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Clinical study

Is occipital bending a structural biomarker of risk for depression and sensitivity to treatment?

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ABSTRACT

Occipital bending (OB) describes asymmetry of the occipital lobes where one lobe wraps across the midline, and has been associated with the presence of mood disorders. We evaluated the relationship between OB and major depressive disorder (MDD) in a large population of subjects from the International Study to Predict Optimized Treatment in Depression. MDD patients (n = 231) and healthy controls (n = 68) underwent MRI and neuropsychiatric evaluation, including response or remission to antidepressant medication at baseline and at 8 weeks. Cortical thickness, ventricular volumes and regional grey matter volumes were measured. OB was visually assessed and OB angle measured using a semi-automated method. Correlations with MDD diagnosis, MRI measures and clinical features were tested. Results demonstrated a greater proportion of rightwards OB in MDD compared to control subjects (p = 0.02). There was no difference in the total prevalence of OB (combined left and rightward bending) between MDD and controls. MDD subjects with right OB had greater cortical thickness in three medial occipital regions (cuneus, lingual gyrus and calcarine sulcus) on the left. Lateral ventricular size was 20% lower bilaterally in right OB MDD subjects compared to non-OB MDD subjects. OB was not associated with severity (HDRS-17). Our data suggest the presence of a strong link between greater rightward occipital bending and MDD. Rightward-OB is associated with greater left medial occipital cortical thickness, and with reduced lateral ventricular size. The cause for greater rightward bending in MDD patients is unclear, however our data suggest a developmental aetiology.

1. Introduction

Occipital bending (OB) is a physical asymmetry of the occipital lobes that is easily visualised on CT and MRI. A number of observational studies have demonstrated that there is a greater prevalence of OB in major depressive disorder (MDD) [1] and in other psychiatric diseases [2–4]. These observations raise the possibility that OB may reflect a structural anomaly relating to brain development or lateralisation; however, the status of occipital bending as a biomarker of MDD has not been formally evaluated. This study utilises a large cohort of depressed subjects from the International Study to Predict Optimized Treatment in Depression (iSPOT-D) to evaluate the role of OB as a disease biomarker in MDD [5,6].

MDD is one of the leading causes of death and disability worldwide: the suicide rate for people hospitalised for depression is 7% [7]. It is predicted that, by 2030, depression will be the highest cause of disability of any physical or mental disorder in the world [8]. Despite immense advances in the pathobiological understanding of MDD over the past three decades, the interplay between the structural and biochemical changes seen in MDD remains unclear [9,10]. Uniquely, neuroimaging biomarkers have the capability of providing a structural map of the brain perturbations present in this disorder and so have the potential to inform treatment options, potentially allowing earlier recognition of disease. OB is an interesting candidate biomarker because it may identify people in whom the brain circuits or cortical development pathways have

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been intrinsically altered long before the development of symptoms [1].

The dominant focus of existing MDD neuroimaging research has been on the frontal and subcortical regions of the brain; however, a growing body of evidence implicates an important involvement of the occipital lobes in the pathobiology of this disorder. For example, greater volume of the right occipital cortex has been positively associated with likelihood of remission [11]. Magnetisation transfer imaging of medication naïve MDD subjects revealed lower structural integrity in left middle occipital gyrus compared to normal controls [12]. Hibar and colleagues demonstrated a reduction in cortical thickness in bipolar disorder with increasing duration of disease in bilateral pericalcarine gyrus, and right cuneus [13]. Lower cortical surface areas in the fusiform gyrus has been seen in a *meta*-analysis of 2148 MDD patients [14]. In addition to these cortical and grey matter volume differences in the occipital region, there are convergent functional fMRI and PET data highlighting functional disturbances of this region in MDD. Greater activation of the right superior occipital lobe has been observed in non-psychotic MDD [15]. Decreased resting state fMRI activity in left middle occipital gyrus may distinguish psychotic MDD from healthy subjects and non-psychotic MDD [16]. PET data also reveal lower cerebral blood flow in the parieto-occipital regions in MDD [17].

This study aims to test the association of OB with a diagnosis of MDD in a large, well-characterised, and highly-powered dataset. We speculate that occipital bending reflects an underlying hard-wired neurodevelopmental or anatomical abnormality. Our hypothesis is that the prevalence of OB will be greater in MDD and that the extent of OB will correlate with altered regional cortical thickness and volume measurements.

2. Methods

2.1. Participants

The Western Sydney Ethics Committee approved this study and all participants provided written informed consent. Participants were drawn from the imaging subset of the iSPOT-D trial, comprising 10% of the 2688 recruited participants [5,6]. The trial aimed to identify pre-treatment bio-markers predicting treatment outcome (response or remission) after eight weeks of randomised antidepressant medication. Adult outpatients (age 18–65) with non-psychotic MDD were the target population. The study commenced in January 2009. MDD was diagnosed following assessment by a psychiatrist using the Mini-International Neuropsychiatric interview (MINI) [18], and a score of $\geq$16 on the Hamilton Rating Scale of Depression (HDRS17) [19]. All MDD individuals were either antidepressant naïve or underwent a washout of greater than five half-lives. MDD subjects had a total HDRS-17 $\geq$16 and met the DSM-IV criteria for single or recurrent non-psychotic MDD established by MINI Plus. Suicidal ideation and/or tendencies, as determined by a score $\geq$8 on Section C of the MINI Plus, a history of bipolar disorder, schizophrenia, schizoaffective disorder or psychosis, a current primary diagnosis of anorexia or bulimia, obsessive-compulsive disorder or primary post traumatic disorder, substance dependence and a history of significant brain injury were among the exclusion criteria. Healthy controls all had an HDRS17 score of <7, and were free from any DSM-IV axis 1 diagnosis. DSM-IV axis 2 diagnoses were not exclusionary.

MDD participants were then randomised to receive flexibly-dosed, open label escitalopram, sertraline or venlafaxine-extended release (venlafaxine-ER) for eight weeks. The study explicitly excluded participants taking any medication likely to affect brain function other than the trial medications, including antipsychotics, anticonvulsants, anxiolytics and clonidine. The study recruited subjects from primary care, community, and academic psychiatry settings with the goal of representing a broad sample of antidepressant treatment seekers. Medications were prescribed, and doses adjusted, by treating clinicians according to routine clinical practice following the recommended dose ranges. A HDRS17 score of $\leq$7 was defined as remission.

Baseline MRI sequences were obtained for a total of 231 MDD participants and 68 healthy controls, all of which had sufficient quality T1-weighted data for the analysis. Of the 231 MDD subjects, 44 did not complete the week 8 follow-up assessment, and were therefore excluded from the remission analysis.

2.2. MRI data acquisition and processing

A 3 Tesla GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin, USA) with an 8-channel phased array head coil was used at Westmead Hospital (Sydney, NSW) to obtain T1-weighted 3-dimensional spoiled gradient recalled (SPGR) MRI data (1 mm isotropic voxels; 256 $\times$ 256 matrix; 180 contiguous slices; TR: 8.3 ms; TE: 3.2 ms; Flip angle: 11°; TI: 500 ms; NEX = 1; Frequency direction: S/I). T1-weighted image data pre-processing incorporated a correction for bias-field inhomogeneity, tissue classification into grey matter, white matter and cerebrospinal fluid, and registration to standard space utilizing the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) and the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm).

2.3. Expert visual evaluation of occipital bending

The presence or absence of occipital bending (OB) was assessed visually with a 3D view of the skull-stripped brain, manually obtained using OSIRIX (http://www.osirix-viewer.com) [20]. Occipital bending, as defined previously [1], was deemed present if one of the occipital lobes protruded across the midline inter-hemispheric fissure, with consequent obscuration or retreat of the contralateral occipital lobe. For OB to be present, the inter-hemispheric fissure was also required to deviate from the midline in the occiput. Consensus on the presence of occipital bending was obtained between two assessors blinded to the psychiatric status of the participants (KF and JM). Leftward vs. rightward bending direction was also noted.

2.4. Quantitative evaluation of angle of occipital deviation

A second semi-automated quantitative measure was taken as the angle of occipital deviation (OBA) on a selected axial T1-weighted slice as follows: axial anatomical images were aligned manually along the anterior commissure – posterior commissure line [21] utilizing OSIRIX (http://www.osirix-viewer.com) [20]. Midline was taken as the line joining the midpoints of the two commissures, bisecting the third ventricle. At the same slice, the maximal point of medial excursion of the visible cuneus, posterior/superior to the calcarine fissure was identified bilaterally. The angles between the midline, and the manually derived points were then calculated using an in-house MATLAB routine (MATLAB, The MathWorks, Natick, MA; Fig. 1). The angle of the left occipital lobe relative to midline was chosen to represent OBA, as it was found to be a better discriminator of the presence and direction of occipital bending, in comparison to the angle of the right occipital lobe, or the average angle made by both occipital lobes, based on visual assessment of distribution plots.

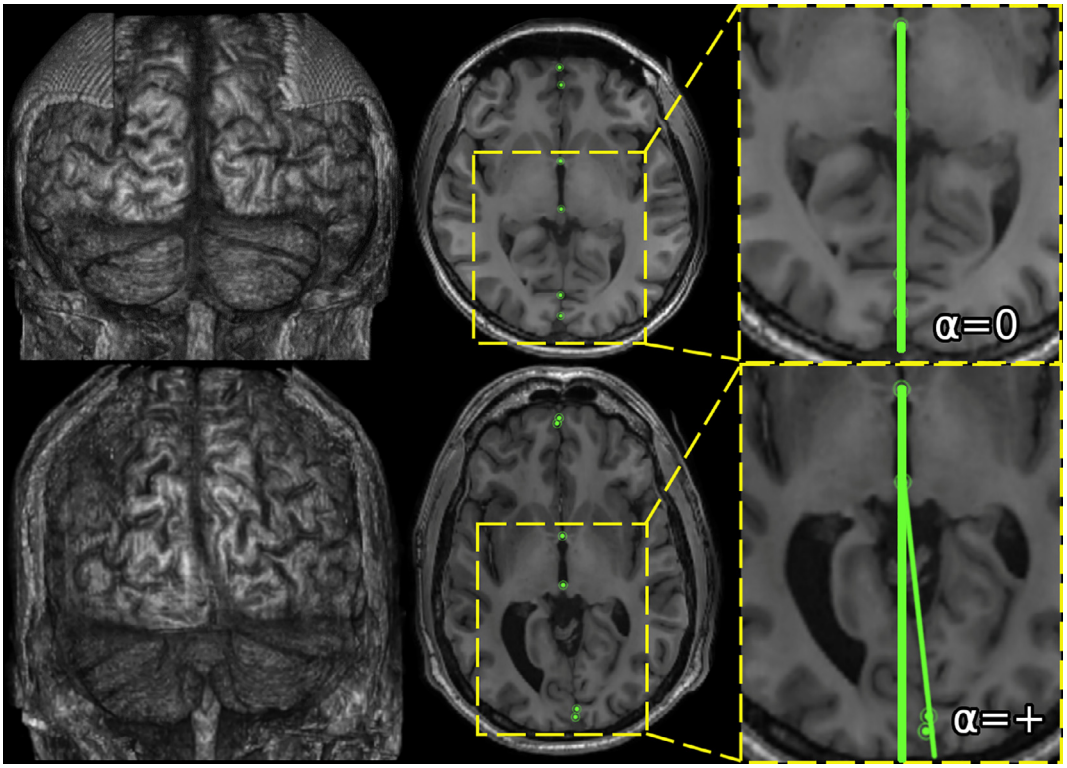

Fig. 1. Illustration of the method used to quantify occipital bending. The occipital bending angle (OBA) is defined as the angle (α) subtended by the midline and the maximal point of medial excursion of the visible cuneus, posterior/superior to the calcarine fissure Top row: no occipital bending. Bottom row: leftwards occipital bending (displayed according to radiological convention).

2.5. Brain volume and cortical thickness analysis

Automated cortical surface reconstruction and volumetric segmentation of the brain was performed in FreeSurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu) [22] as previously described [23]. Whole brain grey matter volumes and ventricular volumes were compared between MDD and controls following normalization to total intracranial volume (ICV). In addition, regional volume (normalized to ICV) and cortical thickness for selected regions of the occipital lobe and surrounding gyri were measured, including the occipital pole, cuneus, lingual gyrus and calcarine sulcus (Fig. 2).

2.6. Statistical analyses

Simple two-tailed t-tests were used to contrast baseline demographic data, whilst one-way ANOVA was utilised in assessment of differences in OBA. Cohort differences in presence/absence of OB were tested using chi-square analysis. OB and OBA were contrasted with the structural imaging data described above using ANOVA, with stratified analyses for MDD and control individuals. Significance was assessed at the 0.05 alpha level, with control for multiple comparisons where appropriate. All statistics were performed in SPSS for Mac version 25 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

3. Results

3.1. Cohort description

Table 1 summarises the group characteristics. Groups were matched for age ($p = 0.09$), gender ($p = 0.14$), years of education ($p = 0.21$), handedness ($p = 0.77$) and age of first visit ($p = 0.09$). The MDD group had an average HDRS17 of 21.5 ± 3.8 at baseline ($t(2\ 9\ 7) = 43.81$, $p < 0.001$ relative to HC), and 10.4 ± 5.2 at 8 weeks ($t(2\ 5\ 3) = 18.76$, $p < 0.001$ relative to HC).

3.2. Prevalence of occipital bending

Table 2 summarises the measures of bending stratified by diagnosis and clinical factors. The overall frequency of bending (left or right bending) was similar for both MDD and control groups. Subjective evaluation identified OB in 22% of all MDD patients ($n = 52$) and in 26% in control subjects ($n = 18$; $\chi^2(1) = 4.59$, $p = 0.50$). Visual bending assessment agreed with our semi-automated method in terms of direction of bending in 99.95% of cases ($n = 70$; $\chi^2(1) = 56.3$, $p < 0.0001$). Excluding left handed individuals did not alter the size or direction of the effect for group-wise OB prevalence ($\chi^2(1) = 0.22$, $p = 0.64$), so subsequent analyses include both left and right handed participants.

The proportion of rightward bending in MDD was more than 3-fold higher than leftward bending, in contrast to an even proportion of right versus left bending in controls. Rightward bending was present in 13.2% of controls and 17.7% of MDD subjects ($p = 0.46$), while leftward bending was present in 13.2% of controls and only 4.8% of MDD subjects ($\chi^2(1) = 5.45$, $p = 0.02$).

3.3. Evaluation of semi-automated measurement of occipital deviation

The mean absolute magnitude of the OBA was 1.6° ± 1.2° in those individuals without visually assessed occipital bending, and 3.1° ± 1.7° in those with visually verified occipital bending ($t(2\ 9\ 7) = -8.29p = 0.004$, including both control and MDD individuals). OBA in those with leftward occipital bending was 2.70° ± 1.73° in HC, and in MDD individuals was 3.92° ± 2.59° ($F_{1,18} = 0.53$, $p = 0.48$). The mean occipital angle of HC with

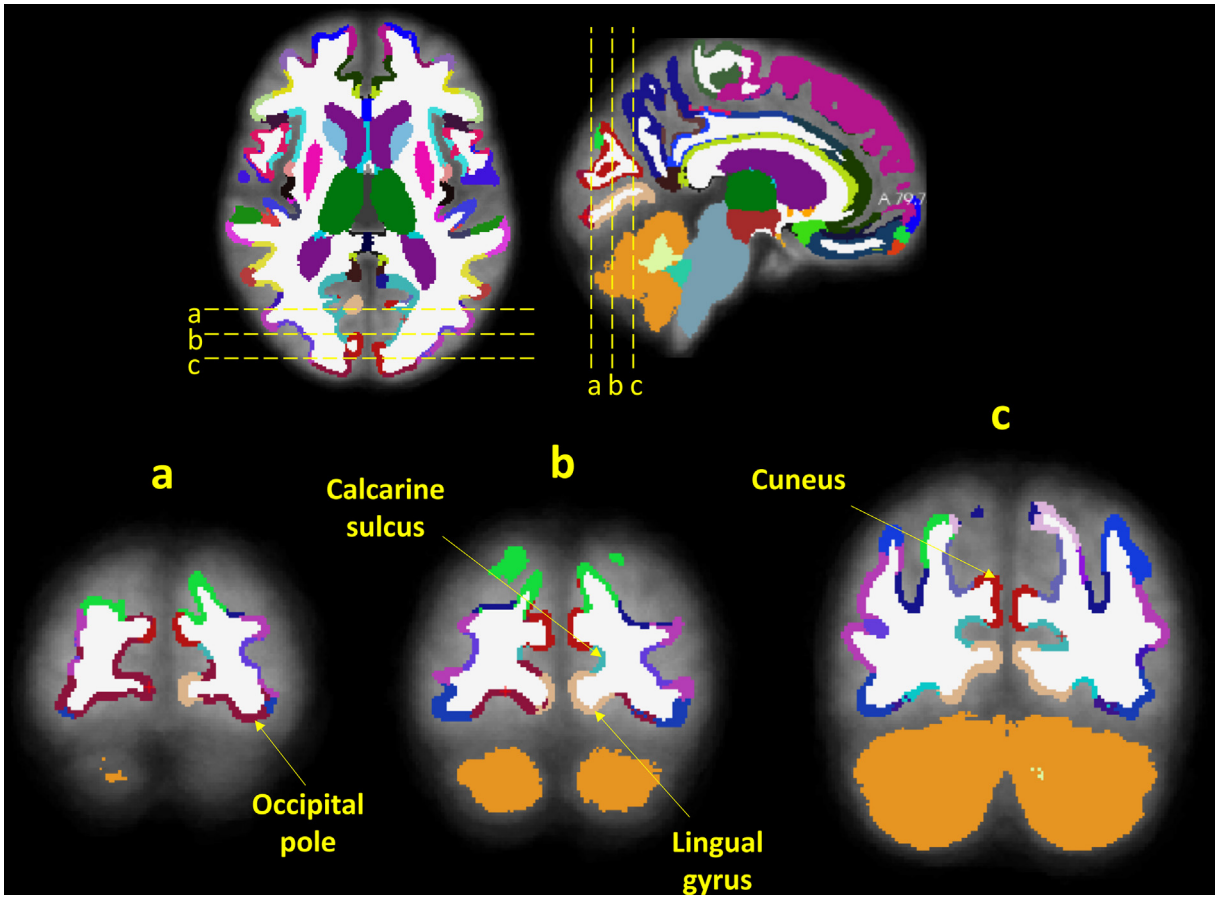

Fig. 2. FreeSurfer segmentation of the occipital lobe in one individual, with segmented regions of interest in the medial occipital lobe highlighted in three representative coronal slices.

Table 1
Demographics and clinical characteristics. SD (standard deviation), N (number of individuals), $HDRS_{17}$ (Hamilton Rating Scale of Depression).

Characteristic	Control	MDD
N (age in years ± SD)	68 (30.6 ± 13.0)	231 (33.4 ± 11.8)
Female gender N (%)	34 (50%)	122 (53%)
Left handed N (%)	7 (10%)	21 (9%)
Years of education ± SD	14.7 ± 2.6	14.2 ± 2.7
Age of first visit ± SD	30.6 ± 12.9	33.4 ± 11.8
Baseline $HDRS_{17}$ ± SD	1.10 ± 1.47	21.54 ± 3.76**
8 week $HDRS_{17}$ ± SD	0.72 ± 1.37	10.40 ± 5.16**
Age of first onset ± SD	–	21.7 ± 10.2
Previous episodes MDD ± SD	–	11.9 ± 18.7
MDD duration ± SD	–	11.7 ± 10.6

** = $p < 0.001$.

rightwards bending was −3.13° ± 1.63°, and −2.85° ± 1.66° in MDD ($F_{1,48} = 0.18$, $p = 0.68$).

Fig. 3 shows the distribution of OBA for subjects with MDD stratified by each category of OB. While considerable overlap is present, it is clear the objective OBA measurements accurately represent the visual categorisation of individuals by occipital asymmetry.

3.4. Characteristics of occipital bending subgroups

Table 2 summarises the measures of bending stratified by diagnosis and clinical factors. For MDD participants, no OB group differences were present for age ($F_{2,228} = 1.559$, $p = 0.21$), gender ($\chi^2(2) = 0.03$, $p = 0.98$), or education ($F_{2,228} = 0.362$, $p = 0.70$). Similarly, no between group differences were present for Control participants (age: $F_{2,65} = 0.647$, $p = 0.53$; gender: ($\chi^2(2) = 0.22$, $p = 0.90$), education: $F_{2,65} = 2.271$, $p = 0.11$). Baseline HDRS-17 did not differ significantly between groups stratified by the presence and direction of occipital bending in Control ($F_{2,65} = 0.573$, $p = 0.57$) or MDD participants ($F_{2,228} = 1.159$, $p = 0.32$).

There was no significant association between OB and remission $\chi^2(1) = 0.01$, $p = 0.93$).

3.5. Characteristics of rightward occipital bending group in MDD

In view of the striking asymmetric distribution of rightward bending in MDD, only differences between rightward-OB MDD subjects (n = 41) and non-OB MDD (n = 179) subjects were evaluated further. A post-hoc comparison between right-OB and non-OB in MDD revealed a borderline difference in remission status ($p = 0.066$) and a significant positive difference in duration of disease ($p = 0.045$). No differences in age of onset ($p = 0.857$), age at MRI measurement ($p = 0.638$), or gender ($p = 0.895$) were seen (Supplementary Table 1).

3.6. Structural correlates of OB

A region-of-interest (ROI) analysis of cortical thickness compared to OB status was performed between the rightwards-OB and non-OB MDD group. All three of most medial occipital regions in the medial/posterior occipital lobe showed greater cortical

Table 2
Clinical and demographic factors stratified by diagnosis and OB. sd (Standard deviation) given where appropriate. Wk0 represents baseline values, Wk8 represents week 8 values. N (number of individuals), HDRS17 (Hamilton Rating Scale of Depression), Wk0_OB % represents the percentage relative to total number of Control and MDD individuals, Wk8_OB % represents the percentage relative to total number of Control and MDD individuals still extant at week 8, Female gender %, response % and remission % represent percentage relative to leftward, nil and rightward OB numbers at baseline and week 8.

Characteristic	Control			MDD		
OB Direction	Leftward	Nil	Rightward	Leftward	Nil	Rightward
Wk0_OB N (%)	9 (13)	50 (74)	9 (13)	11 (5)	179 (77)	41 (18)
OBA ± sd	2.70 ± 1.73	−0.45 ± 1.69	−3.13 ± 1.63	3.92 ± 2.59	−0.24 ± 2.10	−2.85 ± 1.66
Age (years) ± sd	34.3 ± 17.5	29.5 ± 12.0	32.7 ± 13.5	30.1 ± 12.7	34.2 ± 11.7	31.2 ± 11.6
Female gender N (%)	5 (56)	25 (50)	4 (44)	6 (55)	94 (53)	22 (54)
Years of education ± sd	13.7 ± 2.7	15.1 ± 2.4	13.6 ± 3.1	14.6 ± 2.3	14.3 ± 2.8	14.0 ± 2.4
Age of first onset (years) ± sd	–	–	–	20.7 ± 8.7	22.0 ± 10.3	20.6 ± 10.6
Previous MDD episodes ± sd	–	–	–	8.1 ± 10.9	12.7 ± 19.5	9.4 ± 16.6
MDD duration (years) ± sd	–	–	–	9.4 ± 8.8	12.1 ± 11.3	10.6 ± 7.4
Wk0_$HDRS_{17}$ ± sd	1.22 ± 1.39	1.00 ± 1.51	1.56 ± 1.33	21.64 ± 4.70	21.72 ± 3.80	20.73 ± 3.29
Wk8_OB N (%)	9 (13)	50 (74)	9 (13)	7 (4)	146 (78)	34 (18)
Wk8_$HDRS_{17}$ ± sd	1.00 ± 2.35	0.64 ± 1.23	0.89 ± 0.93	12.00 ± 4.55	10.68 ± 5.18	8.88 ± 5.03
Response N (%)	–	–	–	4 (57)	73 (50)	20 (59)
Remission N (%)	–	–	–	1 (14)	46 (32)	16 (47)

** = $p < 0.001$.

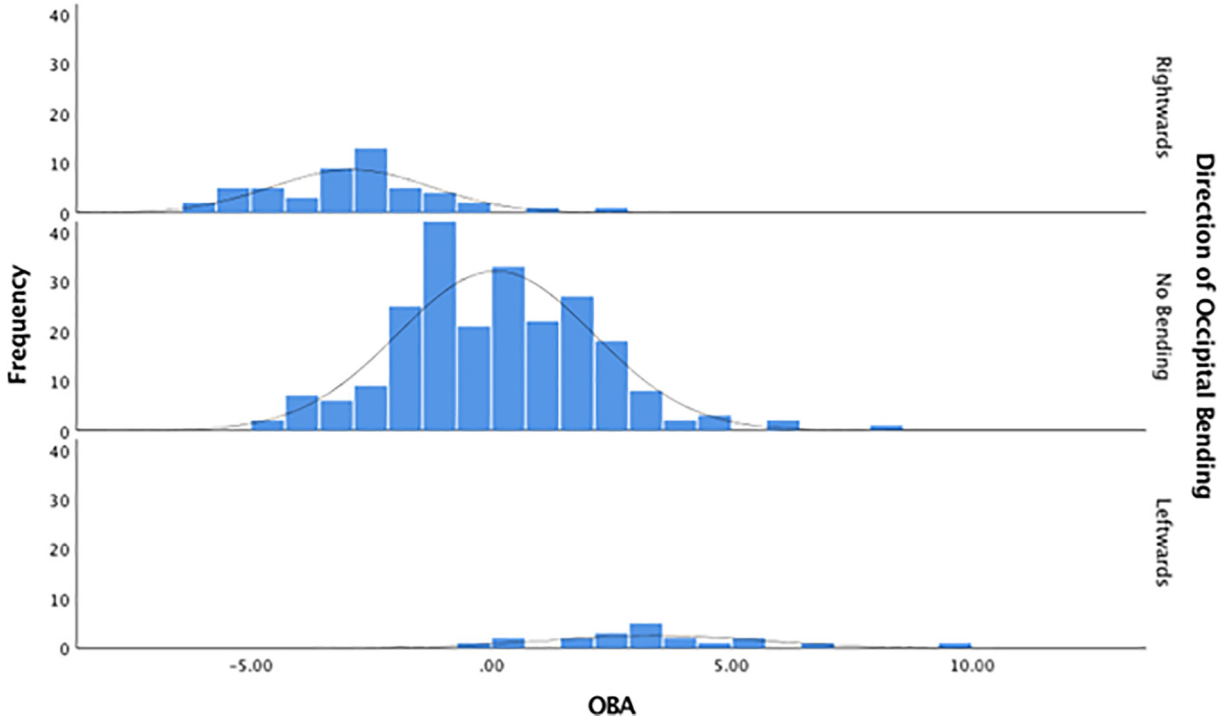

Fig. 3. Histograms showing the distribution of OBA for subjects with MDD, stratified by category of occipital bending. OBA was based on the angle of deviation of the left occipital lobe.

thickness on the left side only. The magnitude of these differences was approximately 4–6% across the three regions, specifically: the left cuneus was 3.5% higher (p = 0.030); the left calcarine sulcus was 4.2% higher (p = 0.002); and the lingual gyrus was 6.4% higher (p = 0.011).

No differences in occipital pole, or the corresponding contralateral structures was detected. A similar trend was seen comparing TBV-adjusted grey matter volume for the same structures, however only the left lingual gyrus reached significance (2.2% higher, p = 0.020).

There was bilaterally reduced lateral ventricular size associated with rightward bending (right: 23% reduction, p = 0.003); left: 17% reduction, p = 0.040). No difference between right-OB and non-OB MDD subjects was found in total CSF volume (p = 0.357), total brain volume (p = 0.258), or for total grey matter (p = 0.568) (all normalised to ICV).

4. Discussion

Our highly-powered study suggests that OB may be a meaningful biomarker in MDD. We demonstrate that rightward OB is threefold more prevalent than leftward OB in MDD compared to an even proportion in controls. We also showed that right OB status was associated with structural features, where the presence of this type of brain asymmetry in MDD is associated with 4–6% greater cortical thickness in the medial posterior occipital region, and with 20% lower bilateral lateral ventricular size. These convergent findings provide strong evidence that OB is not just an isolated incidental finding in MDD, but relates to underlying structural brain changes. The findings call for further future targeted analysis to determine the underlying abnormality causing these structural differences.

While our findings are striking, the underlying causation of OB remains unclear. Possible mechanisms include incomplete neural

pruning during neuronal development, underlying white matter dysfunction, or an acquired, event-related cause for exaggerated rightward asymmetry. A lack of neural pruning could lead to larger cortical volumes which would cause one occipital lobe to wrap around the other due to restricted intracranial space. There is a theory that OB may be ascribed to the development of the endo- and *exo*-cranial venous system [24]. Alternatively, there may be ventricular asymmetry that potentially causes the hemisphere with enlarged ventricular CSF volume to twist around the other [1], but these may be two separate phenomena [4]. Regardless, OB could be the result of shape change than volume [25] or petalia position [26].

The proportion of MDD participants demonstrating OB is less than comparative studies (23% in our study, in comparison to previous estimates of 35% in MDD [1], 34% in bipolar depression [3], and 35% in schizophrenia [4]). Additionally, our control participants demonstrated greater OB than previous studies (27% in comparison to 13%, 8%, and 14%). However, the iSPOT-D participants are derived from a relatively young cohort, and are clinically only moderately depressed, which may also explain the lower rate of OB in our study. The measurements made in the current study employed a very well-described and double read definitions of OB. These observations were additionally validated using a semi-automated methods of angle measurement. Previous investigations of OB in psychiatric disorders have recruited patients who were chronically treatment-resistant and therefore were all severely unwell. Hence, they may represent the more extreme examples of OB prevalence. This study is more highly-powered than previous investigations and has been performed with a great deal of standardisation, hence it is likely our data represent a better estimate of the true prevalence of OB in normal individuals and in outpatient depression. Our results are in keeping with, and further extend and generalise previous studies [11,14,27].

Our data did not show any effect relating to handedness. Brain hemispheric "rightwards" asymmetry has been described in normal adults, with right frontal and left occipital lobes tending to be larger than their respective contralateral structures [28–30]. This asymmetry is thought to have some functional significance relating to handedness [31] and subspecialisation of one hemisphere (often the left) in speech processing, versus spatial processing in the right [2]. However, it must be noted that approximately 10% of right-handers have reversed hemispheric dominance [32] supporting the assumption that brain torque and language dominance rely on different mechanisms [26]. Reversed occipital asymmetry (i.e. "leftwards" occipital bending) has been associated with non-primary ciliary dyskinesia related situs inversus, and left-handedness, implying a possible shared underlying developmental pathway [26]. Reversed occipital asymmetry has also been shown in early CT literature to be related to a number of psychiatric and developmental abnormalities such as autism, delayed speech acquisition and particularly schizophrenia in a number of small, blinded and non-blinded studies [33]. A blinded study involving a heterogeneous population of 45 acute presentation schizophrenic and schizoaffective disorder patients demonstrated an association between reversed occipital asymmetry and measures of drug-free psychopathy relating to language and communication, but not schizophrenia itself [2].

These cortical and functional differences may reflect delayed cortical maturation, which could be either secondary to or result in differences in the underlying complexity of the white matter association tracts. Our previous work demonstrated that OB is distinct from asymmetry of the occipital lobe as such, leading us to suggest that the "bend" may be the result of altered developmental pruning in MDD causing the characteristic wrap-around motif that is specific to OB [1]. Prior data from iSPOT-D is supportive of a functional link between cortical and white matter differences, showing that lower fractional anisotropy in right superior fronto-occipital fasciculus and right superior longitudinal fasciculus is associated with non-remission [34].

Further work is required to evaluate the relationship between the presence of OB and underlying structural factors. Future investigations in this cohort will test the hypothesis that OB is related to differences in the occipital grey matter thickness, and inferior fronto-occipital fasciculus tract abnormalities.

Although highly powered, this is a cross-sectional study and therefore unable to show whether OB is a causative or secondary phenomenon. The latter appears more likely; however, longitudinal data are required to understand the relationship between rightward OB and MDD status. We also did not collect handedness data, which may be related to OB.

5. Conclusions

Rightwards OB is seen at greater frequency in MDD participants and relates to higher local contralateral cortical thickness, together with lower ventricular size bilaterally. Further work is justified investigating OB (or associated more specific brain changes) as a clinical marker for MDD, and elucidating the underlying pathophysiological mechanism.

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Competing interests statement

KF, TW and ML declare no conflicts of interest. JJM is an employee of General Electric Healthcare but declares no conflicts of interest. EG is the CEO of Brain Resource Ltd and has significant equity and stock options in the company. SHK serves as a consultant and has stock options with Brain Resource Ltd. SMG has previously received fees as a consultant for Brain Resource Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2019.02.007.

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