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Overlap of Neuroanatomical Involvement in Frontotemporal Dementia and Primary Psychiatric Disorders: A Meta-analysis

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ABSTRACT

BACKGROUND: Despite significant symptomatic overlap between behavioral variant frontotemporal dementia (bvFTD) and primary psychiatric disorders (PPDs), a potential overlap in their structural anatomical changes has not been studied systematically.

METHODS: In this magnetic resonance imaging-based meta-analysis, we included studies on bvFTD, schizophrenia, bipolar disorder, and autism spectrum disorder that 1) used voxel-based morphometry analysis to assess regional gray matter volumes (GMVs) and 2) reported the coordinates of the regional GMV. Separate analyses were performed comparing clusters of coordinate-based changes in the GMVs (n = 24,183) between patients and control subjects, and overlapping brain regions between bvFTD and each PPD were examined.

RESULTS: We found that GMV alterations in the prefrontal and anterior cingulate cortices, temporal lobe, amygdala, and insula comprise the transdiagnostic brain alterations in bvFTD and PPD.

CONCLUSIONS: Our meta-analysis revealed significant anatomical overlap that paves the way for future investigations of shared pathophysiological pathways, and our cross-disorder approach would provide new insights to better understand the relationship between bvFTD and PPD.

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Frontotemporal dementia (FTD) is a neurodegenerative disorder that predominantly affects the frontal and/or temporal lobes (1,2). The most common subtype is the behavioral variant (bvFTD) that presents with behavioral disturbances such as disinhibition, social awkwardness, loss of insight, apathy, loss of empathy, stereotypical behavior, and changes in eating habits (2). One of the earliest and core symptoms of bvFTD is a gradual loss of social cognition (3), which in turn interferes with behavioral and personality aspects.

From a clinical perspective, a number of major primary psychiatric disorders (PPDs) such as schizophrenia (SZ), bipolar disorder (BD), and autism spectrum disorder (ASD) strongly resemble bvFTD (4,5). More specifically, impaired social cognition is one of the core features of PPD (6). Therefore, both bvFTD and major PPDs might be considered as social brain disorders (7). In addition, in daily clinical practice, the elated mood and lack of insight in mania can strongly resemble bvFTD (8). Finally, both the positive and negative symptoms of SZ (e.g., delusions and hallucinations vs. social withdrawal, paucity of spontaneous speech, and concreteness, respectively) are very similar to what is seen in bvFTD (9). Not surprisingly, approximately 50% of patients with bvFTD receive a prior psychiatric diagnosis (4) owing to similar and overlapping diagnostic criteria for bvFTD and various PPDs (2,10). The relationship between psychiatric symptoms and neurodegenerative disease becomes particularly evident in carriers of a *C9orf72* repeat expansion. It has been shown that family members of *C9orf72* mutation carriers have a higher prevalence of SZ and BD, whereas *C9orf72*-related FTD can present with SZ, BD, or ASD symptoms (11–15). Moreover, young cases with a diagnosis of SZ and BD may have underlying FTD neuropathology (16). Based on this empirical overlap, a potential shared neurobiological background between bvFTD and SZ (16–18), BD (8), and ASD (13) has been postulated by independent authors. Their hypotheses, however, remain to be tested.

Based on the clinical overlap and given the significant structural alterations in the frontotemporal brain regions in patients with a PPD in large-scale studies yielded by the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Consortium (19), in this cross-disorder analysis, we hypothesize that bvFTD and PPDs share a biological vulnerability of specific neuroanatomical networks. The identification of shared neuroanatomical vulnerabilities between bvFTD and PPDs is important because such a finding may support a conceptual framework of how these disorders are related and whether they have common pathophysiological pathways that could be targeted by treatment. Voxel-based morphometry (VBM) is a commonly used neuroimaging method that measures gray matter (GM) structure (20). In this cross-disorder

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comparison, we aimed to identify the overlapping GM differences of bvFTD and PPD including SZ, BD, and ASD by using a voxelwise, coordinate-based meta-analytic approach.

METHODS AND MATERIALS

Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (21). Studies included in this meta-analysis were collected by using MEDLINE (PubMed), Embase, and BrainMap databases, covering the literature until April 2020. We registered our meta-analysis on the Open Science Framework (https://osf.io/9kxrb).

Because different methodologies can affect the volumetric results, we avoided combining various analyses. We, therefore, focused on whole-brain VBM analysis to measure GM volume (GMV) that is widely used within the neuroimaging scientific community. Therefore, to avoid any misinterpretation, we excluded GM alterations when investigated using cortical thickness measurements (using FreeSurfer).

PubMed and Embase. Relevant structural GM neuroimaging studies were retrieved using keywords in the form of medical subject heading or Emtree terms and free text terms in the title and abstract, as follows: "Voxel based Morphometry" OR "VBM" OR "gray matter" in combination with either 1) "Frontotemporal Dementia" OR "Pick disease" OR "Frontotemporal Lobar Degeneration," 2) "Schizophrenia," 3) "Bipolar Disorder" OR "Manic Depression," and 4) "autism spectrum disorder" OR "Asperger syndrome." For overview of the full electronic search strategy, see the Supplement.

BrainMap. A search for BrainMap was conducted by using Sleuth 3.0.3 software to retrieve structural neuroimaging studies (22). Studies were selected from the BrainMap's Voxel-Based Morphometry database. Inclusion criteria for selecting structural GM neuroimaging studies were set as follows: "Experiment + Contrast + Gray Matter" and "Experiments + Imaging Modality + MRI" in combination with 1) "Subjects + Diagnosis + Frontotemporal Dementia" or "Subjects + Diagnosis + Frontotemporal Lobar Degeneration," 2) "Subjects + Diagnosis + Schizophrenia," 3)" "Subjects + Diagnosis + Bipolar Disorder," and 4)" "Subjects + Diagnosis + Autism Spectrum Disorders" or "Subjects + Diagnosis + Asperger's Syndrome."

Study Selection

To be included in our meta-analysis, studies had to fulfill the following inclusion criteria: 1) conducted structural neuroimaging analysis comparing patients with healthy control subjects; 2) used the Rascovsky (2), Neary (1), and McKhann (23) diagnostic criteria for bvFTD; used the Autism Diagnostic Interview-Revised for ASD; or used the DSM-III, DSM-IV, DSM-5 (10), or ICD-10 for SZ, BD, and ASD; 3) conducted a VBM analysis for GMV; 4) reported coordinates in Montreal Neurological Institute (MNI) or Talairach stereotactic standard space; 5) only included patients over age 16 years; 6) reported GM alterations, which reported peak coordinates of statistical significance at the whole-brain level; and 7) were written in English. Studies were excluded when 1) no original data were reported, for example, letters to the editor, meta-analyses, or review studies, and 2) the study sample overlapped with those of another publication. In case of sample duplication, the studies from the same institution/cohort at the same period of time were identified, and the study with the largest sample size was selected.

Endnote database (version 9) was used to register all citations in our search. Duplicated studies were removed based on overlapping authorship, study description, year of publication, and journal. The titles and abstracts of the citations were then screened by 2 independent authors (CT and HU) to determine their relevance for inclusion. Disagreements between authors were resolved through consensus or through the decision of a third author (YALP). Full-text articles of the relevant citations were then assessed to determine whether the study met the predefined inclusion criteria (see PRISMA flow charts in Figures S1–S4).

Patient Selection. In the selection of patients from the included studies, we used several diagnostic criteria. For bvFTD, we only selected subjects who had been diagnosed with bvFTD; subjects with other FTD subtypes such as semantic, logopenic, or nonfluent variant primary progressive aphasia were excluded. Studies including subjects with SZ, psychosis, or schizophreniform disorder were included in the SZ diagnostic group. This included patients with either chronic or first-onset psychosis. Subjects diagnosed with BD type I or II or first-episode mania were included in the BD diagnostic group. For the ASD diagnostic group, subjects were included when diagnosed with ASD, Asperger syndrome, or pervasive developmental disorder (not otherwise specified). Finally, some studies included multiple diagnostic groups. For this case, we included separate patient groups in comparison with healthy control subjects.

Data Recorded in the Database

The following data of study characteristics were extracted from full-text articles: sample size and percentage of females in the group, age of the subjects at the time of magnetic resonance imaging (MRI) (mean age and standard deviation), diagnostic criteria used, global IQ or full-scale IQ (autism studies), mood state at time of MRI (BD studies), field strength of the MRI scanner, slice thickness (in mm), smoothing applied (full width at half maximum in mm), threshold p value, software used for analysis, and nuisance covariates (Tables S1–S8).

Data Extraction and Analysis of VBM Studies

Separate analyses were performed comparing clusters of voxels with alterations in regional GMVs between patient groups and healthy control subjects. The analyses were performed at a cluster-forming threshold (reported with each p value and activation likelihood estimation (ALE) thresholds in the results; clusters with greater ALE values than this threshold were considered statistically significant) computed using a $p < .05$, false discovery rate corrected (with no assumptions to correlations within the dataset), and a conservative minimum cluster volume of 200 mm^3 using BrainMap's GingerALE

(version 3.0.2). Peak coordinates for GMV were extracted from eligible studies and were converted to MNI152 template using the Lancaster transformation before analysis (24). The data in MNI coordinates were entered in BrainMap's GingerALE 3.0.2. The details of the procedure can be found on the website (http://brainmap.org/ale/index.html). In brief, meta-analysis calculations were performed using the latest ALE algorithm in GingerALE. The likelihood of anatomical differences between groups was estimated on the basis of the coordinates reported by the included studies in this meta-analysis (25). A modeled map was constructed by combining foci at each voxel. The statistical maps were thresholded using a cluster-level, familywise error–corrected $p < .05$. The coordinate of the weighed center was generated for each cluster. Within the cluster, the maximum ALE value and its coordinates were identified, which was then assigned to the MNI location of the cluster in the MNI152 atlas. Based on the collected coordinates, single datasets were created by GingerALE for each diagnostic group. Separated single-dataset analyses were conducted to investigate GM alterations within each disorder group. After analyzing the single dataset for each diagnostic group, we performed 3 pairwise conjunction analyses to study the overlap between 1) bvFTD and SZ, 2) bvFTD and BD, and 3) bvFTD and ASD. For the conjunction analyses, we used a voxel threshold of $p < .05$ and a cluster-forming threshold of $p < .001$ (26).

Quality Assessment

The study quality of all included articles was assessed using the Joanna Briggs Institute quality assessment tool (27). The 9-point checklist assesses the rigor of inclusion criteria, subject selection, measurement of exposure, measurement of condition, identification of confounders, strategies for confounders, measurement of outcome, and statistical analysis (Tables S5–S8). Owing to the methodology of our included studies, measurement of exposure has not been taken into account in the final quality assessment. The Joanna Briggs Institute quality assessment tool is a recommended methodological quality (risk of bias) assessment tool and is widely used in VBM studies (28–30).

RESULTS

Search Results

A total of 13,205 studies were retrieved following our systematic search strategy for VBM studies contrasting GMV alterations, of which 2225 were for bvFTD, 7135 were for SZ, 2079 were for BD, and 1766 were for ASD. Ultimately, 258 studies met the final inclusion criteria and were included in our review. Of these, 24 studies concerned bvFTD (patients n = 496, control subjects n = 602), 150 SZ (patients n = 7094, control subjects n = 7332), 64 BD (patients n = 3127, control subjects n = 4248), and 20 ASD (patients n = 643, control subjects n = 641) (Table 1; Figures S1–S4).

Overall, our search yielded a sample size of 11,360 patients and 12,823 control subjects in VBM studies. The details of the collected demographical data are displayed in Table 1, and demographics for each separate study can be found in Tables S1–S4. Of note, some studies lacked information on sex distribution or age. In these cases, estimates of missing values for sex distribution and age were imputed with weighted means.

In addition, PRISMA flowcharts (Figures S1–S4), characteristics of the included studies (Tables S1–S4), images (axial MRI slides) for each analysis (Figures S5–S11), peak coordinates (Tables S9–S15), reported region of interest coordinates for lower and higher values, and related brain regions are displayed in the Supplement, and GingerALE results in NIfTI file format are added as Supplemental Files.

Quality Assessment. The overall scores of the quality assessment for each diagnostic group were displayed in Table 2. Between 93% and 97% of the included studies, for each diagnostic group, fulfilled the quality criteria of the Joanna Briggs Institute quality assessment tool, indicating that the included studies were of high quality. A detailed overview of the quality assessment for each item per study can be found in the Supplement (Tables S5–S8).

Single-Dataset Analysis

Behavioral Variant Frontotemporal Dementia. The number of the studies and sample demographics are displayed in Table 1. Whole-brain coordinate-based meta-analysis of VBM studies demonstrated lower GMV in patients with bvFTD than in control subjects in the brain areas involving the bilateral frontal areas (superior, medial, inferior), bilateral cingulate (especially anterior part), bilateral caudate, putamen, globus pallidus, bilateral insula, temporal cortex (superior, medial, fusiform), amygdala, hippocampus, parahippocampus, and right uncus (Figure 1; Table S9 and Figure S5). No larger GMV in the patient group was detected.

Schizophrenia. The number of the studies and sample demographics are displayed in Table 1. Regions of smaller GMV than those of healthy control subjects were observed in the bilateral cingulate (especially anterior cingulate), bilateral frontal and temporal lobes (superior, medial, inferior), insular, parietal areas (left predominant), bilateral caudate, bilateral thalamus, bilateral amygdala, left hippocampus, and left uncus. Only 1 statistically significant cluster was detected as larger GMV in SZ, pointing out the right precentral gyrus (Table S10 and Figure S6). When all volumetric alterations in SZ were combined, GMVs in the anterior cingulate; frontal, temporal, and insular lobes; thalamus; caudate; amygdala; and hippocampus were significantly different compared with healthy control subjects (Figure 1; Table S10 and Figure S6).

Bipolar Disorder. The number of the studies and sample demographics are displayed in Table 1. Significantly smaller GMV was found in the bilateral frontal lobes (superior, medial, inferior), bilateral cingulate (especially anterior cingulate), bilateral insula, bilateral temporal lobes (superior and medial), amygdala, and hippocampus. Although the larger volumes in the putamen were highly reported in the studies on BD, none of those clusters were significant in our analysis. The combination of smaller and larger GMVs in BD revealed that volumetric brain alterations in BD were related to the bilateral prefrontal

Table 1. Demographic Data of the Diagnostic Groups

	Diagnosis			
Demographics	bvFTD	SZ	BD	ASD
No. of Subjects	1098	14,426	7375	1284
Patients (female)	496 (~160)	7094 (~2617)	3127 (~1820)	643 (101)
Healthy control subjects (female)	602 (~250)	7332 (~2986)	4248 (~2380)	641 (~100)
No. of Studies	24	150	64	20
Age, Mean, Years				
Patients	62.0	~32.8	39.5	28.9
Healthy control subjects	~64.2	~32.5	~37.9	29.1

The number of female subjects and the mean age are approximations because these values were not provided in some studies.
ASD, autism spectrum disorder; BD, bipolar disorder; bvFTD, behavioral variant frontotemporal dementia; SZ, schizophrenia.

areas, anterior cingulate, insula, amygdala, hippocampus, and temporal lobes (Figure 1; Table S11 and; Figure S7).

Autism Spectrum Disorder. The number of the studies and sample demographics are displayed in Table 1. Patients with ASD showed significantly smaller GMV, predominantly in the temporal areas. Lower GMV was observed both in cortical areas including the temporal (especially the fusiform gyrus) and insular areas, and in the subcortical areas including the amygdala, putamen, and hippocampus. Although some studies reported larger GMVs especially in the frontal areas, no significant cluster was detected in the separate analysis of larger GMVs in ASD. The combined analysis pointed out the putamen and the temporal areas including the cortical temporal, fusiform, amygdala, and parahippocampal areas. (Figure 1; Table S12 and Figure S8).

Conjunction Analysis

Across all studies, the clear majority of peak voxels represented GM volumetric changes in patients (bvFTD, SZ, BD, and ASD) compared with control individuals. Consistent GM alterations across all diagnostic groups highlighted included the amygdala, insula, cingulate cortex, and medial prefrontal cortex. (Figure 2; Tables S13–S15 and Figures S9–S11). Although we did not conduct a direct volumetric analysis, basal ganglia involvement including the caudate, putamen, and globus pallidus was more eminent in bvFTD. While GM alterations in the caudate were recorded also in SZ and the putamen in ASD, GM alterations in the globus pallidus were not one of the statistically significant clusters in SZ, BD, and ASD compared with their respective healthy control subjects. Of note, GM changes in thalamic area were more prominent in SZ, whereas statistically significant clusters in this area were not observed in other diagnostic groups.

Overlapping Structural Brain Abnormalities Between bvFTD and SZ. GM differences were indicated by conjunction analysis in the bilateral prefrontal areas (medial and inferior), anterior cingulate, insula, amygdala, hippocampus, caudate, and superior temporal lobe in both bvFTD and SZ compared with control subjects (Figure 2; Table S13 and Figure S9).

Overlapping Structural Brain Abnormalities Between bvFTD and BD. Overlapping GM alterations between bvFTD and BD were observed in the medial and inferior prefrontal areas as well as the insula, anterior cingulate, and left superior temporal lobe (Figure 2; Table S14 and Figure S10).

Overlapping Structural Brain Abnormalities Between bvFTD and ASD. Conjunction analysis revealed overlapping areas with GM alterations between bvFTD and ASD in the temporal medial and inferior area, amygdala, uncus, putamen, and insula (Figure 2; Table S15 and Figure S11).

DISCUSSION

In this cross-disorder analysis, we aimed to identify the overlapping anatomical correlates of bvFTD and PPD. We conducted a meta-analysis of structural neuroimaging studies in bvFTD, SZ, BD, and ASD by using an unbiased technique, anatomical likelihood estimation. Brain GM volumetric alterations in the prefrontal, temporal, insular, and the limbic areas were observed in bvFTD, SZ, and BD, whereas GMV changes prominently in the temporal regions were detected in ASD. Our results identified the prefrontal cortex, temporal lobe, amygdala, insula, and anterior cingulate cortex as overlapping brain areas with structural alterations in bvFTD and PPD, especially in SZ and BD. This shared morphometric signature might

Table 2. Quality Assessment of Voxel-Based Morphometry Studies of Gray Matter Included in the Meta-analysis

Study	Inclusion Criteria	Study Subjects	Exposure	Measurement of Condition	Confounding Factors	Strategies for Confounding Factors	Outcome Measurement	Statistical Analysis	Final Score[a]
bvFTD	100%	83%	NA	100%	100%	92%	100%	100%	96%
SZ	97%	77%	NA	100%	100%	75%	100%	100%	93%
BD	100%	85%	NA	100%	100%	97%	100%	100%	97%
ASD	100%	85%	NA	100%	100%	90%	100%	100%	96%

ASD, autism spectrum disorder; BD, bipolar disorder; bvFTD, behavioral variant frontotemporal dementia; NA, not applicable; SZ, schizophrenia.
[a]Because of the methodology of our included studies, "exposure" has not been taken into account in the final score.

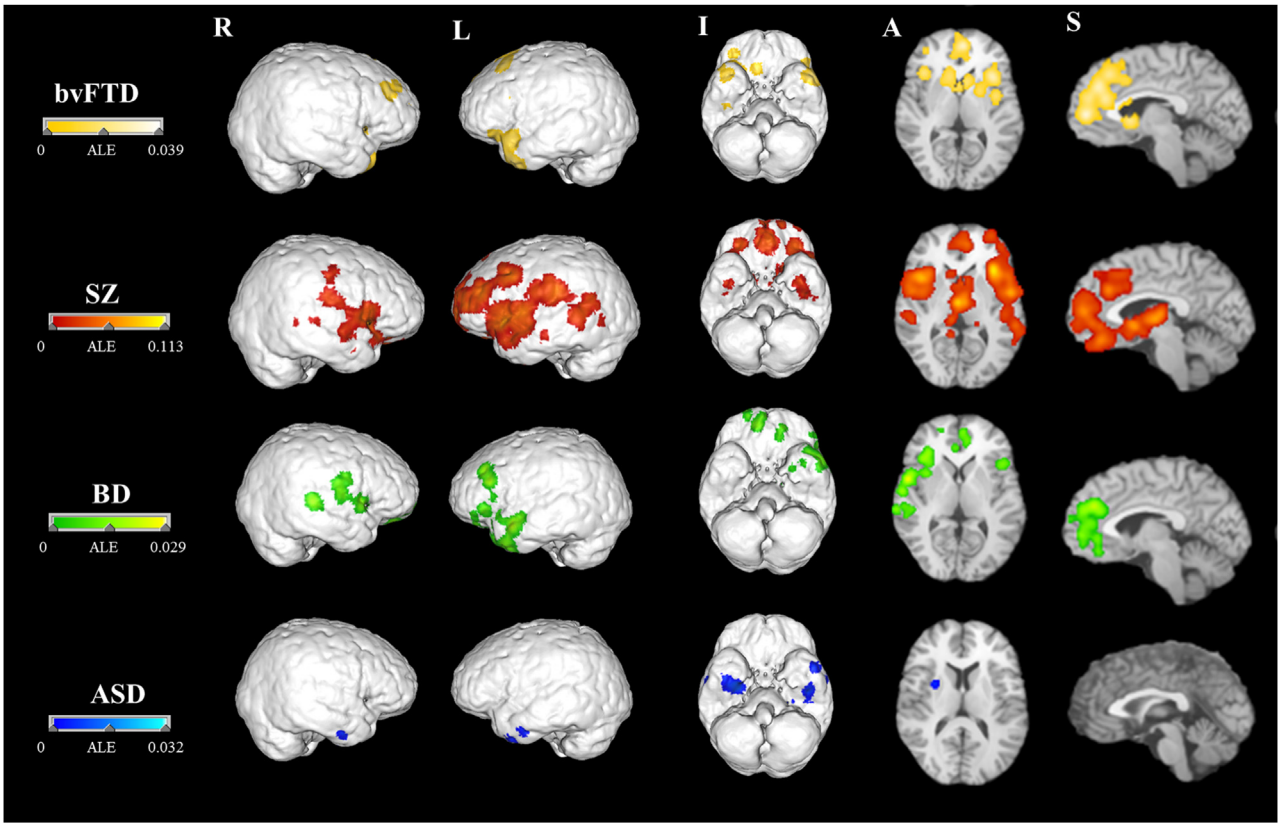

Figure 1. Meta-analytic results of regional gray matter alterations in the diagnostic groups. All results were thresholded at clusterwise threshold $p < .05$ (familywise error–corrected). The activation likelihood estimation (ALE) scores are demonstrated. For the coordinates, brain regions, and detailed presentation of each axial slide for each disorder, see the Supplement. A, axial; ASD, autism spectrum disorder; BD, bipolar disorder; bvFTD, behavioral variant frontotemporal dementia; I, inferior; L, left; R, right; S, sagittal; SZ, schizophrenia.

explain the overlapping clinical phenotypes of those disorders and open the doors for the study of common pathophysiological pathways in both types of disorders.

Brain structural abnormalities have been widely reported in SZ (31), BD (32), and ASD (33), but there is no published meta-analysis reporting the overlapping structural brain abnormalities between bvFTD and those found in PPD, despite their significant clinical overlap. In line with the literature, beyond the frontotemporal cortical areas, the anterior cingulate, insular, and subcortical areas including the caudate, putamen, globus pallidum, and amygdala were affected in bvFTD (34–36). Remarkably, regional volume differences were observed in the same areas in SZ and BD as well. Conjunction analysis confirmed that the prefrontal, cingulate, insular lobes, and amygdala were the shared regions with GM alterations, showing structural alterations in bvFTD and SZ and BD. Not surprisingly, these results have already been published as the overlapping brain areas between SZ and BD (37), but it has not been associated with bvFTD before. Interestingly, over the years, the same anatomical areas have been reported by different authors using different terms such as the neuroanatomical localizations of psychiatric disorders (38,39) and brain morphometric changes in SZ (31,40), BD, (41,42), and ASD (33,43). In addition, similar areas have been reported as the atrophy pattern of bvFTD (34,35), anatomical model of apathy (44–46), disinhibition (47,48), loss of empathy (49,50), emotion regulation system (44,46,50), social cognition (6,51), and limbic-thalamo-prefrontal cortical circuitry (52,53). Another important point is that bvFTD (54,55) and the psychiatric disorders studied here are heritable disorders with variable genetic architectures (56–61). Whereas monogenetic causes underlie bvFTD in 20% to 30% of cases (62), SZ and BD are highly polygenic (57,60). SZ and BD share polygenic overlap, whereas ASD is characterized by both polygenicity and a low percentage (<5%) of rare mutations (57,59–61,63). It is conceivable that through various mechanisms of action, these social brain disorders affect the same neuroanatomical networks (56,61). Our radiological approach is pertinent because neuroimaging studies may offer clues about the effects of the potential shared genetic etiology. Recent ENIGMA-genome-wide association study collaborations have hypothesized that if some brain regions show volumetric case-control differences and others not, these areas may be more vulnerable to the genetic and environmental risk factors, and they have termed it selective brain region vulnerability (64). Indeed, it was found that selective brain region vulnerability overlapped between SZ

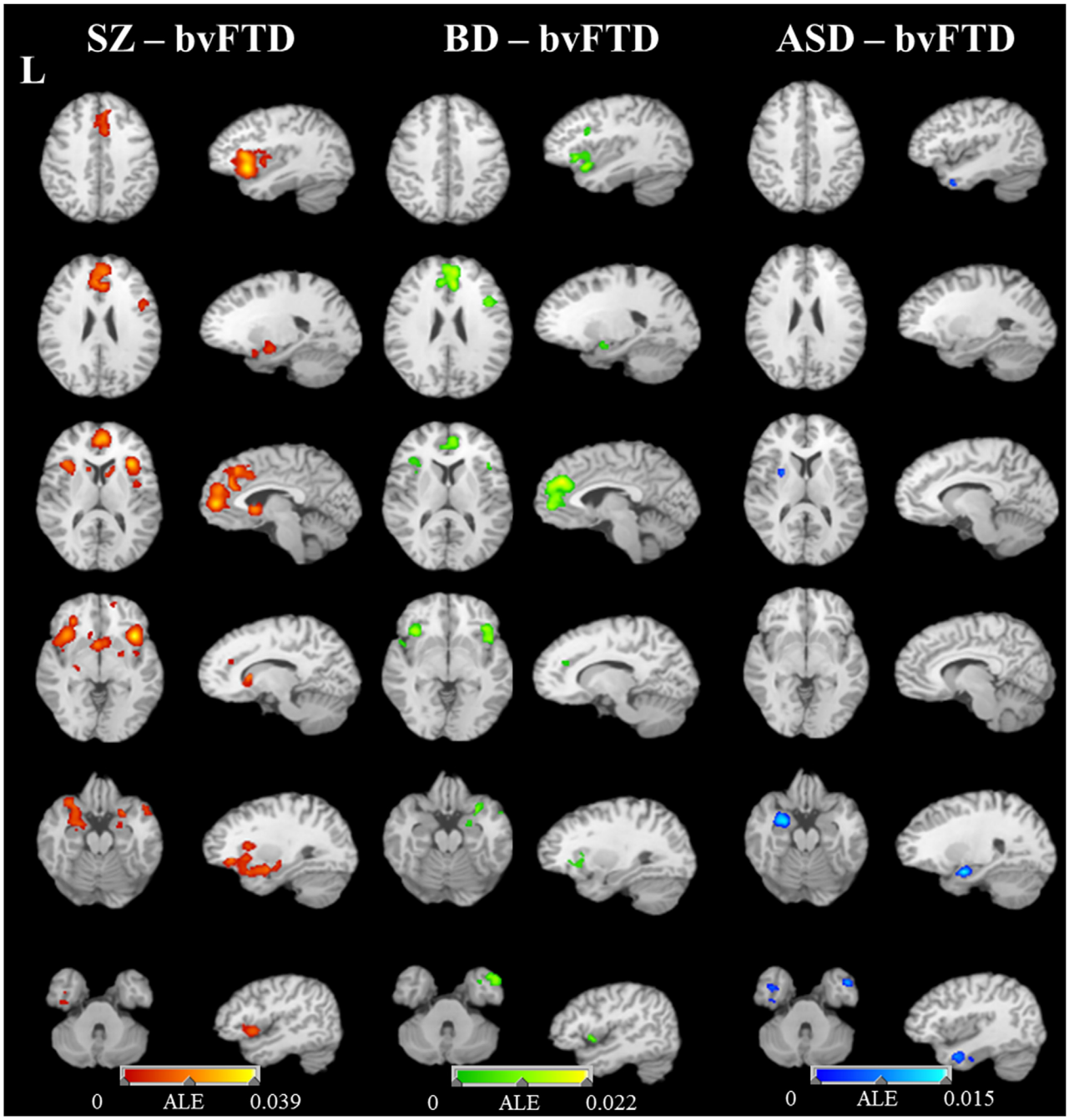

Figure 2. Meta-analytic results of overlapping gray matter alterations among the diagnostic groups. Brain regions involved in the conjunction analysis of behavioral variant frontotemporal dementia (bvFTD) and each psychiatric diagnostic group. All results were thresholded at clusterwise threshold $p < .05$ (familywise error–corrected). The activation likelihood estimation (ALE) scores are demonstrated. For the coordinates, brain regions and detailed presentation of each axial slide for each disease group, see the Supplement. ASD, autism spectrum disorder; BD, bipolar disorder; L, left; SZ, schizophrenia.

and BD and was positively associated with their respective genetic background (64). Consistent with these results, a large body of literature has reported substantial genetic etiologic overlap between SZ and BD (65–68). The results of the present study raise the question whether an etiologic overlap between SZ, BD, and bvFTD might exist.

Apart from the overlapping areas, our separate group analyses were in line with previous meta-analyses focusing on the GM morphometric changes in bvFTD (34), SZ (31,40,69), and BD (41,42,70). However, there was a discrepancy between our results and a large ENIGMA study suggesting larger frontal lobe volumes in ASD (33). The potential explanations of this

inconsistency might be the use of different volumetric-analysis techniques. In this mentioned study (33), FreeSurfer cortical thickness analysis has been used, whereas we only included VBM studies in our meta-analysis to avoid the effect of the different neuroimaging data processing techniques on the results. Second, the effect might be explained by the fact that their sample size was younger than the study populations we included in our meta-analysis. Because our approach is centered on bvFTD, which is an adult-onset disorder, we excluded the pediatric population in our study. Consistent with our interpretation, a large longitudinal neuroimaging study on ASD has shown abnormally high volumes (especially in frontal areas) in early childhood, typical values between ages 10 and 15 years, and then further abnormal decline into adulthood (43). Although numerous explanations such as age and medication effect have been proposed, the mechanism of increased/larger volumes in PPD remains unclear (19). However, this discussion is beyond the scope of this study. Nevertheless, abnormal cortical brain volumes (smaller or larger) in the frontotemporal areas occur in ASD, which supports our argument that ASD is also a frontotemporal lobe disorder.

This is the first study focusing on the overlapping neuroanatomical signatures in bvFTD and PPD. Although our study contains the largest sample size in the literature, there are some limitations that should be addressed. First, we included the studies that reported significant clusters and displayed the region of interest coordinates. Therefore, other large sample size neuroimaging studies that did not display the region of interest coordinates were excluded. Second, we included only VBM studies for the GM structural brain changes analysis. Even though it excluded a large number of studies, we restricted ourselves to those methodologies because variability in the neuroimaging data acquisition, processing, and analysis protocols can affect the sensitivity and apparent variability of other brain imaging measures, making it challenging to compare different studies. Because negative results might likely have not been published, another strong concern in all meta-analyses is publication bias. In contrast, our results were in line with large sample size studies such as ENIGMA that collects and assesses extracted data and other meta-analyses, suggesting that a potential publication bias or our exclusion criteria did not create a major bias. In addition, because the prevalence of bvFTD is lower than that of PPD and owing to our strict inclusion criteria, the bvFTD sample size was smaller than those of SZ and BD. Moreover, because we could not use individual data, we were unable to conduct direct volume comparisons between diagnostic groups. Our methodology provided the statistically significant clusters only between patient groups and their respective age- and sex-matched/corrected control groups. Therefore, the design of the current study does not provide any data to directly compare atrophy severity between bvFTD and PPD. However, we observed GM differences between bvFTD and PPD especially in basal ganglia areas that need to be tested by future better designed methodologies. Moreover, although we cannot generalize our results to all genetic or sporadic subtypes of FTD, this novel approach could initiate more detailed studies in the future focusing on the relationship between bvFTD and PPD.

To conclude, we found considerable overlap in neuroanatomical involvement between 2 diagnostic groups classified as neurodegenerative (bvFTD) versus non-neurodegenerative (PPD), pointing to shared genetic or environmental selective brain region vulnerability that can explain their clinical overlap. We believe that such a cross-disorder point of view might allow identification of shared disease mechanisms and development of analogous disease modifying treatments.

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