Occipital bending in depression

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There are reports of differences in occipital lobe asymmetry within psychiatric populations when compared with healthy control subjects. Anecdotal evidence and enlarged lateral ventricles suggests that there may also be a different pattern of curvature whereby one occipital lobe wraps around the other, termed ‘occipital bending’. We investigated the prevalence of occipital bending in 51 patients with major depressive disorder (males mean age = 41.96 ± 14.00 years, females mean age = 40.71 ± 12.41 years) and 48 age- and sex-matched healthy control subjects (males mean age = 40.29 ± 10.23 years, females mean age = 42.47 ± 14.25 years) and found the prevalence to be three times higher among patients with major depressive disorder (18/51, 35.3%) when compared with control subjects (6/48, 12.5%). The results suggest that occipital bending is more common among patients with major depressive disorder than healthy subjects, and that occipital asymmetry and occipital bending are separate phenomena. Incomplete neural pruning may lead to the cranial space available for brain growth being restricted, or ventricular enlargement may exacerbate the natural occipital curvature patterns, subsequently causing the brain to become squashed and forced to ‘wrap’ around the other occipital lobe. Although the clinical implications of these results are unclear, they provide an impetus for further research into the relevance of occipital bending in major depression disorder.

Keywords: occipital; bending; torque; depression; magnetic resonance imaging
Abbreviation: MADRS = Montgomery-Åsberg Depression Rating Scale

Introduction

Global brain hemispheric asymmetry was first observed on post-mortem specimens by Cunningham (1892) and was described as a greater volume of the left than the right occipital lobe. In certain tasks and neural processes, one hemisphere might be specialized and preferred, and these patterns of dominance are largely common to all humans (Studdert-Kennedy and Shankweiler, 1970; Kinsbourne, 1982). For example, spatial representation is typically performed by the right hemisphere (Mesulam, 1981) whereas speech processing is strongly dominated by left hemisphere processing (Broca, 1865; Wernicke, 1874) in most right-handers and in the majority of left-handers (Knecht et al., 2000). Although the hemispheres have similar volumes, weights and densities, there are visible differences in tissue distribution. These are most obvious at the right frontal and left occipital petalas (impressions in the skull) where there
is protrusion of one hemisphere relative to the other. In many individuals, these can be easily observed on CT and MRI scans (Le May and Kido, 1978; Kertesz et al., 1986). This protrusion may lead to a crossing of the interhemispheric fissure by one hemisphere into the domain of the other, an asymmetry of the brain that has been termed ‘Yakovlevian torque’ or simply ‘brain torque’ by some investigators (Toga and Thompson, 2003). Studies of ‘torque’ have been performed by manual measurement (Bilder et al., 1999) and more recently, by automatic image analysis methods (Deutsch et al., 2000; Thirion et al., 2001; Barrick et al., 2005; Zhao et al., 2009). Although these previous studies stated that Yakovlevian torque was the phenomenon measured, all but two (Deutsch et al., 2000; Zhao et al., 2009) were actually measuring asymmetry. These studies defined brain torque as ‘a global asymmetry of hemispheric volume distribution such that the occipital and frontal lobes are leftwardly and rightwardly asymmetric, respectively’ (Barrick et al., 2009). Often, lengths or widths of the occipital lobes have been measured and compared to yield an asymmetry index, however, lobar length is not equivalent to lobar bending. We define occipital lobe bending with reference to one of the occipital lobes crossing the antero-posterior axis (Corballis and Morgan, 1978). Strictly speaking, the definition of ‘torque’ is ‘cause to twist’ (Merriam-Webster Dictionary, 2013) or ‘a measure of turning force’. Broadly speaking, right-handedness indicates left-hemisphere dominance and hence a larger left hemisphere. Therefore, we would expect that if such torque occurs that it would most likely be the left hemisphere that ‘wraps’ around the right hemisphere. To minimize confusion, we will herein refer to this phenomenon as occipital bending (Fig. 1).

As abnormalities in brain lateralization have been suspected in psychiatric disorders, the concept that patterns of brain asymmetry might be a biomarker for these disorders has been investigated for some years. Lateralization is thought to originate from evolutionary, hereditary, developmental, experience, and pathological factors (Toga and Thompson, 2003). There is a small body of research suggesting that asymmetry may differ between individuals with schizophrenia and matched controls (Luchins et al., 1979, 1983; Crow et al., 1998; Clark et al., 2010). A study by Deutsch et al. (2000) found that the anterior-posterior midline deviation scores in subjects with schizophrenia exceeded control values with a greater prevalence of rightwards occipital bending. Consistent with that finding, Zhao et al. (2009) conducted a study using computerized shape analysis to describe asymmetry in patients with schizophrenia, by estimating the ‘interhemispheric fissure bending’ along the sagittal plane. They found a significantly greater prevalence and extent of occipital bending in patients than in healthy control subjects with bending extent data expressed as ‘H’ and ‘CXY’ scales, although no occipital bending prevalence data were presented.

Occipital bending and occipital asymmetry in affective disorders have not been the focus of substantive research although studies of altered hemispheric activity, especially in anterior brain regions, are common in these disorders (Saletu et al., 2010; Liu et al., 2012). No differences in brain asymmetry have been reported between patients with major depressive disorder and healthy individuals, but significant cortical thinning has been reported to occur in the right lateral parietal and inferior occipital cortex in those with major depressive disorder (Peterson et al., 2009; Truong, 2012). Additionally, total lateral ventricular volume has been shown to be enlarged (Kempton et al., 2011), which may displace the occipital lobes laterally and posteriorly. As the brain asymmetry may be similar to that in healthy people (i.e. larger left than right), the degree of occipital bending would be exacerbated and the width of the interhemispheric fissure narrower as depicted in Fig. 2.

It is possible that differences in occipital bending may differentiate healthy control subjects and patients with major depressive disorder, and we are aware of no other studies that have assessed occipital bending from MRI scans in this patient population. Hence, the current study will be the first to assess the prevalence of occipital bending from MRI scans in healthy and depressed individuals. We hypothesized that occipital bending prevalence would be greater in patients with major depressive disorder than in control subjects and occipital bending would be more rightwards then leftwards.

Materials and methods

Participants

The sample included 51 right-handed subjects (27 males) with a diagnosis of treatment-resistant major depressive disorder aged 19 to 70 years (males, mean age = 41.96 ± 14.00 years; females, mean age =...
age = 40.71 ± 12.41 years) and 48 right-handed control subjects (31 males) matched for age and sex (males, mean age = 40.29 ± 10.23 years; females, mean age = 42.47 ± 14.25 years). All patients with major depressive disorder were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders-Fourth Revision (DSM-IV) criteria by a psychiatrist or clinical psychologist on the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and a score on the Hamilton Depression Rating Scale (Hamilton, 1960). Participants were recruited either by public notice or word of mouth from the clinical services of The Alfred Hospital, Victoria, Australia, or from the clinical services of the Centre for Addiction and Mental Health, University of Toronto, Canada. Exclusion criteria included another current or previous DSM-IV axis I diagnosis, current active medical problem, a known neurological disease or a contraindication to MRI scanning. Healthy control subjects were required to have no history of psychiatric illness. All subjects provided written informed consent on a form approved by the Centre for Addiction and Mental Health Ethics Board or Alfred Human Subjects Research and Ethics Committee.

Magnetic resonance imaging

Two 1.5 T GE Signa Imaging Systems (General Electric Medical Systems) were used to acquire a contiguous sagittal inversion recovery-prepared spoiled gradient T1-weighted sequence for volumetric estimations (repetition time = 8,628 ms, echo time = 1.924 ms, inversion time = 300 ms, matrix size = 256 × 256, 0.94 × 0.94 mm², NEX = 1, slice thickness = 1.5 mm) for each subject.

All T1-weighted scans were viewed in MRicore (http://www.mccauslandcenter.sc.edu/mricro/mricore/) from axial perspective and visually inspected for occipital bending whereby one occipital pole extended across the midline (interhemispheric fissure) which refers to the narrow groove separating the left and right cerebral hemispheres and is identified from axial by looking for a large sulcus between the occipital poles; this is verified from coronal orientation which demonstrates a warped large sulcus in those with occipital bending. Hence, one occipital pole may cross the interhemispheric fissure but the fissure must appear warped to be classified as occipital bending, as demonstrated with 3D cortex rendering. Figure 3 illustrates some examples. A vitamin E pill was attached with tape to the right side of the forehead for each subject, hence the direction of bending (rightwards or leftwards) was always known. One rater (J.J.M.) initially rated each scan unblinded to group membership and then a second rater (R.A.) rated each scan blinded to group membership. Kappa across all scans was 1.0.

The scans rated as having occipital bending were then manually processed in Analyze 9.0 (Brain Imaging Resource, Mayo Clinic) using the calipers feature, which yielded degrees of deviation (Fig. 4). This was completed on the lowest axial slice disclosing both frontal horns and trigone, consistent with Luchsain and Meltzer (1983). Ten scans rated as ‘no occipital bending’ were then randomly selected for measurement of degree of occipital bending in Analyze; they all had 0° occipital bending.

All scans were also processed through SPM2 to automatically calculate grey matter, white matter, and CSF volumes (and added together to yield total intracranial volume) so that groups could be compared in relation to occipital bending prevalence and these volumes.

Statistical analysis

All data were statistically analysed using SPSS for Windows version 19.0 (SPSS). Analyses were two-tailed and evaluated for significance at the 0.05 alpha level. Simple chi-square and ANOVA were used to compare demographics and prevalence of occipital bending between groups.

Results

Demographics

There were no significant differences between the proportion of males and females overall or between their mean ages, between or within groups (all P > 0.05; Table 1).

Prevalence of occipital bending within and between groups

The prevalence of occipital bending was significantly greater within the major depressive disorder group [χ²(1) = 6.996, P = 0.008], and the direction of occipital bending occurred more often (although not statistically significant) in the left-to-right (rightwards) direction in both groups (Table 2).

Although the prevalence of occipital bending was greater among females with major depressive disorder (45.8%) than males with major depressive disorder (25.9%), this difference was not statistically significant; there was also no statistical difference in occipital bending prevalence between males (16.1%) and females (5.9%) within the control group. There was a significant statistical difference in occipital bending prevalence between the females of the groups [χ²(1) = 7.672, P = 0.006]. The mean ages between those with and without occipital bending, between and within groups, did not statistically differ. The maximum degree of occipital bending was 14.66° and statistically differed between the groups [control x = 1.0277 ± 2.98°, major depressive disorder x = 3.0969 ± 4.47°, F(1) = 7.229, P = 0.008], but did not statistically differ between sexes within or between groups (all P > 0.05).

Volumetrics

Although total brain volume did not differ between the major depressive disorder and controls groups (P > 0.05), CSF volumes did (P = 0.008), as did the ratio of CSF to intracranial volume (P = 0.010; Table 1). Results were similar when males were compared between the groups, but there were no such differences between the females of the groups (all P > 0.05).

Within the major depressive disorder group, those who had occipital bending had significantly less total brain volume [F(1) = 5.149, P = 0.028]. Furthermore, females with major depressive disorder with occipital bending had significantly less total brain volume than females with major depressive disorder without occipital bending [F(1) = 9.559, P = 0.005] but this was not significant between males with major depressive disorder with and without occipital bending.

There was no significant difference in Montgomery-Åsberg Depression Rating Scale (MADRS) scores between those with and without occipital bending, but there was between females with major depressive disorder with and without occipital bending [F(1) = 4.627, P = 0.044] such that those with occipital bending had higher MADRS scores. No such difference was observed between males with major depressive disorder with and without occipital bending.
Discussion

The pattern of bending observed in the occipital regions was consistent with our hypothesis that occipital bending prevalence would be greater in patients with major depressive disorder than in controls and that rightwards occipital bending would be more prevalent than leftwards occipital bending, and consistent with occipital bending studies in schizophrenia (Deutsch et al., 2000; Zhao et al., 2009). The study by Zhao et al. (2009) investigated occipital bending in healthy subjects and Deutsch et al. (2000) was
a study in patients with schizophrenia. The unique finding of the current study is that the occurrence of occipital bending is significantly greater (three times as prevalent) for subjects with major depressive disorder than healthy individuals. We also found that there is a far greater prevalence of left-around-right (rightwards) than right-around-left (leftwards) occipital bending (in patients and healthy control subjects), and this is consistent with previous reports of the direction of occipital asymmetry being laterally rightward (Toga and Thompson, 2003).

Only two previous studies have investigated occipital bending: Zhao et al. (2009) used computerized analysis to arrive at significance by means of complex voxel-by-voxel analysis. Hence, our definitions/threshold of ‘occipital bending’ is likely to be different to that of Zhao and colleagues (2009). Additionally, we investigated prevalence, whereas Zhao et al. (2009) looked at mean bending; these are not the same phenomena. Similarly, Deutsch et al. (2000) reported on area of midline deviation (in pixels), which describes the extent of midline shift rather than simple binary prevalence.

We found that there was a trend for females with major depressive disorder to have higher prevalence of occipital bending than males with major depressive disorder, and statistically higher than control females. These results suggest that healthy females have a similar prevalence of occipital bending to that in healthy

Figure 4 Measurement of occipital bending angle in Analyze 9.0. Left: 13.85° occipital bending. Right: 0° (no occipital bending).

Table 1 Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Major depressive disorder</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>27:24</td>
<td>31:17</td>
<td>0.308</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.37 (13.16)</td>
<td>41.06 (11.71)</td>
<td>0.902</td>
</tr>
<tr>
<td>MADRS</td>
<td>32.02 (5.213)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>TBV (l)</td>
<td>1.2059 (0.1005)</td>
<td>1.1926 (0.1470)</td>
<td>0.575</td>
</tr>
<tr>
<td>CSF (l)</td>
<td>0.2932 (0.0744)</td>
<td>0.2559 (0.0593)</td>
<td>0.008</td>
</tr>
<tr>
<td>ICV (l)</td>
<td>1.5001 (0.1317)</td>
<td>1.4485 (0.1858)</td>
<td>0.115</td>
</tr>
<tr>
<td>CSF/ICV (%)</td>
<td>19.4136 (3.963)</td>
<td>17.5686 (2.7332)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

ICV = intracranial volume; TBV = total brain volume; M = Males; F = Females; parenthesized values are standard deviations.

Table 2 Prevalence and direction of occipital bending

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>P-value (controls versus major depressive disorder)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital bending</td>
<td>R or L</td>
<td>R around L R around L</td>
</tr>
<tr>
<td>R or L</td>
<td>R around L</td>
<td>R around L</td>
</tr>
<tr>
<td>R or L</td>
<td>R around L</td>
<td>R around L</td>
</tr>
</tbody>
</table>

*P < 0.05.
R = right; L = left.
males but females with major depressive disorder are more likely to have occipital bending than males with major depressive disorder. This is consistent with Mackay and colleagues (2010) who found female patients with bipolar disorder to have smaller, more asymmetric brains than female control subjects. Hence, the overall results show that those with major depressive disorder have a higher occipital bending prevalence than control subjects. We also found that females with major depressive disorder with occipital bending had significantly less total brain volume, hence more CSF volume (and higher MADRS scores) than females with major depressive disorder without occipital bending; this pattern was not seen between the males with and without occipital bending. This could potentially be explained by the following flow of logic: females have a higher brain volume to intracranial volume ratio than males and therefore less cortex-to-diploe distance. We found that females with major depressive disorder with occipital bending had a greater mean CSF to intracranial volume ratio than those without occipital bending: if this greater relative volume of CSF is due to lateral ventricular enlargement, then the occipital lobe would be displaced laterally and posteriorly resulting in occipital bending. Because of the larger CSF space in males there appears to be more room and hence less possibility for this shift to take place. This is consistent with the scenario depicted in Fig. 2.

It is interesting that one control subject and two patients with major depressive disorder had rightwards occipital bending. It is likely that they represent natural variation within the population. For example, >90% of right-handers show left-hemisphere speech and language localization (Toga and Thompson, 2003), so it may be that the three individuals are within that 10% or less of the population that have reversed hemispheric dominance.

Although there are reports of regional volumetric differences between those with major depressive disorder and controls (Malykhin et al., 2012), the degree of asymmetry in one structure does not always correspond to that of another structure (Corballys and Morgan, 1978). No previous studies have reported lobar asymmetry prevalence in psychiatric and control subjects, hence we cannot compare our finding of 12% (control) and 35% (major depressive disorder) occipital bending prevalence to asymmetry studies. However, in light of Deutsch et al. (2000) who found 48% greater area of midline deviation (in pixels) in those with schizophrenia when compared with matched control subjects, our results are in the right direction. There are a number of possible explanations for why we found a greater occipital bending prevalence (when compared to controls) among our subjects with major depressive disorder than the schizophrenia subjects in the study by Deutsch. First, we rated occipital bending as present only if the extent of bending was clear and obvious. Hence, it may be that some control scans displayed slight occipital bending but not of a great enough extent to be considered as occipital bending ‘present’. Second, published figures that estimate occipital torque to occur in ~70–75% of the healthy population (Mock et al., 2012) only refer to occipital asymmetry and not occipital bending. In our study, we found 12.5% prevalence among controls and 35.3% among patients with major depressive disorder. Although occipital bending may relate to occipital size due to Yakovlevian torque, they are clearly not the same entities. Our future efforts will aim to investigate whether occipital bending and Yakovlevian torque are meaningfully associated with one another. Hence, we have treated occipital bending as a discrete entity on the grounds that the relationship between this and the ‘torque’ and other asymmetries is as yet quite unclear.

Although the groups were matched according to age, sex and handedness in this study, the influence of medication upon neuroanatomy was not controlled for. Although we did not assess frontal bending, previous neuroimaging research has identified similar abnormalities of structure and function at prefrontal cortex in schizophrenia and bipolar disorder that are only separated by underlying cellular pathology (Selemon and Rajkowska, 2003). Frontal regions are frequently implicated in psychiatric disorder and anatomical differences are often reported (Fornito et al., 2009). These differences may be associated with a sex-dependent developmental growth defect in prefrontal cortex (Mackay et al., 2010) that is common to all three disorders. The occipital lobes have been implicated on a physiological level whereby those with major depressive disorder have reduced M2 receptor binding in this region (Nikolaus et al., 2012), reduced fractional anisotropy (an indicator of white matter integrity (Huang et al., 2011)) and reduced magnetization transfer ratios (Kumar et al., 2004).

The origin of this occipital bending difference in major depressive disorder may be elucidated by examining the process of brain maturation. Developmentally, there is little change in overall cerebral volume after 5 years of age; however, there is a significant decrease in grey matter after 12 years compensated by an increase in cerebral white matter throughout childhood and young adulthood (Giedd et al., 1996a, b). Cross-sectional results from 116 subjects aged 59 to 85 years (Resnick et al., 2000) revealed that although age differences were greatest for the parietal area, sex differences tended to be larger for frontal and temporal than parietal and occipital regions. Coffey (1998) reported age-specific changes in brain size to be significantly greater in males than females for CSF volumes [in the peripheral (sulcus) and lateral (sylvian) fissure], and parieto-occipital region area; Mueller et al. (1998) reported no significant correlations between age and intracranial volume, CSF, lateral ventricles, or parietal-occipital region. Hence, although occipital bending is unlikely to be related to age, the lower rate of occipital atrophy in females gives support to the possibility that they are more likely to have occipital bending, or, stated another way, less likely for the bent occipital pole to become unbent (and ‘move’ to the native side of the interhemispheric fissure).

Nine studies of lateral ventricular volume in major depressive disorder and controls were reviewed by Kempton et al. (2011) who reported significantly greater volumes in those with major depressive disorder, although left and right ventricular volumes were not presented separately (only total volume). We postulated that greater ventricular volume would lead to the occipital lobes being displaced in a lateral and posterior manner, eventuating in greater occipital bending prevalence, as depicted in Fig. 2. This would possibly also translate to reduced occipital volume. It would also be expected that the interhemispheric fissure would become narrower; we did not measure this as the current study was one of observation rather than precise measurement. Our future investigations will endeavour to address the relationship between occipital bending, ventricular volume, occipital volume, and width of the...
interhemispheric fissure. However, we did find that a greater percentage of intracranial volume was CSF among the major depressive disorder sample, hence, there was less brain volume. We estimated cranial and brain volumes, and found no differences between the mean intracranial volume of our patients with major depressive disorder and that of healthy, age and sex-matched controls, consistent with our previous investigations between patients with major depressive disorder and healthy control subjects (Maller et al., 2012). It is possible that insufficient neural pruning may trigger changes in the GABAergic system causing abnormalities in cortical inhibition, which is known to be clinically relevant to the underlying neurophysiology in patients with major depressive disorder (Selemon and Rajkowska, 2003; Fitzgerald et al., 2009; Levinson et al., 2010). As the size of the intracranial volume reaches its maximum at ~7 years of age (Gray et al., 1995; Wolf et al., 2003) incomplete neural pruning may lead to the cranial space available for brain growth being restricted, therefore the brain may become squashed and forced to ‘wrap’ around the other occipital lobe.

**Limitations**

We did not assess frontal poles for bending. We also did not consider medication or substance abuse, data that we will collect and control for in future studies. We also only collected demographic data on age and sex, and this is a limitation of the study. Although the assessment of occipital bending was carried out by visual inspection and validated by measurement in the Analyze software, this method may be less sensitive and more error-prone than automatic analyses. Our future investigations will seek to carry out occipital bending assessment using automated analysis.

Furthermore, it would have been useful to have information on IQ and education, lifestyle and personality, childhood disorders/abuse, as well as socioeconomic status. For the clinical group, it would also be useful to have more information on their clinical history including duration of illness and medication. These are all factors that might affect the presence of occipital bending over and above depression per se and are a limitation of the study. Future investigations will also consider family history of depression/schizophrenia present in participants.

Another limitation of this study is that patients and controls may have different motivations for coming forward for a study such as this, and this was not controlled for, yet some of these may represent confounds that are associated with occipital bending.

**Conclusion**

This study is the first to investigate occipital bending in a large sample of patients with major depressive disorder and matched control subjects. We found that occipital bending is three times more prevalent among patients with major depressive disorder and that the direction of this bending is most commonly rightwards, which is consistent with the literature on volumetric asymmetry. Although the clinical implications of this result are unclear, they provide impetus for further research into the relevance of occipital bending in major depression.

**Acknowledgements**

We thank all the patients and volunteers who agreed to participate in this study, and the staff of the MRI facility at the Alfred Hospital, Melbourne, Victoria, Australia, and at the Centre for Addiction and Mental Health, University of Toronto, Canada.

**Funding**

J.J.M. is funded by the NHMRC as a Career Development Fellow; the funding agency had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit this paper for publication.

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