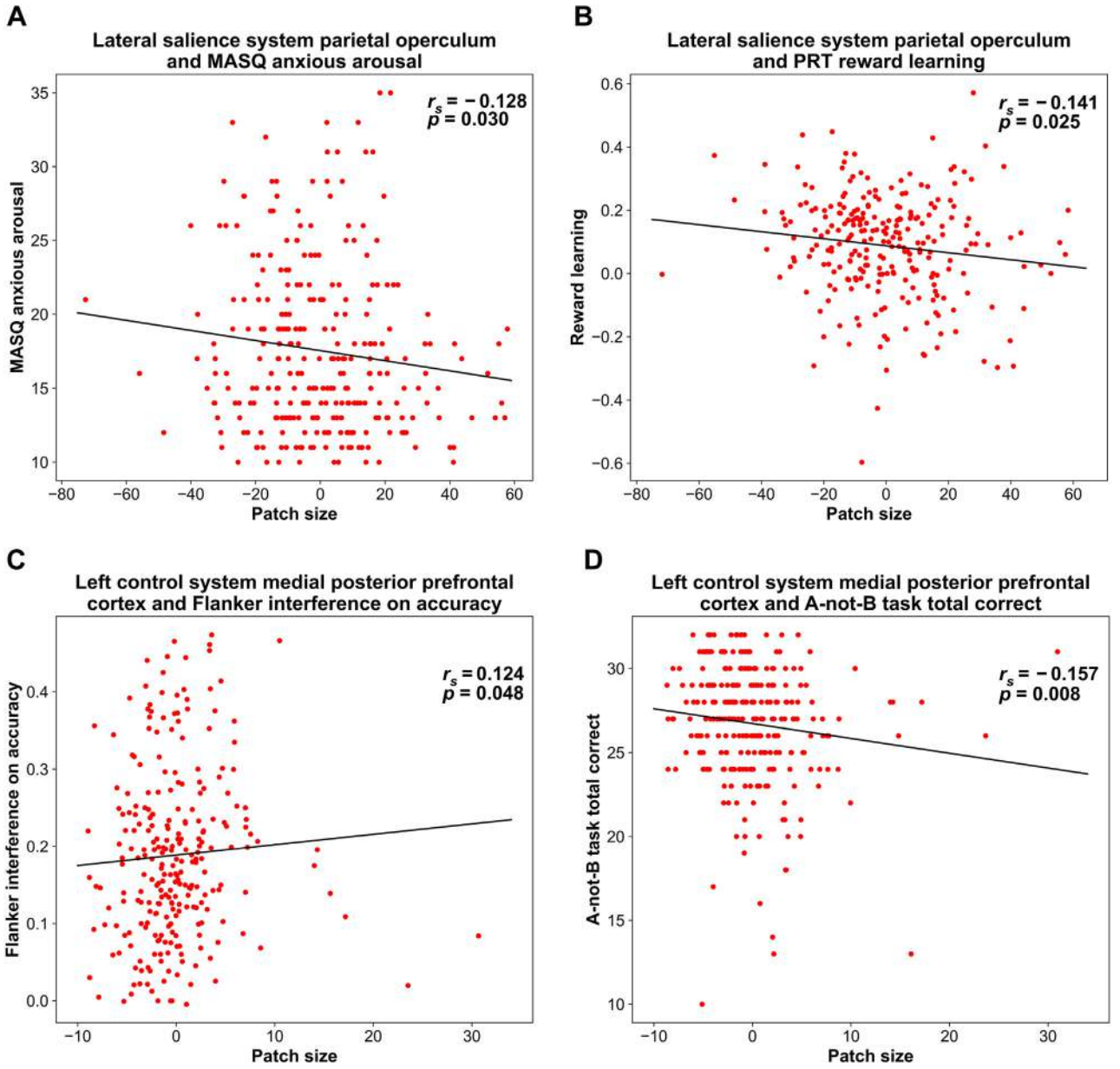


**Figure 3.** Correlations between brain system patches and self-reported symptoms and behavioral task performance. **(A, B)** Spearman correlations ($r_s$) between lateral salience system parietal operculum patch size (residualized number of vertices) and clinical and behavioral measures of **(A)** Mood and Anxiety Symptom Questionnaire (MASQ) anxious arousal and **(B)** probabilistic reward task (PRT) reward learning. **(C, D)** Correlations between control system left medial posterior prefrontal cortex patch size and behavioral measures of **(C)** Flanker interference on accuracy and **(D)** A-not-B task total correct.

reduced working memory and reasoning performance and lower cognitive control as measured by the accuracy scores of the flanker and A-not-B task. While this may seem counterintuitive, it is consistent with previous findings. Prior literature has yielded a pattern that suggests that individuals with depression often perform better on cognitive tasks that require accuracy (44). For example, individuals with depression show slower but more accurate performance on flanker and Stroop tasks (44,45). More critically, our previously published paper on an early subset of the EMBARC study reported that the performance of individuals with depression was characterized by slower reaction time but higher accuracy on the flanker task than healthy control individuals (44). One explanation for this finding has been that depressed groups may be engaging in slower, more deliberate information processing that could protect them from forming inaccurate response biases during cognitive tasks (46). This may explain why smaller patch sizes, which were more characteristic of participants with depression, showed an association with improved flanker and A-not-B task performance, but only in relation to measures of accuracy. However, these findings could also merely reflect the vast heterogeneity in depressive disorders. Various studies

have found inconsistent findings related to cognitive impairment, including discrepancies in severity, the cognitive domains affected, and the directionality of cognitive impairments (47,48).

Collectively, these results relate person-specific brain mapping to several levels of analysis that promise to advance our understanding of heterogeneous mental illnesses (8,9,49–52) and further emphasize the importance of salience- (53) and cognition-related (24) neural functioning in depression. Interestingly, the parietal operculum is one of the only regions found to display higher activation in individuals with MDD during reward anticipation but not in reward outcomes (54). The parietal operculum has also been implicated in positive memory recollection among healthy individuals without depression (55). Thus, individual differences appear to highlight the possible impact of this neural area in depression. In the prefrontal cortex, anatomical analyses have pointed to smaller total volume in medial orbital prefrontal cortex regions for people with geriatric depression (56). While in a different neural area, the findings highlighted in our study complement prior work by identifying similar smaller patches. Finally, our assessment of cortical geometry (i.e., coordinate analysis) indicated that the parietal operculum was located more anteriorly in participants with MDD, and this pattern was significantly associated with general distress. This statistically significant finding provides evidence for the significance of displacement of patches/ROIs in psychopathology. Future person-specific investigations could be useful for identifying the nuanced role of such displacement in clinical presentations of MDD. Taken together, our results indicate that brain mapping at the individual level is related to diagnosis (e.g., patch size of the lateral salience and control systems), symptoms (e.g., anxious arousal and general distress), and behavior (e.g., reward learning and working memory).

NeuroSynth findings produced useful contextualization of the potential meaning for neural regions that differentiated participants with depression from healthy control participants (Table S3). We assessed the highest positive and negative correlating terms for the lateral parietal operculum and left medial posterior prefrontal cortex. Findings linked patch vertices in the lateral salience parietal operculum with sensory, pain, and tactile terms and negatively associated with memory related terms, which may imply that individuals with depression experience functional problems in such areas and potentially experience such problems due to the smaller topological neural areas associated with these functions. While it is difficult to parse causality, these relationships provide insight into differences between healthy and depressed samples and directions for future research.

In sum, individualized brain systems approaches (3–5,30) advance our understanding of the brain and psychopathology and the development of new hypotheses for future research and may inform patient-specific clinical decisions.

### Limitations and Future Directions

Due to the cross-sectional nature of the neuroimaging component in the initial study, it was not possible to assess the causality of the brain regions implicated in MDD. Future studies could utilize an individualized brain systems approach in a longitudinal neuroimaging study of depression to understand causal relationships of these regions in participants with depression. A future longitudinal study could also examine whether these differences in patch sizes represent a trait vulnerability or a state-dependent vulnerability to depression. Additionally, the current study only focused on the implications of cortical regions in individuals with MDD. Future studies should incorporate the cortico-subcortical circuits in similar analyses, which may allow for further insights into individualized functional networks and their role in depression. While the individualized approach overcomes the shortcomings of group-based neuroimaging approaches by accounting for individualized differences in brain mapping, our significant findings were relatively few compared to well-established group-based systems associated with depression (17,19). However, because the patch size metric is not directly comparable to conventional functional connectivity approaches, it is not surprising that our analysis did not replicate the same pattern of results as conventional approaches. Relatedly, another limitation of the current study is that we did not run a traditional functional connectivity analysis to compare results and potentially identify unique contributions of the patch size methodology. However, it is not obvious how to directly relate a measure like patch size, which is a single measure for a given region, to functional connectivity, which conventionally requires the assessment of time courses of activity between 2 regions. Additionally, while it was beyond the scope of our study to integrate treatment outcome data, future studies may benefit from predicting treatment outcomes based on patch sizes derived from individualized approaches. Future studies may also benefit from probing individualized functional organizations on the basis of different variables including but not limited to sex and/or age to identify unique neural differences related to these domains.

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## ARTICLE INFORMATION

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