

Risperidone and Divalproex Differentially Engage the Fronto-Striato-Temporal Circuitry in Pediatric Mania: A Pharmacological Functional Magnetic Resonance Imaging Study

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Objective: The current study examined the impact of risperidone and divalproex on affective and working memory circuitry in patients with pediatric bipolar disorder (PBD). **Method:** This was a six-week, double-blind, randomized trial of risperidone plus placebo versus divalproex plus placebo for patients with mania ($n = 21$; 13.6 ± 2.5 years of age). Functional magnetic resonance imaging (fMRI) outcomes were measured using a block design, affective, N-back task with angry, happy, and neutral face stimuli at baseline and at 6-week follow-up. Matched healthy controls (HC; $n = 15$, 14.5 ± 2.8 years) were also scanned twice. **Results:** In post hoc analyses on the significant interaction in a $3 \times 2 \times 2$ analysis of variance (ANOVA) that included patient groups and HC, the risperidone group showed greater activation after treatment in response to the angry face condition in the left subgenual anterior cingulate cortex (ACC) and striatum relative to the divalproex group. The divalproex group showed greater activation relative to the risperidone group in the left inferior frontal gyrus and right middle temporal gyrus. Over the treatment course, the risperidone group showed greater change in activation in the left ventral striatum than the divalproex group, and the divalproex group showed greater activation change in left inferior frontal gyrus and right middle temporal gyrus than the risperidone group. Furthermore, each patient group showed increased activation relative to HC in fronto-striato-temporal regions over time. The happy face condition was potentially less emotionally challenging in this study and did not elicit notable findings. **Conclusions:** When patients performed a working memory task under emotional duress inherent in the paradigm, divalproex enhanced activation in a fronto-temporal circuit whereas risperidone increased activation in the dopamine (D_2) receptor-rich ventral striatum. Clinical trial registration information—Risperidone and Divalproex Sodium With MRI Assessment in Pediatric Bipolar; <http://www.clinicaltrials.gov>; NCT00176202. *J. Am. Acad. Child Adolesc. Psychiatry*, 2012;51(2):157–170. **Key words:** risperidone, divalproex, pediatric bipolar disorder, fMRI

There is accumulating evidence for the efficacy and effectiveness of divalproex sodium (divalproex)¹⁻³ and risperidone⁴⁻⁶ in pediatric bipolar disorder (PBD). Risperidone has Food and Drug Administration (FDA) approval for use

in pediatric mania, while evidence for divalproex remains more equivocal.^{3,7} Findings from open trials in pediatric mania that showed that divalproex is useful.^{2,3,8,9} are in contrast to those from the double-blind placebo-controlled trial of divalproex extended release showing no benefit relative to placebo.¹⁰ A mechanistic understanding of how these medications affect brain function may offer further insight into how these two medications yield different results. Functional neuroimaging studies using appropriate chal-



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lenge paradigms represent one promising strategy for investigating how brain mechanisms could explain different therapeutic benefit across different classes of medications. Importantly, understanding how treatments can have an impact on the critical interface of affective and cognitive brain circuitries can shed light on how affect regulation is influenced by cognitive operations and vice versa.¹¹ This is especially valuable given the intricate connections between the two underlying neural operations.¹² Such close connectivity between the cognitive and affective brain circuitry explains the combined affective and working memory impairment in PBD.^{11,13,14} Hence, the current study of pediatric mania embraces the emerging trend¹⁵⁻¹⁸ of using task-elicited regional brain activation of a cognitive task (e.g., working memory) under emotional challenge as the primary outcome measure in a pharmacological study.

Working memory has been shown to be impaired in our 3-year longitudinal study of PBD,¹⁹ but pharmacotherapy with lamotrigine was shown to improve working memory in this population.²⁰ In healthy controls (HC), working memory function is supported by fronto-striatal-parietal circuitry.²¹⁻²³ In fact, in a sample that included mixed group of medicated and unmedicated PBD patients, Chang *et al.*²⁴ showed increased activity in PBD patients relative to HC while performing a visuospatial working memory task in several prefrontal regions, including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and anterior cingulate cortex (ACC). Using an N-back working memory task performed under negative emotional challenge with nonmedicated PBD patients, Passarotti *et al.*²⁵ showed that affective regions and cognitive prefrontal regions are less engaged in PBD, suggesting an alteration in the brain circuitry at the interface of affective and cognitive functions. Using another task that probed such an interface, in which colored emotional words were matched with colored dots, lamotrigine monotherapy led to an increase in ventromedial prefrontal cortex (VMPFC) activation in PBD patients relative to HC.¹⁶ Also, decreased activation was noted in the DLPFC in patients, illustrating the additional role of this cognitive region. Furthermore, we and others have documented alterations in fronto-temporal circuitry during facial emotion processing in PBD.²⁶⁻³⁰ These studies further informed us

that emotional faces could be used as an effective probe of affective circuitry function in PBD patients.

Therefore, we compared the effects on brain function of antipsychotic (risperidone) and anti-epileptic (divalproex) medications, using a double-blind randomized controlled trial (DBRCT) in pediatric mania, with a block design, affective, N-back working memory task to probe the interface of cognitive and affective circuitries. Basic neurochemical research implicates fronto-temporal mechanisms of action with divalproex because of its action in the second messenger system³¹ and ventral fronto-striatal systems with risperidone because of its known serotonin-dopamine antagonistic activity in these regions. Serotonin-rich subgenual ACC^{16,32-34} and dopamine (D₂) receptor-rich ventral striatum^{35,36} have been implicated in bipolar disorder and could be predictably involved in the action of risperidone, a known serotonin-dopamine antagonist.

METHOD

Design

This was a 6-week outpatient DBRCT of risperidone plus placebo (that resembled divalproex capsule) versus divalproex plus placebo (which resembled a 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. Written informed consent was obtained after the study was completely described to the participants. Parents and adolescents older than 16 years gave written permission and children younger than 16 years gave assent to participate. The clinical trials registry number is NCT00176202.

Study Sample

Inclusion criteria were a *DSM-IV* diagnosis of mixed or manic bipolar disorder; age 12 through 18 years; and medication free or currently clinically unstable on medication, justifying termination of the ineffective regimen. With consent, all subjects receiving psychotropic medications were washed out and free of any medication for a week before baseline scanning, and for 4 weeks in the case of fluoxetine or aripiprazole. Prior exposure to SGAs and antiepileptic medications was acceptable. Exclusion criteria included: active substance abuse; serious medical problems; autism, and nonaffective psychotic disorders. In addition, HC scoring ≥ 12 on YMRS or ≥ 28 on CDRS-R were excluded. Using these criteria, we recruited 44 subjects into the study. After excluding

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