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Title: Global and local cortical folding alterations are associated with neurodevelopmental subtype in bipolar disorders: a sulcal pits analysis

Short/running title Anatomy of neurodevelopmental subtype of bipolar disorder

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Abstract

Background

Analyzing cortical folding may provide insight into the biological underpinnings of neurodevelopmental diseases. A neurodevelopmental subtype of bipolar disorders (BD-ND) has been characterized by the combination of early age of onset and psychotic features. We investigate potential cortical morphology differences associated with this subtype. We analyze, for the first time in bipolar disorders, the sulcal pits, the deepest points in each fold of the cerebral cortex.

Methods: We extracted the sulcal pits from anatomical MRI among 512 participants gathered from 7 scanning sites. We compared the number of sulcal pits in each hemisphere as well as their regional occurrence and depth between the BD-ND subgroup (N=184), a subgroup without neurodevelopmental features (BD, N=77) and a group of healthy controls (HC, N=251).

Results: In whole brain analysis, BD-ND group have a higher number of sulcal pits in comparison to the BD group. The local analysis revealed, after correction for multiple testing, a higher occurrence of sulcal pits in the left premotor cortex among the BD-ND subgroup compared to the BD and the HC groups.

Conclusion Our findings confirm that BD-ND is associated with a specific brain morphology revealed by the analysis of sulcal pits. These markers may help to better understand neurodevelopment in mood disorder and stratify patients according to a pathophysiological hypothesis.

Keyword

Bipolar Disorder, Neurodevelopment, Early Onset, Psychosis, Imaging, Premotor

1. Introduction

Bipolar disorder (BD) is a heterogeneous disease with various clinical presentations, course of illness, response to treatment and prognosis (1–3). This phenotypic heterogeneity explains to some extent the lack of robust and specific biomarkers in BD and the insufficient knowledge of its pathophysiology (3–5). Defining sub-groups of patients with BD who present more homogeneous characteristics is therefore necessary to better understand the etiologies of BD and advance towards improved treatment outcome and prognosis for patients. Although atypical neurodevelopmental pathways have been more consistently implicated in the pathophysiology of schizophrenia, several lines of evidence indicate that it is also the case for a subset of patients suffering from BD (6,7).

Indeed, genetic and epigenetic studies demonstrated that genes related to neurodevelopmental pathways are involved in the pathophysiology of BD (8). Other etiologic candidates with known or presumed impact on fetal neurodevelopment, such as pregnancy and delivery complications, are more common among patients with bipolar disorders than in controls (9–11). Finally, evidence derived from neuropsychological, neuroimaging, and postmortem studies also point to a neurodevelopmental component in the onset of BD (6). However, the neurodevelopmental insult in BD is probably heterogeneous. While some patients show significant deviations from normal neurodevelopment, others do not, in line with the heterogeneous exposure to putative causal factors of pathological neurodevelopment (7,8). Recent works show that patients with early-onset BD (i.e., patients who had a first episode of depression or mania before the age of 18) and those with psychotic symptoms during mood episodes are more likely to have been exposed to unfavorable genetic and environmental factors associated with impaired neurodevelopmental processes in comparison to other patients with BD (6,7,9,10). They have more cognitive impairment mainly in verbal memory, processing speed and executive function (11). They also have motor or language development preceding the onset of BD (8,9,12). They share

more comorbidities or familial aggregation (13,14) and they are associated with worse prognosis (15–17).

In this context, structural brain imaging can be instrumental to refine the neurodevelopmental phenotype in BD, building on recent works showing that gyrification and sulcation measures derived from MRI provide crucial retrospective information on the early neurodevelopmental trajectory of the patients (18,19). Indeed, the mature morphology of the cortex results from early processes shaping the cortex anatomy from a smooth lissencephalic structure to a highly convoluted surface (20). As a consequence, morphology descriptors of the cortical surface reflect early development (7,20,21). Investigations of cortical folding in BD suggest differences in sulcation (higher right lateral prefrontal local sulcal index and a lower left superior parietal local sulcal index) limited to patients with putative neurodevelopmental impairment (i.e. early-onset and/or psychotic BD) (7).

More recently, more specific descriptors of the cortical surface morphology, namely sulcal pits, have been introduced as markers of the progressive folding of the cortex (22,23). Sulcal pits are defined as the deepest points of the sulcal basins of the cerebral cortex (25,(23), which are allegedly the first to develop embryologically (24). Besides, sulcal pits are under genetic control and might be closely associated with the organization of cortical functional areas and their white matter connections (25,26). Their geometrical features, such as their number and their depth, evolve throughout the gyrification process and can thus be used to track the maturation of each fold. Several studies established that sulcal pits are particularly relevant indicators to distinguish atypical from typical patterns of developmental trajectory, in particular in children with autism spectrum disorder (27), in children with dyslexia (28), and more recently in children with ADHD (29).

In this study, we used sulcal pits to identify potential differences in the cortical folding between a neurodevelopmental bipolar patient subgroup (BD-ND), a bipolar disorder subgroup without neurodevelopmental impairment subgroup (BD) and a healthy comparison group (HC).

2. Material and Method

1. Participants

The MRI data used in this work was obtained from a database of patients consisting of BD and healthy controls previously collected within six international participating university-affiliated psychiatry departments: Assistance Publique-Hôpitaux de Paris (Henri Mondor Hospitals, Créteil, France), University hospital of Grenoble (Grenoble-Alpes University, Grenoble, France), Geneva University Hospital (Switzerland), the Western Psychiatric Institute and Clinic (University of Pittsburgh Medical Center, Pittsburgh, PA, USA), the San Diego Veterans Affairs Healthcare System (San Diego, CA, USA), the Central Institute for Mental Health (Mannheim, Germany), the University Hospital Galway (Galway, Ireland), University of Verona, (Verona, Italy). HC were recruited through media announcements or registry offices and did not have any personal or familial history of axis I mood disorder, schizophrenia or schizoaffective disorder or ongoing alcohol abuse. Trained raters diagnosed patients by using the Diagnostic Interview for Genetic Studies in Creteil and Geneva and the Structured Clinical Interview for DSM-IV in the other sites. History of psychotic features (i.e., patients who had at least one episode of depression or mania with delusions or hallucinations) and early age of onset have been done by a psychiatrist.

Participants presenting a positive history of neurological disease, head trauma with loss of consciousness or magnetic resonance imaging (MRI) contraindications were excluded.

Local ethics committee approvals were obtained within each center and, after receiving a complete description of the study, all participants provided their written consent. As a precautionary measure, participants aged under 18 and over 60 were excluded for this analysis considering risks of incomplete brain maturation for the younger patients and possible effects of physiological brain aging for the older patients. Then, patients with BD were split into two groups. The bipolar neurodevelopmental group (BD-ND) comprised patients who have a history of psychotic features (i.e., patients who had at least one episode of depression or mania

with delusions or hallucinations) or/and early age of onset (9,30), while the bipolar group (BD) was composed of patients presenting none of these neurodevelopmental features.

As cut off to define early age of onset in BD is not consensual, we performed a sensibility analysis with 21 years-old cut off to define early onset (Table S3). We also performed a sensitivity analysis with a more restrictive definition of the BD ND subgroup: patient who have history of psychotic features and early age of onset (Table S4).

2. MRI data collection and preprocessing

High-resolution T1-weighted structural MRI was performed for each subject, as described in (7). MRI sequence parameters details are provided in table S1. The structural MRI data were processed using Freesurfer v5.3.0 <https://freesurfer.net/> and covered the following steps: transformation into standard anatomical referential, intensity normalization, skull stripping, gray-white matter segmentation, cortical surface reconstruction and topology correction, mapping onto a spherical domain and registration across individuals by aligning folds curvature and convexity's geometrical features (Figure 1A).

3. Sulcal pits extraction, labelling and morphometry measures

The procedure is illustrated on Figure 1. The sulcal pits are defined algorithmically as the local maxima of a measure of the depth of the folds on the cortical surface (Figure 1B). Noisy depth maxima corresponding to anatomically irrelevant variations in the folds of the cortical surface are filtered out using a watershed algorithm as described in (22), and implemented in BrainViSa 4.5.0 (<http://brainvisa.info>) (Figure 1C). Once sulcal pits have been extracted from each individual's cortical surface, the next step is to identify homologous pits across participants which is a prerequisite for computing statistics to compare the populations of interest. The goal is to associate to each sulcal pit a label common to all participants, based on an atlas of sulcal pits. In the ideal scenario of a perfect inter-individual match, each of the resulting labels would correspond to only one sulcal pit in each subject. This is a particularly

challenging task in light of the huge variability in the geometry of the cortical surface between individuals and potential residual noise resulting from subtle inaccuracies in brain tissue segmentation, inter-individual registration and sulcal pits extraction processes. The naive pits labeling procedure proposed in (22,23) can associate the same label to several pits in some individuals, such that an additional filtering procedure is required. Different approaches have been proposed such as selecting the deepest pit (29), applying an additional filtering based on the distribution of the depth of the pits across participants for each label (26), or selecting the pit that has the most stable spatial location across the population (23).

In the present study, we benefited from a new sulcal pits labeling technique introduced in (31) which provides a much more consistent labeling across individuals than previous approaches. This technique consists of iteratively matching each sulcal basin from each individual in the population onto an unbiased atlas based on a metric that takes into account the local geometry of the sulcal basin surrounding each pit. In the present study, we use the atlas of sulcal basins and pits that was released in (31) (Figure 1D). Each labeled pit thus corresponds to a unique label among 92 pits labels in the left hemisphere and 90 in the right one respectively. Most importantly, this new approach identifies the noisy sulcal pits left unlabeled and excludes them from the analysis. Note that the present study is the first clinical application of this new sulcal pits labeling approach (31). From these labeled sulcal pits that are matched across individuals, three types of measures are derived: i) The number of sulcal pits is obtained solely by counting the number of labeled sulcal pits per hemisphere and at the entire brain level. ii) The local occurrence of sulcal pits corresponds to a binary coding of the presence-1 or absence-0 of the sulcal pits in each individual, after labeling according to the atlas. iii) The depth of each labeled pit was computed as described in (22) and was compared across the groups.

4. Quality control

We paid specific attention to the quality of the morphometric measures used in this study to prevent potential bias induced by inaccurate processing of MRI data. Indeed, inaccurate tissue segmentation from Freesurfer can lead to a noisy cortical surface that in turn might induce an over-segmentation of too many sulcal basins and pits. The quality of the sulcal pits extraction was assessed carefully. We visualized a scatter plot of the number of sulcal pits as a function of surface area, with the linear regression fit superimposed. Potential outlier participants were identified as the points located far from the regression line. For each of these potential outlier subjects, we visualized the surface with superimposed labeled sulcal pits and corresponding basins in order to assess simultaneously the quality of the cortical mesh and the extraction of sulcal pits. Among the 618 participants, 156 potential outliers were screened visually. A noisy cortical surface and/or inaccurate sulcal basins delineation was detected in 22, who were excluded from the analysis. Since no patients with BD-ND were left for the Verona scanning site and in order to avoid highly unbalanced factors in further statistical analyses (group by scanning site), we decided to also exclude the 116 participants (88 HC and 28 BD) from the Verona site. The final sample thus comprises 512 participants with 184 bipolar BD-ND, 77 BD and 251 HC.

5. Statistical analyses

Statistical analyses were implemented in Python 3.6 using statsmodels 0.10.1. Clinical and demographic continuous variables were compared between BD and BD-NC groups using Student's t-test and categorical variables with the chi-square test when appropriate.

To compare the number of pits per hemisphere and for the whole brain, linear mixed models were used to explore the potential differences between diagnostic group, with the group (BD, BD-ND, HC) modeled as the categorical variable of interest, and age and gender as independent covariates, with the scanning site modeled as a random effect.

To compare local occurrence analysis, logistic regression models were used to explore between-group differences for each sulcal label with the diagnostic group as the variable of interest and age, sex and site as independent covariates with a fixed effect.

To compare the depth of pits, linear regression mixed models were used to explore potential differences between groups for each sulcal pit label with age and sex included as independent covariates and site modeled as a random effect.

Normality of the model's residuals was checked using scatter plots and the Shapiro-Wilk test. In every model, the BD-ND subgroup has been chosen as reference. As proposed by default in statsmodels (<https://www.statsmodels.org/>), we report the Z value and corresponding two-tailed P value. The significance threshold was set at 0.05. When applicable, we corrected for multiple comparisons using the false discovery rate ($pFDR < 0.05$) (32).

3. Results

1. Sample characteristics

After quality controls, the final sample consisted of 512 participants including 184 bipolar BD-ND, 77 BD and 251 HC. No significant difference of gender and age was observed across the three groups (Table 1). Since this is a retrospective multicentric study, the number of participants per group from each site was significantly unbalanced ($Khi = 66.04$, $p < 0.001$) which motivated us to include in our models the site as an independent variable with a random effect (Table 1).

2. Global and hemispheric levels

At the whole brain level, we observed a higher number of pits in the BD-ND compared to the BD group ($z = 2.19$, $p = 0.03$), but no significant difference between the BD-ND and HC ($z = 1.23$, $p = 0.22$). Looking at the two hemispheres separately, the total number of pits was higher in the BD-ND than in the BD ($z = 2.01$, $p = 0.04$) and the HC groups ($z = 2.25$, $p = 0.02$) in the left hemisphere, but no significant differences were observed in the right hemisphere ($z = 1.34$, $p = 0.18$) (see Table 2).

3. Local sulcal pits occurrence

The local occurrence of labelled sulcal pits was compared between groups with the BD-ND group as reference. Exploratory results without FDR correction included the following differences (Table S2 and Figure 2):

- Compared to the BD group, the mean occurrence of sulcal pits in the BD-ND group was higher in three basins of the left hemisphere (L75, L77, L80, see Figure 2 and Figure 1.D for the anatomical location of each basin) and in two basins of the right hemisphere (R34, R49), while it was lower in one basin of the left hemisphere (L90).

- Compared to the HC group, the mean occurrence of sulcal pits in the BD-ND group was higher in three basins of the left hemisphere (L49, L74, L75), in two basins of the right hemisphere (R45, R25), while it was lower in three basins of the left hemisphere (L39, L45, L69) and in one basin of the right hemisphere (R31).

When applying FDR correction across all the sulcal pits labels, we found that the occurrence of sulcal pits was significantly higher in the BD-ND than in the BD ($z = 4.652$ pFDR = 0.00026) and HC groups ($z = 3.66$, pFDR = 0.022) in the left premotor cortex (L75 on Figure 1D, Figure 2A, Figure 2B). The statistics of the occurrence of pits between groups are detailed in Table S2 and illustrated on Figure 2.

4. Sulcal pits depth

Pits depth computed for each sulcal basins was compared between the three groups with BD-ND group as reference.

Exploratory results without FDR correction revealed the following differences across the groups (Table S5 and Figure S4):

- Compared to the BD group, sulcal pits were deeper in the BD-ND group in six basins of the left hemisphere (L10, L36, L60, L62, L67, L72), in eight basins of the right hemisphere (R4, R23, R31, R33, R42, R58, R59, R75), but less deep in two basins of the left hemisphere (L3, L70) and in one basin of the right hemisphere (R7).

- Compared to the HC group, sulcal pits were deeper in the BD-ND group in three basins of the left hemisphere (L16, L62, L76), in seven basins of the right hemisphere (R11, R16, R38, R42, R44, R58, R63), but less deep in two basins of the left hemisphere (L42, L43) and in two basins of the right hemisphere (R56, R81).

None of these differences survived when applying FDR correction across the sulcal pits labels ($p_{FDR} > 0.05$) for all labelled sulcal pits (Table S3).

5. Sensitivity analysis

We assessed the sensitivity of our results to the following two important factors. First, we reproduced the analyses taking 21 years-old as a cut off to define early onset instead of 18 years-old. Results were similar both for the whole brain pits number and local occurrence analysis demonstrating the limited influence of this factor (Table S3).

Second, we reproduced our analyses with a more restrictive definition of BD ND group based on the presence of psychotic features AND early age of onset (instead of OR). With this definition, we didn't find significant difference of whole brain pits number between groups but only a trend (Table S4). Note that this change in the level of significance is at least in part explained by the reduced statistical power consecutive of the lower sample size of the BD ND group in that configuration (44 with AND versus 184 with OR). More importantly, our main result of significant difference in the local occurrence of pits in L75 was still observed despite the lower statistical power (Table S4).

4. DISCUSSION

This large international multicentric study is, to our knowledge, the first to seek for sulcal pits differences, a signature of brain development, in BD with and without neurodevelopmental features.

The higher number of sulcal pits observed at the whole brain and at the left hemisphere levels whatever the cut off age to define early onset (18 or 21 years-old) appears to be a specific marker of the neurodevelopmental subtype of BD, since no such differences exist between BD and HC. Of note, these results are consistent with a previous study showing that bipolar patients with early onset present a higher global index of gyrification than intermediate onset bipolar disorder (33). With a more restrictive definition of BD ND, we found a trend but no significant difference between groups in the whole brain pits number. This variation in the significance of the results could be explained by the reduced statistic power related to the lower sample size. These results at the whole brain level should thus be regarded as exploratory and confirmed by an external validation using larger samples.

Further, our main finding is the localized higher pit occurrence in one single specific fold situated in the left premotor cortex (L75) among the BD-ND group, compared to both the BD and the HC groups. This result was robust to variations in the cut-off used to define the age of onset, as well as to a more restrictive definition of the BD ND group.

Only one previous study has shown sulcation differences between BD-ND and BD but in different brain regions than ours, i.e., the right prefrontal dorsolateral region and the left superior parietal cortex (7). Several factors may explain these discrepancies. Indeed, although both studies support the hypothesis that BD-ND constitutes a distinct subtype of bipolar disorders which may be associated with specific etiology, clinical presentation, prognosis and biomarkers (6), phenotypic definition of the BD-ND patients is not identical across the two studies. Early onset and psychotic features have been analyzed as separate subgroups in (7). We chose to consider both criteria together since they have been described as major features of neurodevelopmental phenotype and frequently associated (6,34). Moreover, early age of onset was set at 21 in (7) while we used a more selective threshold (i.e., age of onset < 18) consistently with previous reports (9,16,30). Furthermore, gyrification index was computed at the scale of sulci in (7), while we referred to a much more local measure: the sulcal pit. In

addition, we used a new method for labelling sulcal pits which provided a more accurate anatomical correspondence across individuals than in previous works. We speculate that using labelled sulcal pits allow us to detect more subtle and localized effects than at scale of sulci. Finally, we imposed stringent correction for multiple comparisons using the false discovery rate (p FDR), thus reinforcing the validity of our findings.

Our main result indicates that a very localized and specific difference in occurrence of pits in the left premotor cortex distinguishes BD-ND from BD and HC. This result is reminiscent of several previous findings supporting the definition of neurodevelopmental subtype of BD. A functional MRI study showed atypical premotor activity or altered resting state network including premotor cortex in ADHD (35) and in patients with autistic spectrum disorder (ASD) (36). Of interest, BD with neurodevelopmental impairment has been associated with these two neurodevelopmental disorders (37). For instance, a recent meta-analysis has shown that nearly one in six adults with BD had ADHD and one in thirteen adults with ADHD was also diagnosed with BD (38) and a prospective study has demonstrated that BD with comorbid ASD presented earlier BD onset than BD without comorbid ASD (39). Also, the involvement of the premotor cortex in the pathophysiology of BD-ND is supported by several previous findings. Recent neuroimaging studies reported an abnormal functional connectivity in resting-state networks involving the premotor cortex as well as the sensorimotor network (40,41) in patients with BD. In addition, hyper connectivity of the sensorimotor network in children with BD (very early age of onset) compared to controls has been reported in (42). Premotor cortex thus seems to be involved in the pathophysiology of bipolar disorder with putative deviation in neurodevelopmental trajectories.

Finally, we found trends of differences (without FDR corrections) both in the occurrence and the depth of sulcal pits in several cortical areas, mainly situated within the frontal lobe. Some of these differences agree with previous results obtained in ADHD and in autism spectrum disorder. Specifically, the depth of the pits located in the left ascending ramus of the Sylvian

fissure (Broca area) distinguish children with autism spectrum disorder from typically developing children in (27). Here, we observed a higher occurrence of pits in the BD-ND subgroup compared to the BD group in this same region (L80). Also, (29) reported differences in the depth of pits between ADHD and typically developing children localized in the left superior frontal junction. We also observe a difference in the depth of pits between the BD-ND and the BD groups in this area (L3). All these results confirm that impaired neurodevelopment might have led to local differences in the organization of sulcal pits which may later mediate the phenotypic presentation. Some alterations appear to be common to several neurodevelopmental disorders while others seem specific to one disorder as it is the case for the L75 in neurodevelopmental subtype of bipolar disorder. Future analyses of sulcal pits across neurodevelopmental disorders such as (43) will allow to refine these observations.

Although our results are consistent with our main hypothesis, they must nevertheless be tempered by the following limitation.

Our study is based on the hypothesis of a neurodevelopmental subgroup in BD. Clearly, this field remains incipient. Replication studies with larger samples and longitudinal investigations of neurodevelopmental trajectories are needed to confirm these results and to establish that sulcal pits could be used as a neurodevelopmental marker of BD.

Another important limitation we should acknowledge, is the definition of neurodevelopmental subtype according to the presence of one of two features, namely psychotic features and early age of onset defined by age of onset. Given the post-hoc nature of this analysis, several neurodevelopment features reported in previous works as perinatal complication, early life trauma minor physical anomalies (MPAs), dermatoglyphic anomalies, soft neurological signs were not available in this study. In the same way cognitive, motor, and language impairments were not available, making the interpretation of the results in premotor cortex limited (6). These relevant neurodevelopmental features were not available to classify our patients but also to exclude minor neurodevelopmental features in healthy controls. Nevertheless, psychotic features or early age of onset are consistently considered to be robust manifestations of the neurodevelopmental phenotype of BD (6,7).

New studies involving extensive assessment of the neurodevelopmental phenotype, including relevant clinical data, should be pursued to refine the characterization of this subpopulation of patients with BD.

5. CONCLUSION

As a conclusion, we conducted the first ever sulcal pits analysis revealing a very specific cortical morphological abnormality in patients with BD presenting a neurodevelopmental phenotype. These morphological markers of early brain development could be instrumental to refine our diagnostic classifications not only in BD but also in other psychiatric disorders associated with neurodevelopmental impairment.

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		BD-ND n= 184	BD n= 77	HC n= 251	Total n= 512	Test	pvalue
Gender,	n(% Female)	108 (58.7)	47 (61.04)	139 (55.38)	294 (57.4)	Khi = 0.96	0.963
Âge,	mean(sd)	37.4 (10.1)	38.1(10.7)	38.4 (10.8)	38.05 (10,5)	F = 0.48	0.62
Sample size by site,	n(% of the site)	25 (28.7)	9 (10.3)	53 (60.9)	87 (100)	Khi = 66.04	<0.001
	Créteil						
	Galway	25 (36.7)	3 (4.4)	40 (58.8)	68 (100)		
	Genève	12 (24)	11 (22)	27 (54)	50 (100)		
	Mannheim	20 (26.7)	19 (25.3)	36 (48)	75 (100)		
	Pittsburgh	57 (50.0)	20 (17.5)	37 (36.5)	114 (100)		
	Sandiego	35 (40.7)	2 (2.3)	49 (28.1)	86 (100)		
	Grenoble	10 (31.2)	13 (40.6)	9 (28.1)	32 (100)		

Table 1 : Sample characteristic

Number of pits	BD-ND mean (sd)	BD mean (sd)	HC mean (sd)	Group comparaison	Z value	pvalue
Whole brain	150.52 (5.19)	148.92 (4.53)	150.17 (4.65)	BD ND vs BD	2.129	0.033
				BD ND vs HC	1.234	0.217

Left Hemisphere	75.93 (3.09)	74.94 (3.07)	75.31 (3.09)	BD ND vs BD	2.008	0.045
				BD ND vs HC	2.253	0.024
Right Hemisphere	74.59 (3.36)	73.97 (2.96)	74.87 (2.96)	BD ND vs BD	1.345	0.179
				BD ND vs HC	-0.436	0.663

Table 2: Statistics of the number of sulcal pits between the three groups (BD-ND, BD and HC) at the whole brain and hemisphere levels.

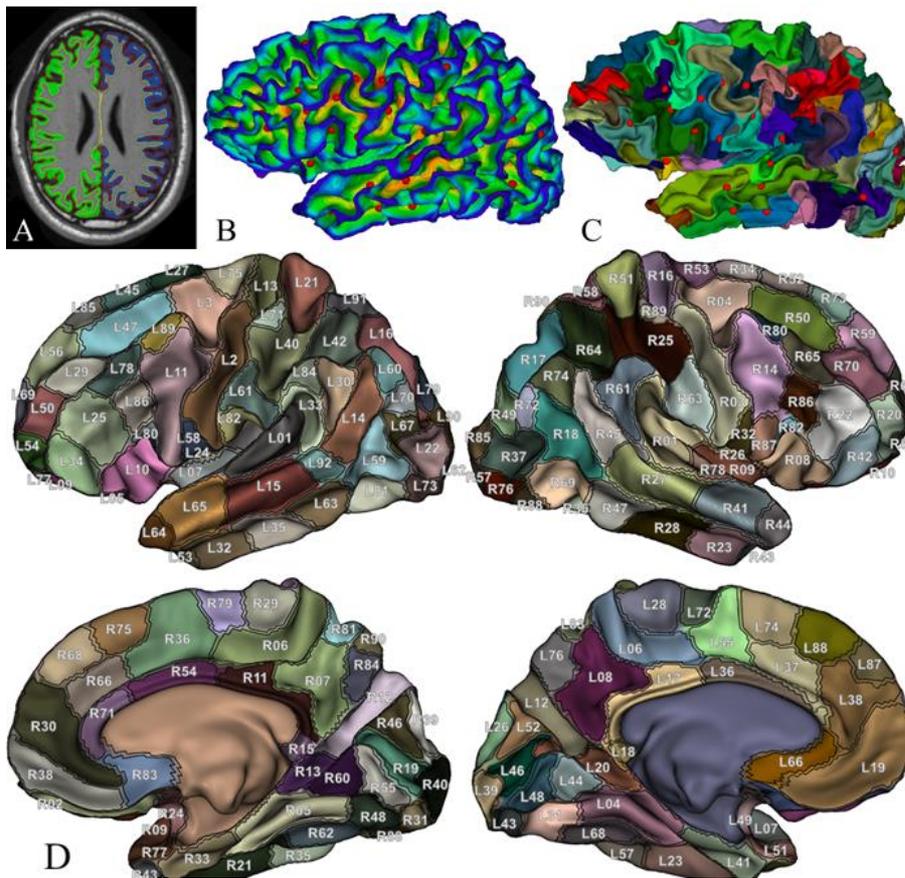


Figure 1: The procedure for extracting the sulcal pits and the atlas showing the anatomical location of the sulcal pits labels. A) Brain tissues and cortical surfaces are segmented using freesurfer. B) The sulcal pits correspond to local depth maxima. C) Each sulcal pit is the deepest point of its corresponding sulcal basin. The sulcal pits and corresponding basins are matched across individuals using a dedicated pipeline described in (34). D) The atlas of sulcal pits used in this study.

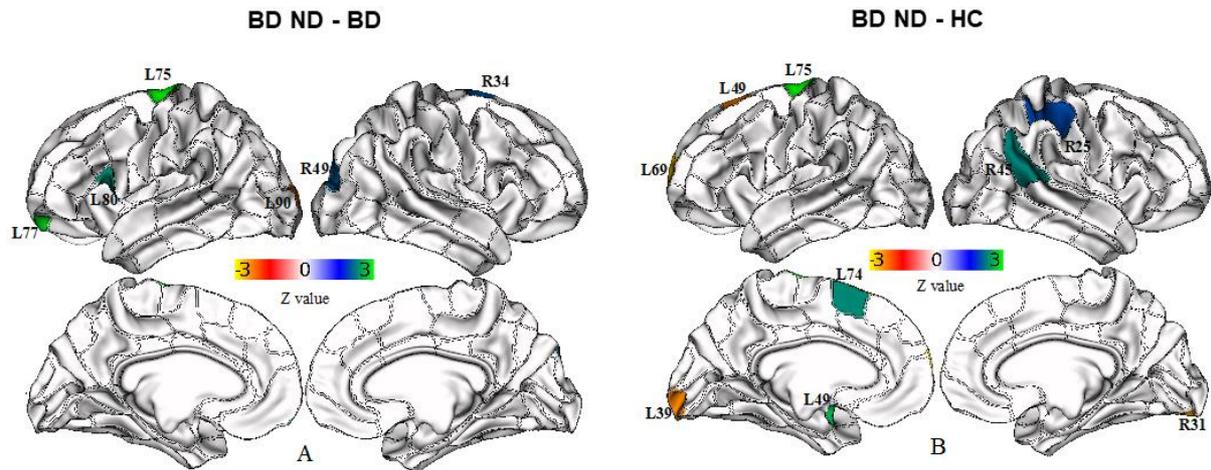


Figure 2: The analysis of local pits occurrence. The occurrence of each labelled pits was computed and compared between (A) the BD-ND group and the BD group (B) the BD-ND group and the HC group. The color encodes the Z value. The basin is colored when the difference is significant ($p < 0.05$). After applying the FDR correction across all the sulcal pits labels, we only get a higher occurrence of pits for the label L75 in the BD-ND compared to the BD group ($z = 4.652$, $p\text{FDR} = 0.00026$) and to the HC group ($z = 3.66$, $p\text{FDR} = 0.022$)