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No alterations of brain structural asymmetry in Major Depressive Disorder: An ENIGMA consortium analysis

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Abstract

Magnetic resonance imaging (MRI) studies have shown subtle differences of brain anatomy between people with major depressive disorder (MDD) and healthy controls, but few studies have specifically examined brain anatomical asymmetry in relation to this disorder, and results from those studies have remained inconclusive. Asymmetry is a subtle but pervasive aspect of the human brain, and it may be altered in several psychiatric conditions. At the functional level, some electroencephalography studies have indicated left fronto-cortical hypo-activity and right parietal hypo-activity in depressive disorders, so that aspects of lateralized anatomy might also be affected. In the current study, we investigated 2256 individuals with MDD and 3504 controls, from 31 separate datasets, for differences in the laterality of thickness and surface area measures of 34 cerebral cortical regions. We also investigated volume asymmetries of eight subcortical structures, in 2540 MDD individuals and 4230 controls, from 32 datasets. T1-weighted MRI data were processed with a single protocol using FreeSurfer software and the Desikan-Killiany atlas. The unprecedented sample size provided 80% power to detect effects of the order of Cohen's d = 0.1. However, the largest effect size of MDD diagnosis was Cohen's d = 0.085 for the thickness asymmetry of the superior temporal cortex, which was not significant when adjusting for multiple testing. Asymmetry measures were also not significantly associated with medication use, acute versus remitted status, first episode versus recurrent status, or age at onset. Altered brain macro-anatomical asymmetry may therefore be of little relevance to MDD aetiology in most cases.

Keywords: laterality, left-right asymmetry, major depressive disorder, MRI

Introduction

Major Depressive Disorder (MDD) is a common and debilitating psychiatric disorder, characterized by a persistent feeling of sadness or a lack of interest in outside stimuli (DSM-V) (1). The disorder is often characterized by recurrent episodes and can become a chronic condition (2). Worldwide, lifetime prevalence varies considerably. A WHO World Mental Health survey across 18 countries found an average lifetime prevalence ranging from 6.6% in Japan to 21.0% in France, with an average lifetime prevalence of 14.6% across high-income countries (3).

Much of the neurobiology of MDD is unknown, but subtle alterations of brain structure may be involved, and various MRI-based studies have observed regional brain differences between MDD individuals and healthy controls. A recent review of the literature by Zhang (4) described various possible structural alterations in the brains of MDD individuals, such as case-control differences in the thickness of the medial orbitofrontal cortex and inferior parietal gyrus. However, it was also noted that the results of structural MRI studies in MDD have often been inconsistent (4). This inconsistency is likely due to the use of small study sample sizes in relation to subtle effects, and also heterogeneity among studies in terms of clinical characteristics and methodological aspects. For example, hardware and software differences between scanners and distinct data processing pipelines can contribute to heterogeneity (5).

In the ENIGMA (Enhancing Neuro-Imaging Genetics through Meta-Analysis) consortium (http://enigma.ini.usc.edu), researchers from around the world collaborate to analyse many separate datasets jointly, and to reduce some of the technical heterogeneity by using harmonized MRI preprocessing protocols. Two recent studies by the ENIGMA consortium's MDD working group showed differences in cerebral cortical and subcortical brain structures between more than 1700 MDD individuals and 7000 controls. Relative to controls, MDD individuals had significantly smaller hippocampal volumes (6). In addition, adults with MDD had thinner cortical grey matter than controls in the orbitofrontal cortex, anterior and posterior cingulate cortex, insula and temporal lobes (7), and adolescent MDD individuals had a lower total cortical surface area than age-matched controls, driven particularly by regional reductions of the medial orbitofrontal cortex and superior frontal gyrus, as well as primary and higher-order visual, somatosensory and motor surface areas (7).

Left-right asymmetry is an important aspect of human brain organization, that may be altered in various psychiatric and neurocognitive conditions, including schizophrenia, autism and dyslexia (8-10). There are indications that altered brain asymmetry might also play a role in MDD. On a functional level, EEG studies have reported that asymmetry in frontal brain resting activity differs between MDD individuals and healthy controls, although not always in a consistent direction, and

moderated by age and sex (see e.g. (11-14), reviewed in (15, 16)). Such findings have led to the development of stimulation protocols targeted at the left dorso-lateral prefrontal cortex, which are now used in the clinic for the treatment of MDD (17). Moreover, a recent review considered studies based on dichotic listening, visual hemifield analysis, electrophysiology, and neuroimaging, and concluded that there was evidence for reductions of left frontal and right parietotemporal function in depressive disorders (18). A reduction of left frontal activity is in accordance with approach/withdrawal models of MDD, in which the normal balance of left frontal activity underlying positive reactions to positive stimuli, and right frontal activity underlying negative reactions to negative stimuli, might be disturbed (19, 20).

Some of the average brain anatomical differences between MDD individuals and controls, described in the review by Zhang *et al.*(4), involved only one of the two hemispheres. Zhang *et al*. concluded that the right medial orbitofrontal cortex was often found to be thinner in MDD individuals than controls, while the volumes of the left middle frontal gyrus and the right thalamus were lower in MDD individuals (4). The ENIGMA consortium study of the cerebral cortex found, in adults, that the thickness of the inferior temporal gyrus and caudal anterior cingulate was significantly thinner in MDD individuals only on the right side, but not on the left (7). However, in these analyses it was not tested whether effect sizes of diagnosis were significantly different on the left and right sides, nor was asymmetry quantified as a trait in its own right. Rather, the unilateral patterns were reported on the basis that one hemisphere achieved statistical significance against the null hypothesis of no effect of diagnosis, and the other side did not. Such patterns can reflect insufficient statistical power to detect small but uniform bilateral effect sizes, and do not necessarily indicate differences in brain laterality *per se*. Furthermore, to analyze asymmetry alterations in MDD, a post hoc statistical comparison of the left and right-sided effect sizes reported by the previous studies would not yield the same level of statistical power as can be provided by utilizing the individual-level paired left and right data. Meanwhile the ENIGMA study of subcortical volumes did not consider left and right hemisphere measures separately, as they were combined together for bilateral averages (6).

Brain structural asymmetry in MDD has only been investigated in a small number of individual studies with limited sample sizes. These include a study of grey matter volume of the dorsolateral prefrontal cortex in 39 treatment-naive MDD individuals, 31 medicated MDD individuals, and 49 controls, in which the treatment-naive individuals had increased rightward asymmetry (i.e., the extent of right>left asymmetry was larger) relative to controls (21). Another study reported that the frontal lobe volume was on average less rightward asymmetric in MDD individuals (N=34) than in controls (N=30) (22). No large-scale studies of brain asymmetry in MDD have been performed to date.

To systematically investigate structural asymmetries in the brains of MDD individuals vs healthy controls, we used data available through the ENIGMA consortium's MDD Working Group, and targeted brain regional and global hemispheric lateralities as assessed by the asymmetry index AI=(Left-Right)/(Left+Right). In healthy populations, some regional brain asymmetries show mean sex differences (23, 24). In addition, MDD is often reported to be more common in women than men; for example, a sex ratio of 1.6:1 was found in a Canadian survey (25). The disorder can also present differently in men and women (25, 26). These observations prompted us to perform secondary - analyses separately by sex. Furthermore, some structural brain differences between MDD individuals and controls were found to be distinct between adolescent and adult groups (see above)(7). Asymmetries of the brain also change with age in healthy populations, for some subcortical (23) and cortical regions (24). We therefore carried out secondary analyses in separate subgroups of MDD individuals and controls under and over age 21 years at the time of scanning. As MDD is a clinically heterogeneous disorder, we also tested whether structural brain asymmetries are different in medicated versus non-medicated MDD individuals, acute MDD individuals versus those in remission, first episode MDD individuals versus those with recurrent episodes, or in relation to age at onset of the disorder.

Methods

Datasets

For this study, we pooled individual-level data from 32 non-overlapping datasets collected around the world, of which one dataset included only subcortical volumes, and all others had both subcortical and cerebral cortical measures. See Online supplement Table S1 for the geographic locations and demographics of the different samples. All participating sites obtained approval from local institutional review boards and ethics committees, and all study participants provided written informed consent.

In total, the combined dataset for cortical measures contained 2256 MDD individuals and 3504 controls after local quality control at each centre (see below), but before central quality control, which was performed specifically for the present study (further explained below). The combined dataset for subcortical measures consisted of 2540 cases and 4230 controls, before central quality control. Eleven of the study centres contributing to this analysis were also involved in the previous study of cortical differences between MDD individuals and controls (7), while eight of the current study centres also contributed to the previous ENIGMA MDD subcortical study (6). The mean age at sampling across datasets was 37.1 years (s.d. 16.1) for MDD individuals and 39.0 (s.d. 17.3) for controls, respectively. Of the MDD individuals, 36% were male, and of the controls 47% were male.

Descriptive information per dataset is presented in Online supplement Table S1, and diagnostic instruments are described in Online supplement Table S2. Data on antidepressant medication use at time of scanning, recurrent episodes, acute versus remitted status, and age of MDD onset can be found per dataset In Online supplement Table S3.

Image processing

Structural T1-weighted brain MRI scans were acquired at each study site. Images were acquired at different field strengths (1.5 T or 3 T), and with various acquisition parameters as shown in Online supplement Table S4. All sites then applied harmonized processing and quality control protocols developed or adopted by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols). The data used in the current study were left and right volumes of eight bilaterally paired subcortical structures (strictly seven subcortical structures plus the lateral ventricles), and thickness and surface area measures for each of 34 bilaterally paired cortical regions, the latter as defined with the Desikan-Killiany atlas (27). In addition, the average cortical thickness and total surface area per entire hemisphere were analysed. Subcortical segmentation and cortical parcellations were performed with the freely available and validated software FreeSurfer (versions 5.1 or 5.3) (28, 29). Parcellation of cortical grey matter regions were visually inspected and statistically evaluated for outliers following the standardized ENIGMA protocol (http://enigma.ini.usc.edu/protocols/imaging-protocols).

Data preparation, visualization and statistical analysis

De-identified data were sent from all datasets to a central analysis team. As a measure of asymmetry for each bilaterally paired measure, we then calculated the asymmetry index: AI=(L-R)/(L+R), where L and R are the left and right measures, respectively. Thus, positive and negative AI values indicate leftward and rightward asymmetry, respectively. It is important to note that in the definition of the AI, the difference (i.e., L-R) was normalized by use of the bilateral measure as denominator (i.e., L+R), such that the measure does not scale with the overall magnitude of L and R. For this reason, we did not adjust for intracranial volume in our analyses. Furthermore, we were interested to detect the full extent of any case-control effects on AIs, without removing variance in the AIs that might be correlated with other brain measures potentially affected in MDD.

Quality control at the sites had excluded individual datapoints. Centrally, subjects with more than four entries missing for the eight subcortical volumes were excluded from the analysis of subcortical regions, as having possibly unreliable subcortical data. Similarly, subjects with more than eight missing values out of 34 regional cortical thickness measures were removed altogether from the analysis of cortical thickness, and likewise for surface area measures. Exclusion of subjects by this

step varied from 1% of both MDD individuals and controls for the subcortical data, up to 3% of controls for the surface area data. The total remaining numbers were, 3399 controls and 2217 MDD individuals for the cortical surface areas, 3427 controls and 2229 MDD individuals for the cortical thickness values, and 4185 controls and 2517 MDD individuals for the subcortical volumes. The numbers of individual missing values then varied by structure: from 0.16% missing values for the surface area of the lateral orbitofrontal cortex to 14.3% missing values for the surface area of the entorhinal cortex: Full numbers can be found in Online supplement Table S5.

To prevent large effects of possible outliers, all AIs were winsorized to 2.2 times the inter-quartile range, as recommended in (30). Frequency histograms of each AI are shown in Supp. Figure 1. The per-dataset means for each AI were computed, and multidimensional scaling-plots were created separately for cortical thickness AIs, cortical surface AIs, and subcortical volume AIs, to visualize whether any datasets were obvious outliers in terms of their population-level laterality, as considered over multiple regions.

Using individual-level data from all available datasets, for each structure separately, a linear mixed model was fitted using R (version 3.4.0), with AI as the dependent variable, and Sex, Age, Age^2 and Diagnosis (MDD or control) as fixed factors, with 'dataset' as a random factor (random intercept). As Age and Age^2 are highly correlated, we made use of the poly()-function in R for these two predictors, which created a pair of uncorrelated variables to model age effects (so-called orthogonal polynomials)(31), where one variable was linear and one non-linear'. Model fit was checked visually by inspection of the plots of residuals vs fitted values, and the QQ plots for the residual values. Cook's distance plots by dataset (R command CookD (lme_model, group="dataset") were used to visualize whether any of the datasets were obvious outliers at the level of individual structures. To interpret the results of our analysis, we used a false discovery rate (FDR) of 0.05 within all AIs of a given structural measure, so separately within 35 cortical thickness AIs, 35 cortical surface area AIs, and eight subcortical volume AIs. A global FDR assessment was also planned, over all AIs tested in the main analysis of all subjects, but no effects of diagnosis on AIs proved significant within the separate FDR corrections (see Results), so that a global assessment was not needed. We calculated Cohen's d for the effect size of diagnosis on each AI, as *t*sqrt(1/n1 + 1/n2),* where n1 and n2 are the sample sizes of the MDD individuals and the controls respectively, and *t* is the *t* statistic for the diagnosis term in the model for a given AI. Brain anatomical figures were generated using Freesurfer functions and triangular surface plotting (trisurf) in Matlab R2015b, with the Cohen's d statistics for cortical regions projected onto the pial surface.

We used the pwr() command in R to calculate *a priori* the minimal effect size that we had 80% power to detect with the available data. (As each linear model included multiple predictor variables, including a random effect, the *a priori* power could not be computed exactly, but this calculation assumed the use of simple t-tests to provide a useful indication). For the cortical measures we set a significance level of 0.001 (roughly 0.05/35 in the context of multiple testing over all 34 regional AIs and one global hemispheric AI). This showed that the indicative minimum effect at 80% power was Cohen's d=0.112. For the subcortical AIs (corrected at 0.05/8=0.006), the indicative minimum effect at 80% power was d=0.090.

For secondary analysis of the effects of MDD diagnosis on AIs within demographic subsets, we separated the data into females only, males only, individuals ≤ 21 years of age or individuals >21 years at the time of scanning. The same linear mixed model as above was applied to each of these subsets separately, except that the factor 'sex' was not included for the male- or female-only subsets.

Secondary analyses of AIs in relation to clinical variables were carried out within MDD individuals only (see Supp. Table S3). For binary clinical variables (recurrent versus first episode, medicated versus un-medicated with antidepressants at time of scanning, acute versus remitted), we used the same linear mixed model approach described above, except now replacing the diagnosis status with the binary clinical variable in question. For this purpose we only included datasets with at least ten MDD individuals of each subgroup. Age at onset within MDD individuals was tested as a linear effect on AIs, otherwise using the same linear mixed model as for the main analysis. See Supp. Tables S6a-c and S7a-c for the sample sizes used for each linear mixed model in these secondary analyses. FDR adjusted p-values are presented, for the 8 (subcortical) or 35 (cortical) AIs within each separate analysis.

Results

MDS-plots based on per-dataset AI means showed that none of the datasets were extreme outliers, viewed across all brain structures (Supp. Figure 2).

In the main analysis (all MDD individuals versus controls), no significant effects of diagnosis were found for any of the cortical thickness, cortical surface or subcortical volume AIs, after multiple testing correction (Tables 1-3, Table S5). The subset analyses by age and sex also showed no significant effects of diagnoses on AIs (Tables 1-3, Table S5). A small number of nominal (unadjusted) P values for effects of diagnosis on AIs were below 0.01, but none survived FDR correction for multiple comparisons. The strongest effect of diagnosis on asymmetry in the main analysis was for

the superior temporal gyrus thickness asymmetry, with an unstandardised effect of diagnosis on AI (i.e. the mean AI difference between cases and controls after adjustment for the other model effects) of 0.002, nominal (unadjusted) p=0.003, Cohen's d = 0.085. For this region, the right surface area was larger than the left in controls, and also in cases but to a lesser extent (Table S5). Similar effects were found for the caudal anterior cingulate thickness AI (Cohen's d = 0.079; L>R in controls and more so in cases) and the cuneus surface area asymmetry (Cohen's d = -0.081; R>L in controls and more so in cases)(Table S5). Some of the subset analyses also produced nominally significant effects, such as for hippocampal volume asymmetry in males only (Cohen's d = -0.112) (Tables 1-3, Table S5). However, in the context of multiple testing, these cannot be considered reliable effects. Full model results are included in Table S5.

We visualized the Cohen's *d* values from the main analyses (all subjects combined, i.e. the left-most columns of Tables 2 and 3) against a cortical brain image, to help assess whether any multi-region patterns were discernible which might have spanned neighbouring regions, or corresponded with the frontal-occipital or dorso-ventral axes (Figure 1). No clear patterns were visible.

The analysis of clinical variable effects on AIs within MDD individuals (Supp. Tables 6abc-7abc) showed only one significant P value <0.05 after multiple testing adjustment: the cortical thickness of the fusiform gyrus was more rightward asymmetric in persons using antidepressants at time of scanning (adjusted p-value 0.046). However, this p-value was only adjusted within this particular analysis (i.e., 35 cortical thickness AIs tested for effects of medication use) and should be interpreted with care, given the degree of study-wide testing involved. Full results from these analyses can be found in Supp. Tables 6abc-7abc.

Discussion

In this study, no significant differences of brain structural asymmetry were found between individuals with MDD and unaffected controls, for any cerebral cortical or subcortical asymmetry measure, in an unprecedented sample size of over 5,000 subjects. Power analysis indicated that we had 80% power *a priori* to detect a case-control Cohen's *d* of roughly 0.1 for a given AI, in the main analysis. However, the strongest effect of diagnosis involved Cohen's *d* = 0.085 for the superior temporal gyrus thickness AI, which was too subtle to be statistically significant when considering multiple testing, even with this large sample size (adjusted P value of 0.104). There were similarly small and non-significant changes of caudal anterior cingulate thickness asymmetry (Cohen's *d* = 0.079) and cuneus surface area asymmetry (Cohen's *d* = -0.081). We are not aware of previous findings in the literature which are concordant with these effects. If differences in the asymmetry of brain structures between individuals with MDD and unaffected controls do exist, they were too small

to be detected reliably in this analysis. Our study illustrates the importance of taking large-scale and systematic approaches to the study of brain-disorder associations.

We found no support for alterations of asymmetry that are consistent with those reported in two previous, small studies (see Introduction) of the dorsolateral prefrontal cortex (21) or frontal lobe (22). In our data, sub-regions that are part of the dorsolateral prefrontal cortex showed merely tentative case-control differences for cortical surface area, in opposite directions across sub-regions (Figure 1). It may therefore be that the earlier studies reported false positive findings in the context of small datasets, although the cortical atlas that we used did not have a perfect equivalent for the measures defined in these studies, and we did not consider grey matter volumes as such. Rather, we studied regional cortical thicknesses and surface areas as distinct measures, which together drive grey matter volumetric measures, but have been shown to vary relatively independently (32), such that separate analyses are well motivated.

The possibility remains that altered brain functional or structural asymmetry might be related, as cause, correlate or effect, to MDD in some etiological subgroups of individuals. The previous ENIGMA consortium analyses of brain structural changes in MDD (in which asymmetry was not investigated; see Introduction) found case-control differences particularly in the context of multiple episodes of depression and/or in relation to age of onset of depression (6, 7). One possibility is therefore that brain changes in MDD may be driven by long-term stress associated with the disorder. Following our main analysis, we sub-divided the data by sex and age groups, and we also analyzed various clinical variables within MDD individuals (recurrent versus first episode, on antidepressant medication versus antidepressant-free at time of scanning, acute versus remitted, age at onset), but found no convincing evidence for effects within these subgroups. Sample sizes for these secondary analyses were reduced relative to the main analysis, due to either subsetting or limited availability of clinical variables (Supp. Tables S6a-S7c), while multiple testing for these secondary analyses was substantial. We found one tentative effect involving thickness asymmetry of the fusiform gyrus, with respect to medication status of MDD individuals (FDR adjusted P= 0.046). In a previous study, medication naïve persons with MDD (N=37) showed a greater thickness of the left fusiform gyrus than healthy controls (N=41)(33), while in our analysis, MDD individuals using antidepressant medication had a rightward change of thickness asymmetry of the fusiform cortex compared to MDD individuals that were not using antidepressants at time of scanning. Given the degree of multiple testing in our secondary analyses, and that this finding has no previous support in the literature, we regard it as tentative. Furthermore, we had no systematic information on past use of medication or other treatments, nor dose levels at the time of scanning, both of which may relate to disorder duration and severity, such that this finding must be interpreted with caution. We did not have information on other diagnostic

subtypes such as melancholia or atypical depression, which may be important with respect to the biological heterogeneity of MDD, and will need further research.

While we did not find case-control differences of brain structural asymmetry in this study, functional asymmetries may still play an important role in MDD. Relations between structural and functional variability of the brain are subtle and complex (34-37). As mentioned in the introduction, various studies of depression have reported case-control differences in the asymmetry of frontal electrophysiological patterns (11, 14). The number of pyramidal cells, the number of synapses per cell, and their firing patterns are thought to influence cortical EEG recordings (38). A difference in the number of pyramidal cells may also affect cortical thickness (39). In fact, an inverse relation between cortical thickness and EEG alpha power has been reported for some cortical regions (40). However, a recent meta-analysis of frontal alpha asymmetry as a diagnostic marker in depression (16 studies, MDD: n = 1883, controls: n = 2161) found no significant difference between individuals with MDD and controls (16). Other reviews also point to inconsistencies or problems in studies of frontal alpha asymmetries in depression (15, 41), although most have been studies of the resting state, while there is evidence that EEG differences are stronger during cognitive or emotional processing tasks (42, 43). A recent study which made use of resting state fMRI reported that certain bilateral changes, which were found between 709 MDD individuals and 725 controls, would require a minimum of 400 individuals per group to be detectable, and also that brain–clinical variable relationships exhibited poor cross-centre reproducibility (44). Clearly, large scale studies are necessary for brain imaging research into disorder associations, to reach reliable conclusions.

As regards asymmetry specifically, it is unclear how altered functional laterality might relate to MDD in terms of cause, effect, or correlation due to shared underlying factors. The average form of human brain laterality is probably established in the embryo, as indicated by *in utero* behavioural data (45, 46), as well as neuroanatomical studies of foetuses (47, 48), and gene expression analysis in which left and right-sided samples from the embryonic central nervous system are contrasted (49-51). The typical form of human brain asymmetry is characterised by left-hemisphere language dominance (in more than 85% of people) (52), right-handedness (also roughly 85% of people) (53), and a particular anatomical pattern involving both subcortical and cerebral cortical features (23, 24). However, human brain laterality is also highly variable between individuals. Factors that cause variation around the average form are largely unknown, and heritability estimates are generally low to modest for both functional and structural aspects, while age and sex have significant but subtle effects (10, 23, 24).

We did not consider handedness as a factor in our models, as handedness did not show an effect on brain anatomical laterality in an analysis of over 17,000 subjects from healthy control and population datasets, also performed by the ENIGMA consortium (24). Data on handedness were limited for many of the datasets in the present study.

In a multi-centre study such as ours, the between-centre variability may result in reduced statistical power relative to an equally sized single-centre study, but no single centre has been able to collect such large samples alone. In addition, multi-centre studies can be representative of real-world heterogeneity, with potentially more generalizable findings than single-centre studies (54).

Conclusions

Although the present study examined a large sample size, with 80% power *a priori* to detect case-control differences in the order of Cohen's *d*=0.1, we found no significant differences between individuals with MDD and controls in asymmetries of cerebral cortical thickness and surface area measures, nor for subcortical volume asymmetries. Our study illustrates how high-powered and systematic studies can yield clearer findings in human clinical neuroscience, where previous studies had provided a mixed picture.

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Conflicts of interest

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Figure Legends

Figure 1. Effect sizes (as Cohen's d) for regional asymmetry differences in cortical thickness and surface area, between MDD individuals and unaffected controls. A positive effect means that

individuals with MDD were more leftward/less rightward asymmetrical than controls. From top to bottom: lateral, medial, inferior, fronto-lateral views. Note that all Cohen's d values ranged from -0.081 to 0.085, and that none of the differences between individuals with MDD and controls were significant after adjustment for multiple testing across regions.

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Tables

Table 1 Cohen's d and p-values for the effects of diagnosis on AIs of subcortical volumes. A positive effect means that cases are more leftwards/less rightwards asymmetrical than controls.

	All		Males		Females		> 21 years		≤ 21 years	
Region	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**
accumbens	0.0009	0.972	-0.026	0.541	0.023	0.492	0.012	0.679	-0.004	0.948
amygdala	0.0163	0.523	0.041	0.324	0.001	0.986	0.009	0.759	0.029	0.646
caudate	-0.0159	0.534	-0.018	0.654	-0.011	0.737	-0.008	0.771	-0.072	0.258
hippocampus	-0.0414	0.105	-0.112	0.007	-0.003	0.928	-0.037	0.187	-0.029	0.652
lateral ventricles	0.0584	0.021	0.057	0.168	0.059	0.072	0.046	0.106	0.089	0.156
pallidum	-0.0224	0.391	-0.088	0.037	0.009	0.782	-0.003	0.930	-0.087	0.186
putamen	-0.0278	0.286	-0.099	0.018	0.012	0.723	-0.025	0.382	-0.026	0.691
thalamus	0.0010	0.969	0.019	0.640	-0.016	0.631	0.002	0.934	-0.029	0.647

Table 2 Cohen's d and p-values for the effects of diagnosis on AIs of cortical surface areas. A positive effect means that cases are more leftwards/less rightwards asymmetrical than controls.

	All		Males		Females		> 21 years		≤ 21 years	
Region	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**
total surface area	0.017	0.543	-0.035	0.475	0.052	0.188	0.017	0.580	0.069	0.295
banks sts	0.004	0.879	0.009	0.858	-0.010	0.812	-0.013	0.680	0.072	0.300
caudal anterior cingulate	-0.022	0.434	-0.079	0.109	-0.012	0.763	-0.030	0.336	0.015	0.817
caudal middle frontal	0.058	0.036	-0.024	0.634	0.104	0.009	0.044	0.152	0.139	0.035
cuneus	-0.081	0.003	-0.124	0.012	-0.051	0.201	-0.071	0.022	-0.047	0.480
entorhinal	-0.005	0.864	0.068	0.195	-0.029	0.498	-0.008	0.803	-0.009	0.888
frontal pole	-0.045	0.102	-0.044	0.371	-0.056	0.158	-0.027	0.379	-0.126	0.057
fusiform	-0.002	0.944	0.060	0.241	-0.041	0.309	0.030	0.341	-0.122	0.065
inferior parietal	-0.031	0.273	0.008	0.877	0.007	0.862	-0.044	0.159	0.028	0.668
inferior temporal	0.037	0.185	0.057	0.246	0.035	0.379	0.029	0.343	0.085	0.197
insula	0.046	0.098	0.072	0.141	0.013	0.744	0.065	0.035	0.008	0.899
isthmus cingulate	0.003	0.918	0.068	0.166	0.055	0.167	0.004	0.890	0.039	0.553
lateral occipital	0.000	0.986	0.033	0.500	-0.018	0.652	-0.003	0.930	0.029	0.659
lateral orbitofrontal	0.004	0.891	0.034	0.488	-0.015	0.713	0.003	0.923	0.001	0.982
lingual	0.010	0.730	-0.022	0.649	0.069	0.080	-0.003	0.913	0.069	0.297
medial-orbitofrontal	-0.019	0.503	0.025	0.612	-0.036	0.369	-0.045	0.152	0.082	0.212
middle temporal	-0.042	0.140	0.008	0.868	-0.099	0.016	-0.047	0.139	-0.038	0.578
para-central	0.031	0.261	0.020	0.689	0.030	0.463	0.041	0.190	0.027	0.686
parahippocampal	-0.003	0.925	0.051	0.303	0.005	0.901	-0.028	0.372	0.078	0.239
pars opercularis	0.023	0.409	0.013	0.794	0.024	0.541	0.009	0.757	0.051	0.440
pars orbitalis	0.022	0.420	-0.014	0.773	0.022	0.571	0.019	0.526	0.023	0.727
pars triangularis	0.006	0.841	-0.021	0.671	-0.015	0.701	-0.001	0.978	-0.001	0.990
pericalcarine	-0.031	0.265	0.018	0.718	-0.036	0.372	-0.025	0.424	-0.015	0.826

post-central	-0.021	0.447	0.029	0.554	-0.013	0.744	-0.020	0.518	-0.001	0.985
posterior cingulate	-0.044	0.110	-0.060	0.216	-0.046	0.243	-0.046	0.136	-0.004	0.947
pre-central	0.038	0.172	0.063	0.206	0.022	0.578	0.045	0.144	0.059	0.370
pre-cuneus	0.005	0.851	-0.047	0.341	0.071	0.072	-0.021	0.498	0.084	0.202
rostral anterior cingulate	0.014	0.626	-0.064	0.198	0.045	0.266	0.018	0.566	-0.005	0.941
rostral middle frontal	-0.062	0.026	-0.094	0.055	-0.026	0.506	-0.073	0.017	-0.005	0.944
superior frontal	0.064	0.021	0.107	0.032	0.047	0.242	0.061	0.050	0.061	0.358
superior parietal	-0.020	0.463	-0.121	0.014	0.040	0.316	-0.015	0.620	-0.021	0.748
superior temporal	0.017	0.565	-0.052	0.309	0.052	0.206	0.009	0.789	0.029	0.676
supra-marginal	0.038	0.177	0.030	0.558	0.031	0.441	0.064	0.043	-0.093	0.166
temporal pole	-0.003	0.908	0.079	0.112	0.003	0.950	-0.016	0.609	0.041	0.530
transverse temporal	0.008	0.770	-0.076	0.117	-0.018	0.651	0.017	0.569	-0.046	0.487

Table 3. Cohen's d and p-values for the effects of diagnosis on AIs of cortical thickness. A positive effect means that cases are more leftwards/less rightwards asymmetrical than controls.

	All		Males		Females		> 21 years		≤ 21 years	
Region	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**
average thickness	0.028	0.307	0.070	0.111	-0.005	0.893	0.024	0.431	0.055	0.400
banks sts	0.016	0.582	0.011	0.810	0.014	0.711	0.049	0.122	-0.103	0.134
caudal anterior cingulate	0.079	0.004	0.083	0.059	0.077	0.030	0.070	0.021	0.097	0.142
caudal middle frontal	0.017	0.537	-0.008	0.859	0.036	0.314	0.009	0.771	0.056	0.392
cuneus	-0.027	0.325	-0.020	0.655	-0.025	0.477	-0.019	0.529	-0.029	0.660
entorhinal	0.010	0.733	0.018	0.691	0.006	0.868	0.004	0.894	0.046	0.492
frontal pole	0.016	0.563	0.054	0.215	-0.018	0.609	0.020	0.513	0.051	0.442
Fusiform	0.002	0.954	0.022	0.614	-0.009	0.802	0.004	0.905	-0.008	0.909
inferior parietal	-0.052	0.057	-0.048	0.273	-0.045	0.209	-0.050	0.104	-0.070	0.290
inferior temporal	0.048	0.080	0.071	0.109	0.028	0.430	0.045	0.140	0.037	0.579
Insula	0.005	0.850	0.039	0.378	-0.018	0.614	-0.003	0.924	0.039	0.560
isthmus cingulate	-0.017	0.527	-0.009	0.831	-0.033	0.348	-0.018	0.561	-0.064	0.328
lateral occipital	-0.013	0.645	-0.087	0.048	0.045	0.202	-0.027	0.370	0.022	0.738
lateral orbitofrontal	0.044	0.108	0.068	0.119	0.033	0.350	0.058	0.056	0.049	0.456
Lingual	0.019	0.482	-0.027	0.544	0.051	0.152	0.035	0.246	-0.030	0.648
medial-orbitofrontal	-0.053	0.054	-0.091	0.040	-0.021	0.562	-0.032	0.289	-0.076	0.249
middle temporal	-0.008	0.766	-0.019	0.676	-0.006	0.865	-0.003	0.926	-0.067	0.321
para-central	0.001	0.983	0.062	0.160	-0.037	0.299	0.001	0.966	0.034	0.602
parahippocampal	0.032	0.245	0.096	0.029	-0.002	0.946	0.038	0.215	0.064	0.336
pars opercularis	-0.041	0.135	-0.091	0.038	-0.024	0.494	-0.065	0.032	0.096	0.145
pars orbitalis	-0.010	0.714	-0.013	0.770	-0.011	0.765	-0.020	0.511	0.069	0.300
pars triangularis	-0.004	0.891	0.017	0.693	-0.024	0.501	-0.006	0.832	0.053	0.423
pericalcarine	0.008	0.768	-0.013	0.772	0.025	0.484	0.012	0.693	-0.030	0.648
post-central	0.047	0.091	0.063	0.151	0.026	0.461	0.044	0.149	0.064	0.330
posterior cingulate	0.038	0.165	0.055	0.211	0.027	0.444	0.041	0.176	0.029	0.660
pre-central	0.026	0.336	0.011	0.800	0.025	0.475	0.016	0.592	0.044	0.509

pre-cuneus	-0.051	0.063	-0.007	0.881	-0.076	0.033	-0.055	0.070	-0.019	0.777
rostral anterior cingulate	-0.007	0.808	0.031	0.483	-0.027	0.451	-0.016	0.600	0.063	0.341
rostral middle frontal	-0.030	0.268	-0.039	0.378	-0.036	0.309	-0.021	0.493	-0.045	0.492
superior frontal	-0.011	0.691	0.063	0.153	-0.059	0.098	-0.008	0.781	0.028	0.674
superior parietal	0.004	0.872	0.081	0.066	-0.047	0.188	0.011	0.711	-0.032	0.629
superior temporal	0.085	0.003	0.090	0.049	0.071	0.056	0.068	0.033	0.133	0.051
supra-marginal	0.021	0.445	0.077	0.084	-0.016	0.651	0.011	0.712	0.029	0.667
temporal pole	-0.010	0.730	-0.024	0.581	0.009	0.804	-0.003	0.924	-0.033	0.618
transverse temporal	0.037	0.174	0.078	0.078	0.008	0.825	0.019	0.537	0.111	0.092

Figure 1