# Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder: fMRI outcomes

Mani N. Pavuluri*[a,b], Alessandra M. Passarotti[a,b], Lisa H. Lu[b,c], Julie A. Carbray[a], John A. Sweeney[b]

[a] Institute for Juvenile Research, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL USA;

[b] Center for Cognitive Medicine, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL USA;

[c] Department of Psychology, Roosevelt University, Chicago, IL USA

**Corresponding Author:**

Mani N. Pavuluri, M.D., PhD.

1747 West Roosevelt Road

Institute for Juvenile Research

Department of Psychiatry

Chicago, IL 60608 USA

Phone: (312) 413-0064

Fax: (312) 413-0063

Email: mpavuluri@psych.uic.edu

**ABSTRACT**

The aim of this research was to determine the relative effects of risperidone and divalproex on brain function in pediatric mania. This is a double-blind 6-week fMRI trial with 24 unmedicated manic patients randomized to risperidone or divalproex, and 14 healthy controls (HCs) matched for IQ and demographic factors (mean age: 13.1±3.3 years). A pediatric affective color matching task, in which subjects matched the color of a positive, negative or neutral word with one of two colored circles, was administered. The primary clinical measure was the Young Mania Rating Scale (YMRS). The risperidone group, relative to HC, showed an increase in activation from pre- to post-treatment in right pregenual and subgenual anterior cingulate cortex and decreased activation in bilateral middle frontal gyrus during the negative condition; and decreased activation in left inferior and medial, and right middle frontal gyri, left inferior parietal lobe, and right striatum with positive condition. In the divalproex group, relative to HC, there was an increased activation in right superior temporal gyrus in the negative condition; and in left medial frontal gyrus and right precuneus with the positive condition. Greater pre-treatment right amygdala activity with negative and positive condition in the risperidone group, and left amygdala activity with positive condition in divalproex group, predicted poor response on YMRS. Risperidone and divalproex yield differential patterns of prefrontal activity during an emotion processing task in pediatric mania. Increased amygdala activity at baseline is a potential biomarker predicting poor treatment response to both the risperidone and divalproex.

Key words: mania, child, treatment, medication, adolescent, prefrontal

## 1. INTRODUCTION

Functional alterations in frontostriatal and limbic circuitry are beginning to be clarified in pediatric bipolar disorder (PBD) (Rich et al., 2006; Pavuluri et al., 2007, 2008; Leibenluft et al., 2007; Chang et al., 2008). However, while evidence for the efficacy of anti-epileptic mood stabilizers (Wagner et al., 2002, 2009; Pavuluri et al., 2006, 2010a; Findling et al., 2006) and second generation antipsychotics (SGAs) for this condition (Chang et al., 2008; DelBello et al., 2002, 2009; Findling et al., 2009; Tohen et al., 2008; Haas et al., 2009; Pavuluri et al., 2010a) is accruing, knowledge of how these medications impact brain systems in this population remains poorly understood. Mechanistic understanding of the interface of cognitive and affective brain operations is now possible using the fMRI paradigms that probe these functional operations. Examining the brain function before and after treatment will illustrate the individual influence of each pharmacotherapeutic agent, with brain oxygen level dependent (BOLD) signal serving as an outcome measure. The rationale behind the study, therefore, is to determine the level of impairment of brain function at baseline and the extent of normalization or alternative functional brain activity due to a specific medication.

Primate studies (Ongur and Price, 2000; Petrides and Pandya, 2002) as well as our previous studies in youths with PBD and healthy controls (HCs) (Pavuluri et al., 2007, 2008, 2010a) have demonstrated the specific role of prefrontal cortical regions and their direct or indirect influence on amygdala. Baseline pathophysiology in PBD illustrated hyperactive amygdala, poorly controlled by the interfacing higher cortical emotional and cognitive control regions i.e., ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal cortex (DLPFC), especially in response to negative stimuli relative to neutral or positive stimuli (Pavuluri et al.,

2007, 2008, 2010a). Further, Phillips, Ladouceur and Drevets (2008) offered a framework in line with our previous findings in PBD indicating that lateral cortical regions (VLPFC and DLPFC) are involved in voluntary emotional control, while the dorsal and ventral medial prefrontal regions (MPFC) are involved in processing of emotional salience of the stimuli, mediation of autonomic responses and generation of emotional state. Indeed, strong connections exist between VLPFC, MPFC, pregenual and subgenual anterior cingulate cortex (ACC), and the amygdala, with indirect connections to DLPFC (Ongur and Price, 2000). Therefore, it is plausible that manic mood state in PBD will present with a loss of top-down control involving reduced MPFC, VLPFC and DLPFC activity and hyperactive amygdala, and reverse may be true in treated euthymic patients. An important observation from our previous studies was a reduced VLPFC activity (with inability to control amygdala) in severe manic patients relative to HC (Pavuluri et al., 2007, 2010a) and an increased VLPFC activity (with some preserved ability to exert effort) among samples inclusive of hypomanic patients (Pavuluri et al., 2010a; Rich et al., 2006). Additionally, our previous work has also illustrated compensatory increased activity in the intermediary cortex i.e., ACC in PBD relative to HC with treatment (Pavuluri et al., 2007, 2010a; 2010b), or in supplementing the VLPFC activity in an effort to control increased amygdala activity relative to HC or patients with attention deficit hyperactivity disorder (Passarotti et al., 2009, 2010a, 2010b).

There is only one pharmacological fMRI study that probed the interface of affective and cognitive circuitry in PBD. Pavuluri et al. (2010a) examined the effects of lamotrigine in manic and hypomanic patients by probing the interface of affective and cognitive systems using a pediatric affective color matching paradigm. These patients demonstrated

increased bilateral DLPFC and MPFC activity relative to HC after lamotrigine therapy (Pavuluri et al., 2010b).

The current fMRI study compared the SGA, risperidone, with an anticonvulsant, divalproex sodium (divalproex), using a double-blind randomized controlled trial (DBRCT) design and a pediatric emotion processing task during fMRI studies. In parallel, HC were scanned before and after the 8 weeks, but without receiving treatment. The first aim of the study was to map the treatment related changes in brain activity among PBD patients relative to changes in HC followed over a similar time interval. Based on the preliminary studies of lamotrigine effects in PBD using a similar task in an independent sample (Pavuluri et al., 2008; 2010a), we predicted that patients receiving divalproex in the current study would demonstrate increased MPFC activity. No studies are yet available in mapping the action of SGAs in mania. Based on the effects of serotonin enhancement on subgenual cortex in adult depression (Konarski et al., 2009), we expected to see increased subgenual activity with risperidone. However, increased subgenual activity was also noted with improved mood on lamotrigine monotherapy (Pavuluri et al., 2010a, 2010b). Given the scant data on treatment studies, and bearing with the fact that there may be commonalities in mood states regardless of medication specific changes, our hypotheses remain exploratory in nature. Our second aim, therefore, was to determine potential neuroimaging predictors of treatment response within the patient groups. Based on the previous treatment studies in PBD, we predicted that increased amygdala activity (Chang et al., 2008) and/or decreased prefrontal activity at baseline (Pavuluri et al., 2010a, 2010b) would be associated with poor treatment response, regardless of the type of medication. Given that the color matching task in the current study probed the interface of cognitive and affective circuitry regions, and since

these regions are known to be highly connected at the cortical level, it was premature to predict the relative differences in activation within the PFC contingent on illness state or medication type.

## 2. METHODS

### 2.1 Design

This was a 6-week out-patient DBRCT of risperidone plus placebo (that resembled divalproex capsule) vs. divalproex plus placebo (that resembled risperidone tablet) for manic and mixed episodes of bipolar disorder. This study was approved by the University of Illinois at Chicago's Institutional Review Board (IRB). Parents and adolescents older than 16 years gave written permission; adolescents younger than 16 years and children gave assent to participate in this trial.

### 2.2 Sample

Inclusion criteria were a DSM-IV diagnosis of mixed or manic bipolar disorder; 12 to 18 years old; and medication free or currently clinically unstable on medication, justifying termination of the ineffective regimen (with consent, all subjects were washed out and free of any medication for a week prior to baseline scanning, and 4 weeks in case of fluoxetine or aripiprazole). Prior exposure to SGAs and anti-epileptic medications was acceptable. Exclusion criteria included: active substance abuse; serious medical problems; autism and non-affective psychotic disorders. Using these criteria, we recruited 46 subjects into the study. There were three subjects who were medication naïve. After excluding subjects whose data were unusable due to motion artifacts (HC: n=2; risperidone group: n=3; divalproex group: n=3), the final sample included in the analyses consisted of 14 HC, and 24 patients randomized to either risperidone (n=12) or

divalproex (n=12). No subjects dropped out of the study. Sample characteristics are summarized in Table 1.

### 2.3 Assessment and efficacy measures

Each child and their parent or legal guardian were interviewed using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Geller et al., 1998) supplemented by the episode characterization of bipolar disorder from the KSADS - Present and Lifetime version (Kaufman et al., 2000). Diagnostic interviews were completed by doctoral level clinicians with established inter-rater reliability (MNP, JAC). The primary clinical efficacy measure was the Young Mania Rating Scale (YMRS; Young et al., 1978). The Child Depression Rating Scale-Revised was also administered (CDRS-R; Poznanski and Mokros, 1995). Three masters-level independent clinical raters with established reliability administered these clinical outcome measures on a weekly basis.

### 2.4 Pediatric affective color matching fMRI paradigm

This block design task assessed the ability to match the color of a word to one of two colored circles presented on the left and right side of the word on a display screen (Pavuluri et al., 2008). Negative words targeted affective domains relevant to PBD, such as feelings of depression, disappointment, and rejection. Positive words reflected feelings of happiness, energy, accomplishment, and success. Words were at an eight-year-old reading level, and were equivalent across affect conditions in frequency of usage (Klein, 1964; Kucera and Francis, 1967; Gilhooly and Logie, 1980; Bradley and Lang, 1999). No word was repeated during the task. Subjects were presented with separate blocks (30 sec each) of positive, negative, and neutral word conditions (5 blocks of each condition) in a pseudo-random order, with each block consisting of 10 trials. Each block was separated by a 10 second fixation period (total of 15

fixation blocks) to provide rest periods during testing, and to allow for hemodynamic responses to return toward resting level before the next block of trials. In each 3 second trial, a word was presented for 200 ms, followed by a response period of 2800 ms, during which subjects pressed a button (left or right) to match the color of the word to the correct color dot (Figure 1, Panel A). Subjects were told to "respond as quickly as possible". Trials were balanced for correct responses (left or right dots) and colors used. The total duration of the task was approximately 10 min.

**2.5 MRI protocol**

MRI studies were performed using a 3.0 Tesla whole body scanner (Signa, General Electric Medical System, Milwaukee, WI). Functional images were acquired using echo-planar imaging, which is sensitive to regional alterations in blood flow via blood oxygenation level dependent (BOLD) contrast effects. Twenty-five axial slices were acquired. Parameters for functional scans were: TE=25ms; flip angle=90°; field of view=20x20cm; acquisition matrix=64x64; TR=2.5s; 5mm slice thickness with 1mm gap. Anatomical images were acquired in the axial plane (three-dimensional spoiled gradient recalled [SPGR], 1.5mm thick contiguous axial slices) to coregister and normalize the functional data.

**2.6 Image processing and data analysis**

For functional imaging data, FIASCO software (Functional Imaging Analysis Software-Computational Olio; Eddy et al., 1996) was used to implement 3D motion estimation and correction, and to remove slow signal drift. Individual volumes were excluded from the analysis if head displacement from the median head position in the time series was greater than 1.5mm, or if head rotation from the median head position was greater than 0.5 degrees. The number of volumes retained after discarding those with motion artifact did not significantly differ across

groups. To evaluate subject-wise activation effects for statistical analyses, voxel-wise effect size (r) maps were calculated for each subject by contrasting activation for the negative and positive conditions separately with the neutral condition, at baseline and then at follow-up. A Fisher z transform was applied to the r values to more closely approximate a normal distribution (zr; Rosenthal, 1991). Subjects' zr-maps (effect size) and SPGR anatomical images were warped into Talairach space using AFNI's (Analysis of Functional Neuroimages) automated procedure (Talairach and Tournoux, 1988). Functional maps were re-sampled to an isotropic 3x3x3 mm grid to provide a voxel dimension similar to that of the in-plane resolution of the acquired data.

We conducted two whole-brain repeated measures voxel-wise ANOVAs in AFNI. A first omnibus ANOVA compared the three groups (risperidone, divalproex, healthy controls) for each condition (negative vs neutral words, positive vs neutral words) and testing time (Baseline, Follow-up) was carried out in order to examine differences in neural activation due to risperidone or divalproex treatment relative to HC. Based on the significant three-way interaction of group by condition by testing time, a second ANOVA with the same condition and testing time factors, but with just the two patient groups (risperidone, divalproex) was carried out in order to elucidate differential treatment effects on neural activation in the two patient groups. For each ANOVA, and only for clusters that were significant in the three-way interaction, we carried out pair-wise comparisons to further decompose the significant interaction. To correct for multiple comparisons, whole brain Monte-Carlo simulations using AlphaSim (Mayberg et al., 1999) were used to achieve a corrected cluster threshold of $p<0.001$. Therefore we report only clusters reaching a contiguous volume of at least 351 cubic mm at a voxelwise threshold of $p<0.01$, resulting in a corrected probability of $p<0.001$.

Finally, based on clusters that emerged as significant in the whole-brain ANOVA within the two patient groups, we performed Spearman correlation analyses to determine the relationship between symptom response as assessed by clinical measures (YMRS, CDRS-R) and the changes in fMRI activation in significant regions of interest (ROIs). Anatomical ROIs were defined in standard Talairach space using AFNI tools. These regions in AFNI format, as well as anatomical ROI definitions, are available at:

http://ccm.psych.uic.edu/Research/NormalBrain/ROI_rules.htm;

http://ccm.psych.uic.edu/Research/ResearchProgram/NormalBrain/ROIaffect_rules.aspx

## 3. RESULTS

### 3.1 Demographic and clinical data

Table 1 summarizes clinical and demographic data for the three groups.

**Study dosing of risperidone and divalproex**

The mean (standard deviation, SD) risperidone dose at endpoint was 1.58 (±0.40) mg/day in non-responders and 1.55 (±0.44) mg/day in responders (defined as improvement ≥50% on the YMRS scores). The mean (S.D.) divalproex dose at endpoint was 856.77 (±215.58) mg/day in non-responders and 834.13 (±359.03) mg/day in responders. The mean serum valproic level at end point was 98 $\mu$g/mL, and 92% of patients achieved a therapeutic serum valproic level of > 75 $\mu$g/mL by the 5$^{th}$ day. No titration of medications was allowed after day 7. One subject in the divalproex group received lorazepam as a rescue medication at a dose of 2 mg for severe agitation during the first week of the trial.

### 3.2 Behavioral results

### 3.2.1 Reaction time

A repeated measures ANOVA with group (risperidone group, divalproex group, HC) as a between-subjects' factor, and testing time (baseline, follow-up) and word condition (negative, positive, neutral) as within-subjects' factors, was carried out on median RT and accuracy data (Table 2). With regard to median RT data, there was only a significant group effect [$F(1,35)=5.56$, $p=0.008$] in that the risperidone (548 ms) [$F(1,35)=11.40$, $p=0.002$] and divalproex groups (561 ms) [$F(1,35)=4.55$, $p=0.04$] exhibited overall slower RT than HC across testing times (483 ms), but did not differ from each other. Other than the main effect of group, no other significant effects or interactions were found, indicating that group differences did not change significantly based on word condition or over time.

### 3.2.2 Accuracy

After normalizing the accuracy distributions using an arcsine transformation, a repeated measures ANOVA with the same factors as for the RT ANOVA was conducted on the accuracy data. There was a significant group effect [$F(2,36)=9.20$, $p=0.0006$] but the interaction of group by time was not significant ($p>0.05$). Follow-up analyses revealed that the risperidone group was significantly less accurate than the divalproex group [$F(1,36)=4.89$, $p=0.03$] and the HC group [$F(1,36)=18.40$, $p=0.0001$], whereas there was only a non-significant trend for accuracy to be lower in the divalproex group relative to HC [$F(1,36)=3.83$, $p=0.06$]. The main effect of time was significant [$F(1,36)=4.69$, $p=0.04$] but the interaction of group by time was not significant ($p>0.05$). Planned comparisons on the significant time effect revealed that accuracy was higher at follow-up compared to baseline in all groups.

## 3.3 fMRI results

A significant group by word valence by time interaction was found for the first ANOVA [$F(2,36)=5.39$, $p<0.01$], which compared all groups, and for the second ANOVA [$F(1,22)=5.75$, $p<0.025$], which contrasted the two patient groups only. For each ANOVA, and only for clusters that were significant in the three-way interaction, we carried out pair-wise comparisons to decompose the significant interaction and main effects for the negative or positive word versus the neutral word contrast at baseline and follow-up. A list of the clusters that were significant based on the omnibus ANOVA and the relative within- and between-group differences in activation are reported in Table 3.

### 3.3.1 Exploratory analyses of differences between the two patient groups at baseline.

*3.3.1.1 Risperidone vs. Divalproex groups at baseline*.

First, in order to ensure there was no baseline heterogeneity between groups that could explain group differences in outcome, based on the significant three-way interaction in the first ANOVA we conducted pair-wise comparisons to examine whether the two patient groups differed at baseline. Both for the negative (negative vs. neutral) and positive (positive vs. neutral) conditions, there were no significant differences in activation at baseline.

*3.3.1.2 Risperidone and divalproex groups combined vs. HC at baseline.*

Pairwise comparisons on the significant clusters in the three-way interaction for the second ANOVA revealed that for the negative condition at baseline, the PBD patients, relative to HC, exhibited no increased activation, and decreased activation in left medial frontal gyrus and bilateral superior temporal gyrus. For the positive condition at baseline, relative to HC, the PBD patients exhibited increased activation in right superior frontal gyrus and decreased activation in left medial frontal gyrus.

### 3.3.2 Treatment effects in the patient groups relative to HC

We examined differential treatment effects in the risperidone and divalproex groups relative to HC by decomposing the significant three-way interaction of group by time by condition in the second ANOVA.

*3.3.2.1 Risperidone group vs. HC at follow-up relative to baseline (Table 3)*

For the negative condition at follow-up relative to baseline, the risperidone group showed an increase in activation, relative to HC, in right subgenual ACC and perigenual ACC (Figure 1, Panel B), and decreased activation in bilateral middle frontal gyrus (DLPFC) and right precuneus. For the positive condition at follow-up relative to baseline, the risperidone group, compared to HC, showed no increased activation but showed decreased activation in left inferior frontal gyrus (BA 44/6; VLPFC) and medial frontal gyrus (MPFC), right DLPFC, in right mid-cingulate gyrus, right striatum and in posterior regions (right superior temporal gyrus and left inferior parietal lobule).

*3.3.2.2 Divalproex group vs. HC at follow-up relative to baseline (Table 3)*

For the negative condition at follow-up relative to baseline, the divalproex group showed an increased activation, relative to HC, in right superior temporal gyrus. For the positive condition at follow-up relative to baseline, relative to the HC group, divalproex group showed increased activation in right precuneus, and in left MPFC (Figure 1, Panel C), and decreased activation in right DLPFC.

### 3.3.3 Differential treatment effects in the two patient groups

We examined differential treatment effects between the risperidone and divalproex groups by decomposing the significant three-way interaction of Group by Time by Condition in the second ANOVA. For the negative condition at follow-up relative to baseline, the two patient groups did

not differ significantly in activation. For the positive condition at follow-up relative to baseline, divalproex group showed increased activation relative to risperidone group in left MPFC (Figure 2 and Table 3) and left inferior parietal lobule.

### 3.3.4 Baseline neural correlates of improvements in global YMRS score with treatment

For each of the patients groups Pearson's correlation analyses were performed between activation (i.e., number of significantly active voxels) in amygdala at baseline and improvements in YMRS scores over time (i.e., baseline score – follow-up score) for the Negative or Positive vs Neutral contrast. Because of the exploratory nature of these analyses, we report the results with corrected p values ($p$<0.01) and with uncorrected p values (uncorrected $p$>0.01).

*3.3.4.1 Risperidone group*

For the risperidone group, for the negative vs neutral words condition at baseline, there was a significant negative correlation between improvement in YMRS scores and baseline activation in right amygdala ($r$=-0.75, with corrected $p$<0.01), indicating that the lower the amygdala activation was at baseline, the greater the YMRS improvement was with treatment. Similar results were found for the positive vs neutral words at baseline, but only with an uncorrected p ($r$=-0.62, uncorrected $p$=0.03).

*3.3.4.2 Divalproex group*

For negative vs neutral word matching condition, there was a significant positive correlation between improvement in YMRS scores and baseline activation in right ($r$=0.74, corrected $p$<0.01) and left ($r$=0.60, uncorrected $p$=0.04) VLPFC. For positive vs. neutral word matching at baseline, there was a significant negative correlation between YMRS improvement and baseline activation in left amygdala ($r$=-0.61, uncorrected $p$=0.03).

*3.3.4.3 HC group at follow-up relative to baseline.*

First, given that HC served as the reference point against which each of the two patient groups were measured over time, it is relevant to examine the pre-post changes within HC. Relative to baseline, on follow-up, increased activity was noted in right middle frontal gyrus with negative condition and in bilateral inferior parietal lobule with positive condition (Table 4).

Additional analyses of each treatment group's pre-post changes are available on our web page: http://ccm.psych.uic.edu/Research/ResearchProgram/MoodDisorder/AdditionalResults.aspx.

**Exploratory Analyses on differences in brain activation between "Responders" and "Non-responders" based on YMRS global scores improvements with treatment**

In an exploratory fashion, based on the significant interaction in the second ANOVA, we also evaluated differences in brain activation between responders and non-responders based on YMRS global scores. For the Divalproex group 33% of patients were responders and 66% were non responders, whereas for the Risperidone group 75% were responders and 25% were non-responders (Table 5). The results are posted at the above CCM web page. In short, for the negative vs neutral word condition in the Divalproex group responders relative to non-responders showed increased activation in temporal and orbito-frontal regions, and decreased activation in VLPFC and DLPFC regions. For the Risperidone group responders relative to non-responders showed increased activation in supramarginal gyrus and decreased activation in bilateral amygdala, right orbito-frontal and temporal cortex, and parahippocampal gyrus. Similar results were obtained for the positive vs neutral word conditions and are listed on the CCM web page. For the present study, due to the small sample sizes and uneven percentages of responders and non-responders within each patient group, we cannot draw any robust conclusions based on the

results of these comparisons. Therefore further studies are warranted on this issue with larger samples and comparable numbers of responders and non-responders, and we will not discuss the present results further.

## 4. DISCUSSION

This is the first fMRI study to directly compare the effects of an anti-epileptic mood stabilizer and an SGA on brain function in pediatric mania. There are three central findings from this study that inform the treatment mechanisms of the drugs. First, with treatment, both patient groups have recruited alternative neural circuitry regions relative to HC. Second, when the drugs were directly compared, divalproex lead to increased activity in left MPFC relative to risperidone while modulating positive emotions, although both drugs were comparable in modulating the negative emotions. Third, increased pre-treatment activity in right amygdala with negative and positive condition in the risperidone group, and left amygdala with positive condition in divalproex group predicted poor response on YMRS. Comparable to our other studies using this paradigm (Pavuluri et al., 2008; Passarotti et al., 2010a), the task did not elicit group differences on behavioral data that could account for the differences in brain activation. Thus, task difficulty effects are not the likely cause for group differences. In fact, accuracy improved across all groups over time indicating practice effects.

### 4.1 Risperidone: functional brain mechanism

Similar to our previous results in treated patients (Pavuluri et al., 2007, 2008, 2010a, 2010b) and also as predicted in our first hypothesis (Konarski et al., 2009), patients treated with risperidone, relative to HC during the negative word matching, showed increased subgenual and pregenual activity (i.e., among the compensatory emotional

control regions) and decreased DLPFC activity (i.e., the cognitive control region). It may be that the patient group was deploying resources for emotion control at the expense of cognitive control while modulating negative emotions. While performing a similar task that involved negative word matching (Pavuluri et al., 2008) or incidentally processing emotions during a cognitive task (Pavuluri et al., 2010a), we have shown a similar decrease in activity in DLPFC and a compensatory increase in the activity in ACC. Also, subgenual and pregenual ACC that were deployed with risperidone were implicated in adult mood disorders where gray matter, especially the glia, was reduced (Mayberg et al., 1999; Strakowski et al., 2004). Indeed, subgenual ACC was shown to be underactive in untreated patients with bipolar disorder while performing an attentional task (Strakowski et al., 2004) and appeared to be a critical region concerned with modulating autonomic responses and neurotransmission in animals (Drevets et al., 2008). Risperidone may deploy this region to gain emotional control through serotonin – dopamine antagonism. Indeed, stimulation of subgenual ACC ameliorated symptoms in adult depression (Mayberg et al., 2005) and perfusion was normalized with a serotonin reuptake inhibitor in the same region (Drevets et al., 2002; Mayberg et al., 2000). Unlike negative word matching, positive word matching led to the lack of deployment of both the emotional and the cognitive regions in patients relative to HC. This may mean decreased effort and/or deployment of brain regions while modulating positive emotions in the case of risperidone.

**4.2 Divalproex: functional brain mechanism**

Pattern of increased activity in left MPFC in divalproex group relative to HC in positive condition was similar to that of another anti-epileptic drug, lamotrigine, while performing

a similar task (Pavuluri et al., 2010a). The MPFC was deployed during emotional evaluation (Northoff et al., 2004; Deppe et al., 2005; Bermpohl et al., 2006; Kross et al., 2009) posed by the positive emotional stimuli in this study. In the negative condition, increased activity in right superior temporal gyrus in patients receiving divalproex, relative to HC, may suggest increased effort in pre-lexical perception of the intense emotional words. (Price, 2010).

### 4.3 Comparing the treatment effects of risperidone *vs.* divalproex on brain function

#### 4.3.1 Differences.

Increased MPFC activity shown by divalproex group on direct comparison relative to risperidone group was also noted in divalproex group relative to HC during the positive word matching. Increased MPFC activation in divalproex group, similar to that shown with lamotrigine in our previous study (Pavuluri et al., 2010a), may play a critical role in emotion regulation in PBD as mentioned above, with its direct connectivity to amygdala (An et al., 1998; Freedman et al., 2000; Passarotti et al., 2003). Within divalproex group, bilateral increased VLPFC predicted improvement on YMRS. Indeed, the anterior language center is a part of VLPFC which may have been engaged to improve cognitive control through self-talk (Barkley, 2000). This increase in pre-treatment VLPFC activity did not correlate with YMRS change in risperidone group.

This differential pattern either on direct or parallel comparison of both drugs illustrates how two types of medications engage different brain regions while performing "a cognitive task under positive emotional challenge" and how responders in each group engage different prefrontal regions towards change in clinical symptoms. It may be that

these results need to be interpreted with care given that the treatment response rates may have contributed to differential pattern of brain function across the two medications, especially given that there were only four responders within divalproex group (Table 6). However, the pattern of differential response was consistent across the two groups in overall group response or by dichotomous grouping with responders vs. non-responders.

### 4.3.2 Commonalities

Increased pre-treatment activity in amygdala predicted poor response on YMRS in both the groups, although these findings are lateralized to the left and the right in divalproex and risperidone groups respectively. Increased amygdala activity may serve as a potential biomarker of treatment response. In line with our results, Chang et al (2008) demonstrated a correlation between the reduction in amygdala activity and depressive symptoms with lamotrigine treatment in PBD patients, illustrating treatment efficacy. However, impaired MPFC and VLPFC activity may also explain poor emotion regulation regardless of the level of activity in amygdala given the systems level abnormalities reported above.

This is a "proof of concept" study to examine the mechanism of brain circuitry function in response to an antiepileptic and SGA in PBD. Limitations include the fact that we used a block design study that did not allow us to distinguish between correct and incorrect responses and to study the effect of affective response specifically to positive or negative words while performing the cognitive tasks. The vital reason for using block design in this study was to minimize the risk of switching between emotions with interspersed trials posing trial-wise impact from the most recent trials. Further, studying medication

naïve patients is desirable in future trials to avoid the confound of previous medications that could have already altered brain function.

In conclusion, this DBRCT demonstrated that divalproex engaged MPFC relative to risperidone while modulating positive emotions in pediatric mania. Risperidone engaged pre and subgenual ACC and divalproex engaged superior temporal gyrus while modulating negative emotions in patients relative to HC, although the medication groups did not differ on direct comparison. Greater pre-treatment right amygdala activity with negative and positive condition in the risperidone group, and left amygdala activity with positive condition in divalproex group, predicted poor response on YMRS.

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**FIGURE CAPTIONS:**

1. The pediatric color matching task and treatment effects of risperidone and divalproex.

Panel A: Pediatric Color Matching Task

Panel B: Risperidone vs. HC in Negative Condition*

Panel C: Divalproex vs. HC in Positive Condition*

Legend: *=Group by Time Interaction; SG ACC=subgenual anterior cingulate cortex PACC=pregenual ACC; MPFC=medial prefrontal cortex; red indicates significantly greater activation in the PBD group v HC

2. Divalproex group vs. risperidone group in both negative and positive conditions.

Legend: blue indicates significantly greater activation in Divalproex group vs. Risperidone group; Left MPFC= Left medial prefrontal cortex; RISP=Risperidone group; DVPX=Divalproex group; *$p$<0.01

References

An, X., Bandler, R., Ongur, D., Price, J.L., 11-30-1998. Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. Journal of Comparative Neurology 401, 455-479.

Barkley, R., 2000. Genetics of childhood disorders: XVII. ADHD, Part 1: The executive functions and ADHD. Journal of the American Academy of Child & Adolescent Psychiatry 39, 1064-1068.

Bermpohl, F., Pascual-Leone, A., Amedi, A., Merabet, L.B., Fregni, F., Gaab, N., Alsop, D., Schlaug, G., Northoff, G., 2006. Attentional modulation of emotional stimulus processing: an fMRI study using emotional expectancy. Human Brain Mapping 27, 662-677.

Bradley, M.M., Lang, P.J., 1999. Affective norms for English words (ANEW): Stimuli, instruction manual and affective ratings.

Chang, K.D., Wagner, C., Garrett, A., Howe, M., Reiss, A., 2008. A preliminary functional magnetic resonance imaging study of prefrontal-amygdalar activation changes in adolescents with bipolar depression treated with lamotrigine. Bipolar Disorders 10, 426-431.

DelBello, M.P., Chang, K., Welge, J.A., Adler, C.M., Rana, M., Howe, M., Bryan, H., Vogel, D., Sampang, S., Delgado, S.V., Sorter, M., Strakowski, S.M., 2009. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disorders 11, 483-493.

DelBello, M.P., Schwiers, M.L., Rosenberg, H.L., Strakowski, S.M., 2002. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. Journal of the American Academy of Child and Adolescent Psychiatry 41, 1216-1223.

Deppe, M., Schwindt, W., Kugel, H., Plassmann, H., Kenning, P., 2005. Nonlinear responses within the medial prefrontal cortex reveal when specific implicit information influences economic decision making. Journal of Neuroimaging 15, 171-182.

Drevets, W.C., Bogers, W., Raichle, M.E., 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. European Neuropsychopharmacology 12, 527-544.

Drevets, W.C., Savitz, J., Trimble, M., 2008. The subgenual anterior cingulate cortex in mood disorders. CNS Spectrums 13, 663-681.

Eddy, W.F., Fitzgerald, M., Genovese, C.R., Mockus, A., Noll, D.C., 1996. Functional image analysis software - computational olio. 39-49.

Findling, R.L., McNamara, N.K., Stansbrey, R., Gracious, B.L., Whipkey, R.E., Demeter, C.A., Reed, M.D., Youngstrom, E.A., Calabrese, J.R., 2006. Combination lithium and divalproex sodium in pediatric bipolar symptom re-stabilization. Journal of the American Academy of Child and Adolescent Psychiatry 45, 142-148.

Findling, R.L., Nyilas, M., Forbes, R.A., McQuade, R.D., Jin, N., Iwamoto, T., Ivanova, S., Carson, W.H., Chang, K., 2009. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 70, 1441-1451.

Freedman, L.J., Insel, T.R., Smith, Y., 5-29-2000. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. Journal of Comparative Neurology 421, 172-188.

Geller, B., Warner, K., Williams, M., Zimerman, B., 1998. Prepubertal and young adolescent bipolarity versus ADHD: Assessment and validity using the WASH-U-KSADS, CBCL, and TRF. Journal of Affective Disorders 51, 93-100.

Gilhooly, K.J., Logie, R.H., 1980. Age of acquisition, imagery, concreteness, familiarity and ambiguity measures for 1,944 words. Behavior Research Methods and Instrumentation 12, 395-427.

Haas, M., DelBello, M.P., Pandina, G., Kushner, S., Van, H., I, Augustyns, I., Quiroz, J., Kusumakar, V., 2009. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disorders 11, 687-700.

Kaufman, J., Birmaher, B., Brent, D.A., Ryan, N.D., Rao, U., 2000. K-SADS-PL. Journal of the American Academy of Child and Adolescent Psychiatry 39, 1208-

Klein, G.S., 1964. Semantic power measured through the interference of words with color-naming. American Journal of Psychology 77:576-88., 576-588.

Konarski, J.Z., Kennedy, S.H., Segal, Z.V., Lau, M.A., Bieling, P.J., McIntyre, R.S., Mayberg, H.S., 2009. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. J Psychiatry Neuroscience 34, 175-180.

Kross, E., Davidson, M., Weber, J., Ochsner, K., 3-1-2009. Coping with emotions past: the neural bases of regulating affect associated with negative autobiographical memories. Biological Psychiatry 65, 361-366.

Kucera H., Francis N.W., Carroll, J.B., 1967. **Computational Analysis of Present-Day American English**. Brown University Press, Providence, R.I.

Leibenluft, E., Rich, B.A., Vinton, D.T., Nelson, E.E., Fromm, S.J., Berghorst, L.H., Joshi, P., Robb, A., Schachar, R.J., Dickstein, D.P., McClure, E.B., Pine, D.S., 2007. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. American Journal of Psychiatry 164, 52-60.

Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 10-15-2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biological Psychiatry 48, 830-843.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 156, 675-682.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 3-3-2005. Deep brain stimulation for treatment-resistant depression. Neuron 45, 651-660.

Northoff, G., Heinzel, A., Bermpohl, F., Niese, R., Pfennig, A., Pascual-Leone, A., Schlaug, G., 2004. Reciprocal modulation and attenuation in the prefrontal cortex: an fMRI study on emotional-cognitive interaction. Human Brain Mapping 21, 202-212.

Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex 10, 206-219.

Passarotti, A.M., Paul, B.M., Bussiere, J.R., Buxton, R.B., Wong, E.C., Stiles, J., 2003. The development of face and location processing: an fMRI study. Developmental Science 6, 100-117.

Passarotti, A.M., Sweeney, J.A., Pavuluri, M.N., 2009. Neural Correlates of Incidental and Directed Facial Emotion Processing in Adolescents and Adults. Social Cognitive and Affect Neuroscience 4, 387-98.

Passarotti, A.M., Sweeney, J.A., Pavuluri, M.N., 2010a. Differential engagement of cognitive and affective neural systems in pediatric bipolar disorder and attention deficit hyperactivity disorder. Journal of International Neuropsychological Society 16, 106-117.

Passarotti, A.M., Sweeney, J.A., Pavuluri, M.N., 1-30-2010b. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. Psychiatry Research. 181, 36-43.

Pavuluri, M., Passarotti, A.M., Harral, E., Parnes, S., Sweeney J.A., 2010a. A pharmacological fMRI study probing the interface of cognitive and emotional brain systems in pediatric bipolar disorder. Journal of Child and Adolescent Psychopharmacology 20, 395-406.

Pavuluri, M., Passarotti, A.M., Harral, E., Sweeney J.A., 2010b. Enhanced Prefrontal Function with Pharmacotherapy on a Response Inhibition Task in Adolescent Bipolar Disorder. Journal of Clinical Psychiatry 71, 1526-1534.

Pavuluri, M., Passarotti A.M., Mohammed T, Carbray J.A., Sweeney J.A., Enhanced working and verbal memory after lamotrigine treatment in pediatric bipolar disorder. Bipolar Disorders 12, 213-220.

Pavuluri, M.N., O'Connor M.M., Harral, E.M., Sweeney J.A., 7-15-2007. Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. Biological Psychiatry 62, 158-167.

Pavuluri, M.N., O'Connor, M.M., Harral, E.M., Sweeney, J.A., 2008. An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. Psychiatry Research 162, 244-255.

Petrides, M., Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. European Journal of Neuroscience 16, 291-310.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Molecular Psychiatry 13, 829, 833-829, 857.

Poznanski, E.O., Mokros, H.B., 1995. Children's Depression Rating Scale, Revised (CDRS-R).

Price, C.J., 2010. The anatomy of language: a review of 100 fMRI studies published in 2009. Annals of the New York Academy of Sciences 1191, 62-88.

Rich, B.A., Vinton, D.T., Roberson-Nay, R., Hommer, R.E., Berghorst, L.H., McClure, E.B., Fromm, S.J., Pine, D.S., Leibenluft, E., 6-6-2006. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proceedings of the National Academy of Sciences of the United States of America 103, 8900-8905.

Rosenthal, R., 1991. *Meta-analytic procedures for social research.*

Strakowski, S.M., Adler, C.M., Holland, S.K., Mills, N., DelBello, M.P., 2004. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. Neuropsychopharmacology 29, 1734-1740.

Talairach, J., Tournoux, P., 1-15-1988. Co-Planar Stereotactic Atlas of the Human Brain.

Tohen, M., Vieta, E., Goodwin, G.M., Sun, B., Amsterdam, J.D., Banov, M., Shekhar, A., Aaronson, S.T., Bardenstein, L., Grecu-Gabos, I., Tochilov, V., Prelipceanu, D., Oliff, H.S., Kryzhanovskaya, L., Bowden, C., 2008. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. Journal of Clinical Psychiatry 69, 1776-1789.

Wagner, K.D., Redden, L., Kowatch, R.A., Wilens, T.E., Segal, S., Chang, K., Wozniak, P., Vigna, N.V., Abi-Saab, W., Saltarelli, M., 2009. A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar

disorder in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 48, 519-532.

Wagner, K.D., Weller, E.B., Carlson, G.A., Sachs, G., Biederman, J., Frazier, J.A., Wozniak, P., Tracy, K., Weller, R.A., Bowden, C., 2002. An open-label trial of divalproex in children and adolescents with bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry 41, 1224-1230.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. British Journal of Psychiatry 133, 429-435.

**Table 1: Demographic variables and clinical characteristics**

| | HC (n=14) | Risperidone Group (n=12) | Divalproex Group (n=12) | Analysis | |
|---|---|---|---|---|---|
| | **Mean (SD/%)** | **Mean (SD/%)** | **Mean (SD/%)** | ***F*** | ***p* value** |
| ***Variables*** | | | | | |
| **Age (years)** | 13.9 (3.4) | 12.6 (1.6) | 12.7 (2.5) | 1.11 | *p*=0.34 |
| **WASI - FSIQ**[a] | 106.5 (12.0) | 94.67 (9.7) | 96.17 (18.2) | 2.96 | *p*=0.07 |
| **SES**[b] | 2.1 (1.2) | 2.3 (0.8) | 2.2 (1.6) | 1.0 | *p*=0.21 |
| **YMRS (pre, post)** | | | | 14.95 | *p*=0.00001 |
| Pre YMRS | 1.3 (1.8) | 27.8 (6.7) | 23.0 (8.5) | Risp vs HC: *p*=0.0001<br>Dvpx vs HC: p=0.0001<br>Risp vs Dvpx: *p*=0.14 | |
| Post YMRS | 1.3 (2.1) | 11.8 (11.1)* | 14.2 (11.8)* | Risp vs HC: *p*=0.004<br>Dvpx vs HC: *p*=0.0006<br>Risp vs Dvpx: *p*=0.50 | |
| **CDRS (pre, post)** | | | | 7.47 | *p*=0.002 |
| Pre CDRS-R | 19.6 (2.7) | 45.1 (14.4) | 39.5 (15.0) | Risp vs HC: *p*=0.0001<br>Dvpx vs HC: *p*=0.0001<br>Risp vs Dvpx: *p*=0.25 | |
| Post CDRS-R | 18.9 (1.6) | 26.8 (7.3)* | 37.4 (16.1) | Risp vs HC: *p*=0.006<br>Dvpx vs HC: *p*=0.0001<br>Risp vs Dvpx: *p*=0.02 | |
| ***Variables*** | **N (%)** | **N (%)** | **N (%)** | **Fisher's Exact Test (two-tailed)** | |
| **Sex** | | | | *p*>0.05 | |
| Male | 7 (50%) | 7 (58%) | 9 (75%) | | |
| Female | 7 (50%) | 5 (42%) | 3 (25%) | | |

| | | | | |
|---|---|---|---|---|
| **Race** | | | | $p>0.05$ |
| Caucasian | 9 (64%) | 7 (58%) | 8 (67%) | |
| Other | 5 (36%) | 5 (42%) | 4 (33%) | |
| **Handedness** | | | | |
| Right | 14 (100%) | 11 (92%) | 11 (92%) | $p>0.05$ |
| Left | 0 (0%) | 1 (8%) | 1 (8%) | |

**Legend:** [a]Wechsler Abbreviated Scale of Intelligence Full Scale Intelligent Quotient (WASI-FSIQ; Matrix Reasoning and Vocabulary Subtests); [b]Mean revised Hollingshead socio-economic status; Risp.=Risperidone; Dvpx= Divalproex sodium; HC = Healthy Control; YMRS = Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale-Revised. * = follow-up scores differ from baseline scores at p=0.00001.

**Table 2: Behavioral results.** Median RT and accuracy for the risperidone group, the divalproex group and healthy controls (HC). SD=standard deviation.

| | **Risperidone Group** | **Divalproex Group** | **HC** |
|---|---|---|---|
| **Reaction Time (in ms)** | Median (SD) | Median (SD) | Median (SD) |
| ***Baseline*** | | | |
| Positive words | 586 (102) | 571 (92) | 482 (94) |
| Negative words | 551 (168) | 561 (94) | 494(107) |
| neutral words | 507 (161) | 552 (88) | 473 (88) |
| ***Follow-up*** | | | |
| Positive words | 531 (105) | 619 (190) | 481 (123) |
| Negative words | 516 (123) | 609 (155) | 474 (109) |
| neutral words | 589 (167) | 615 (113) | 480 (107) |
| **Accuracy (% correct)** | % (SD) | % (SD) | % (SD) |
| ***Baseline*** | | | |
| Positive words | 87 (8) | 90 (4) | 96 (1) |
| Negative words | 75 (10) | 90 (5) | 97 (2) |
| neutral words | 88 (8) | 90 (5) | 96 (2) |
| ***Follow-up*** | | | |
| Positive words | 81 (14) | 94 (2) | 96 (3) |
| Negative words | 87 (9) | 94 (2) | 94 (5) |
| neutral words | 80 (15) | 96 (2) | 96 (4) |

**Table 3: Group by time by condition interactions: Illustrating significant clusters of activation**

| | Talairach Coordinates for peak values | Area | BA | Volume (mm3) | *t* value for peak values |
|---|---|---|---|---|---|
| *Negative vs Neutral* | | | | | |
| **Risperidone Group** | | | | | |
| **> HC** | 2, 8, -7 | R subgenual ACC | 25 | 486 | 3.20 |
| | 2, 23, 2 | R perigenual ACC | 24 | 378 | 2.84 |
| **HC> Risperidone Group** | | | | | |
| | 41, 41, 35 | R middle FG | 9 | 648 | 3.80 |
| | -40, 20, 35 | L middle FG | 9 | 378 | 2.91 |
| | 14, -76, 56 | R precuneus | 7 | 378 | 3.56 |
| *Positive vs Neutral* | | | | | |
| **Risperidone Group** | | | | | |
| **> HC** | None | None | None | None | None |
| **HC > Risperidone Group** | | | | | |
| | -46, -1, 14 | L inferior FG | 44/6 | 378 | 3.31 |

| | | | | | |
|---|---|---|---|---|---|
| | 41, 17, 50 | R middle FG | 9 | 1134 | 3.32 |
| | 47, 41, 26 | R middle FG | 46 | 621 | 3.68 |
| | -1, 53, 14 | L medial FG | 10 | 378 | 4.01 |
| | -1, 11, 44 | L mid-cingulate gyrus | 32 | 756 | 3.20 |
| | 23, -7, 20 | R caudate | | 1323 | 4.00 |
| | 26, -13, 17 | R putamen | | 513 | 3.53 |
| | -40, -28, 26 | L inferior PL | 40 | 2322 | 3.07 |
| | 41, -73, 29 | R superior TG | 21 | 351 | 3.22 |
| *Negative vs Neutral* | | | | | |
| **Divalproex Group >** | | | | | |
| **HC** | 20, 8, -28 | R superior TG | 38 | 405 | 3.47 |
| | | | | | |
| **HC > Divalproex** | | | | | |
| **Group** | None | None | None | None | None |
| *Positive vs Neutral* | | | | | |
| **Divalproex Group >** | | | | | |
| **HC** | 23, -85, 26 | R precuneus | 7 | 540 | 3.22 |
| | -10, 55, 3 | *L medial FG | 10 | 486 | 3.72 |
| | | | | | |
| **HC > Divalproex** | | | | | |
| **Group** | 1, 30, 54 | R middle FG | 9 | 351 | 2.57 |
| *Negative vs Neutral* | | | | | |
| **Risperidone Group** | None | None | None | None | None |

| | | | | | |
|---|---|---|---|---|---|
| **> Divalproex Group** | | | | | |
| **Divalproex Group >** | | | | | |
| **Risperidone Group** | | | | | |
| | None | None | None | None | None |
| *Positive vs Neutral* | | | | | |
| **Risperidone Group** | | | | | |
| **> Divalproex Group** | None | None | None | None | None |
| **Divalproex Group >** | | | | | |
| **Risperidone Group** | | | | | |
| | -1, 53, 14 | L medial FG | 10 | 459 | 3.55 |
| | -37, -31, 29 | L inferior PL | 40 | 459 | 3.50 |

**Legend:** *=Significant clusters at corrected p<0.001 with contiguity threshold; FG=frontal gyrus; PL=parietal lobule; TG=Temporal gyrus; ACC=anterior cingulate cortex; HC= Healthy Control group; BA= Brodmann's Area; L= Left; R= Right.

**Table 4. Differences at follow-up vs. baseline for the healthy controls**

| | **Talairach Coordinates for peak values** | **Area** | **BA** | **Volume (mm3)** | ***t* value for peak values*** |
|---|---|---|---|---|---|
| **HC** | | | | | |
| *Negative vs Neutral* | | | | | |
| Follow-up > Baseline | 44, 5, 44 | R middle FG | 9 | 486 | 5.86 |
| Baseline > Follow-up | None | None | None | None | None |
| *Positive vs Neutral* | | | | | |
| Follow-up > Baseline | 53, -49, 38 | R inferior PL | 40 | 567 | 3.36 |
| | -46, -55, 47 | L inferior PL | 40 | 432 | 4.46 |
| Baseline > Follow-up | None | None | None | None | None |

**Legend:** *=Significant clusters at corrected p<0.001 with contiguity threshold; FG=frontal gyrus; PL=parietal lobule HC= Healthy Control group; BA= Brodmann's Area; L= Left; R= Right.

**Table 5.**

**Additional Findings: within group differences for each treatment group at follow-up vs. baseline**

| | **Talairach Coordinates for values** | **Area** | **BA** | **Volume (mm3)** | ***t* value for peak values*** |
|---|---|---|---|---|---|
| **Risperidone Group** | | | | | |
| *Negative vs Neutral* | | | | | |
| Follow-up > Baseline | 2, 21, -1 | R perigenual ACC* | 24 | 270 | 3.57 |
| | 2, 6, -7 | R subgenual ACC* | 25 | 270 | 2.92 |
| Baseline > Follow-up | none | none | none | None | None |
| *Positive vs Neutral* | | | | | |
| Follow-up > Baseline | none | none | none | None | None |
| Baseline > Follow-up | 26, 5, 17 | R putamen | | 675 | 3.52 |
| | -28, -10, 17 | L putamen | | 587 | 3.82 |
| | 17, -46, 26 | R cingulate gyrus | | 621 | 3.41 |
| **Divalproex Group** | | | | | |
| *Negative vs Neutral* | | | | | |
| Follow-up > Baseline | none | none | none | None | None |
| Baseline > Follow-up | none | none | none | None | None |
| *Positive vs Neutral* | | | | | |
| Follow-up > Baseline | -19, 29, -4 | L inferior FG* | 47 | 351 | 3.03 |

| | | | | |
|---|---|---|---|---|
| -49, -34, 50 | L inferior PL* | 40 | 432 | 2.93 |

**Legend:** *=Significant clusters at corrected p<0.001 with contiguity threshold; FG=frontal gyrus; PL=parietal lobule; ACC=anterior cingulate cortex; BA= Brodmann's Area; L= Left; R= Right.

**Table 6. Within group differences in activation among responders vs. non-Responders based on YMRS global scores.**

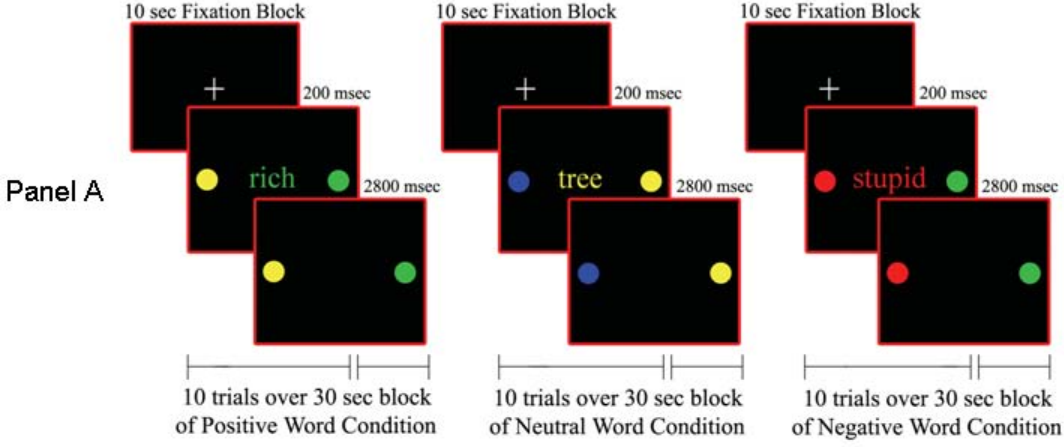
| | Talairach Coordinates for peak values | Area | BA | Volume (mm3) | t value for peak values* |
|---|---|---|---|---|---|
| ***Negative vs Neutral Condition*** | | | | | |
| ***Divalproex Group*** | | | | | |
| **Responders (N=4) > Non-Responders (N=8)** | -37, -4, -34 | L middle TG | 21 | 324 | 3.11 |
| | -1, 59, -7 | L orbital FG | 10 | 270 | 4.31 |
| **Non-Responders > Responders** | | L inferior FG | 47 | 675 | 3.53 |
| | -40, 20, -1 | | | | |
| | 14, 50, 26 | R superior FG | 9 | 378 | 2.74 |
| ***Risperidone Group*** | | | | | |
| **Responders (N=9) > Non-Responders (N=3)** | 59, -52, 23 | R supramarginal gyrus | 40 | 459 | 2.65 |
| **Non-Responders > Responders** | 23, 53, -10 | R orbital FG | 11 | 324 | 4.56 |
| | 23, -1, -13 | R amygdala | | 1512 | 3.39 |
| | -22, -22, -10 | L amygdala | | 3348 | 3.68 |
| | 29, -19, -13 | R parahippocampal | 28 | 837 | 3.78 |

| | | | | | |
|---|---|---|---|---|---|
| | | gyrus | | | |
| | 53, -10, 5 | R superior TG | 22 | 459 | 3.03 |
| | -4, -10, 20 | L thalamus | | 270 | 4.44 |
| ***Positive vs Neutral*** | | | | | |
| ***Divalproex Group*** | | | | | |
| **Responders (N=4) >** | 2, 5, -4 | R subgenual anterior | 25 | 756 | 3.84 |
| **Non-Responders** | | cingulate cortex | | | |
| **(N=8)** | | | | | |
| | 11, 29, -16 | R medial FG | 25 | 297 | 4.83 |
| | -4, 53, -13 | L medial FG | 11 | 891 | 3.04 |
| | 35, -19, -19 | R parahippocampal | 20 | 756 | 3.47 |
| | | gyrus | | | |
| **Non-Responders >** | -43, 17, 2 | L inferior FG | 45, | 432 | 2.89 |
| **Responders** | | | 47 | | |
| | -4, 53, 26 | L superior FG | 9 | 297 | 3.35 |
| | 17, -22, 41 | R cingulate gyrus | 31 | 1593 | 2.82 |
| | 53, 17, -13 | R superior TG | 38 | 351 | 2.72 |
| | -49, -4, -7 | L superior TG | 38 | 621 | 2.82 |
| | -16, 2, 23 | L caudate body | | 459 | 2.49 |
| | 35, 38, 38 | R middle FG | 9 | 459 | 2.50 |
| ***Risperidone Group*** | | | | | |
| **Responders (N=9) >** | -28, 62, 8 | L middle FG | 9 | 459 | 2.69 |
| **Non-Responders** | | | | | |
| | 35, -43, 32 | R inferior PL | 40 | 270 | 2.87 |

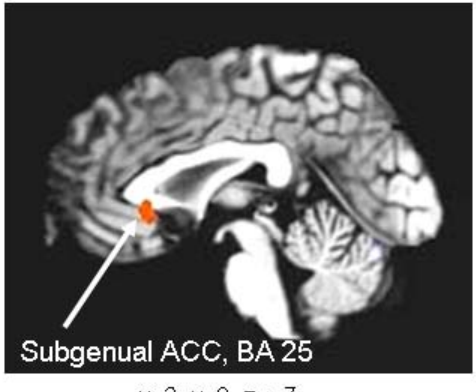
| | | | | | |
|---|---|---|---|---|---|
| **(N=3)** | | | | | |
| **Non-Responders >** | 29, 8, -13 | R Inferior FG | 47 | 918 | 2.93 |
| **Responders** | | | | | |
| | 35, 38, -13 | R orbital FG | 11 | 810 | 3.86 |
| | 35, -25, -13 | R amygdala | | 1593 | 4.10 |
| | -22, -22, -10 | L amygdala | | 1647 | 2.97 |

**Legend:** *=Significant clusters at corrected $p<0.01$ with contiguity threshold; ACC=anterior cingulate cortex; FG=frontal gyrus; PL=parietal lobule; BA= Brodmann's Area; L= Left; R= Right.

Figure 1

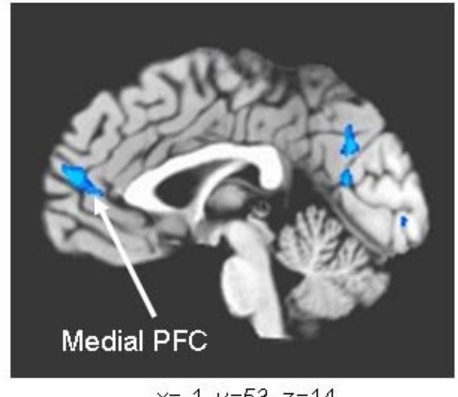



Panel B



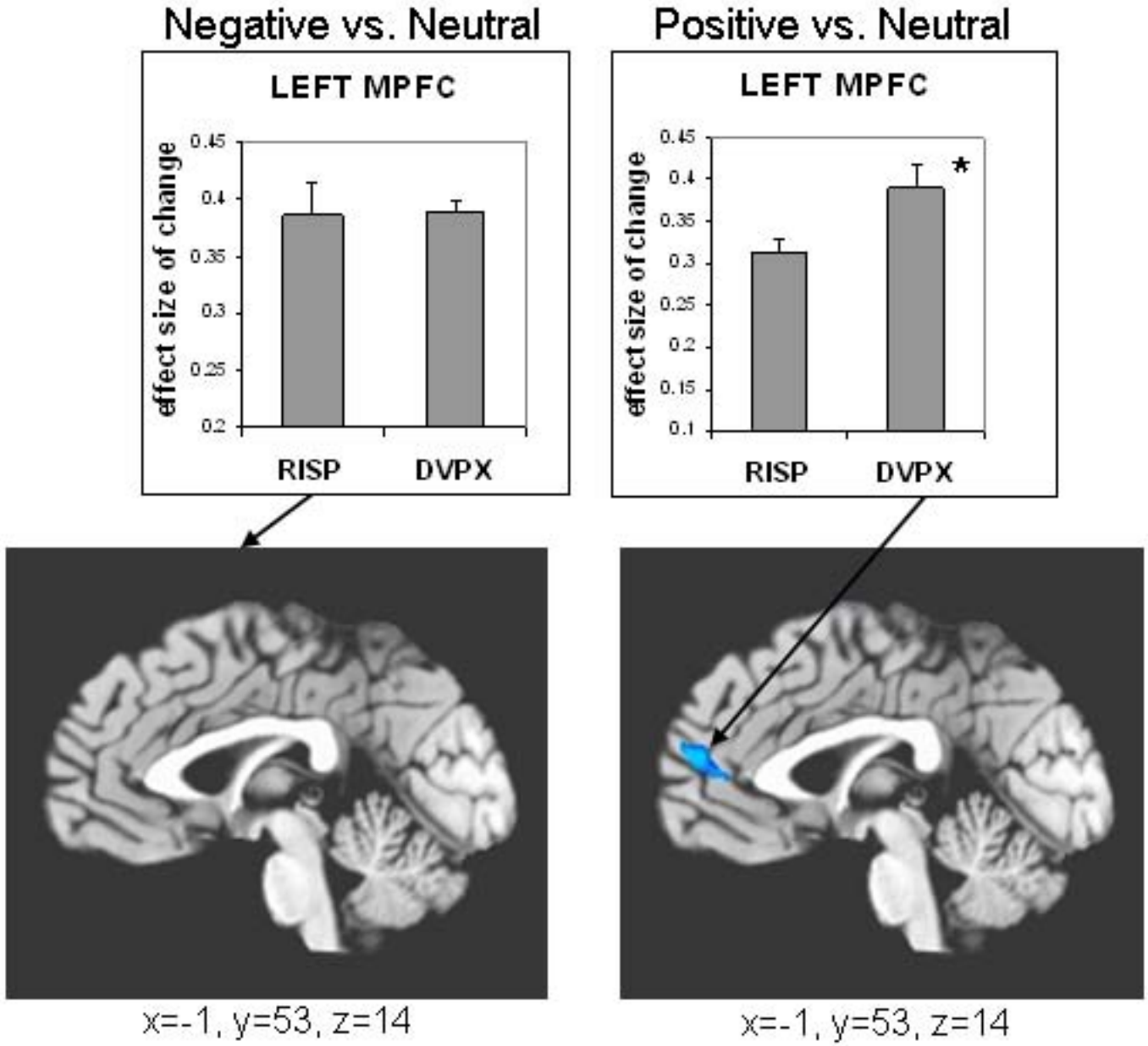

x=2, y=8, z= -7

Panel C




x=-1, y=53, z=14

Figure 2


Negative vs. Neutral
LEFT MPFC
effect size of change
0.45
0.4
0.35
0.3
0.25
0.2
RISP
DVPX
Positive vs. Neutral
LEFT MPFC
effect size of change
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
*
RISP
DVPX
x=-1, y=53, z=14
x=-1, y=53, z=14