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Author/s:
Van Rheenen, TE;Cotton, SM;Dandash, O;Cooper, RE;Ringin, E;Daglas-Georgiou, R;Allott, K;Chye, Y;Suo, C;Macneil, C;Hasty, M;Hallam, K;McGorry, P;Fornito, A;Yücel, M;Pantelis, C;Berk, M

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# Increased cortical surface area but not altered cortical thickness or gyrification in bipolar disorder following stabilisation from a first episode of mania

Tamsyn E. Van Rheenen*[1,2] PhD, Sue M Cotton[3,4] PhD, Orwa Dandash[1,6] PhD, Rebecca E Cooper[1] BSc (hons), Elysha Ringin[1] BSc(hons), Rothanthi Daglas-Georgiou[3,4] PhD, Kelly Allott[3,4] DPsych, Yann Chye[6] PhD, Chao Suo[6] PhD, Craig Macneil[5] PhD, Melissa Hasty[5] DPsych, Karen Hallam[9] PhD, Patrick McGorry[3,4] PhD, Alex Fornito[6] PhD, Murat Yücel [6] PhD, Christos Pantelis[1,7,$] PhD and Michael Berk[3,4,9,$] PhD.

[1]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia
[2]Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia
[3]Orygen, Parkville,VIC, Australia;
[4]Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia
[5]Orygen Youth Health Clinical Program, Parkville, VIC, Australia
[6]Turner Institute for Brain and Mental Health, School of Psychological Sciences and Monash Biomedical Imaging Facility, Monash University.
[7]Florey Institute of Neuroscience and Mental Health, Clayton, VIC, Australia
[8]The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, Australia
[9]Barwon Health, PO Box 281, Geelong, Victoria, 3220, Australia
[$] Equal contribution

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* Corresponding author current postal address:
Dr Tamsyn Van Rheenen
Melbourne Neuropsychiatry Centre, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Vic 3053, Australia, tamsyn.van@unimelb.edu.au

**Abstract**

*Background:* Despite reports of altered brain morphology in established bipolar disorder (BD), there is limited understanding of when these morphological abnormalities emerge. Assessment of patients during the early course of illness can help to address this gap, but few studies have examined surface-based brain morphology in patients at this illness stage.

*Methods:* We completed a secondary analysis of baseline data from a randomised control trial of BD individuals stabilised after their first episode of mania (FEM). The magnetic resonance imaging scans of n=35 FEM patients and n=29 age-matched healthy controls were analysed. Group differences in cortical thickness, surface area and gyrification were assessed at each vertex of the cortical surface using general linear models. Significant results were identified at $p<.05$ using cluster-wise correction.

*Results:* The FEM group did not differ from healthy controls with regards to cortical thickness or gyrification. However, there were two clusters of increased surface area in the left hemisphere of FEM patients, with peak coordinates falling within the lateral occipital cortex and pars triangularis.

*Conclusions:* Cortical thickness and gyrification appear to be intact in the aftermath of a first manic episode, whilst cortical surface area in the inferior/middle prefrontal and occipitoparietal cortex is increased compared to age-matched controls. It is possible that increased surface area in the FEM group is the outcome of abnormalities in a premorbidly occurring process. In contrast, the findings raise the hypothesis that cortical thickness reductions seen in past studies of individuals with more established BD may be more attributable to post-onset factors.

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*Keywords:* surface-based morphology; bipolar disorder; neuroprogression; lithium; quetiapine; Freesurfer; neurodevelopment

## Introduction

Bipolar disorder (BD) is a complex mood disorder that is often conceptualised as involving neuroprogression, which refers to the cumulative clinical and cognitive deterioration that occurs alongside neuroanatomical change in some individuals during the years following illness onset; and which may reflect the neurotoxic effects of repeated mood episodes (Berk, 2009; Berk et al., 2011; Michael Berk, Robert Post, et al., 2017; Kapczinski et al., 2017; Kozicky et al., 2016; Van Rheenen et al., 2020). The neurobiology underlying BD is not well-understood, although numerous studies have reported cortical and subcortical brain morphological abnormalities in patients with predominantly 'established' illness (i.e. those that have had one or more mood episodes following the initial mania), particularly those with a psychosis history (Arnone et al., 2009; Bora et al., 2010; Hanford et al., 2016; Hibar et al., 2018; Ivleva et al., 2013; Lim et al., 2013; Zwanzger et al., 2014). However, illness stage and episode history are often not well-controlled within these studies. There is also relatively limited longitudinal structural neuroimaging data across the illness course, which hampers understandings of the time at which these morphological abnormalities begin to emerge (Van Rheenen et al., 2020). Explicit examination of individuals at the onset of BD can help to resolve this, where deviations from normative brain change may reflect the outcome of premorbid alterations, or rapid neurobiological change occurring alongside the emergence of the core mania symptoms that define the illness.

The literature on structural brain changes in the early stages of BD is relatively sparse compared to that of established samples (Van Rheenen et al., 2020), although there is some evidence indicating control-equivalent brain *volume* around the time of the first manic episode, including in patients with co-occurring psychosis (Arumugham et al., 2017; Goikolea et al., 2018; Keramatian et al., 2020; Kozicky et al., 2016; Strakowski et al., 2002).

While this finding suggests that the grey matter volume reductions seen in patients with established BD are influenced by post-onset factors, there are also some studies indicating pathology prior to and at the time of the initial onset of mania. Indeed, increases and decreases in inferior frontal gyrus volume, surface area and thickness have been observed in young individuals at genetic high risk for BD (Drobinin et al., 2019; Hajek et al., 2013; Roberts et al., 2016). In first episode BD cohorts, there are also reports of both increases and decreases in various global estimates of brain volume (De Peri et al., 2012; Vita et al., 2009), as well as regionally in the amygdala, basal ganglia, thalamus, precuneus, cerebellum and temporal and fusiform gyri (Adler et al., 2007; Chen et al., 2012; Farrow et al., 2005; Rosso et al., 2007; Watson, Anderson, et al., 2012; Watson, Bai, et al., 2012). Recent work from our group showed reduced brain volume in young individuals following a first episode of mania in the orbitofrontal cortex, anterior cingulate and the inferior frontal gyrus compared to controls (M Berk et al., 2017).

Other studies have reported preliminary evidence that individuals with BD may have thinner cortex in the lingual gyrus (Qiu et al., 2013) and anterior cingulate (Fornito et al., 2009) at illness onset. However, surface-based characterisation of brain changes in the early illness course of BD is generally lacking (e.g., Achalia et al., 2020; Haukvik et al., 2016). Such an analysis allows a more fine-grained distinction between cortical thickness and surface area, the constituent measures of grey matter volume. Several studies suggest that cortical thickness and surface area have different rates of heritability, are influenced by distinct genetic, environmental and developmental factors, and do not clearly track with one another over time (Grasby et al., 2020; Panizzon et al., 2009; Andreas B. Storsve et al., 2014; Wierenga et al., 2014). Thus, they can help to more clearly pinpoint the component neurobiological processes underlying gross changes in cortical volume.

Alterations in cortical thickness, and to a much lesser extent, surface area, have been reported in BD patients with established illness (Abé et al., 2016; Fung et al., 2015; Hartberg et al., 2011; Hibar et al., 2018; Rimol et al., 2012; Yalin et al., 2019). There is evidence that cortical thickness in BD is influenced by post-onset variables including psychotropic medication and illness duration (Hibar et al., 2018; Van Erp et al., 2018; van Haren et al., 2011). In contrast, cortical surface area is proposed to have a relatively stronger neurodevelopmental basis in that it scales to some degree with gyrification and the number or ontogenetic cortical columns; both of which are established during foetal gestation and early postnatal maturation (Hogstrom et al., 2012; Mota & Herculano-Houzel, 2015; Mountcastle, 1997; Striedter et al., 2015). Indeed, large scale genetic studies show that cortical surface area is influenced by genetic variants that regulate neural progenitor cell activity during foetal development (Grasby et al., 2020; Makowski et al., 2022).

Normative changes in surface area and gyrification have also been documented at later stages of the lifespan and may index underlying cellular processes including synaptogenesis, dendritic branching and myelination (Cafiero et al., 2019; White et al., 2010). However, surface area and gyrification are generally shown to be less influenced by changeable factors such as socioeconomic status or medication as is cortical thickness (Hibar et al., 2018; Piccolo et al., 2016). Hence, simultaneous examination and comparison of cortical thickness, surface area and gyrification in the early course of BD can provide insight into the extent to which the brain abnormalities seen at the later illness stages are influenced by premorbid neurodevelopmental processes or factors associated with manifest illness progression.

In this *exploratory* study, we aimed to extend our previous work showing prefrontal grey matter *volume* reductions in young individuals after stabilisation from a first episode of mania with psychotic features, hereafter collectively referred to as the FEM group for

simplicity (M Berk et al., 2017). In that study we used Voxel-Based Morphometry (VBM), a technique that can quantify gross volumetric characteristics but not the anatomical properties of the cortex itself. Here we build on this using Freesurfer, a method capable of comparing *surface-based* brain morphology (i.e. cortical thickness, surface area and gyrification) between this FEM group and age-matched healthy controls. This patient sample is relatively homogenous in terms of its low-symptom load, narrow diagnosis of BD-I, and the use of the same predominant medication regime in all patients since the onset of their illness. Thus, in this work we overcome some of the limitations of past research on early-course BD, in which mixed samples of patients with varied medication use or degrees of acute illness symptomatology (e.g., Adler et al., 2007; Keramatian et al., 2020; Kozicky et al., 2016) in already small samples (n's typically <30, e.g. see Vita et al., 2009) have been employed. Further, we adopted a spatially unconstrained whole-brain approach for examining cortical thickness, surface area and gyrification, to provide a comprehensive picture of morphological brain changes in this cohort. In doing so, we overcome bias in previous studies using region of interest approaches, in which there is potential for the averaging out of sub-regional signals. We hypothesised that surface-based abnormalities would be apparent in the FEM group in the prefrontal cortex, although the precise measure affected remained an open question.

## Materials and Methods

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

This study involved secondary analysis of the *baseline* data of young individuals that participated in a 12-month long single-blind randomised control trial comparing lithium

carbonate to quetiapine fumarate monotherapy following stabilisation from their first episode of mania (Michael Berk, Rothanthi Daglas, et al., 2017). Although individuals with substance induced mania or mania in the context of schizoaffective disorder were included in the trial, only those with mania occurring in the context of BD-I were included in the analyses described in this paper. This group of individuals is collectively referred to as the FEM group or FEM patients hereafter. The trial was conducted between 2006 and 2013 and registered with the Australian and New Zealand Clinical Trials Registry ACTRN12607000639426. All clinical measures and scans were obtained at baseline sessions occurring at the time FEM patients were randomised to monotherapy of either lithium *or* quetiapine as part of the trial; this occurred after patients had been clinically stabilised on a combination treatment of lithium *and* quetiapine for a period of at least 1 month prior to randomisation, but up to 1.2 years. Clinical stabilisation was based on the global impression of the treating clinician and/or team as indicating clinical appropriateness to discontinue one of either lithium or quetiapine. Imaging data were also collected on a separate healthy comparison group that was not part of the trial, using the same time-points and measures. Healthy controls were recruited after an initial period of FEM patient recruitment. Thus, there was some overlap in the assessment timeframes of both clinical and healthy control groups, although the overlap length was not substantial.

*Participants*

The clinical sample included n=35 individuals aged 15-25[1] and meeting DSM-IV-TR criteria for a first manic episode with psychotic features in the context of BD-I, as confirmed by Structured Clinical Interview for DSM-IV-TR – Patient Edition (First et al., 2002).

[1] The Orygen early psychosis clinics from which patients were recruited operationalises this age range as the criterion for service entry. Parental consent was obtained from both FEM patients and healthy control individuals that were under 18 years of age.

Patients were recruited from Monash Health and Orygen specialist early psychosis clinics located within the South Eastern, Western and North Western suburbs of Melbourne. Other inclusion criteria for entry into the trial included clinical stabilisation from a first manic episode (on a combination of lithium and quetiapine) for a period of *at least* one month prior to randomisation, a Young Mania Rating Scale (YMRS) score of at least 20 during the first manic episode[2], and no previously treated manic episode(s); capacity to provide informed consent to the study and comply with study procedures; and utilization of effective contraception if female and sexually active. The Orygen early psychosis clinics from which patients were recruited were designed as a clinical service for individuals with first episode psychosis. Hence, the first episode mania sample encompassed those with psychotic features. Because high levels of substance/alcohol use are common in this population, substance/alcohol abuse/dependence was allowed in this cohort to enhance generalizability. Patients were excluded if they were pregnant or lactating, were not fluent in English, had organic mental disease including intellectual disability (full scale intelligence quotient <70); an absolute neutrophil count of $\leq 1.5 \times 10^9$ per liter, or other clinically relevant biochemical or haematological abnormalities. Further exclusion criteria are detailed in the supplementary material.

A sample of *n*=29 psychiatrically healthy individuals were included for comparison purposes. Healthy controls were recruited by general advertisement and friends of current service users. No control was outside the age range of 15-25 or had a current psychiatric illness as confirmed by the screening tool of the Structured Clinical Interview for DSM-IV-TR. Other exclusion criteria for the control group included a past history of psychiatric

[2] FEM patients were included as part of a clinical trial of acute mania, and therefore severity criteria were used to ensure that patients had clinically meaningful mania symptoms.

illness, current substance abuse or dependence, and/or a full-scale intelligence quotient score <70 as indicated by the Wechsler Abbreviated Scale for Intelligence (Wechsler, 1999).

*Clinical measures*

Baseline clinical assessment measures included the Young Mania Rating Scale (YMRS: Young et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979) as measures of manic and depressive symptomatology. Overall psychopathology was also assessed using the Brief Psychiatric Rating Scale (BPRS: Ventura et al., 1993) and the Clinical Global Impressions Scale modified for BD (CGI-BP: Spearing et al., 1997). General functioning was assessed with the Global Assessment of Functioning (GAF: Jones et al., 1995), which was the standard functional assessment tool at the time of participant recruitment. Length of hospitalization for initial mania, time from first mania admission discharge to MRI scan, other psychotropic medication use, and comorbid illnesses were also recorded.

*MRI data acquisition and processing*

Baseline T1-weighted Magnetisation-Prepared RApid Gradient-Echo (MPRAGE32) structural neuroimaging scans were acquired using a Siemens Trio Tim 3T scanner (32 channel head coil) at the Murdoch Children's Research Institute in Melbourne, Australia. Image acquisition parameters were as follows: 192 sagittal slices with a voxel size of 1 $mm^3$; repetition time =2000 ms; echo time = 2.24 ms; field-of-view = 256 x 232 $mm^2$; matrix size = 256 x 192. The structural images of 25 patients were sampled at twice the resolution due to an acquisition error, resulting in a matrix size of 512 x384 384 pixels and an in-plane resolution of 0.5 mm x 0.5 mm (see supplementary material for further detail).

The FreeSurfer image analysis suite, version 6.0, was used for cortical surface reconstruction and subcortical segmentation (http://surfer.nmr.mgh.harvard.edu/). These processes have been described previously (Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 1999). Briefly, the processing pipeline involved intensity normalisation, removal of non-brain tissue, automated Talairach transformation, correction for motion and signal intensity and topology correction. Cortical surfaces were then reconstructed between the white- and grey-matter boundaries to create the white matter surface layer, and between the grey matter and cerebrospinal fluid boundaries to create the pial surface layer. All reconstructed surfaces were visually inspected by trained raters for white and grey matter segmentation, adequate removal of non-brain tissue, motion artefact and intensity. Inaccuracies in outlining cortical surfaces were manually corrected with FreeSurfer's editing tools, where the identification of motion artefacts or pre-processing errors in segmentation and skull stripping were appropriately edited and subsequently reprocessed and then visually inspected again, with this process continuing until no further editing was required. Full details of the surface correction protocol can be found in the supplementary material. Following image reconstruction, automated segmentation of cortical and subcortical structures were extracted based on the Desikan-Killiany atlas system (Desikan et al., 2006). Inter-rater reliability of final volume estimates (after correction) was calculated from a subset of 9 randomly selected volumes. The strength of the intra-class coefficient (ICC) was considered to be very high, with a value of >0.97 across all measures.

Estimates of cortical thickness were obtained using the shortest distance between the grey/white matter boundary and the pial surface at vertices on a uniform triangular grid with 1mm spacing across the cortex. Estimates of surface area were obtained using the shortest distance between vertices on the pial surface. Gyrification was also computed via the FreeSurfer analysis suite according to the process described by Schaer et al. (2012). Briefly,

an outer hull is wrapped around the pial surface of the cortex following cortical reconstruction. Circular regions of interest are then defined at each vertex of the surface of this hull, and the corresponding areas of each region of interest are located on the pial surface. These data are then used to compute the local gyrification index (LGI) at each vertex on the pial surface, where LGI is the ratio of buried cortex surface area (inner) to convex hull (outer) surface area.

*Statistical Analysis*

The demographic and clinical characteristics of each group were compared using one-way analysis of variance (ANOVA) or Chi Square ($\chi^2$) tests in the Statistical Package for the Social Sciences (SPSS: v25). Global brain measures (intracranial volume, total cortex volume, total white matter volume, total grey matter volume, total LGI, total cortical surface area and mean cortical thickness) were imported from Freesurfer into SPSS and compared across groups using univariate ANCOVA with Bonferroni correction (7 comparisons: $\alpha_{adj}$ =.007). Comparisons of intracranial volume controlled for age and sex, while comparisons of the other global brain measures controlled for age, sex and intracranial volume[3].

[3] Intracranial volume was selected as a covariate for all imaging measures for a) consistency across the models, b) based on advice provided in the Freesurfer documentation citing that 'volume scales with head size which is mostly due to changes in surface area', (https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV), c) in light of evidence from the literature explicitly indicating increased surface area, thickness, volume and sulcal depth in larger brains (Im et al., 2008), d) due to the often found correlation between intracranial volume and disease status (e.g., Vita, De Peri, & Sacchetti, 2009). Indeed, in this sample intracranial volume was significantly different between the BD and control groups (t[59]=2.13, p=0.0373), indicating it as a confounding factor and warranting its inclusion as a covariate, and e) for consistency with previous literature estimating group differences in gyrification in schizophrenia and BD samples (for example, see Bartholomeusz et al., 2013; Nanda et al., 2014; Palaniyappan et al., 2013; Vita et al., 2009).

Vertex-wise analyses were performed for cortical surface area, thickness and gyrification (LGI) using the Query Design Estimate Contrast (QDEC) program within the FreeSurfer imaging suite. A vertex-wise approach was used to identify specific coordinates of brain alteration in a spatially unbiased manner. First, the cortical surface of each participant was registered to the fsaverage template. General Linear Models were then used to test the effect of diagnosis at each vertex of the cortical surface, controlling for age, sex and intracranial volume *a-priori*. For the measures of thickness and surface area, smoothing at full-width half-maximum (FWHM) 10mm was applied. No smoothing was applied for gyrification because LGI is already smoothed during pre-processing. Cluster-wise correction for multiple comparisons was performed using cluster-forming and cluster-level thresholds of $p<0.05$, implemented using Monte Carlo simulation with 10,000 permutations (Hagler Jr et al., 2006). Right and left hemispheres were analysed separately. Exploratory vertex-wise correlational correlations (cluster-wise correction at $p<0.05$) were then conducted to identify associations between clinical indices and the surface-based measures showing significant between-group differences.

## Results

*Demographic and clinical variables*

Table 1 shows the demographic and clinical descriptives for the sample. There were no significant group differences in age, but there was an overrepresentation of males in the FEM group compared to controls. In the FEM group, the mean MADRS score was 7, and the mean YMRS score was 2. A mean CGI-BP score of 2 indicated that patients were, on average, 'minimally ill'. At the time of the baseline MRI assessment, 17 FEM patients had been randomized to receive lithium and 18 to receive quetiapine (in the days immediately

prior)[4]; 4 patients were also using antidepressants, and 5 were using benzodiazepines. Fifteen patients met criteria for comorbid cannabis use/dependence and 12 met criteria for comorbid alcohol abuse/dependence.

*Global brain measures*

Table 2 shows the group comparisons and effect sizes of the global brain measures. No between group differences were evident, although effect sizes in the medium range were evident for total LGI (Cohen's d=0.41) and total cortical surface area (Cohen's d=0.38) favoring subtle increases in FEM patients, and for mean cortical thickness (Cohen's d=0.50) favoring decreases in FEM patients.

*Vertex-wise analyses*

FEM patients did not differ from healthy controls with regard to cortical thickness or LGI. There were two clusters of increased surface area in the left hemisphere in the FEM group compared to controls. The peak coordinates for these clusters (Fig 1) fell within the pars triangularis (size = 2128.9 $mm^2$, X= -51.3, Y= 25.8, Z= -7.2, cluster corrected $p<.05$) and the lateral occipital cortex (size =1886.39 $mm^2$, X=-17.1, Y= -86.8, Z= 20.7, cluster corrected $p<.05$), but extended across the rostral middle frontal and pars opercularis, as well as the superior parietal and slightly into the inferior parietal cortex (supplementary Fig 1), respectively. Effect sizes for these clusters were; d=0.21 (pars triangularis) and d=0.51 (lateral occipital). No other clusters were found to significantly differ between the FEM and control groups.

[4] Note that the baseline assessment occurred at the same time as randomisation to either lithium or quetiapine monotherapy, after all participants had been stabilised on a combination of *both* lithium *and* quetiapine. Thus, all participants had been on the same medication regime since their initial manic episode. Note the mean time from hospital discharge to baseline MRI scan was 1.2 years.

*Exploratory analyses*

Given surface-based group-differences, in the FEM group, vertex-wise correlations between regional surface area and the following variables were examined: MADRS, YMRS, BPRS, length of mania admission (days) and duration between hospital discharge and baseline MRI scan (years). No significant correlations were revealed for any variable.

**Discussion**

There exists a limited literature on brain structural changes during or after a first episode of mania, and even fewer studies have used sensitive, surface-based techniques. Grey matter volume reductions have been found in some, but not all cohorts of this nature, but many studies are confounded by sample heterogeneity, particularly with respect to medication use and acute illness effects (Keramatian et al., 2020; Kozicky et al., 2016). Here we examined surface-based brain morphology in a sample of young BD outpatients with a low symptom load who were all stabilised on a standardised combination of lithium and quetiapine following their first manic episode.

We found no group differences in global or regional estimates of brain volume, thickness or gyrification. We did, however, identify two clusters of increased surface area - circumscribed to the left lateral middle/inferior prefrontal and occipitoparietal cortex in FEM patients compared to controls. These findings are, in part, regionally aligned to the outcomes of our previous work in this cohort showing reduced right inferior frontal gyrus volume using VBM (M Berk et al., 2017). However, the effects are in opposing hemispheres and in opposing directions, such that our previous findings do not appear to be explained by underlying surface-based changes. It is possible that this discrepancy in results can be accounted for by the strict focus on BD-I patients here, whereas our previous work also comprised patients with schizoaffective disorder or substance-induced mania. Alternatively,

it may relate to our covarying of intracranial volume here (to control for variation in head size within the sample) but not in the previous work. To explore this, we re-ran the surface area analysis excluding intracranial volume as a covariate, but no significant clusters were identified at all using this method.

Differences in the statistical packages employed to analyse the data might also offer some explanation, as there is evidence that only a proportion of variance in VBM derived-grey matter volume (used in the previous analyses) is explained by the Freesurfer derived surface-based morphology measures used here (Palaniyappan & Liddle, 2012). Indeed, similar findings of an absence of regional overlap in Freesurfer or VBM-derived brain measures have been documented in other psychiatric and neurological illnesses, where it has been argued that grey matter volume effects may not be apparent since the combined effects of thickness and surface area may occur in opposite directions (Gerrits et al., 2016; Palaniyappan & Liddle, 2012; Palaniyappan et al., 2011). Equally, it has been argued that small, non-significant changes in multiple surface-based measures could combine to produce significant grey matter reductions as assessed by VBM (Palaniyappan & Liddle, 2012).

Surface area is proposed to be influenced by the number of ontogenetic cortical columns situated perpendicular to the surface of the brain (Mountcastle, 1997). While the organisation of these columns is influenced by neurogenesis, cell proliferation, and neuronal migration from the ventricular zone during early foetal development, ongoing cellular processes including synaptogenesis, intra-cortical myelination and dendritic arborization are thought to continue to shape cortical surface area expansion beyond this early time window (Cafiero et al., 2019; Rakic, 1988). Although cortical surface area and gyrification are positively related, the former has been found to reach maturity during late childhood/early adolescence, while the development of gyrification is greatest in the third trimester of pregnancy and peaks prior to toddlerhood (Bethlehem et al., 2022; Cafiero et al., 2019;

Raznahan et al., 2011; Wierenga et al., 2014). Hence, when considered relative to each other, measures of gyrification and surface area appear to index very early and slightly later peaking neurodevelopmental processes, respectively.

Extrapolating to our data, the absence of group differences in gyrification in the context of surface area expansion in FEM patients, provides some *preliminary* evidence that brain maturational processes occurring *after* the typical gyrification peak *may* be impacted prior to the onset of mania. In typically developing individuals there is evidence of a gradual decline in surface area following its maturational peak during late childhood/early adolescence (Brown & Jernigan, 2012; Østby et al., 2009; Wierenga et al., 2014). This evidence raises the possibility that the increased surface area in FEM patients seen here represents the outcome of developmental lag in, or developmental arrest of, the normative contraction of surface area with increasing age (Cropley & Pantelis, 2014; Pantelis et al., 2005). However, this assertion is purely speculative and will need to be rigorously tested in future work, as alternative explanations for the effect include a possible influence of prior depressive symptom history (which was not recorded) and/or the use of drugs or alcohol. The latter was an exclusion criterion for controls but not the FEM group, in whom 43% reported comorbid cannabis abuse/dependence and 34% reported comorbid alcohol abuse/dependence. Further, given recent evidence that head motion partially influences between-group differences in surface area and thickness, it is also possible that the effects seen here are attributable to methodological factors rather than developmentally influenced-neurobiological processes underpinning mania (Yao et al., 2017).

Nonetheless, the increases in surface area seen in the left inferior and rostral middle frontal gyri here is partially consistent with increases in surface area and volume in the right hemisphere of these regions seen in young people at genetic high risk for BD (Hajek et al., 2013). Relevantly, both the left and right inferior frontal gyrus and the rostral middle frontal

gyrus affect subcortical functioning by mediating inhibitory processes that are critical for regulating emotional arousal (Breakspear et al., 2015; Chikazoe et al., 2007; Swick et al., 2008; Wager et al., 2008). Left inferior frontal gyrus activity has been shown to be deficient in response to emotional stimuli in genetically at-risk youth (Roberts et al., 2013); and left ventral prefrontal activity has also been found to predict hypomania symptoms in young people by increasing impulsive reactivity (Edmiston et al., 2020). In the context of our findings, these data provide further credence to the possibility that lateral inferior/middle frontal gyri abnormalities represent a factor predating the onset of mania. The lateral-occipitoparietal surface area finding in FEM patients is novel however, and requires further exploration as this is not a brain region that has been consistently linked to BD. Nonetheless, this region is implicated in face and object processing (Nagy et al., 2012), abnormalities of which have been demonstrated in youth and adults with BD (Joshua et al., 2016; Rich et al., 2008; Van Rheenen et al., 2017).

The finding of increased surface area in FEM patients in this sample is consistent with some existing evidence of abnormal surface area in patients with established BD (Abé et al., 2016), including increases specifically in the left pars triangularis (Yalin et al., 2019). However, it is also contrary to that of several other studies that have not found patient-control differences, including a recent large-scale ENIGMA analysis of 2447 BD patients and 4056 controls (Hibar et al., 2018; Karantonis et al., 2021; Madre et al., 2020; Rimol et al., 2012). Notably, in that study, an effect of illness length was not evident for surface area, however, other secondary analyses revealed circumscribed regional surface area decreases in individuals with a history of psychosis. This finding, taken alongside other evidence that morphological brain abnormalities tend to be more extensive in the primary psychotic disorders, schizophrenia and schizoaffective disorder, compared to BD (Ivleva et al., 2013),

raises the possibility that the surface area results in our work relate to the psychotic features that accompanied the first manic episodes of our clinical sample.

Further, in the ENIGMA study, patients that were taking lithium had greater surface area in select regions compared to those who were not, while the opposite was true for patients using atypical antipsychotics. Nonetheless, regions of surface area affected by psychotropic medication were less widespread across the cortex compared to that of thickness (Hibar et al., 2018). This finding, in the context of other work indicating that surface area contraction relative to cortical thinning occurs quite gradually over time (Andreas B Storsve et al., 2014), suggests that that the combination pharmacological treatment used to stabilise the FEM group in our study is unlikely to have had strong effects on surface area given the relatively limited length of exposure prior to the baseline assessment. Indeed, we saw no correlation between surface area and time length since first mania (and by proxy, time on medication for mania) in this data. This is consistent with our abovementioned assertion that increased surface area in FEM patients likely reflects the outcome of a premorbidly occurring process, rather than one in response to intervention immediately following the onset of mania. In future work we plan to examine whether cortical surface morphology is differently affected by the use of lithium or quetiapine using the longitudinal trial data in this sample.

The number of studies of cortical surface area in patients with established BD is limited. However, we speculate that the inconsistency between our findings of increases in FEM patients and of decreases or an absence of the effect altogether in some studies of established BD, might be explained by the conflation of established patient groups with different long-term exposures to either lithium versus antipsychotic medication in the latter. Further, while gyrification abnormalities were not evident in the current study, there is some evidence indicating both increases (Madeira et al., 2020) and reductions (McIntosh et al.,

2009; Nenadic et al., 2015) in established BD cohorts. A recent study indicated that this may be specific to individuals with an earlier age of onset (Sarrazin et al., 2018), but in our analyses we controlled for this effect by including age as a covariate of no-interest. Hence, our findings are consistent with the conclusions of that study positing that BD is not associated with generalised abnormalities in cortical folding (Sarrazin et al., 2018).

Cortical thickness reductions were also not evident in this FEM cohort, but are apparent and widespread in BD patients with more established illness (Hanford et al., 2016). For example, the recent ENIGMA study showed thinner cortex in adult BD patients in frontal, temporal and parietal regions bilaterally (Hibar et al., 2018). Within this, frontal, occipital and medial-parietal thickness reductions were perpetuated by a longer duration of illness and associated with common BD-indicated medications from the mood stabiliser and antiepileptic drug classes (increases and decreases, respectively). In the context of the relatively limited evidence of thickness reductions at the onset of BD in the sparse extant literature on the topic, the pattern of findings across these studies raise the possibility that post-onset factors represent the main drivers of the BD-associated cortical thickness reductions seen in the literature.

The findings of this work should be interpreted in the context of a number of limitations. First, we employed an LGI approach that is limited by its potential to capture neighbouring sulci/gyri that are not functionally or structurally related as a result of the use of a spherical kernel at each vertex. While this approach is commonly used in psychiatric imaging studies, future research should consider implementing shape-adaptive kernels or other similar models to measure LGI, as these may more accurately capture cortical folding patterns (Lyu et al., 2018). Second, the study was very modestly powered, as the FEM sample was analysed in the context of baseline data from a randomised controlled trial. It is thus possible that a) the localised subregional effects seen here represent type I errors, or b)

the absence of widespread group differences is due to power limitations in detecting effects. Caution is therefore recommended in interpreting the findings, pending replication in larger confirmatory analyses. Third, there was an imbalance across the FEM group and controls in terms of the sex distribution. Although we covaried for sex as well as intracranial volume - which varies by sex - in the analyses, we cannot completely discount that this imbalance may have affected the results. Fourth, the history of psychotic features in the FEM group and the diagnostic inclusion of only those with BD I, limits the generalisability of results to patients with these characteristics. Nonetheless, that the FEM sample was relatively homogenous in that it comprised outpatients with a low symptom load at the time of their scan and who had been stabilised on the same medication regime early in their illness course, overcomes some of the heterogeneity issues that have hampered the interpretation of findings in prior related studies.

Finally, up to 43% of the FEM group had comorbid alcohol or cannabis abuse/dependence. Owing to the small sample, we could not statistically compare these patients to those without this comorbidity. Thus, it is possible that the significant results observed here were driven by the presence of substance use disorder and not FEM per se. Past history of depressive episodes was also not explicitly recorded, nor was information about psychotherapy, antidepressant use, family psychiatric or trauma history, or past presence of childhood behavioural or learning disorders that are known to affect neurodevelopment. We were thus unable to determine the impact that variation within these factors may have had on the results. Our inability to determine the influence of prior depression is a particularly important caveat, given that previous work in FEM cohorts has shown a trend toward decreased grey matter volume in a circumscribed region only in patients with previous depression (Keramatian et al., 2020). Hence, it is possible that unaccounted prior depression in our sample had a non-negligible influence on the findings.

That said, there is some preliminary evidence in more established adult samples showing that lifetime mania history, rather than that of depression, is a more important correlate of cortical morphology (Ekman et al., 2010). This debate notwithstanding, a strength of the study was that no FEM patients had a past history of treatment for mania (typically antipsychotics or mood stabilizers), given this was an exclusion criterion for the trial.

In sum, our findings indicate that cortical thickness and gyrification are intact in the aftermath of a first manic episode with psychotic features, whilst cortical surface area in the inferior prefrontal and parieto-occipital cortex is increased compared to age-matched controls. These findings highlight the relevance of studying component measures of brain volume, as past research in FEM cohorts have either shown limited grey matter volume reductions in different areas to those identified here; or have not shown patient-control differences at all. Future work explicitly examining the impact of lithium and antipsychotic medications on surface-based brain morphology over time is needed. At the very least, studies of surface-based morphology in more established patients should examine the extent to which there are differences in surface area between patients using or not using these medications. This will help to better contextualise the findings observed here from a trajectory-based perspective; and will thus facilitate a better understanding of the course of change in surface-based brain characteristics in BD over time.

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**Conflict of Interest**

Dr Van Rheenen has received grants unrelated to the current study from Club Melbourne, the Henry Freeman Trust, Jack Brockhoff Foundation, University of Melbourne, Barbara Dicker Brain Sciences Foundation, Rebecca L Cooper Foundation and the Society of Mental Health Research. Professor Berk has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal

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**Author contributions**

Dr Van Rheenen conceptualized the paper, oversaw the statistical analysis and wrote the first draft of the manuscript. Prof Berk conceived of the initial trial and oversaw it in its entirety. Prof Cotton oversaw the data collection and was involved in the statistical analysis. Prof's Fornito, Yucel, McGorry and Pantelis, as well as Dr's Hallam, Hasty, MacNeil, Allot and Daglas contributed intellectually to the study protocol, design and recruitment of patients. Dr's Chye and Suo, and Miss Cooper and Miss Ringin contributed to the imaging processing and quality control. All authors contributed intellectually to the manuscript and have approved its final form.

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**Table 1**. *Demographic and clinical characteristics of the sample*

| | Healthy controls (n=29) | | | First episode mania (n=35) | | | Comparisons | |
|---|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Proportion*** | ***Mean*** | ***SD*** | ***Proportion*** | ***Test statistic (F/ $\chi^2$)*** | ***p value*** |
| **Age (years)** | 21.34 | 2.48 | | 21.43 | 2.29 | | .02 | .889 |
| **Sex (m/f)** | | | 12/17 | | | 28/7 | 10.09 | .001 |
| **Baseline YMRS** | - | - | | 2.40 | 3.55 | | | |
| **Baseline MADRS** | - | - | | 7.43 | 9.29 | | | |
| **Baseline BPRS** | - | - | | 32.74 | 9.26 | | | |
| **Baseline CGI-BP (overall severity)** | - | - | | 2.06 | 1.57 | | | |
| **Baseline GAF** | - | - | | 68.46 | 14.05 | | | |
| **Length of hospitalisation for initial manic episode (days)**[*] | - | - | | 25.13 | 13.34 | | | |
| **Duration between hospital discharge and baseline MRI scan (years)** | - | - | | 1.21 | 0.70 | | | |
| **Randomisation (quetiapine/lithium)**[^] | | | | | | 18/17 | | |
| **Current antidepressants (# using)**[$] | | | | | | 4 | | |
| **Current benzodiazepines (# using)**[$] | | | | | | 5 | | |
| **Comorbid cannabis abuse/dependence (# meeting criteria)**[$] | - | - | - | | | 15 | | |
| **Comorbid alcohol abuse/dependence (# meeting criteria)**[$] | - | - | - | | | 12 | | |
| **Comorbid other substance abuse/dependence (# meeting criteria)**[$] | - | - | - | | | 6 | | |
| **Comorbid anxiety disorder (# meeting criteria)**[$] | - | - | - | | | 7 | | |

Note: MADRS = Montgomery Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI-BP = Clinical Global Impressions scale – modified for bipolar disorder; GAF = Global assessment of functioning; MRI = magnetic resonance imaging

[*]First episode mania patients were initially identified during an inpatient admission for a first manic episode, but did not complete their baseline assessments until they were considered to be completely clinically stable; [^]baseline assessments occurred immediately after randomisation, thus participants had all been recently on the combination lithium and quetiapine treatment used for stabilisation; [$]refers to use/comorbidity recorded at baseline

**Table 2**. *Comparison of global brain measures*

| | Healthy controls | | First episode mania | | Comparisons | | |
|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | ***Test statistic ($F/X^2$)*** | ***P value*** | ***Effect size (Cohen's d)*** |
| **Intracranial volume[a]** | 1517943.57 | 146974.94 | 1558315.53 | 145746.75 | 1.11 | .296 | 0.28 |
| **Total cortex volume[b]** | 525670.72 | 23821.62 | 526423.17 | 23602.41 | .02 | .904 | 0.03 |
| **Total white matter volume[b]** | 466356.09 | 30751.54 | 469896.7 | 30468.55 | .19 | .661 | 0.12 |
| **Total grey matter volume[b]** | 709657.65 | 27787.15 | 706014.03 | 27531.43 | .25 | .618 | 0.13 |
| **Total LGI[b]** | 207.21 | 5.94 | 209.65 | 5.88 | 2.47 | .122 | 0.41 |
| **Total cortical surface area[b]** | 174485.83 | 6989.95 | 177131.59 | 6925.62 | 2.10 | .153 | 0.38 |
| **Mean cortical thickness[b]** | 2.68 | 0.08 | 2.64 | 0.08 | 2.81 | .099 | 0.50 |

a = controlling for age and sex; b = controlling for age, sex and intracranial volume; LGI = Local gyrification index. P values are uncorrected

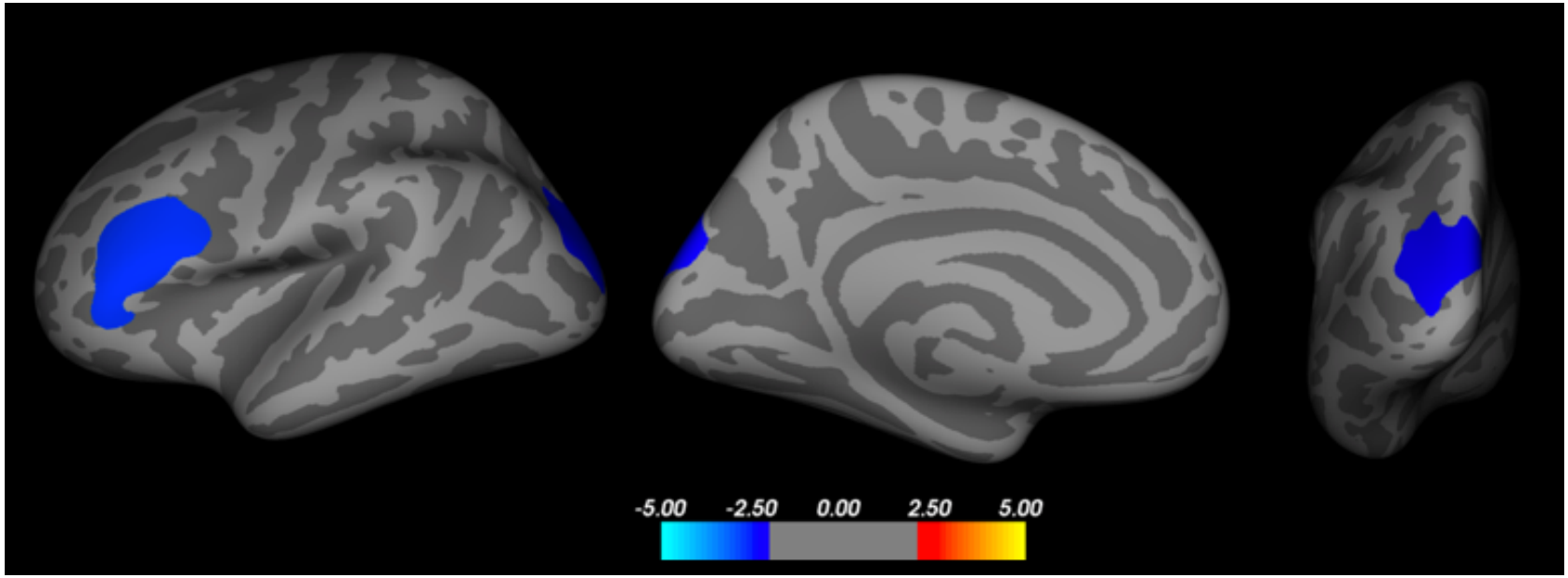



**Figure 1**. *Statistical map of cortical surface area expansion in the left lateral middle/inferior prefrontal and lateral parietal-occipital-regions of the cortical surface in the first episode mania group compared to age-matched healthy controls*. The map indicates lateral, medial and posterior views of the inflated surface using the Desikan Killiany atlas. It was generated from a general linear model specifying cortical surface area as the dependent variable at each vertex of the surface, covarying for age, sex and intracranial volume and correcting for multiple comparisons using Monte Carlo cluster-wise correction ($p$<.05). The peak talairach (MNI305) coordinates for the significant clusters fell within the left pars triangularis (X= -51.3, Y= 25.8, Z= -7.2) and the left lateral occipital cortex (X=-17.1, Y= -86.8, Z= 20.7). Note the colour bar reflects significance of the clusters in log (10) values (e.g., -2 = p< 0.01, -5 = p<0.00001).

***Supplementary Material***

# Increased cortical surface area but not altered cortical thickness or gyrification in bipolar disorder following stabilisation from a first episode of mania

*Running title: Surface-based brain morphology and first episode mania*

Tamsyn E. Van Rheenen*[1,2], Sue M Cotton[3,4], Orwa Dandash[1,6], Rebecca E Cooper[1], Elysha Ringin[1], Rothanthi Daglas-Georgiou[3,4], Kelly Allott[3,4], Yann Chye[6], Chao Suo[6], Craig Macneil[5], Melissa Hasty[5], Karen Hallam[9], Patrick McGorry[3,4], Alex Fornito[6,] Murat Yücel [6], Christos Pantelis[1,7] and Michael Berk[3,4,9]

[1]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia
[2]Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia
[3]Orygen, Parkville,VIC, Australia;
[4]Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia
[5]Orygen Youth Health Clinical Program, Parkville, VIC, Australia
[6]Turner Institute for Brain and Mental Health, School of Psychological Sciences and Monash Biomedical Imaging Facility, Monash University.
[7]Florey Institute of Neuroscience and Mental Health, Clayton, VIC, Australia
[8]The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, Australia
[9]Barwon Health, PO Box 281, Geelong, Victoria, 3220, Australia

* Corresponding author current postal address:
Dr Tamsyn Van Rheenen
Melbourne Neuropsychiatry Centre, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Vic 3053, Australia, tamsyn.van@unimelb.edu.au

Exclusion criteria for patients with diabetes mellitus

Further exclusion criteria included a known or suspected clinically relevant systemic medical disorder; a prior sensitivity or allergy to quetiapine, lithium or their components; a history of epilepsy, or an immediate risk of self-harm. Use of cytochrome P450 3A4 inhibitors in the 14 days preceding enrolment was not permitted including ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, fluvoxamine and saquinavir. The use of cytochrome P450 inducers was also not permitted in the 14 days preceding enrolment including phenytoin, carbamazepine, barbiturates, rifampacin, St John's Wort or glucocorticoids. Additional exclusion criteria was applied to patients with diabetes mellitus (DM), as uncontrolled diabetes mellitus can affect emotional, cognitive and brain health. For these patients, the extra exclusion criteria included: admission to hospital for treatment of DM or DM-related illness in the previous 12 weeks; unstable DM defined as enrolment glycosylated haemoglobin (HbA1c) 48.5; not on the same dose of oral hypoglycaemic drug(s) for the 4 weeks before randomisation (8 weeks for thiazolidinediones); daily insulin more than 10% outside their mean monthly dose on one or more occasions in the preceding 4 weeks; and/or not under physician care for DM or the physician responsible for patient's DM care did not indicate that patient's DM was controlled or did not approve the patient's participation in the study.

Acquisition error resulting in the structural images of 25 patients sampled at twice the resolution[5]

Structural images were acquired at two different resolutions as a result of the inadvertent selection of the interpolation box during the reconstruction process. *All* images were acquired in the k-space (frequency space) at the same rate, then reconstructed into the image space using Fourier transform in which two matrices (mesh-like frames) were applied, resulting in some images being reconstructed with a matrix that had double the number of spatial units to that when interpolation was not applied. Although it was anticipated that interpolation would not affect the quality of structural neuroimaging results, the following were carried out to assess this as a precaution:

1) Acquisition of phantom images with and without interpolation;
2) Acquisition of human data with and without interpolation;
3) Statistical analyses involving co-registration of both image types (to minimize head motion effect) and subtraction to investigate resulting residuals using trilinear interpolation when subtracting the images from each other. Other methods e.g. B-spline as well as nearest neighbor were also used and to a large degree produced similar results.

Other than slight differences in non-brain tissues and around the edges of the head, no other differences were evident. Given successful removal of non-brain tissues using the skull-stripping feature in Freesurfer and the use of a 10mm smoothing kernel for the current analysis, as well as the strong inter-rater reliability of volume estimates (after correction) in 9

[5] Note that this error occurred only in patients because the healthy control cohort was recruited after the majority of the patient sample had been scanned.

randomly selected regions, the discrepancy in scan resolutions is unlikely to have had any effect on the analysis.

Copy of in-house image editing protocol used to manually correct surfaces delineated by Freesurfer.

## Editing in Freeview

Freeview is the interface that you will use to make edits in Freesurfer. You will need an active Freesurfer environment for it to load. Use the following command to load each brain to view. Each back slash represents a new command, allowing many commands to be run in one go.

```
freeview -v \
subjectID/mri/T1.mgz \
subjectID/mri/wm.mgz \
subjectID/mri/brainmask.mgz \
subjectID/mri/aseg.mgz:colormap=lut:opacity=0.2 \
-f subjectID/surf/lh.white:edgecolor=blue \
subjectID/surf/lh.pial:edgecolor=red \
subjectID/surf/rh.white:edgecolor=blue \
subjectID/surf/rh.pial:edgecolor=red
```

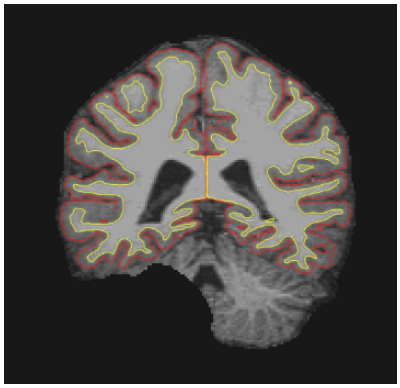
Once Freeview loads up, you will be making three types of edits: pial surface edits, white matter edits, and control point edits. Pial surface errors are the most common, and fortunately with the higher quality 3T scans, errors in the white matter are less common than they used to be. How to make these corrections are thoroughly described in the tutorials provided below.

## Tutorial Links

- General editing
- Pial surface edits
- White matter edits
- Control point normalisation
- Topological errors
- Skull stripping errors

## Skull stripping errors

**Problem:** When skull stripping step removes more than just the skull, causing part of the brain to be removed, or removes too little, leaving behind portions of the skull.



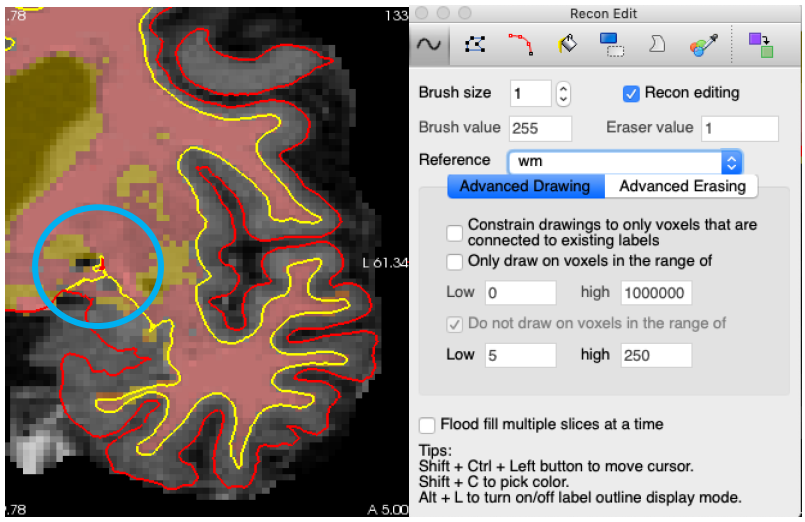
**Solution:** Adjust the watershed parameters. Either make the threshold more conservative if part of the brain has been removed by decreasing the preflooding height percentage, or more aggressive if part of the skull has been left behind by increasing the height. Height is 1-50, default is 25. If part of brain missing, start around 35, and if too much skull is remaining, start around 25.

> recon-all -skullstrip -wsthresh <*height*> -clean-bm -subjid <*subject_ID*>
> recon-all -autorecon-pial -subjid *subject_ID*

## Segmentation errors

**Problem:** White matter voxels are excluded, or voxels that are not white matter are included. Check in all three views to ensure they are holes and not sulcus.

**Solution:** Open 'recon edit' and make sure you are editing the white matter volume. Click to add white matter voxels on all affected areas.
> recon-all -autorecon2-wm -autorecon3 -subjid *subject_ID*

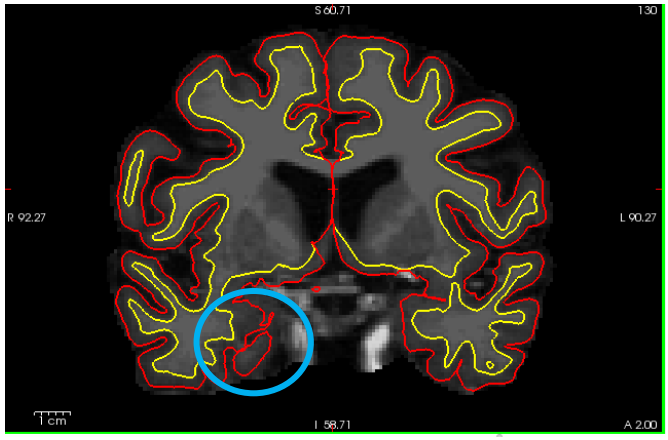


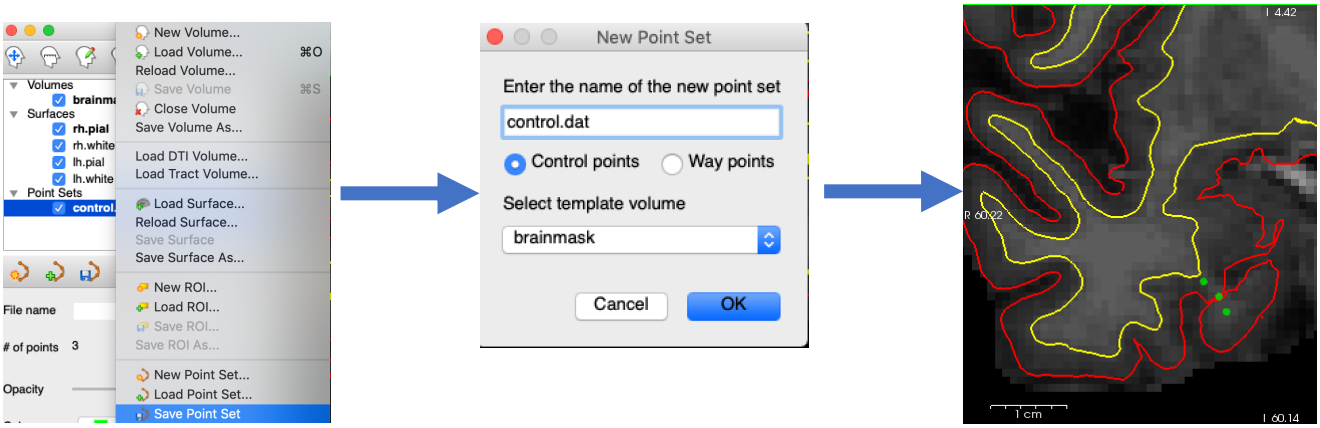

## Intensity Normalisation Errors

**Problem:** White matter not registering properly, erroneously segmented.

**Solution:** Go to file > save point set, make the file name 'control.dat', then click to add data points.

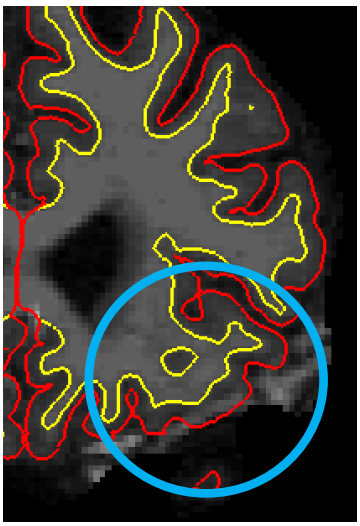
> recon-all -autorecon2-cp -autorecon3 -*subject_ID*





## Pial surface errors

**Problem:** When non-cortex things like skull or dura are included in the pial surface.



**Solution:** Select the 'recon-edit' button, make sure the reference is set to 'brainmask', brush size 1 or 2 (depending on how fine you'd like to edit), hold down shift key + left click to remove voxels.

> recon-all -autorecon-pial -subjid pial_edits_before

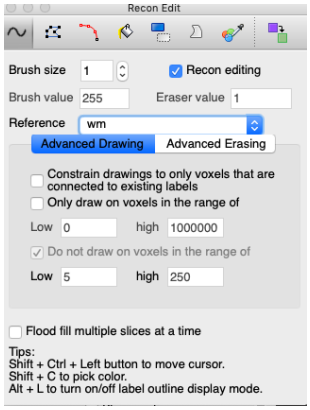
## Topological Defect

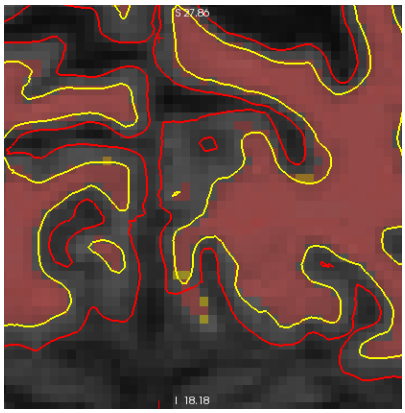
**Problem:** White matter surface excludes voxels that are white matter.

**Solution**: Open 'recon-edit', make sure you're editing the white matter layer, toggle back between brainmask.mgz and wm.mgz to see where to make edits, click to add white matter voxels.

> recon-all -autorecon2-wm -autorecon3 -subjid *subject_ID*





**Things to note:**

- Always click on and make edits on the 'brainmask' layer. Do not edit any other layers.
- Always save!
- You can adjust the contrast to make seeing the grey/white matter boundaries clearer…

## Recon-all, again and again

Once you've made edits, you will need to re-run recon-all so it can take into account the new changes. You can tell recon-all to run from a certain step in the pipeline to save you time. For example, if you've only made pial surface edits, you can use this command:

> recon-all subjid *subject_ID* -autorecon3-pial

If you've made white matter edits *and/or* grey matter edits, you can use this command:

> recon-all subjid *subject_ID* -autorecon2-wm

However, if you've made multiple edits, you will need to use the '-all' command to capture all relevant processes.

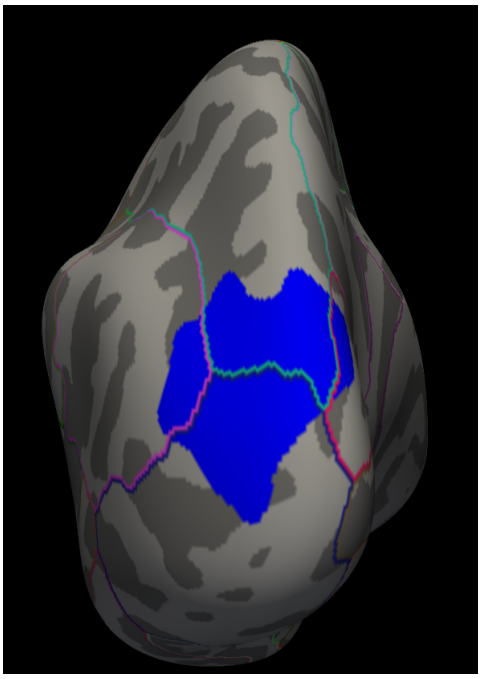
> recon-all -all subjid *subject_ID*

### Using the quality control log

This process of editing and running recon-all can happen two or three times, and each time this happens, certain details must be recorded.

- Participant ID
- Initials – *person who made the edits*

Location – *path file to the subject directory*



**Supplementary Figure 1.** Location of the occipitoparietal cortex surface area cluster overlaid on the Desikan Killiany atlas regions. Aqua lines delineate the superior parietal region, dark blue delineate the lateral occipital cortex, pink delineates the inferior parietal cortex and red delineates the cuneus.

**Highlights**

- Cortical thickness and gyrification appear intact following a first manic episode
- Prefrontal and occipitoparietal cortex surface area is increased after a first manic episode
- Increased surface area may be the outcome of premorbid abnormalities