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FURTHER UNDERSTANDING OF THE COMORBIDITY BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND BIPOLAR DISORDER IN ADULTS: AN MRI STUDY OF CORTICAL THICKNESS

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1. INTRODUCTION

A substantial and bi-directional overlap has been documented between attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BPD) in adults (Sachs et al. 2000) and children (Biederman et al. 2003). In adults, BPD comorbid with ADHD has an early age of onset in childhood and adolescence (Sachs et al. 2000). Family studies suggested that BPD comorbid with ADHD might be an early onset, familially distinct subtype of BPD (Faraone et al. 2003), given that co-segregation between BPD and ADHD has been demonstrated.

Although ADHD and bipolar disorder co-occur frequently and represent a particularly morbid clinical form of both disorders (Biederman et al. 2005) neuroimaging research addressing this co-morbidity is scarce, and no studies have used measures of cortical thickness. In a previous volumetric MRI study of the current sample we found that BPD was associated with a significantly smaller orbital prefrontal cortex and larger right thalamus, and that this pattern was also found in comorbid subjects with ADHD+BPD (Biederman et al. 2008). Likewise, ADHD was associated with significantly less neocortical gray matter, less overall frontal lobe and superior prefrontal cortex volumes, a smaller right anterior cingulate cortex, and less cerebellar gray matter, as was comorbid ADHD+BPD (Biederman et al. 2008). These results support the hypothesis that ADHD and BPD independently contribute to volumetric alterations of selective and distinct brain structures. Yet, whether these results will extend to cortical thickness alterations remains unknown.

Given the architectonic nature of cortical and subcortical connections with respect to cortical lamination, cortical thickness could be an indicator of integrity of cytoarchitecture in the cortex and thus an indirect assessment of cortical connectivity (Makris et al. 2006). Recent neuroimaging studies of cortical thickness in ADHD, including our own, have shown consistent abnormalities in prefrontal and parietal regions associated with corticostriatal, attention and executive neural networks (Sowell et al. 2003; Makris et al. 2007; Shaw et al. 2007; Almeida et al. 2010; Batty et al. 2010). In contrast, in BPD, cortical thinning was shown in left rostral paracingulate and right dorsal paracingulate regions in one study (Fornito et al. 2008), whereas other studies of cortical thickness have found BPD-related thinning in left dorsal-anterior and posterior cingulate regions, left occipital region, left precentral area, right medial frontal, frontopolar and frontoorbital cortex (FOC), right postcentral and angular regions, right lateral occipital areas as well as right and left middle frontal areas (Lyoo et al. 2006; Fornito et al. 2008). To date, none of these studies evaluated individuals with combined ADHD+BPD.

The main aim of this study was to identify a network of MRI measures of cortical thickness in adults with ADHD comorbid with bipolar disorder (ADHD+BPD), and the independent contribution of each disorder to this network of alterations. Based on the existing, limited neuroimaging literature on comorbidity, we expected that each contributing disorder would be associated with disorder specific findings. Specifically, ADHD will be associated with abnormalities in the supervisory networks involved in generalized control of multiple

cognitive functions involved in attentional and executive processing (e.g., prefrontal, inferior parietal lobule and anterior cingulate cortices (Strange et al. 2001; Seidman 2006; Burgess et al. 2007)). We also expected that BPD will be associated with abnormalities in the limbic and paralimbic cortices involved in emotion processing including anterior cingulate, and anterior insula, as well as the ventral PFC regions including FOC. To the best of our knowledge, this represents the first examination of cortical thickness measurements in adults with ADHD and BPD attending to the issue of the comorbidity.

2. METHOD

As previously reported, (Biederman et al. 2008), subjects (ages 18–59) were stratified into four groups based on diagnostic status: BPD+ADHD (n=31), BPD only (n=18), ADHD only (n=26), and controls with neither ADHD nor BPD (n=23). This paper presents entirely new cortical thickness analyses on the same sample as in our previous volumetric study using identical brain acquisitions carried out at Massachusetts General Hospital (MGH) as reported in Biederman (Biederman et al. 2008). Data from 43% of the participants in this study without BPD (24 with ADHD and 18 controls) have additionally been reported in other papers (Seidman 2006; Makris et al. 2007). Briefly, exclusion criteria were neurological disorders, sensorimotor handicaps, inadequate command of the English language, or a Full Scale IQ estimate less than 75 as measured by the Wechsler Adult Intelligence Scale-Revised (Wechsler 1981). No ethnic or racial group was excluded. Socioeconomic status (SES) was assessed with the Hollingshead scale (Hollingshead, 1975).

We recruited ADHD probands (including those with comorbid BPD) through referrals to the Adult ADHD program at Massachusetts General Hospital (MGH) and advertisements in the greater Boston area. A subset of the bipolar probands was recruited through a follow-up to a birth cohort study (Thermenos et al. 2010) that used identical imaging methods during the same time period. We recruited control probands through advertisements in the greater Boston area. These were selected by not having BPD or ADHD as is customary in case-control studies. ADHD adults were included if they met full criteria for current ADHD according to the DSM-IV, with childhood onset and persistence into adulthood. Written informed consent was obtained for all subjects after a complete description of the study, and all participants received an honorarium for participating. The MGH human subjects committee approved this study. All BPD subjects met full criteria for DSM-IV bipolar I disorder.

Regarding medication history for the 23 controls, 19 had never received psychotropic medications, 4 had received medications in their lifetime, including anti-depressants (n=4), anti-anxiety (n=1) and stimulant (n=1) medications. For the 26 ADHD participants, 12 had never received psychotropic medications, and 14 had received some medications including anti-depressants in the past only (n=2), stimulants until the 24 hours prior to imaging when they were washed out (n=8), and stimulants in the past (n=4). For the 18 BPD participants, 6 had never received psychotropic medications, and 12 were on multiple medications including anti-depressants (n=10), anti-psychotics or mood stabilizers (n=10), stimulants (n=1), and anti-anxiety medications (n=2). For the 31 ADHD+BPD participants, 3 had never received psychotropic medication, 5 had missing data, and 23 were on multiple medications including stimulants (n=10), anti-depressants (n=23), anti-anxiety medications (n=3), and anti-psychotics or mood stabilizers (n=17).

2.1 Clinical Assessment Measures

Trained interviewers, blind to ascertainment status, interviewed subjects with the Structured Clinical Interview for DSM-IV (First et al. 1997) and modules from the Kiddie SADS-E (Orvaschel 1994). The structured interview data were reviewed by a diagnostic committee

blind to the subject's ascertainment group and all non-diagnostic data. We computed kappa coefficients by having board certified child and adult psychiatrists diagnose subjects from audio taped interviews. Kappa coefficients for ADHD and BPD were 0.88 and 0.95, respectively. We estimated IQ from the Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981) to assess comparability of the groups.

2.2 MRI Protocol

Whole brain MR images were collected on a Siemens 1.5 Tesla scanner at the MGH/HST A. Athinoula Martinos Center for Biomedical Imaging. A sagittal localizer scan was performed for placement of slices, followed by a coronal T2-weighted sequence to rule out unexpected neuropathology. Two sagittal 3D MP-RAGE (T1-weighted, non-selective inversion-prepared spoiled gradient echo pulse) sequences were collected and averaged (TR/TE/T1/flip = 2.73 s/3.39 ms/1.0 s/7, bandwidth = 190 Hz/pixel, sampling matrix = 256 × 192 pixels, FOV = 256 × 256 mm, effective slice thickness = 1.33 mm on a 170 mm slab of 128 partitions) and used for analyses conducted at the MGH Center for Morphometric Analysis (CMA).

2.3 Image Analysis

Structural scans were transferred to the CMA and coded and catalogued for blind analysis. Image analysis, including preprocessing and segmentation of cerebral cortex and white matter was done in workstations using Cardviews software (Filipek et al. 1994; Caviness et al. 1996).

2.4 Cortical Thickness Analysis Procedure

The technique implemented herein is a method using a combination of automated routines and supplemented by semi-automated and manual procedures (Makris et al. 2008). Briefly, steps include: 1). Segmentation of the cerebral cortex using Cardviews; 2). Computation of cortical thickness differences using FreeSurfer (Dale et al. 1999) and; 3). Caret (Van Essen 2004) implementation for robust surface registration. For a more detailed and complete description of the methods we refer to previous publications of our groups (Makris et al. 2006; Makris et al. 2007; Makris et al. 2008) and to the detailed methods in the supplemental materials of this manuscript. Once segmentation is executed in Cardviews following a semi-automated procedure (see Figure 1A, 1B), the outline files created by the segmentation are converted to a FreeSurfer volume segmentation (Figure 1C). A surface is tessellated, smoothed (Figure 1D) and inflated (Figure 1E) from the converted FreeSurfer volume. An intensity gradient is then created throughout the cortex as a function of the distance from the white matter surface according to the manual segmentation of the cerebral cortex (Figure 1F) and the exterior surface is generated to be consistent with the manual segmentation (Figure 1G). These surfaces enable the computation of cortical topographical measurements such as cortical thickness, curvature, gyrification index and folding index (Dale et al. 1999). With the white and gray surfaces in place, thickness maps are created across the cerebral cortex.

The registration was done using the Caret software package (Van Essen 2004) by manually tracing visible anatomical landmarks, i.e., sulci, on the cortical surface of each subject (see Figure 2) and then registering to the Population Average, Landmark- and Surface-based (PALS) atlas (Van Essen 2005). This approach has been shown to be more robust in surface registration as compared to fully automated methods of registration (Pantazis et al. 2010). Given our *a priori* ROI driven hypothesis and neural systems-based approach, we think that this study benefits the most from the landmark-based technique as the anatomical regions adjacent to the landmarks are optimally registered (Zhong et al. 2010). The registration

method uses a deformable, spherical registration that is constrained by the landmarks. This landmark-based spherical registration to the PALS atlas generates a deformation map of each subject's cortical surface to align each subject into the common space (Figure 1H), and allows inter-subject averaging for computation of cortical thickness differences between groups. Colored regions show significant differences in cortical thickness from an omnibus F-test with red representing $p < .05$ and yellow $p < .001$. A parcellation scheme is mapped onto the template brain, which depicts the 49 cortical parcellation units (PUs), per hemisphere, as labeled by the CMA methodology and their approximate corresponding Brodmann's areas, to localize results regionally (Figure 1I). It should be noted that this hybrid method is different from other available techniques, such as FreeSurfer, (which perform similar cortical measurements), with respect to two principal aspects. First, semi-automated and manual routines (Filipek et al. 1994; Caviness et al. 1996), which have been implemented as the gold standard to validate fully automated methodologies for segmentation (Fischl et al. 2002) were necessary to reliably and accurately obtain the cortical ribbon in each subject (Caviness et al. 1996; Makris et al. 2006). Furthermore, we used the Caret software to improve surface registration by manually drawing sulci on each subject's cortical surface (Van Essen 2004). In all, this combined method allows for the interoperation between volume-based and surface-based topographic analysis, and extends the functionality of many existing segmentation schemes.

2.5 Reliability of sulci

In our study, the 32 landmarks (16 for each hemisphere), i.e., principally cerebral sulci, of five subjects were delineated twice by rater1 (DB), and once by rater2 (MG) in the Caret domain. To test intra-rater reliability of the manual delineation, for each landmark, we computed the Hausdorff distance between the two delineations of rater1. For inter-rater reliability, we calculated the Hausdorff distance between the first delineation of rater1 and the corresponding delineation of rater2. Hausdorff distance measures how close the two curves are, and would be zero if they were perfectly matched. So we would expect to see a smaller value if a landmark delineation reliability is high.

2.6 Data Analysis

Each subjects' native space cortical thickness map was transformed to a target subject (PALS) using the Caret registration technique described above, and then smoothed using a Gaussian with fwhm of 10mm (full width at half maximum). Using a general linear model (GLM) we implemented a vertex-wise omnibus F-test to find regions that differed between controls and any psychopathological group (i.e., ADHD, BPD, or BPD+ADHD). The four group omnibus test was advantageous because it provided a single map that identified any areas where thickness differences were due to effects of ADHD, effects of BPD, or the interaction of the two disorders. A cluster was significant if each contiguous vertex had $p < 0.05$ and a total area of at least 31.77 mm^2 (Makris et al. 2008). Additionally, the surface of the target subject was parcellated in order to localize group differences. Each cluster is identified and labeled by the PU that is the primary constituent of that cluster.

For each subject, the mean cortical thickness of a cluster was calculated from all vertices that comprise that cluster. In each cluster, the subjects' mean thickness was then modeled as a function of their ADHD status, BPD status, and an interaction term using linear regression. No covariates were used in the model. If the interaction term was not significant, it was removed from the regression model, and the independent effects of ADHD and BPD were reported in the form of beta weights. Using a model with the two main effects and their interaction allowed us to quantify the specific contribution of ADHD or BPD on the cortical thickness in each cluster, independent of the presence or absence of the other disorders. All tests were two-tailed with alpha set at 0.05.

3. RESULTS

3.1 Demographic Characteristics, Intellectual Functioning and Psychiatric Comorbidity

There were no significant group differences on age, sex, or handedness. Not surprisingly, significantly different IQ scores were shown across the 4 groups, and a trend difference was found in personal SES (i.e., subjects own occupational and educational status) and race ($p < .10$). Whole brain volume between the groups was comparable (Table 1).

3.2 Reliability of sulci

Intra-rater and inter-rater reliability for sulci tracing using the Hausdorff distance was high. Specifically, the overall mean difference was 1.32 mm for intra-rater and 1.68 mm for inter-rater measurements. Table 2 shows reliability measures for each one of the 32 landmarks.

3.3 Cortical Thickness

ROIs: By using the omnibus F-test we found 23 clusters of vertices in the right hemisphere and 13 in the left, which became the ROIs used in these analyses as shown in figure 3. Colored regions show significant differences in cortical thickness (Figure 3).

The 23 clusters of vertices localized to the *right hemisphere* comprised frontal, parietal, temporal and occipital regions (Figure 3). Frontal lobe regions included the frontal pole (FP, BA 10, 11), superior frontal gyrus (F1, BA 6, 8, 9), middle frontal gyrus (F2, BA 6, 8, 9, 46), perigenual anterior cingulate gyrus (perigACC or perigCGa, BA 24), dorsal anterior cingulate gyrus (dACC or dCGa, BA 24, 33) and paracingulate gyrus (PAC, BA 32), supplementary motor cortex (SMC, medial BA 6), and precentral gyrus (PRG, BA 4, and Caudal BA 6). Parietal cortical areas comprised the angular gyrus (AG, BA 39), and posterior part of supramarginal gyrus (SGp, caudal BA 40), superior parietal lobule (SPL, BA 5, 7). Temporal lobe regions included the temporal pole (TP, BA 38), posterior insula (pINS) and posterior part of parahippocampal gyrus (PHp, BA 27, 35). Several areas in the occipital lobe were involved, including the dorsolateral occipital area (OLs, BA 18, 19), lingual gyrus (LG, BA 17, 18) and the occipital pole (OP, BA 17, 18). Finally, there were also two clusters localized within temporooccipital transition areas, namely the dorsolateral temporooccipital region (TO2, BA 37) and the temporooccipital fusiform gyrus (TOF, BA 37). Of the above regions several were localized *bilaterally*. These were the frontal pole, precentral gyrus, caudal part of the supramarginal gyrus, temporooccipital fusiform gyrus, dorsolateral occipital and occipital pole areas. Finally, the cortical regions lateralized uniquely on the *left hemisphere* involved principally the parietal lobe at the posterior cingulate gyrus (CGp, BA 23, 31, 26, 29, 30), and precuneus (PCN, medial BA 7). The mean cortical thickness in each ROI is shown for each of the four groups (Table 3).

3.4 Effect of ADHD and BPD

For each ROI an analysis was performed to examine separately the effect of ADHD and BPD. In the regression model the intercept represents the average thickness of the ROI without either ADHD or BPD effects (control average). The beta coefficients for ADHD and BPD represent the average increase or decrease in cortical thickness due to the respective factors. In all but one ROI showing an interaction effect in the ventrolateral surface of the visual association occipital region (OLi, BA 18, 19), there was no interaction between ADHD and BPD. Of note, the effects of ADHD were all decreases in cortical thickness, though not all statistically significant (Figure 4a and Table 4). In contrast, effects of BPD included increases and decreases in cortical thickness, however, all but one area that were statistically significant were increases (Figure 4a and Table 4). The one ROI, in which the BPD effect was decreased cortical thickness was the right ventral frontal pole.

3.5 Comorbid ADHD plus BPD condition-Additive Effect

Because there was only one statistical interaction (as noted above) between the effects of ADHD and BPD in cortical thickness, cortical thickness of the comorbid condition can be accurately predicted by combining the individual effect of each condition (Figure 4c). This resulted in three classes of findings. 1) In most ROIs, ADHD decreased cortical thickness and BPD increased cortical thickness and thus the combination of the two produced an intermediate effect; 2) in some areas there was little effect of one of the conditions and the combination of the two produced an effect very similar to the predominant condition, and 3) in a few ROIs, the effect of both conditions was a decrease in cortical thickness for both conditions and the combined condition produced a much thinner cortex than either condition alone (notably the frontal pole).

4. DISCUSSION

In this cortical thickness analysis, we found a striking pattern of different effects attributable to ADHD and BPD that were independent of the other condition. The ADHD effect was a statistically significant *decrease* in cortical thickness in a number of regions across the cortex that support executive and attentional functions. In contrast, the BPD effect was a statistically significant *increase* in cortical thickness in several brain regions with the exception of the frontal pole, which showed a decrease in both BPD and ADHD. Given that there were minimal interaction effects, these results indicate that the cortical thickness of the comorbid group can be accurately predicted by combining the individual effects of ADHD and BPD observed individually.

Our observations with respect to the ADHD effect replicated already published observations (Sowell et al. 2003; Makris et al. 2007; Almeida et al. 2010; Batty et al. 2010), which indicate cortical thinning of frontal and parietal cortical regions in both the dorsolateral and dorsomedial aspects of the hemispheric surface. Likewise, the BPD effects demonstrated cortical thinning in frontopolar areas (FP) and cortical thickening in an array of temporal, parietal and occipital regions in this sample of adults with BPD. This reduction in cortical thickness in the FP is predicted and largely consistent with the neurobehavioral literature (Lyoo et al. 2006; Fornito et al. 2008; Rimol et al. 2010), however the presence of significant cortical thickening is less well established. However, the findings of a pattern following a dorsal and a ventral stream of distribution in the cortical surface are novel. Future studies will need to assess whether this pattern is associated with neural systems alterations involving both cortical and white matter fibers (Makris et al. 2009).

The cortical thinning abnormalities in the dorsal-cortical and the ventral-limbic system are consistent with the neuroimaging literature on ADHD and bipolar disorders. Cortical thinning has been shown in ADHD in dorsal systems involving DLPFC and medial frontal regions (Makris et al. 2007). Likewise, cortical alterations have been reported in BPD in left rostral paracingulate and right dorsal paracingulate regions using a semi-automated approach (Fornito et al. 2008). Cortical abnormalities have also been shown in BPD using a fully automated method in left dorsal-anterior and posterior cingulate regions, left occipital region, left precentral area, left and right middle frontal area, right medial frontal, frontopolar and orbitofrontal cortex, right postcentral and angular regions as well as right lateral occipital areas (Lyoo et al. 2006).

Our findings indicate that comorbid ADHD with BPD presents a morphometric profile reflecting an additive effect of both ADHD and BPD cortical abnormalities (Lyoo et al. 2006; Makris et al. 2007; Fornito et al. 2008), similar to what we observed in the same sample with volumetric imaging (Biederman et al. 2008). Individuals with comorbid ADHD +BPD showed cortical thinning within both the dorsal-cortical system (i.e., DLPFC,

dorsolateral and medial frontal pole, anterior cingulate gyrus and paracingulate gyrus) as well as in the ventral-limbic system (i.e., medial frontal cortex and ventral frontopolar cortices) bilaterally. These alterations in prefrontal limbic circuitry reflect a disruption in regions governing cognitive control of affective and hedonic functions, as well as self-monitoring, attention and executive functions.

The dorsal-cortical system (including the DLPFC, dorsal FP, ACC and PAC) has been associated with cognitive aspects of negative emotion such as apathy, psychomotor slowing as well as attentional and executive function deficits. In contrast, the ventral-limbic system containing limbic and paralimbic structures (such as the ventral FP, ventral prefrontal cortex, subcallosal cortex, insula, and temporal pole) deals with aspects of autonomic behavior (Mayberg 2002).

Interestingly, among all structures, the most affected structure was the frontal pole (FP, BA 10) bilaterally, which belongs to both dorsal-cortical and ventral-limbic systems. This cortical region shows unique features in terms of its topography, histology, anatomical connections and function (Ramnani and Owen 2004). Topographically, it unites its dorsolateral and ventral aspects bridging BA 10 with BA 9 and 46 of the DLPFC with BA 32 of the mPFC and BA 11 and 47 of the ventral PFC. Structurally, its high content and density in dendritic spines (Jacobs et al. 2001) and functionally, its role in a variety of cognitive and emotional processes such as memory (Duzel et al. 1999; Burgess et al. 2001), attention (Koechlin et al. 1999), planning and reasoning, relational integration between objects or thoughts (Kroger et al. 2002), and processing of internal states (Christoff and Gabrieli 2000), make the frontopolar region a potential processor for the integration of cognitive and emotional information. Future studies are needed to determine whether these abnormalities are specific to this particular comorbid diagnosis.

Although the exact etiology of the cortical thinning findings remains unclear, it can be hypothesized that they represent alterations of cells, neuropil, synaptic densities as well as local fibers or long corticocortical fiber pathways. More work is needed to elucidate the etiology of these neurobiological changes in the cortex in subjects with ADHD+BPD.

Our findings should be interpreted in light of some methodological limitations such as registration errors inherent to inter-subject mapping due to a high degree in inter-individual variability of cortical surface topography. Limitations are also due in part to the transformation procedure, as well as the potentially ill-posed nature of inter-subject correspondence in topology. While inferior parietal lobule alterations have been documented in both ADHD and BPD, in the present study of comorbid ADHD with BPD, we did not find any significant cortical alterations in this region. Whether this may be due to population criteria differences or differences in method remains an open question. Also, differences in our findings may have resulted from the fact that these are comorbid cases rather than ADHD or BPD alone. Furthermore, because the medication status was heterogeneous, we could not address the impact of medication adequately. More work is needed to further elucidate these important issues.

Despite these considerations, our study shows that the effects of ADHD and BPD on cortical thickness are primarily independent and often in contrasting directions. Since ADHD was consistently associated with decreased cortical thickness, and BPD was predominantly associated with increased cortical thickness, the additive effects resulted in less cortical thickness alterations. A notable exception was the frontal pole in which cortical thickness was decreased by both conditions. To the best of our knowledge, this is the first neuroimaging documentation showing that in comorbid ADHD+BPD subjects, the cerebral cortex is affected in networks that support cognitive and emotional processes and in cortical

centers responsible for vital cortical-limbic interactions and integration localized principally in the frontal lobe.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Illustration of the topological cortical parcellation (TCP) system. The overall approach is to segment and parcellate the cerebral cortex using *Cardviews* and then use *FreeSurfer* to compute cortical thickness differences. 1A shows an intensity normalized T1-weighted MR coronal image. Segmentation (1B) of the cerebral cortex is done in the *Cardviews* domain following mainly a manual procedure. The outline files created by the segmentation procedure (using *Cardviews*) is converted to a *FreeSurfer* volume (1C). A surface is tessellated, smoothed (1D) and inflated (1E) from the converted *FreeSurfer* volume. An intensity gradient is created throughout the cortex as a function of the distance from the white matter surface according to the manual segmentation of the cerebral cortex (1F). The exterior surface is generated to be consistent with the manual segmentation (1G). Using Caret software (Van Essen 2002); (Van Essen 2004) we draw manually visible anatomical landmarks, i.e., sulci, on the cortical surface of each subject. Then we run Caret surface registration to the Population-Average, Landmark- and Surface-based (PALS) atlas (Van Essen 2005) (1H). By registering each subject to a common space, each vertex on each subject can be mapped together to allow for inter-subject averaging. Maps are then created showing the cortical thickness differences between groups of subjects; colored regions show significant differences in cortical thickness between the two groups with red representing $p < .05$ and yellow $p < .001$. These regions are localized by overlaying the cortical parcellation map on the inflated surface (1I). Significant clusters from a vertex-wise omnibus F test of all four groups were identified using a general linear model.

Figure 2.

Example illustrating the landmarks traced on the right hemispheric surface of a single subject. Lateral and medial views shown. Landmarks with a '*' indicate the six standard sulci supplied with Caret.

Abbreviations: SF STSant – Sylvian Fissure, Superior Temporal Sulcus anterior.

Figure 3.

Significant clusters from a vertex-wise omnibus F test of all four groups using a general linear model, identifying clusters that differed between controls and any psychopathological group (i.e., ADHD, BPD, or BPD+ADHD). Shown are the 36 significant clusters that surpassed a significance level of $p < 0.05$ for each contiguous vertex and an area of at least 31.77 mm^2 (Makris et al. 2008). Mean thickness values from these clusters were used as regions of interest for the regression model.

Figure 4a

Figure 4b

Figure 4c

Figure 4.

Figure 4a. Effect of ADHD controlling for BPD. Colored regions show clusters with significant ($p < 0.05$) cortical thinning due to an independent ADHD effect. Color bar represents beta values from regression model.

Abbreviations: CGp – cingulate gyrus, posterior division; F1 – superior frontal gyrus; F2 – middle frontal gyrus; FP – frontal pole; LG – lingual gyrus; OLS – occipital lateral gyrus, superior division; OP – occipital pole; PCN – precuneus; perigACC – perigenual anterior cingulate cortex; PHp – parahippocampal gyrus, posterior division; pmCGa_dACC2 – posterior middle cingulate gyrus, anterior division, dorsal anterior cingulate cortex; PRG – precentral gyrus; SGp – supramarginal gyrus, posterior division; SMC – supplementary motor cortex; SPL – superior parietal lobule; TP – temporal pole.

Figure 4b. Effect of BPD controlling for ADHD. Colored regions show clusters with significant ($p < 0.05$) independent BPD effect. Red colors represent thinning and blue colors represent thickening. Color bar represents beta values from regression model.

Abbreviations: AG – angular gyrus; CGp – cingulate gyrus, posterior division; FP – frontal pole; LG – lingual gyrus; OP – occipital pole; PHp – parahippocampal gyrus, posterior division; pINS – posterior insula; SGp – supramarginal gyrus, posterior division; TO2 – middle temporal gyrus; TOF – temporo-occipital fusiform gyrus.

Figure 4c. Additive effect of ADHD+BPD. Cortical thickness of the comorbid condition depicted by combining the individual effect of each condition. Blue represents areas in which the comorbid group has thicker cortices than the control group. Red, orange and yellow represents areas in which the comorbid group has thinner cortices than the control group.

Abbreviations: AG – angular gyrus; CGp – cingulate gyrus, posterior division; F1 – superior frontal gyrus; F2 – middle frontal gyrus; FP – frontal pole; LG – lingual gyrus; OLs – occipital lateral gyrus, superior division; OP – occipital pole; PCN – precuneus; perigACC – perigenual anterior cingulate cortex; PHp – parahippocampal gyrus, posterior division; pINS – posterior insula; pmCGa_dACC2 – posterior middle cingulate gyrus, anterior division, dorsal anterior cingulate cortex; PRG – precentral gyrus; SGp – supramarginal gyrus, posterior division; SMC – supplementary motor cortex; SPL – superior parietal lobule; TO2 – middle temporal gyrus; TOF – temporo-occipital fusiform gyrus; TP – temporal pole.

Table 1
Demographic Characteristics Comparing ADHD vs. Controls vs. Bipolar vs. Bipolar & ADHD *

<i>Demographic Characteristics</i>	Controls N=23	ADHD N=26	Bipolar N=18	ADHD & Bipolar N=31	Test Statistic (df), p value
Mean (Standard Deviation)					
Age	34.0 (9.6)	36.9 (11.1)	39.9 (6.5)	35.7 (12.0)	F(3,94)= 1.16, p=0.329
SES ¹	1.7 (0.5)	2.0 (1.1)	2.4 (1.0)	2.3 (1.2)	F(3,91)= 2.20, p=0.094
Full Scale IQ Estimate	115.6 ± 12.1	117.2 ± 13.5	102.7 ± 11.8 ^{ab}	107.9 ± 12.0 ^{ab}	F(3,93)=6.5, p<0.001
Whole Brain Volume	1311.3 (149.1)	1292.4 (90.2)	1247.9 (155.4)	1314.2 (131.3)	F(3,94)= 1.11, p=0.347
Frequency (Percent)					
Gender (male)	13(57)	13(50)	8(44)	19(61)	$\chi^2_{(1)}= 1.6$, p=0.670
Handedness (right)	21(91)	25(96)	16(89)	24(80)	$\chi^2_{(3)}= 3.9$, p=0.278
Race (Caucasian)	19(83)	26(100)	15(83)	29(97)	$\chi^2_{(3)}= 7.5$, p=0.057
Medication status at scan	1(4)	1(4)	11(61) ^{ab}	13(42) ^{ab}	$\chi^2_{(3)}= 27.5$, p<0.001
Frequency (Percent)					
Psychiatric Comorbidity					
Multiple (2) Anxiety Disorder ²	0 (0)	4 (15)	2 (25)	4 (15)	$\chi^2_{(3)}= 5.0$, p=0.174
Antisocial Personality Disorder ²	0 (0)	0 (0)	0 (0)	0 (0)	n/a
Substance Use Disorders ³	7 (30)	13 (50)	9 (50)	7(23)	$\chi^2_{(3)}= 6.4$, p=0.094

^a p<0.05 vs. ADHD;

^b p<0.05 vs. BPD

* Table is identical to that presented in Biederman et al (2008).

¹ Social class as measured by the Hollingshead scale (1975).

² Presence of the disorder within one month of diagnostic interview. Due to missing data, sample sizes for the Bipolar and ADHD & Bipolar groups are 8 and 26, respectively.

³ Lifetime history of alcohol or drug abuse or dependence

Table 2

The mean (in unit of mm) and standard deviation (std) of Hausdorff distances over five subjects are listed to quantify intra-rater and inter-rater reliability of the manual landmark delineation in Caret.

landmark	hemisphere	Intra-Reliability		Inter-Reliability	
		mean	std	mean	std
cingulate	left	1.1852	0.4635	1.8180	1.0275
cingulate	right	1.7086	0.5053	2.3540	1.2997
i_frontal	left	0.7077	0.1885	1.0483	0.6054
i_frontal	right	0.7136	0.1098	0.7997	0.1840
inparietal	left	1.2301	0.6217	1.7682	0.6505
inparietal	right	1.0295	0.3596	1.2269	0.2642
LANDMARK.CalcarineSulcus	left	1.5289	0.5693	2.3250	0.6082
LANDMARK.CalcarineSulcus	right	1.3415	0.6510	1.7009	0.4304
LANDMARK.CentralSulcus	left	1.3632	0.4059	1.7613	0.5633
LANDMARK.CentralSulcus	right	1.4654	0.5678	1.8872	0.7342
LANDMARK.MedWall.DORSAL	left	0.6495	0.1097	1.0429	0.3791
LANDMARK.MedWall.DORSAL	right	0.8447	0.1058	0.8516	0.4251
LANDMARK.MedWall. VENTRAL	left	2.8389	1.1521	2.5844	1.1094
LANDMARK.MedWall. VENTRAL	right	1.5977	0.4583	3.4432	1.2592
LANDMARK.SF_STSant	left	3.3281	2.3943	3.4782	1.0056
LANDMARK.SF_STSant	right	4.6988	1.6450	4.9360	3.6711
LANDMARK.SylvianFissure	left	0.9833	0.1077	1.5376	0.8652
LANDMARK.SylvianFissure	right	0.8748	0.2852	1.7063	1.0940
latorbdl	left	0.8229	0.3424	1.0449	0.3626
latorbdl	right	1.2689	0.7963	1.2322	0.6156
olfactory	left	1.0255	0.3604	1.8162	0.9977
olfactory	right	0.8838	0.2727	1.0773	0.5495
postcentral	left	1.3935	0.5920	1.6769	0.5800
postcentral	right	1.0974	0.3714	1.4340	1.0509
precentral	left	0.9420	0.2396	1.0111	0.3980
precentral	right	0.9371	0.2429	1.1427	0.3905

landmark	hemisphere	Intra-Reliability		Inter-Reliability	
		mean	std	mean	std
sbparietal	left	0.6939	0.2326	0.9939	0.2844
sbparietal	right	0.4673	0.1144	0.8568	0.3962
s_frontal	left	0.9522	0.2694	1.0293	0.5581
s_frontal	right	0.9758	0.3910	1.3251	0.4923
s_temporal	left	1.4186	0.5119	1.3575	0.4022
s_temporal	right	1.3132	0.1598	1.4926	0.7422
Overall		1.32	0.85	1.68	0.89

Table 3

Mean cortical thickness in each significant cluster for each group.

	Controls (N=23)	ADHD (N=26)	BPD (N=18)	Comorbid (N=31)
	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)
ADHD Significantly Thinner				
Right F1	3.58 $\pm$ 0.41	3.35 $\pm$ 0.34	3.76 $\pm$ 0.45	3.44 $\pm$ 0.48
Right F2	3.86 $\pm$ 0.45	3.43 $\pm$ 0.56	3.77 $\pm$ 0.49	3.67 $\pm$ 0.58
Right F2	4.05 $\pm$ 0.52	3.67 $\pm$ 0.63	4.03 $\pm$ 0.7	3.57 $\pm$ 0.68
Right FP/BA 9/10/11	3.72 $\pm$ 0.45	3.4 $\pm$ 0.58	3.49 $\pm$ 0.47	3.28 $\pm$ 0.5
Right PRG/BA 4	3.62 $\pm$ 0.44	3.2 $\pm$ 0.47	3.67 $\pm$ 0.54	3.43 $\pm$ 0.76
Right perigACC	4.22 $\pm$ 0.44	4.03 $\pm$ 0.82	4.16 $\pm$ 0.64	3.66 $\pm$ 0.74
Right pmCGa_dACC2	3.62 $\pm$ 0.39	3.49 $\pm$ 0.46	3.93 $\pm$ 0.51	3.55 $\pm$ 0.51
Right SMC/BA 6	4.22 $\pm$ 0.55	3.81 $\pm$ 0.48	4.27 $\pm$ 0.63	3.94 $\pm$ 0.68
Right SGp/BA 40	3.37 $\pm$ 0.45	3.15 $\pm$ 0.4	3.53 $\pm$ 0.42	3.31 $\pm$ 0.42
Right SPL/BA 7	3.39 $\pm$ 0.41	3.06 $\pm$ 0.44	3.43 $\pm$ 0.44	3.29 $\pm$ 0.55
Right OLs/BA 18/19	3.29 $\pm$ 0.37	2.99 $\pm$ 0.31	3.32 $\pm$ 0.44	3.07 $\pm$ 0.44
Right OLs/BA 18/19	3.01 $\pm$ 0.41	2.64 $\pm$ 0.36	3.04 $\pm$ 0.54	2.83 $\pm$ 0.59
Right TP	4.11 $\pm$ 0.44	3.92 $\pm$ 0.5	4.31 $\pm$ 0.34	3.89 $\pm$ 0.58
Right TP	4.31 $\pm$ 0.44	4.11 $\pm$ 0.57	4.55 $\pm$ 0.64	4.07 $\pm$ 0.59
Left FP/BA 9/10/11	4.05 $\pm$ 0.51	3.96 $\pm$ 0.73	4.21 $\pm$ 0.71	3.63 $\pm$ 0.72
Left FP/BA 9/10/11	4.18 $\pm$ 0.49	3.97 $\pm$ 0.87	4.12 $\pm$ 0.66	3.61 $\pm$ 0.78
Left PRG/BA 4	3.48 $\pm$ 0.34	3.19 $\pm$ 0.44	3.69 $\pm$ 0.67	3.33 $\pm$ 0.6
Left CGp/BA 23	3.55 $\pm$ 0.38	3.38 $\pm$ 0.4	3.77 $\pm$ 0.41	3.41 $\pm$ 0.35
Left PCN/BA 7	3.77 $\pm$ 0.48	3.48 $\pm$ 0.45	3.91 $\pm$ 0.5	3.67 $\pm$ 0.43
Left PCN/BA 7	3.7 $\pm$ 0.48	3.45 $\pm$ 0.53	3.94 $\pm$ 0.55	3.51 $\pm$ 0.7
Left OLs/BA 18/19	3.23 $\pm$ 0.45	2.89 $\pm$ 0.33	3.22 $\pm$ 0.35	2.98 $\pm$ 0.53
BPD Significantly Thicker				
Right AG/BA 39	3.12 $\pm$ 0.31	2.97 $\pm$ 0.33	3.4 $\pm$ 0.38	3.27 $\pm$ 0.46
Right pINS	3.94 $\pm$ 0.47	3.78 $\pm$ 0.45	4.28 $\pm$ 0.38	4.07 $\pm$ 0.52
Right TO2	3.15 $\pm$ 0.29	2.96 $\pm$ 0.27	3.25 $\pm$ 0.32	3.26 $\pm$ 0.45
Right TOF/BA 37	2.8 $\pm$ 0.51	2.69 $\pm$ 0.45	3.16 $\pm$ 0.46	3.03 $\pm$ 0.63
Left CGp/BA 23	3.41 $\pm$ 0.43	3.34 $\pm$ 0.41	3.77 $\pm$ 0.37	3.54 $\pm$ 0.49
Left TOF/BA 37	2.43 $\pm$ 0.37	2.23 $\pm$ 0.39	2.55 $\pm$ 0.39	2.47 $\pm$ 0.3
Right OLi	2.99 $\pm$ 0.36	2.61 $\pm$ 0.41	2.83 $\pm$ 0.36	2.92 $\pm$ 0.61
ADHD Thinner and BPD Thicker				
Right PHp	2.66 $\pm$ 0.31	2.43 $\pm$ 0.25	2.85 $\pm$ 0.36	2.63 $\pm$ 0.32
Right LG	2.99 $\pm$ 0.31	2.88 $\pm$ 0.33	3.26 $\pm$ 0.31	3.07 $\pm$ 0.31
Right OP	2.63 $\pm$ 0.29	2.44 $\pm$ 0.36	2.86 $\pm$ 0.36	2.56 $\pm$ 0.52
Left CGp/BA 23	2.92 $\pm$ 0.36	2.66 $\pm$ 0.37	3.01 $\pm$ 0.31	2.92 $\pm$ 0.35
Left SGp/BA 40	3.27 $\pm$ 0.36	3.16 $\pm$ 0.41	3.58 $\pm$ 0.48	3.31 $\pm$ 0.49

	Controls (N=23)	ADHD (N=26)	BPD (N=18)	Comorbid (N=31)
	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)	Mean $\pm$ SD (mm)
Left OP	2.73 $\pm$ 0.34	2.51 $\pm$ 0.34	3.04 $\pm$ 0.42	2.69 $\pm$ 0.59
Left OP	2.56 $\pm$ 0.4	2.34 $\pm$ 0.4	2.86 $\pm$ 0.69	2.56 $\pm$ 0.74
BPD Significantly Thinner				
Right FP/BA 9/10/11	4.14 $\pm$ 0.49	3.87 $\pm$ 0.77	3.84 $\pm$ 0.53	3.58 $\pm$ 0.85

Abbreviations: AG – angular gyrus; BA – Brodmann's area; CGp – cingulate gyrus, posterior division; F1 – superior frontal gyrus; F2 – middle frontal gyrus; FP – frontal pole; LG – lingual gyrus; OLs – occipital lateral gyrus, superior division; OP – occipital pole; PCN – precuneus; perigACC – perigenual anterior cingulate cortex; PHp – parahippocampal gyrus, posterior division; pINS – posterior insula; pmCGa_dACC2 – posterior middle cingulate gyrus, anterior division, dorsal anterior cingulate cortex; PRG – precentral gyrus; SGp – supramarginal gyrus, posterior division; SMC – supplementary motor cortex; SPL – superior parietal lobule; TO2 – middle temporal gyrus; TOF – temporo-occipital fusiform gyrus; TP – temporal pole.

Table 4

Cortical thickness in total sample of four groups of subjects (n=98), predicted by ADHD and BPD

	ADHD Effect β [95% CI]	BPD Effect β [95% CI]	Intercept β [95% CI]
ADHD SIGNIFICANTLY THINNER			
Right F1	-0.28 [-0.45, -0.10]**	0.12 [-0.05, 0.29]	3.61 [3.46, 3.76]
Right F2	-0.27 [-0.49, -0.05]*	0.10 [-0.12, 0.31]	3.78 [3.59, 3.97]
Right F2	-0.42 [-0.68, -0.16]**	-0.07 [-0.32, 0.19]	4.07 [3.84, 4.30]
Right FP/BA 9/10/11	-0.27 [-0.47, -0.06]*	-0.17 [-0.37, 0.04]	3.69 [3.51, 3.87]
Right PRG/BA 4	-0.33 [-0.57, -0.10]**	0.15 [-0.08, 0.39]	3.58 [3.37, 3.78]
Right perigACC	-0.34 [-0.62, -0.06]*	-0.24 [-0.52, 0.03]	4.30 [4.01, 4.55]
Right pmCGa_dACC2	-0.25 [-0.45, -0.06]	0.17 [-0.03, 0.36]	3.68 [3.51, 3.85]
Right SMC/BA 6	-0.37 [-0.61, -0.13]**	0.10 [-0.14, 0.34]	4.20 [3.99, 4.41]
Right SGp/BA 40	-0.22 [-0.39, -0.05]*	0.16 [-0.01, 0.33]	3.37 [3.22, 3.52]
Right SPL/BA 7	-0.24 [-0.43, -0.04]*	0.15 [-0.04, 0.34]	3.34 [3.17, 3.51]
Right OLs/BA 18/19	-0.28 [-0.43, -0.12]***	0.06 [-0.10, 0.22]	3.28 [3.14, 3.41]
Right OLs/BA 18/19	-0.29 [-0.49, -0.10]**	0.12 [-0.07, 0.32]	2.97 [2.79, 3.14]
Right TP	-0.30 [-0.50, -0.10]**	0.07 [-0.13, 0.27]	4.17 [3.99, 4.34]
Right TP	-0.33 [-0.56, -0.10]**	0.08 [-0.15, 0.30]	4.38 [4.18, 4.58]
Left FP/BA 9/10/11	-0.35 [-0.61, -0.04]*	-0.12 [-0.40, 0.16]	4.17 [3.93, 4.42]
Left FP/BA 9/10/11	-0.35 [-0.65, -0.05]*	-0.23 [-0.53, 0.06]	4.25 [3.99, 4.51]
Left PRG/BA 4	-0.32 [-0.54, -0.11]**	0.17 [-0.04, 0.38]	3.50 [3.31, 3.69]
Left CGp/BA 23	-0.26 [-0.42, -0.11]**	0.11 [-0.04, 0.27]	3.60 [3.46, 3.73]
Left PCN/BA 7	-0.26 [-0.45, -0.08]**	0.17 [-0.01, 0.36]	3.75 [3.59, 3.92]
Left PCN/BA 7	-0.34 [-0.57, -0.10]**	0.14 [-0.10, 0.37]	3.75 [3.54, 3.95]
Left OLs/BA 18/19	-0.29 [-0.47, -0.11]**	0.05 [-0.13, 0.22]	3.20 [3.05, 3.36]
BPD SIGNIFICANTLY THICKER			
Right AG/BA 39	-0.15 [-0.30, 0.01]	0.30 [0.14, 0.45]***	3.12 [2.98, 3.25]
Right pINS	-0.19 [-0.38, 0.002]	0.31 [0.12, 0.50]***	3.95 [3.79, 4.12]
Right TO2	-0.10 [-0.24, 0.05]	0.21 [0.07, 0.35]**	3.10 [2.98, 3.23]
Right TOF/BA 37	-0.12 [-0.33, 0.10]	0.34 [0.13, 0.56]**	2.81 [2.62, 3.00]
Left CGp/BA 23	-0.14 [-0.32, 0.04]	0.27 [0.09, 0.44]**	3.45 [3.29, 3.60]
Left TOF/BA 37	-0.14 [-0.30, 0.008]	0.19 [0.04, 0.34]*	2.40 [2.27, 2.53]
Right OLi	Interaction effect p=0.02[‡]		
ADHD THINNER AND BPD THICKER			
Right PHp	-0.22 [-0.35, -0.10]***	0.20 [0.07, 0.32]**	2.65 [2.55, 2.76]

	ADHD Effect β [95% CI]	BPD Effect β [95% CI]	Intercept β [95% CI]
Right LG	-0.15 [-0.27, -0.02] *	0.22 [0.10, 0.35] ***	3.01 [2.90, 3.12]
Right OP	-0.24 [-0.41, -0.08] **	0.17 [0.006, 0.33] *	2.66 [2.51, 2.80]
Left CGp/BA 23	-0.18 [-0.32, -0.04] *	0.18 [0.04, 0.32] *	2.88 [2.76, 3.00]
Left SGp/BA 40	-0.18 [-0.36, -0.005] *	0.21 [0.04, 0.39] *	3.31 [3.15, 3.47]
Left OP	-0.28 [-0.47, -0.10] **	0.23 [0.05, 0.41] *	2.77 [2.61, 2.93]
Left OP	-0.26 [-0.50, -0.03] *	0.26 [0.02, 0.49] *	2.58 [2.37, 2.79]
BPD SIGNIFICANTLY THINNER			
Right FP/BA 9/10/11	-0.26 [-0.55, 0.02]	-0.29 [-0.57, -0.008] *	4.14 [3.89, 4.39]

*
p 0.05,

**
p 0.01,

***
p 0.001

Abbreviations: AG – angular gyrus; BA – Brodmann's area; CGp – cingulate gyrus, posterior division; F1 – superior frontal gyrus; F2 – middle frontal gyrus; FP – frontal pole; LG – lingual gyrus; OLs – occipital lateral gyrus, superior division; OP – occipital pole; PCN – precuneus; perigACC – perigenual anterior cingulate cortex; PHp – parahippocampal gyrus, posterior division; pINS – posterior insula; pmCGa_dACC2 – posterior middle cingulate gyrus, anterior division, dorsal anterior cingulate cortex; PRG – precentral gyrus; SGp – supramarginal gyrus, posterior division; SMC – supplementary motor cortex; SPL – superior parietal lobule; TO2 – middle temporal gyrus; TOF – temporo-occipital fusiform gyrus; TP – temporal pole.