

Common neural dysfunction in psychiatric disorders: Insights from a meta-analysis of resting-state fMRI studies

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1 **Common neural dysfunction in psychiatric disorders: Insights from a meta-**
2 **analysis of resting-state fMRI studies**

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23 **Abstract:** A central challenge in psychiatry is the need for improved diagnostic
24 accuracy and treatment efficacy. Recent dimensional frameworks like the Research
25 Domain Criteria (RDoC) initiative address this by promoting a transdiagnostic
26 approach to identify shared neural mechanisms across psychiatric disorders. Here, we
27 conducted a transdiagnostic meta-analysis of resting-state fMRI studies that employed
28 amplitude-based measures of spontaneous brain activity—the amplitude of low-
29 frequency fluctuations/fractional ALFF (ALFF/fALFF) and regional homogeneity
30 (ReHo). Our results revealed that patients, compared to healthy controls, exhibited
31 significantly elevated ALFF/fALFF in the lateral orbitofrontal cortex, anterior insula,
32 and caudate, as well as increased ReHo in the ventrolateral prefrontal cortex but
33 reduced ReHo in the middle occipital gyrus. These regions were then subjected to
34 resting-state functional connectivity and functional decoding analyses based on a
35 dataset of 110 healthy participants, allowing for a data-driven inference on
36 psychophysiological functions. These regions and their networks are mapped onto
37 systems implicated in cognitive control, social functioning, emotional processing, and
38 sensory perception. Collectively, our findings delineate a suite of transdiagnostic
39 neural aberrations reflected in resting-state activity, thereby advancing the
40 neurobiological validation of the dimensional frameworks and highlighting potential
41 common targets for therapeutic intervention.

42 **Keywords:** Psychiatric disorder; Meta-analysis; ALFF/fALFF; ReHo; Resting-state
43 functional connectivity

44 **1 Introduction**

45 The rising prevalence of psychiatric disorders poses significant challenges to global
46 healthcare systems. The World Health Organization (2022) estimates that
47 approximately 970 million people are affected worldwide, with major depressive
48 disorder (MDD), anxiety disorders, attention-deficit/hyperactivity disorder (ADHD),
49 and schizophrenia being the most common. These conditions cause substantial
50 functional impairments, increase premature mortality risk [1,2], and drive significant
51 socio-economic losses [3]. Yet increased investment in mental-health services has not
52 resolved underdiagnosis and misdiagnosis [4,5], a problem amplified by reliance on
53 subjective clinical interviews. Objective neuroimaging biomarkers are therefore
54 imperative.

55 Resting-state functional magnetic resonance imaging (rs-fMRI) offers a powerful
56 tool to address this need. By circumventing task-performance confounds inherent to
57 task-based fMRI and enabling standardized data acquisition [6,7,8], rs-fMRI is
58 particularly well-suited for probing the neurobiological substrates of psychiatric
59 disorders [9]. This suitability has contributed to the rapid expansion of the literature,
60 which in turn has fueled numerous disorder-specific meta-analyses aimed at delineating
61 common and reliable resting-state alterations in regional activity and/or functional
62 connectivity.

63 A clear pattern emerges from synthesizing these meta-analyses: the same core
64 neural regions/functional connectivity exhibit convergent pathological alterations
65 across traditional diagnostic boundaries. Repeatedly reported resting-state alterations
66 are localized to brain regions that form the core of the default-mode (DMN), salience
67 (SN), and subcortical (SCN) networks. Dysfunctions within these networks appear to

68 correspond to the impairments in social adaptation, executive control, and emotion
69 processing commonly observed across psychiatric disorders. For instance, functional
70 disruptions in core DMN nodes (e.g., medial prefrontal cortex [mPFC]) and reduced
71 DMN integrity are observed in schizophrenia, ADHD, MDD, and post-traumatic stress
72 disorder (PTSD), and are associated with social-cognitive impairments such as social
73 avoidance and alienation [10,11,12,13,14]. Similarly, impaired connectivity between
74 the SN and prefrontal cortex is repeatedly reported across these disorders, contributing
75 to executive dysfunction [15,16,17]. In mood disorders such as bipolar disorder and
76 MDD, aberrant reward and emotional processing within subcortical structures (e.g.,
77 caudate) is consistently documented [11,18]. Taken together, findings from disorder-
78 specific meta-analyses suggest that resting-state functional abnormalities in key neural
79 regions/circuits may represent a shared pathological substrate.

80 This is consistent with emerging transdiagnostic frameworks in psychopathology.
81 For instance, the p-factor theory proposes a general psychopathology factor underlying
82 comorbidity across multiple psychiatric disorders [19], while the National Institute of
83 Mental Health (NIMH) Research Domain Criteria (RDoC) initiative advocates for
84 understanding mental disorders via dimensional constructs spanning neurobiology and
85 behavior, moving beyond conventional diagnostic classifications [20,21]. Collectively,
86 these perspectives support the view that psychiatric disorders are not discrete, mutually
87 exclusive categories but rather overlapping manifestations of shared abnormalities in
88 key transdiagnostic neurobiological dimensions or functional circuits [22,23]. This
89 view is supported by recent transdiagnostic meta-analyses based on task-based fMRI
90 or structural neuroimaging, which have revealed common abnormalities in core brain
91 regions regulating emotional processing, cognitive control, and social functioning

92 across disorders [24,25,26,27,28]. However, it remains unclear whether these
93 transdiagnostic alterations are consistently observed as resting-state functional
94 signatures.

95 Here, we used activation likelihood estimation (ALE) to delineate transdiagnostic
96 convergence of resting-state functional signatures, indexed by amplitude of low-
97 frequency fluctuations/fractional ALFF (ALFF/fALFF) and regional homogeneity
98 (ReHo) [29,30,31], across psychiatric disorders. Furthermore, to characterize the
99 physiological functions of regions derived from meta-analyses following a brain
100 network perspective, resting-state functional connectivity (RSFC) analysis was
101 incorporated into the current study, which was tested on an independent rs-fMRI dataset
102 collected from healthy participants, see also [25,32,33,34,35]. This network perspective
103 is particularly relevant to the transdiagnostic approach, since it is likely that
104 psychopathology factors such as symptoms of depression, anxiety, or psychosis are
105 increasingly understood in terms of alterations in large-scale brain networks rather than
106 a small number of regions [28,36,37,38,39,40]. Lastly, we examined psychological
107 functions of regions identified herein and their networks with functional decoding
108 analyses based on large-scale datasets from the Neurosynth database [41]. Taken
109 together, these complementary analytical schemes aimed to provide data-driven
110 quantitative inference on psychophysiological functions of identified regions.

111

112 **2 Materials and Methods**

113 ***2.1 Literature search and selection***

114 Following the PRISMA guidelines, we performed systematic and comprehensive
115 searches of the PubMed, ISI Web of Science, and Google Scholar databases in

116 November 2022. The following two categories of pertinent terms were combined as the
117 keywords for the search: (1) imaging modalities: “rs-fMRI” OR “rest state fMRI” OR
118 “rest state imaging” OR “rest state functional magnetic resonance imaging” OR “ALFF”
119 OR “amplitude low frequency fluctuations” OR “fALFF” OR “fractional amplitude of
120 low frequency fluctuation” OR “ReHo” OR “regional homogeneity”; and (2) disorder
121 diagnosis: “schizophrenia” OR “schizophreniform” OR “attention deficit hyperactivity
122 disorder” OR “ADHD” OR “conduct disorder” OR “conduct problems” OR “disruptive
123 behavior disorders” OR “affective disorders” OR “bipolar disorder” OR “unipolar
124 disorders” OR “mania” OR “manic disorder” OR “dissociative disorder” OR “major
125 depressive disorder” OR “MDD” OR “depression” OR “obsessive compulsive disorder”
126 OR “OCD” OR “generalized anxiety disorder” OR “GAD” OR “mood and anxiety
127 disorders” OR “anxiety disorder” OR “post-traumatic stress disorder” OR “stress
128 disorder” OR “PTSD” OR “post-traumatic stress”. In addition, we explored several
129 other sources, including the bibliography and citation indices of the pre-selected articles,
130 as well as the reference list of relevant reviews, and direct searches on the names of
131 frequently occurring authors.

132 It should be noted that we center on two core categories of local activity indices in
133 rs-fMRI studies: ALFF/fALFF and ReHo [29,30,31]. These indices were selected for
134 their clear neurobiological foundations and methodological suitability.
135 Neurobiologically, they quantify low-frequency oscillation properties of the BOLD
136 signal, providing markers of intrinsic local brain activity [42]: ALFF measures the
137 absolute amplitude of oscillations [30]; fALFF reflects the relative contribution of low-
138 frequency components to the total frequency spectrum [29]; and ReHo assesses the
139 synchrony of signals among adjacent voxels [31].

140 The significance of these indices lies in the fact that they are not merely
141 quantitative metrics but reflections of the brain's intrinsic physiological processes.
142 Low-frequency BOLD oscillations are closely linked to spontaneous fluctuations in
143 neuronal activity and, via neurovascular coupling, to concomitant changes in local
144 cerebral blood flow, volume, and oxygenation [43]. The magnitude of ALFF/fALFF
145 values is therefore associated with local energy metabolism, whereas ReHo captures
146 the spatial synchrony of adjacent voxels, indexing the integrative function of local
147 circuits. Both metrics correlate with regional glucose metabolism and oxygen
148 consumption [44,45], providing a valuable window into brain physiology and
149 pathology. In depression, schizophrenia, and other disorders, alterations (increases or
150 decreases) in ALFF/fALFF or ReHo are consistently observed in key areas such as the
151 prefrontal and parietal cortices, and correlate with symptom severity [12,46,47].
152 Critically, these indices tend to normalize toward healthy-control levels as symptoms
153 improve [47,48], supporting their potential as state or treatment-response biomarkers.

154 From a methodological standpoint, these indices require no predefined seed
155 regions or network templates, enabling unbiased whole-brain exploration, and
156 demonstrate good test-retest reliability [49]. Furthermore, as indicators of local activity
157 characteristics, they avoid the statistical heterogeneity and interpretative challenges
158 arising from mixing different metric types (e.g., local activity and functional
159 connectivity) in meta-analyses [50].

160 The obtained studies were further assessed according to the following criteria.
161 First, the publication reported rs-fMRI studies and was published in a peer-reviewed
162 English language journal. Second, each study referred to at least one psychiatric
163 disorder versus control group comparisons. Third, the study conducted the analyses at

164 the regional level, particularly the ALFF/fALFF or the ReHo analyses. Fourth, we
165 restricted the meta-analysis to studies that reported the whole brain functional
166 neuroimaging data (rather than region of interest [ROI] analyses). Finally, brain
167 imaging results were presented in a standardized stereotaxic space (Talairach or
168 Montreal Neurological Institute, MNI). For studies using Talairach coordinates, we
169 converted them to MNI coordinates using the icbm2tal algorithm [51] implemented in
170 the GingerALE software (version 3.0.2, <http://www.brainmap.org/>). Subsequently,
171 several additional steps were employed to further refine the selection of the reported
172 results, such that results were excluded if (i) participants in the psychiatric group had a
173 history of neurological diseases such as epilepsy, brain tumor, brain lesion or meningitis;
174 (ii) studies did not adopt ALFF/fALFF or ReHo analyses; (iii) studies covered the range
175 of frequencies higher than 0.10 Hz or lower than 0.01 Hz. Applying these inclusion and
176 exclusion criteria to filter the search results yielded a total of 303 experiments (i.e.,
177 contrasts), comprising 163 contrasts from 77 studies measuring ALFF/fALFF and 140
178 contrasts from 63 studies measuring ReHo (Figure 1). These procedures were
179 independently performed by two investigators, with discrepancies resolved by
180 discussion with a third reviewer. Detailed information on each study is provided in
181 Tables S1 and S2.

182

183 **2.2 Activation Likelihood Estimation (ALE) meta-analyses**

184 A coordinate-based meta-analysis of available fMRI research was conducted,
185 employing the ALE algorithm implemented with in-house MATLAB scripts [52,53].
186 Applying the ALE algorithm, the published coordinates of the brain regions correlated
187 to each meta-analysis were independently converged across different contrasts [54,55].

188 Specifically, ALE interprets reported foci as three-dimensional Gaussian spatial
189 probability distributions with widths based on empirical estimates of the spatial
190 uncertainty resulting from the heterogeneity of the neuroimaging data across subjects
191 and between templates [52]. Within each contrast included in the analysis, a modulated
192 activation (MA) map is initially produced by taking the maximum probability
193 associated with any one focus (always the closest one) for each voxel [54]. The
194 improved ALE algorithm has the benefit of preventing multiple foci from a single
195 contrast collectively affecting the individual MA value of a single voxel. Additionally,
196 rather than being considered as independent contrasts for each meta-analysis, distinct
197 contrasts from the same subject sample were pooled into a single contrast to prevent
198 studies with multiple contrasts based on the same subject sample from impacting ALE
199 values more than others [54].

200 To generate an ALE map across studies, the union of the individual modulated
201 activation maps was first created from the maximum probability associated with any
202 one focus (always the nearest one) for each voxel. Using a non-linear histogram
203 integration approach, this ALE map was evaluated against a null distribution of random
204 spatial connections across studies [54,56]. To limit the potential excessive contribution
205 of a single contrast, the average non-linear contribution of each contrast for each cluster
206 was also calculated using the percentage of the ALE values for the cluster with and
207 without the relevant contrast [57]. Based on the calculated contribution, we employed
208 two additional criteria to select significant clusters: (1) the contributions for one cluster
209 should be from at least two experiments so that the finding would not only be driven
210 by one single contrast; and (2) the average contribution of the most dominant
211 experiments (MDE) should not exceed 50%, whereas the average contribution of the

212 two most dominant experiments (2MDEs) should not exceed 80% [57].

213 Applying the ALE algorithm, the reported coordinates of brain areas associated
214 with differences between patients with psychiatric disorders and healthy controls
215 converged across different contrasts. Specifically, we evaluated transdiagnostic
216 alterations in ALFF/fALFF or/and ReHo with two directional relationships: (1)
217 ALFF/fALFF increases among patients relative to healthy controls (patients > healthy
218 controls: 82 contrasts, 318 foci, 6193 subjects); (2) ALFF/fALFF decreases among
219 patients relative to healthy controls (patients < healthy controls: 81 contrasts, 276 foci,
220 5649 subjects); (3) ReHo increases among patients relative to healthy controls (patients >
221 healthy controls: 71 contrasts, 255 foci, 5436 subjects); and (4) ReHo decreases among
222 patients relative to healthy controls (patients < healthy controls: 69 contrasts, 276 foci,
223 5257 subjects).

224

225 **2.3 Validation analyses**

226 To examine the robustness of our ALE findings, we conducted several additional
227 analyses, including i) leave-one-experiment-out (LOEO) analysis to verify the stability
228 of the results; ii) fail-safe N (FSN) analysis to quantify the resilience against publication
229 bias; and iii) modulation analyses to exclude the confounding effects.

230 First, we conducted an LOEO analysis for each ALE meta-analysis to ensure that
231 conclusions derived from the primary meta-analysis were not driven by coordinates
232 from any single experiment. In this approach, one experiment from each fold was
233 eliminated, and the rest of the $N-1$ experiments were subjected to the ALE meta-analysis.

234 Aiming to determine the brain regions substantially engaged, we performed

235 conjunction analysis on the ALE results for each fold. In the LOEO study, the indicated
236 brain regions were identified in more than 70% of the folds.

237 Next, to examine the publication bias of our ALE findings, we applied FSN
238 analysis. The amount of contra-evidence that the ALE can tolerate (i.e., FSN) was
239 calculated by introducing null pseudo-studies as noise into the ALE cohort to assess the
240 robustness of ALE clusters [58,59]. A higher FSN indicates more stable results and
241 hence a higher robustness [58]. See Supplementary methods for details.

242 Finally, to examine demographic, clinical, and imaging-specific moderators of the
243 observed effects, we extracted per-voxel probabilities from all meta-analytically
244 identified regions. The assessed factors encompassed: mean age, sex ratio, clinical
245 diagnoses, medication status, comorbidity, band-pass settings, eye state, and MRI
246 magnetic field strength, see also [25,26,28,32,60,61,62]. Nonparametric analyses such
247 as Kruskal-Wallis *H*, Mann-Whitney *U*, and Spearman's *rank* correlation were applied
248 based on data characteristics. Notably, potentially influential factors such as age of
249 onset and illness duration were not evaluated due to insufficient reporting across studies.
250

251 **2.4 Resting-state functional connectivity analysis and functional decoding**

252 To further characterize the functional connectivity and network organization of brain
253 regions derived from ALE meta-analyses, we performed RSFC analysis using an
254 independent rs-fMRI dataset from healthy participants. Resting-state scans were
255 collected from 116 right-handed, neurologically healthy adults (57 males, mean age =
256 21.80 ± 2.41 years, range = 18-30 years) at Beijing Normal University. Participants
257 underwent a 5-minute resting-state fMRI scan, with instructions to keep their eyes
258 closed, remain still, stay awake, and avoid structured thought. Sixteen participants (8

259 males) were excluded due to excessive head motion, yielding a final sample of 100
260 individuals for analysis. All procedures complied with the Declaration of Helsinki and
261 were approved by the Ethics Committee of Beijing Normal University
262 (ICBIR_A_0016_018). Written informed consents were obtained from all participants.
263 Details on image acquisition/preprocessing are provided in the Supplementary Methods.

264 Specifically, for each of the ALE meta-analyses (transdiagnostic increases in
265 ALFF/fALFF, increases in ReHo, and decreases in ReHo, see Results), significant
266 clusters were binarised and separately used as seed regions. The mean BOLD time
267 series across all voxels within each corresponding seed mask was extracted and
268 correlated with every voxel-wise time series in the brain using Pearson's bivariate
269 correlation. The resulting Pearson's correlation coefficients were transformed into
270 Fisher's z -scores to quantify connectivity strength. Finally, one-sample t -tests were
271 performed against zero to identify brain regions significantly connected to the seeds.
272 Resulting t -maps were thresholded using cluster-level family-wise error correction
273 ($cFWE < 0.05$, cluster size ≥ 20 voxels).

274 Next, to assess the underlying large-scale network correlates, RSFC results (i.e.,
275 resulting t -maps) were overlaid onto seven canonical functional cortical networks and
276 a collection of subcortical areas [63,64,65]. Canonical networks include the fronto-
277 parietal network (FPN), dorsal attention network (DAN), ventral attention network
278 (VAN), somatomotor network (SMN), visual network (VN), cortical affective network
279 (AFN), and default mode network (DMN), in addition to a subcortical network (SCN)
280 [65]. The relative distribution was computed by the proportion of activated voxels of a
281 given network versus all activated voxels, while the absolute distribution was calculated
282 by the proportion of activated voxels of a given network versus voxels of that template

283 network [34,66].

284 Meanwhile, to explore which psychological topics were most relevant to these
285 RSFC results, functional decoding analyses were performed based on the Neurosynth
286 database (version 0.6) [41] with codes from a set of IPython Notebooks
287 (<https://github.com/adelavega/neurosynth-lfc>) [67]. Psychological topics with $p < 0.01$
288 (FDR corrected) were reported. See Supplementary methods for details.

289

290 **3 Results**

291 ***3.1 Studies included in meta-analyses and sample characteristics***

292 In the present meta-analysis, we included studies that compared ALFF/fALFF or ReHo
293 between individuals with psychiatric conditions and healthy controls. Specifically, the
294 included clinical conditions were as follows: (i) mood-related conditions, including
295 bipolar disorder and major depressive disorder; (ii) psychosis-related conditions,
296 including schizophrenia; (iii) anxiety-related conditions, including anxiety disorder,
297 post-traumatic stress disorder, and obsessive-compulsive disorder; and (iv) behavior
298 disorders, including attention-deficit/hyperactivity disorder and conduct disorder. The
299 age range of the samples spanned from children/adolescents (mean age < 18 years) to
300 the elderly (mean age > 50 years). The distribution of the number of studies for each
301 clinical condition is presented in Table S3, and the age range distribution across clinical
302 samples is detailed in Table S4.

303

304 ***3.2 ALE meta-analyses across psychiatric disorders***

305 In transdiagnostic changes of ALFF/fALFF (Table 1 & Figure 2A), ALE meta-analysis
306 indicated that the increased ALFF/fALFF in patients compared to healthy controls

307 identified convergent clusters in the left orbitofrontal cortex (lOFC), right anterior
308 insula (AI), and caudate. Of the 82 included contrasts, 10 contributed to the cluster in
309 the lOFC (MDE = 18.39%; 2MDE = 35.40%), 12 contrasts contributed to the cluster in
310 the AI (MDE = 15.35%; 2MDE = 29.57%), and 12 contrasts contributed to the cluster
311 in the caudate (MDE = 15.05%; 2MDE = 30.03%; Table S5). The results of the LOEO
312 approach corroborated these findings (Table S7 & Figure S1). Subsequent FSN
313 analyses revealed region-specific differences in robustness (Table 1): the lOFC
314 remained statistically significant following the inclusion of null studies equivalent to
315 70% of the original number of studies in the meta-analysis (i.e., 0.7k, where k denotes
316 the number of original studies in the meta-analysis); the right AI retained statistical
317 significance after incorporating 0.5k null studies; and the caudate even maintained
318 statistical significance upon the inclusion of 1.7k null studies. In contrast, no consistent
319 peak activations were observed when comparing patients versus healthy controls in the
320 decreased ALFF/fALFF.

321 Regarding transdiagnostic changes of ReHo (Table 1 & Figure 2B), ALE meta-
322 analysis indicated that the increased ReHo in patients compared to healthy controls
323 identified convergent clusters in the left ventral lateral prefrontal cortex (vlPFC).
324 Among 71 contrasts, 7 contributed to the cluster in the vlPFC (MDE = 20.27%; 2MDE
325 = 40.44%; Table S6). In contrast, the decreased ReHo in patients compared to healthy
326 controls identified consistent peak activations in the left middle occipital gyrus (MOG),
327 with 8 out of 69 contrasts contributing to this cluster (MDE = 16.44%; 2MDE = 30.76%;
328 Table S6). The results of the LOEO approach corroborated these findings (Table S7 &
329 Figure S1). In addition, FSN analysis revealed that the vlPFC showed lower robustness;
330 conversely, the MTG remained significant even after incorporating 2.1k null studies

331 (Table 1).

332

333 **3.3 Modulation effects**

334 Modulation analyses of per-voxel probabilities from meta-analytic clusters revealed
335 limited effects of demographic, clinical, and imaging-specific factors (Table S8).
336 Clinical diagnoses showed no significant moderating effects overall (Kruskal-Wallis H :
337 all $H < 6.274$, $p > .511$), except for increased ALFF/fALFF in the caudate associated
338 with psychotic diagnoses. Furthermore, neither comorbidity status nor medication
339 exposure accounted for spatial patterns of aberrant spontaneous neural activity (Mann-
340 Whitney U : all $U < 1.560$, $p > .119$). Lastly, demographic and imaging parameters
341 demonstrated no significant associations, such that spontaneous neural activity
342 alterations were unrelated to mean age or sex ratio (nonparametric correlations: all $|\rho|$
343 < 0.119 , $p > .292$), and similarly unaffected by band-pass filtering settings, eye state
344 during scanning, or MRI magnetic field strength (Mann-Whitney U : all $U < 1.556$,
345 $p > .119$).

346

347 **3.4 RSFC results**

348 To interpret the meta-analytic findings within large-scale networks, we conducted
349 RSFC analysis and projected the resulting statistical maps onto canonical networks.
350 Results showed that regions associated with transdiagnostic increases in ALFF/fALFF
351 exhibited strong functional connectivity with the lOFC, lPFC, AI, anterior cingulate
352 cortex (ACC), inferior parietal lobule (IPL), caudate, and putamen (Table 2). These
353 connectivity patterns were predominantly distributed in the FPN (relative: 36.98%;
354 absolute: 24.72%), DMN (relative: 29.90%; absolute: 12.96%), and SCN (relative:

355 28.07%, absolute: 40.57%; Figure 3A). Functional decoding analysis revealed that
356 these networks were predominantly associated with the psychological functions such
357 as conflict, inhibition, switching, working memory, mentalizing, emotion, reward, and
358 fear processing (Figure 4A).

359 Regions associated with transdiagnostic increases in ReHo exhibited strong
360 functional connectivity with ACC, supplementary motor area (SMA), lPFC, AI, and
361 caudate (Table 2). These connectivity patterns were predominantly distributed in the
362 FPN (relative: 51.10%, absolute: 26.61%) and VAN (relative: 27.60%, absolute:
363 20.55%; Figure 3B), which were focused on conflict, inhibition, switching, cues, and
364 learning processing (Figure 4B). In contrast, regions associated with transdiagnostic
365 decreases in ReHo exhibited strong functional connectivity with MOG, lingual, and
366 fusiform gyrus (Table 2). These connectivity patterns were predominantly distributed
367 in the VN (relative: 73.06%, absolute: 61.03%; Figure 3C), which were associated with
368 visual-motion, action, motor, spatial, sensory, and gaze processing (Figure 4C).

369

370 **4 Discussion**

371 Within a transdiagnostic framework, the neurobiological substrates of spontaneous
372 neural activity—quantified through amplitude-based indices (ALFF/fALFF) and
373 regional synchronization (ReHo)—remain incompletely characterized. To address this
374 gap, we conducted a transdiagnostic meta-analysis of rs-fMRI studies conducted in
375 psychiatric disorders. Results demonstrated that, compared with healthy controls,
376 patients exhibited significantly elevated ALFF/fALFF in the lOFC, AI, and caudate,
377 alongside increased ReHo in the vlPFC and decreased ReHo in the MOG. These
378 findings proved robust after validation approaches to eliminate effects solely due to a

379 single experiment. In addition, FSN analysis indicated that, to a large extent, the
380 findings are robust to publication bias and remained consistent after adjusting for
381 demographic, clinical, and imaging-specific variables.

382 These findings are consistent with transdiagnostic/dimensional models of
383 psychopathology advocated in recent years [21,68,69,70]. For instance, RDoC proposes
384 that mental disorders may reflect dysfunctions in a limited number of core
385 transdiagnostic functional dimensions, such as cognitive control, social functioning,
386 and negative/positive valence. These dimensions can be assessed using various
387 indicators, including neuroimaging measures [21,22,23,71,72]. In this regard, the brain
388 regions showing abnormal local activity and synchronization identified in our study
389 likely map onto the RDoC core functional dimensions; as such, they solidified the
390 evidence that a shared neural substrate underlies symptoms cutting across conventional
391 diagnostic boundaries. Furthermore, RSFC analysis and functional decoding revealed
392 that these aberrant brain regions, along with their associated connectivity patterns, are
393 implicated in multiple large-scale brain systems. These include networks involved in
394 cognitive control (FPN, VAN), social and emotional processing (DMN, SCN), and
395 sensory functions (VN). Collectively, by integrating meta-analytic findings with
396 functional connectivity and decoding analyses, the present study not only identifies
397 convergent, transdiagnostic alterations in local brain activity but also provides data-
398 driven quantitative inference on psychophysiological functions of these brain regions.

399 First, our results revealed transdiagnostic alterations in regional brain activity, as
400 measured by ALFF/fALFF, within the IOFC, AI, and caudate. Subsequent RSFC
401 analyses showed that these regions are functionally embedded in several large-scale
402 networks, including the FPN, DMN, and SCN. Specifically, the FPN supports high-

403 level cognitive control, including task-set maintenance, response inhibition, and aspects
404 of long-term planning [73,74,75]. Dysfunction within this network (and in hub regions
405 like the IOFC) may weaken top-down inhibition and thus contribute to the impulsive
406 aggression observed across ADHD, anxiety disorders, and schizophrenia [76]. This is
407 consistent with recent transdiagnostic neuroimaging meta-analyses that report both
408 alterations (e.g., reduced gray matter volume in the IOFC [25]) and functional
409 abnormalities (e.g., reduced gray matter volume in the IOFC [27]) within this
410 network. Moreover, altered functional connectivity between the FPN and SCN may
411 further contribute to dysregulated emotional processing and regulation [27,77,78]. The
412 DMN, closely involved in value-based decision-making [79], self-referential thought
413 [80], and theory of mind [81], supports social and adaptive functioning [82,83].
414 Impairments in DMN have been consistently documented across psychiatric conditions
415 [25,27,84] For instance, early-life stress has been shown to exert long-term effects on
416 the development of core DMN regions (e.g., mPFC), increasing vulnerability to diverse
417 psychopathological outcomes [85]. In summary, the patterns of ALFF/fALFF
418 abnormalities observed in our study suggest that dysfunctions in critical nodes (e.g.,
419 IOFC, AI, caudate) and related networks may underlie common impairments in
420 cognitive control, emotion processing, and social functioning across psychiatric
421 disorders.

422 Using ReHo to assess local functional synchronization, the present study identified
423 transdiagnostic alterations in the vIPFC and the MOG. Further RSFC analysis revealed
424 that these regions are primarily embedded within the FPN, VAN, and VN. The recurrent
425 involvement of the FPN further supports its central role in cognitive control deficits
426 across psychiatric disorders. In addition, the FPN interacts dynamically with the VAN,

427 and coordinated activity between these networks supports stimulus-outcome
428 anticipation, response preparation, and inhibitory control [73,74,75]. Dysfunctions in
429 these networks may underlie transdiagnostic impairments in cognitive flexibility and
430 emotion regulation. For instance, in patients with depression, hypoactivity in key FPN
431 nodes (e.g., vLPFC) is associated with recurrent rumination [86], whereas in anxiety
432 disorders, hyperactivity in core VAN regions (e.g., AI) is linked to persistent
433 hypervigilance [87]. Interestingly, VN dysfunction has also been observed. Given the
434 fundamental role of visual processing in interpreting external information and guiding
435 behavior, it is not surprising that VN abnormalities have been consistently documented
436 across various psychiatric disorders [88,89,90]. Notably, neuromodulation targeting
437 regions of the VN has recently emerged as a promising therapeutic approach, showing
438 potential for rapid symptom alleviation in depressive episodes [91]. Collectively, these
439 findings suggest that psychopathology involves multilevel network disturbances—from
440 low-level perceptual processing to higher-order regulatory mechanisms—with
441 significant clinical relevance across psychiatric disorders.

442 Overall, by quantifying the neurobiological basis of spontaneous neural activity,
443 our findings provide evidence for common functional disruptions underlying
444 psychiatric disorders. Interestingly, the transdiagnostic relevance of regions identified
445 in the current study is further bolstered by their convergence with findings from other
446 modalities. The observed abnormalities (e.g., lOFC, AI) significantly overlap with
447 those reported in prior transdiagnostic studies using task-based fMRI and structural
448 MRI, a consistency validated across diverse age samples from childhood to adulthood
449 [24,25,26,27,28,92]. Psychiatric genetics research further indicates that these brain
450 regions are convergence zones for polygenic risks associated with multiple psychiatric

451 disorders, suggesting that different diagnostic categories may share a common genetic
452 basis [93]. Thus, this multimodal evidence strongly suggests that abnormalities in these
453 regions and relevant networks reflect a common neural mechanism that cuts across
454 diagnostic labels, rather than methodological artifacts or mere symptom overlap.

455 At a neurophysiological level, ALFF/fALFF and ReHo are closely tied to
456 fundamental processes like neurovascular coupling and metabolic homeostasis
457 [43,44,45]. Therefore, their alterations may represent objective markers of
458 dysfunctional baseline neuronal excitability and metabolism. In this context, it is
459 reasonable to speculate that local resting-state activity abnormalities may act as an
460 intermediate phenotype, bridging genetic risks and behavioral symptoms, which offers
461 a neurobiological account for the common co-occurrence of cognitive and emotional
462 symptoms (e.g., attentional deficits, emotion dysregulation) across various psychiatric
463 diagnoses.

464 Several limitations warrant cautious interpretation and further investigation. First,
465 given that our sample spans childhood/adolescence (a critical period for
466 neurodevelopment [94]) to older adulthood (involving neurodegenerative changes [95]),
467 constructing age-stratified transdiagnostic models is essential. However, the current
468 meta-analytic approach was constrained by uneven availability of rs-fMRI data across
469 age groups in the primary literature. Although modulation analyses indicated no
470 significant association between spontaneous neural activity differences and mean age
471 of patient, future research would benefit from larger samples to characterize specific
472 patterns of resting-state brain activity abnormalities across different lifespan stages in
473 psychiatric disorders. Second, the cross-sectional nature of included studies precludes
474 causal inferences regarding whether observed neural alterations constitute precursors

475 or consequences of psychopathology—a critical question awaiting resolution through
476 longitudinal designs incorporating multimodal biomarkers. Several methodological
477 limitations warrant acknowledgment: (i) the ALE meta-analysis quantifies spatial
478 convergence but does not incorporate effect size estimation; (ii) imbalanced distribution
479 of experiments across diagnostic categories necessitates caution against
480 overgeneralizing findings; (iii) modulating effects of potentially influential factors such
481 as illness duration and age of illness onset could not be assessed comprehensively as
482 this information was not consistently included across primary studies; and (iv) the
483 current meta-analysis was not prospectively registered on PROSPERO. Although we
484 rigorously adhered to the PRISMA guidelines and maintained full transparency to
485 mitigate bias, we recognize that these measures cannot fully substitute for the value of
486 prior registration. In light of this, we believe it would be prudent to adopt prospective
487 registration as a standard practice in future research.

488

489 **5 Conclusion**

490 Through a meta-analysis of spontaneous neural activity, the present study reveals neural
491 correlates of functional impairments in psychiatric disorders—these correlates are not
492 confined to specific diseases but may reflect universal deficits in sensory functions,
493 emotional processing, cognitive control, and social functioning across psychiatric
494 conditions. This research perspective aims to provide a valuable complement to existing
495 classification frameworks by elucidating shared underlying mechanisms, thereby
496 advancing a more systematic and in-depth understanding of mental disorders.

497

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504

505 **Data and code availability statement**

506 The analysis code supporting the findings of this study is available from the
507 corresponding author upon reasonable request. The resting-state fMRI data are also
508 available from the corresponding author upon reasonable request; however, they are
509 not publicly deposited due to privacy regulations and restrictions specified in the
510 participants' informed consent.

511

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531 **Contributions**

532 LW: Methodology, Data analysis, Writing- Original Draft, Writing-Review & Editing;
533 QL: Methodology, Data analysis, Writing-Review & Editing; ZZ: Writing-Review &
534 Editing; WC: Writing-Review & Editing; YS: Writing-Review & Editing; TL:
535 Investigation, Methodology, Writing-Review & Editing, Supervision & Fund
536 Application; CF: Conceptualization, Writing-Review & Editing, Supervision & Fund
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541 **Ethics declarations**

542 **Conflicts of interest**

543 The authors declare that they have no conflict of interest.

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785 **Table 1. Significant clusters from the meta-analysis of patients versus healthy controls**
 786 **contrast.**

Lateral ity	Brain Regions	BA	MNI Coordinates x y z	Peak Z Score	Cluster- level <i>p</i> (FEW- corrected)	Cluster Size (mm ³)	FSN
<i>ALFF/fALFF increased</i>							
L	lateral orbitofrontal cortex	47	-38 42 -12	5.05	.001	1176	$0.7k_1 < FSN < 0.8k_1$
R	anterior insula	13	36 14 -8	4.31	.001	1192	$0.5k_1 < FSN < 0.6k_1$
R	caudate	-	14 14 12	6.07	<.001	1480	$1.7k_1 < FSN < 1.8k_1$
<i>ALFF/fALFF decreased</i>							
-	-	-	- - -	-	-	-	-
<i>ReHo increased</i>							
L	ventral lateral prefrontal cortex	10	-30 46 10	4.52	.041	696	$0.1k_2 < FSN < 0.2k_2$
<i>ReHo decreased</i>							
L	middle occipital gyrus	19	48 -70 2	5.33	<.001	1592	$2.1k_3 < FSN < 2.2k_3$

787 *P(cFWE) < .05 at the cluster level with a cluster-forming threshold of P < .001 using 10,000*
 788 *permutations. FSN, fail-safe N; K₁ = 82; K₂ = 71; K₃ = 69; BA, Brodmann; MNI, Montreal*
 789 *Neurological Institute; L, left; R, right.*

790

Table 2. Resting-state functional connectivity.

Laterality	Brain Regions	BA	MNI Coordinates (mm)			Peak Intensity	Cluster Size (mm ³)
			x	y	z		
Regions associated with transdiagnostic increases in ALFF/fALFF							
L/R	caudate/putamen/ventral striatum/thalamus/anterior insula/lateral orbitofrontal cortex/anterior cingulate cortex/lateral prefrontal cortex	47/13/ 24/10	10	12	10	29.86	117072
	inferior parietal lobule/angular gyrus		40	-54	-56	48	9.74
L	inferior parietal lobule/angular gyrus	40	60	-44	50	9.45	3688
R	middle temporal gyrus	37	-56	-38	-12	7.96	1016
Regions associated with transdiagnostic increases in ReHo							
L/R	anterior cingulate cortex/supplementary motor area	32/24/ 22	2	22	42	14.66	25176
L	lateral prefrontal cortex/medial frontal cortex	10/9	-32	48	12	32.62	25144
R	lateral prefrontal cortex/medial frontal cortex	10/9	34	58	12	15.62	19904
L	lateral orbitofrontal cortex/anterior insula	47/13	-44	16	4	10.12	8480
R	lateral orbitofrontal cortex/anterior insula	47/13	34	18	0	9.48	4800
R	inferior parietal lobule/angular gyrus	40	50	-48	44	8.48	3920
L	inferior parietal lobule/angular gyrus	40	-54	-54	42	8.33	3752
L	caudate	-	-16	14	6	10.18	4584
R	caudate	-	18	12	14	9.49	2440
Regions associated with transdiagnostic decreases in ReHo							
R	middle occipital gyrus/lingual gyrus/fusiform gyrus/middle temporal gyrus/inferior temporal gyrus/posterior cingulate cortex	19/18/ 37/30	50	-68	4	30.19	141280
	precentral gyrus/supplementary motor area						
	precentral gyrus		6	-56	-12	44	9.56
L	anterior insula	13	-40	-34	16	8.03	1480
L	precentral gyrus	6	-14	-30	64	7.88	1184

791 Clusters exceeding 1000 mm³ in volume are presented to summarize the primary results. BA,
 792 Brodmann; L, left; R, right.

793 **Figure legends**

794

795 **Figure 1. Flow chart of the study selection process for the meta-analysis.** rsMRI, resting
796 magnetic resonance imaging.

797

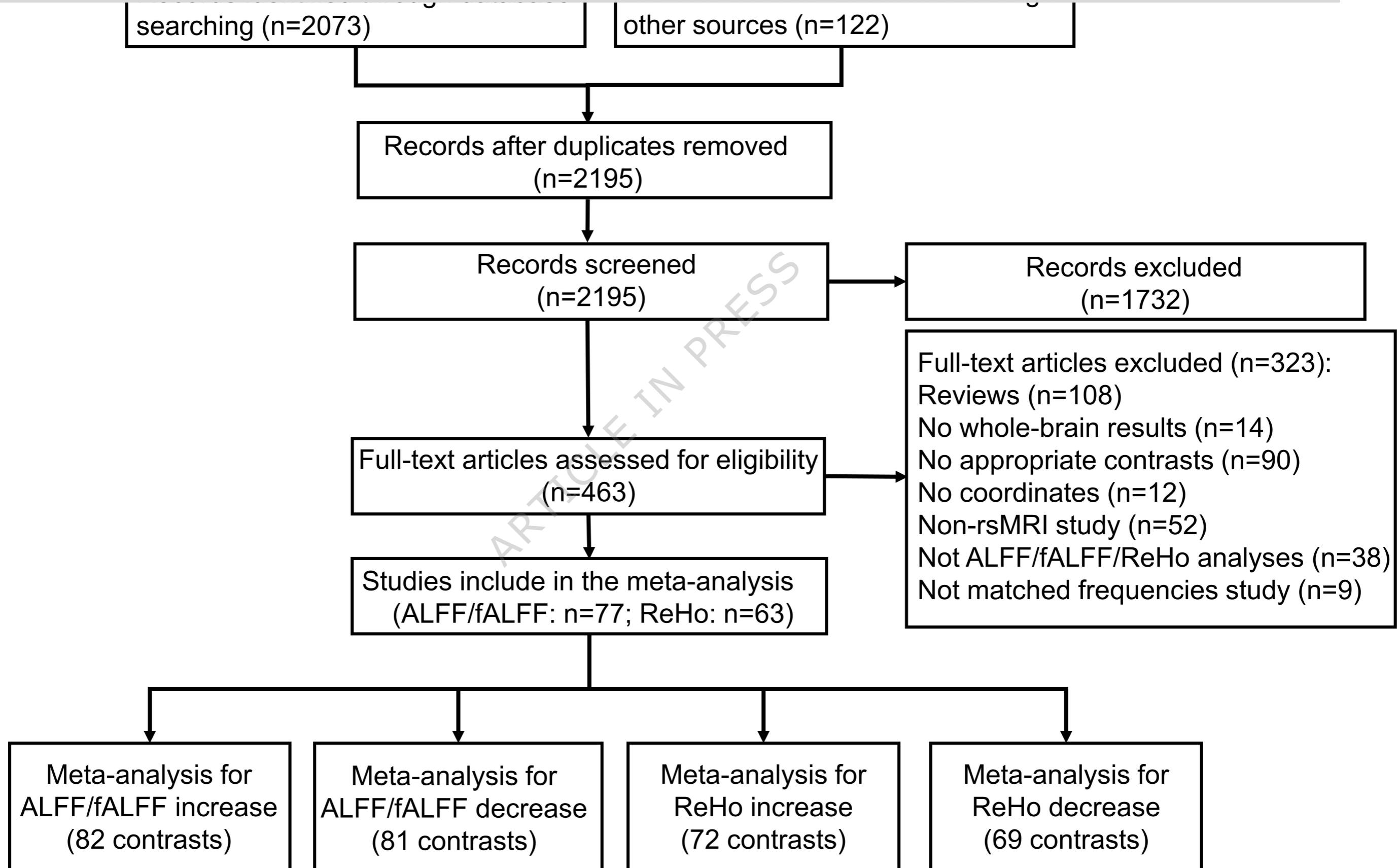
798 **Figure 2. Significant clusters from the main meta-analysis of patients versus healthy controls**
799 **in (A) Transdiagnostic changes in ALFF/fALFF, and (B) Transdiagnostic changes in ReHo**
800 **(cluster-level family-wise error correction ($P < .05$) with a cluster-forming threshold of P**
801 **< .001 using 10000 permutations).** lOFC, lateral orbitofrontal cortex; AI, anterior insula; vLPFC,
802 ventral lateral prefrontal cortex; MOG, middle occipital gyrus; BA, Brodmann; MNI, Montreal
803 Neurological Institute; L, left; R, right.

804

805 **Figure 3. Overall resting state functional connectivity and network distributions.** (A) RSFC
806 results for the regions derived from meta-analysis of transdiagnostic increases in ALFF/fALFF (left
807 panel), and relative/absolute distribution (right panel). (B) RSFC results for the regions derived from
808 meta-analysis of transdiagnostic increases in ReHo (left panel), and relative/absolute distribution
809 (right panel). (C) RSFC results for the regions derived from meta-analysis of transdiagnostic
810 decreases in ReHo (left panel), and relative/absolute distribution (right panel). L, left; R, right; FPN,
811 fronto-parietal network; DAN, dorsal attention network; VAN, ventral attention network; SMN,
812 somatomotor network; VN, visual network; AFN, cortical affective network; DMN, default mode
813 network; SCN, subcortical network.

814

815 **Figure 4. Functional decoding for contributing networks.** WM, working memory.



(A) ALFF/fALFF: Patients > healthy controls

(B) ReHo: Patients > healthy controls

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