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Psychotropic Medications and Their Effect on Brain Volumes in Childhood Psychopathology

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The heightened awareness of psychopathology in childhood has been paralleled by an upsurge of prescriptions for psychotropic medications in this population (Olfson, Blanco, Liu, Wang, & Correll, 2012). Although medications are evidence-based treatments which in many disorders effectively ameliorate symptoms and impairment, their mounting use in pediatrics has been controversial (Rapoport, 2013). This is based on the lack of adequately powered randomized controlled trials combined with concerns for children's greater sensitivity to side effects of psychotropic agents and the unclear ramifications for the developing brain. Physicians treating pediatric populations are thus charged with the challenge of weighing potentially far-reaching risks of medications against their benefits in children struggling with impairments that in and of themselves stand to impede development. To exercise sound clinical judgment, physicians should be informed about the neurobiological mechanisms and effects of psychotropic medications on the brain, particularly in children and adolescents.

Advances in neuroimaging methods have provided the opportunity to begin to investigate the neural correlates of psychopathology as well as the impact of treatments on brain development. To examine the question of how pediatric psychopharmacology affects structural brain development, we searched the literature for structural neuroimaging studies that analyzed the effect of medication on brain volumes in children with psychiatric conditions. This literature is relatively small due to the tendency for imaging studies that focus on the neural correlates of psychopathology to exclude children on medications based on the concern that medication use will alter the fundamental changes in brain function and structure under investigation.

Psychotropic Medication Effects: Cellular and Animal Models

As a foundation for understanding how psychopharmacology could impact structural brain development, we first review basic research on neuronal effects of psychotropic medication.

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This work has generally relied on cellular and animal models to investigate whether these agents can promote neuronal survival and growth and how they interact with signaling pathways mediating these processes.

Two relevant pathways for promoting neuronal survival and growth are the mitogen activated protein kinase/extracellular-regulated kinase (MAP/ERK) pathway and the phosphatidylinositol-3 kinase (PI3K) pathway. These cascades can inhibit molecules that trigger cell death and induce transcription of neuroprotective signals. Interestingly, both have been linked to psychopathology (Tanis & Duman, 2007), and multiple psychotropic medications interact with these pathways. Lithium and valproate, for example, upregulate these pathways in several neuronal cell types (Hunsberger, Austin, Henter, & Chen, 2009). Chronic lithium and valproate promote inactivation of the pro-apoptotic protein GSK-3 β , a downstream target of the PI3K pathway, in vitro (De Sarno, Li, & Jope, 2002) and in rodent cortex and hippocampus, regions widely implicated in psychopathology (Dash et al., 2010; Kozlovsky, Amar, Belmaker, & Agam, 2006). Typical and atypical antipsychotics also activate this pathway in neuronal cell culture, leading to neurite outgrowth (Lu & Dwyer, 2005). Haloperidol and clozapine also increase activation of the MAP/ERK pathway in rodent prefrontal cortex (Browning et al., 2005; Valjent, Pages, Herve, Girault, & Caboche, 2004). Recent work in neural stem cells demonstrates that fluoxetine promotes activation of both MAP/ERK and PI3K pathways (Huang et al., 2013).

Lithium's and valproate's activation of these pathways can increase levels of bcl-2, an anti-apoptotic protein (Chen et al., 1999), and brain-derived neurotrophic factor (BDNF) (Shaltiel, Chen, & Manji, 2007), a prominent growth factor implicated in neuronal development, resiliency, plasticity and the pathophysiology of several neuropsychiatric disorders (Autry & Monteggia, 2012). Rats treated with clinically relevant doses of lithium or valproate demonstrate activation of the MAPK/ERK pathway and increased transcription of BDNF (Einat et al., 2003). Antipsychotics, particularly atypical antipsychotics, and SSRIs have also been shown to increase BDNF in rodent hippocampus (Nibuya, Nestler, & Duman, 1996; Pillai, Terry, & Mahadik, 2006).

Stimulants have also been linked to increased neuronal growth in several studies of juvenile rats, albeit through different mechanisms. One study showed that methylphenidate induced dendritic elaborations of pyramidal neurons in the cingulate cortex (Zehle, Bock, Jezierski, Gruss, & Braun, 2007). Amphetamine has also been shown to provoke dendritic growth in pyramidal neurons (Diaz Heijtz, Kolb, & Forssberg, 2003) as well as dopaminergic neurons of the ventral tegmental area through basic fibroblast growth factor (Mueller, Chapman, & Stewart, 2006).

Finally, several psychotropics promote neurogenesis in rodents. At least for lithium and valproate, this also involves the MAPK/ERK pathway (Chen, Rajkowska, Du, Seraji-Bozorgzad, & Manji, 2000; Hao et al., 2004). Fluoxetine can increase neurogenesis in rodent hippocampus (Malberg, Eisch, Nestler, & Duman, 2000) and reverse the decline in neurogenesis observed in rodent stress paradigms (Hitoshi et al., 2007). Both d-amphetamine and methylphenidate can promote neurogenesis in adolescent rodents, which,

in the case of methylphenidate was associated with increased BDNF (Dabe, Majdak, Bhattacharya, Miller, & Rhodes, 2013; Lee et al., 2012).

While there is consensus from a large body of studies supporting that psychotropic medications can promote neuronal viability, other studies have identified neurotoxic effects of certain medications, most commonly typical antipsychotics (Dean, 2006) and stimulants (Advokat, 2007). It is worth noting that these are often observed at supra-therapeutic doses, or in the case of stimulants, at levels consistent with abuse. The reasons for these inconsistencies, particularly when contrasted with clinical improvement, remain unresolved. Given that dysfunction and that loss of neurons figure prominently in psychiatric disorders, the overall findings from animal and cellular studies support a mechanism whereby psychotropic medications can boost neuronal resilience and plasticity and ameliorate symptoms.

Neuroimaging Studies of Children and Adolescents with Psychopathology

While the majority of neuroimaging studies have been done in adults, there is an accumulating database for children and adolescents. The authors conducted literature searches in PubMed and PsychInfo databases using the phrases “brain volume and psychotropic drugs” or “child brain volume” plus “pediatric psychotropic drugs.” All structural neuroimaging studies using brain MRI in children and adolescents up to age 19 that analyzed medication effects and contained a healthy control group were included. For attention deficit hyperactivity disorder (ADHD), three meta-analyses that reviewed predominantly child studies were also included. A total of 25 studies (plus three meta-analyses) met our criteria across four disorders: bipolar affective disorder (BPAD), schizophrenia, ADHD, and obsessive compulsive disorder (OCD).

Bipolar Affective Disorder

Neuroimaging of children and adults with BPAD has frequently demonstrated decreased brain volumes in emotion-related neurocircuitry, including limbic regions, such as the amygdala, which is responsible for emotion processing; prefrontal cortical regions hypothesized to exert a top-down role in emotion regulation; and interconnected regions, such as the basal ganglia.

One study investigated differences in subcortical volumes in 20 children with and without BPAD and found that bilateral amygdala volumes were decreased in children with BPAD. Prior treatment with lithium or valproate was associated with increased amygdala volume in the BPAD group (Chang et al., 2005). Another study demonstrated that treatment with stimulants in children with BPAD was also associated with increased amygdala volume (Geller et al., 2009). A third study comparing 21 children with BPAD vs. 30 controls found decreased amygdala volume in BPAD but no relationship to psychotropic medication at the time of the scan (Kalmar et al., 2009). Unlike the other reports, this study did not examine the effect of different types of medication separately.

The effect of lithium was explored in 17 adolescents with BPAD versus 12 controls. Here, illness duration was negatively correlated with hippocampal volume, and affected

adolescents treated with lithium had larger right hippocampal volume than untreated individuals (Baykara et al., 2012). This finding replicated work in adults (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012; Yucel et al., 2007).

Studies of the basal ganglia in BPAD obtained conflicting results for the nucleus accumbens (NAcc), with two studies demonstrating increased right NAcc volume (Ahn et al., 2007; Frazier et al., 2008), while another found decreased NAcc volume (Geller et al., 2009). In the latter study, stimulant treatment was associated with increased NAcc volume, a normalizing effect.

The subgenual prefrontal cortex (sgPFC) is also of interest, as work in adults has repeatedly shown decreased volume in mood disorders. Two pediatric studies provide evidence that pharmacologic treatment is associated with increases in volume of sgPFC. The largest study, involving 51 individuals with BPAD and 41 controls, found smaller left sgPFC volume in affected individuals with familial BPAD (Baloch et al., 2010). Those treated with a mood stabilizer showed greater right sgPFC volume compared to untreated individuals. Another study showed increased volume of posterior subgenual cingulate, a subdivision of sgPFC, in individuals treated with lithium or valproate vs. untreated individuals and healthy controls (Mitsunaga et al., 2011). A smaller study found no difference in sgPFC volume between groups or any relationship between sgPFC volume and medication (Sanches et al., 2005). This study included a heterogeneous patient population with milder forms of bipolar disorder.

Two additional studies showed decreased volumes, one in anterior cingulate cortex (ACC) (Chiu et al., 2008), and the other in corpus callosum (Lopez-Larson et al., 2010), with no relationship between volumes and medication. The study on ACC did not examine medication effects according to medication type while the study on corpus callosum only compared volumes based on dosage of antipsychotics. A longitudinal study of individuals with BPAD following their first psychotic episode showed no difference in rates of volumetric change and no effect of antipsychotics (Arango et al., 2012).

Hence, in BPAD, there is some evidence that medications can help to normalize decreased brain volumes in the amygdala, hippocampus, and sgPFC, which comprise neurocircuitry important for emotion regulation, a major domain of impairment. Mood stabilizers, in particular lithium and valproate, have the most support. A number of studies failed to find any effect of medication, although many of these had a small sample size or did not examine the effect of specific medications.

Schizophrenia

Childhood schizophrenia is rare and consists of childhood onset schizophrenia (COS), starting before age 13, and early onset schizophrenia (EOS), starting between ages 13 and 18. As in adults, childhood schizophrenia is characterized by progressive gray matter loss, but to a more serious degree (Rapoport & Gogtay, 2011). The few available studies often had small sample sizes and a high proportion of medicated subjects, so that medication effects were evaluated by amount of neuroleptic exposure.

Most studies of COS involved overlapping subjects from a longitudinal cohort collected by the National Institute of Mental Health. Three of these studies demonstrated progressive gray matter loss in several areas, including frontal, parietal, and temporal lobes (Rapoport et al., 1999; Sporn et al., 2003) and left hippocampus (Jacobsen et al., 1998). The rate of gray matter reduction in several of these regions correlated with baseline symptom severity, although none of the studies showed any correlation between the rate of gray matter loss and the amount of exposure to neuroleptics.

One report from this group did support a normalizing effect of clozapine on volume of the caudate (Frazier et al., 1996). Eight adolescents with COS and 8 matched comparison subjects were scanned twice; the first scan occurred prior to the experimental group's initiation of clozapine and the second scan two years later. At scan 1, patients with COS had larger mean caudate volumes than controls. At scan two, all had clinically improved and their caudate volumes had decreased so that they did not differ from the controls.

For EOS, one cross-sectional study demonstrated lower temporal gyrus volume that correlated with increased positive symptoms (Tang et al., 2012), and another demonstrated decreased volume of thalamus and, in affected males, the left amygdala (Frazier et al., 2008). Neither study found a correlation between neuroleptic exposure and volumes. A longitudinal study of individuals following their first psychotic episode showed greater loss of gray matter in the frontal and left parietal lobes and also failed to find a correlation with level of neuroleptic exposure (Arango et al., 2012).

Thus, only one study, unique in that it investigated a single medication, demonstrated an association between medication and normalization of brain structure. No studies demonstrated disturbances in brain volume associated with medication. The observation that most studies fail to support any association between neuroleptics and changes in gray matter volumes suggests that the progressive decline in gray matter is inherent to the disorder.

Attention Deficit Hyperactivity Disorder

Structural neuroimaging studies of ADHD, which is primarily diagnosed during childhood, were most common in children and adolescents. This work has consistently shown decreases in global brain volume and volumes within a fronto-striatal-cerebellar brain circuit responsible for executive function, a central deficit in ADHD (Krain & Castellanos, 2006).

We identified 6 studies examining differences in brain volumes between medicated and unmedicated children and adolescents with ADHD, and the majority detected a relationship between brain volumes and stimulants. The largest of these studies, which included 152 subjects with ADHD and 139 age and sex matched controls, found that individuals with ADHD who were not on medication had smaller total white matter volume than individuals with ADHD treated with stimulants (Castellanos et al., 2002). The authors also noted that both medicated and unmedicated children with ADHD had smaller total cerebral and cerebellar volumes than controls but did not differ from each other, suggesting that stimulant treatment did not account for these differences. A previous study by the same investigators involving 50 females with and without ADHD had not found decreased white matter volume

or a relationship to stimulant treatment, although it was limited by a smaller sample size (Castellanos et al., 2001).

Two studies have reported that unmedicated children with ADHD have smaller right ACC volume than controls, while medicated children demonstrate relative increases in right ACC volume (Semrud-Clikeman, Pliszka, Bledsoe, & Lancaster, 2012; Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006). Another group showed a similar finding for the posterior inferior vermis of the cerebellum, whereby untreated individuals with ADHD, but not those who received stimulants, showed a smaller volume in this area than controls (Bledsoe, Semrud-Clikeman, & Pliszka, 2009). Additionally, a study examining the thalamus, due to its fronto-striatal connections, found that compared to treated children, untreated subjects had smaller volume of the pulvinar nuclei, which was associated with greater hyperactivity (Ivanov et al., 2010).

Finally, several meta-analyses have examined the impact of stimulant treatment on brain volumes in ADHD. The earliest, from 2007, failed to detect any effect but acknowledged that very few studies reported treated and untreated subjects separately (Valera, Faraone, Murray, & Seidman, 2007). Another meta-analysis that reviewed studies performing whole brain analyses found decreased right caudate volume in ADHD, with increased volume associated with stimulants (Nakao, Radua, Rubia, & Mataix-Cols, 2011). The most recent meta-analysis (Frodin & Skokauskas, 2012) included studies using whole brain analysis or manual tracing of the basal ganglia, the latter a more sensitive technique. Consistent with the prior meta-analysis, it showed decreased caudate volume in children with ADHD relative to controls, which was attenuated in studies with higher percentages of treated children.

The studies described here correspond to a larger literature that supports decreased brain volumes in a variety of brain regions in individuals with ADHD. Of note, only one of the six individual studies examining the effect of stimulants failed to find any normalization of decreased brain volumes. Further, the two meta-analyses with sufficient data on medication support improved basal ganglia volumes in patients on stimulants. Therefore, the largest body of available evidence supports the ameliorative effect of stimulants on structural brain development in childhood ADHD.

Obsessive Compulsive Disorder

Current neuroanatomical models postulate that derangements in fronto-subcortical circuits underlie OCD. Two studies prospectively measured the effect of paroxetine in treatment-naïve children and adolescents, each employing a region of interest analysis for specific subcortical structures. Gilbert et al. found that treatment-naïve children with OCD had significantly larger thalamic volume than healthy controls and that after 12-weeks of paroxetine, thalamic volume decreased and was associated with reduced symptom severity (Gilbert et al., 2000). In a study of the amygdala (Szeszko et al., 2004), treatment-naïve children with OCD, but not controls, exhibited significantly larger left amygdala volume than right. After 16 weeks of paroxetine, subjects with OCD displayed decreases in left amygdala volume correlating with the dosage of paroxetine. Both findings support a normalizing effect of paroxetine on brain volumes in regions implicated in OCD.

Clinical Implications and Future Directions

Current understanding of cellular mechanisms of psychotropic agents coupled with structural neuroimaging data reviewed here converges on a model in which psychotropic medication can normalize brain structures presumed to be altered by psychopathology during early development. Although some studies did not show a compensatory effect of medication, none of the studies detected disturbances in brain volume related to medication. These observations, in light of clinical efficacy and accumulating functional neuroimaging studies demonstrating normalized brain function with medication (Singh & Chang, 2012), suggest that judicious pharmacological management in children is more likely to restore rather than disrupt brain development. This stands in contrast to concerns that use of psychotropic medication in childhood might be deleterious to normative structural brain development; however, given the small number of studies available, more investigation is needed to draw firm conclusions. Cell and animal studies should incorporate more developmentally timed approaches, to clarify whether neuroprotective and neurotrophic effects occur in both juveniles and adults. Exploring whether sensitive periods occur in which the ameliorative effects of psychotropics are more powerful at specific developmental stages is of great interest. If such periods could be identified, they could have important clinical implications. Within reason, given logistic and ethical issues, the specific effects of individual medications on brain structural development should be studied to help guide psychopharmacologic management during childhood. More longitudinal and prospective neuroimaging studies are needed, and ideally, these studies should integrate structural and functional methods to clarify the significance of structural differences. Disentangling the mechanisms by which interventions counter psychopathology and promote neurodevelopment is important not only to optimize safety and efficacy of treatment, but also to advance understanding of normative brain development.

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Figure 1.

Normalization of regional brain volumes following pharmacologic treatment in childhood and adolescence. Sagittal T1-weighted brain MRI images depict more medial regions on left and more lateral regions on right. Labeled areas indicate structures for which medication has been associated with normalization of differences in brain volume observed in childhood psychopathology. Relevant disorders are listed with each structure (ADHD=Attention Deficit Hyperactivity Disorder, BPAD=Bipolar Affective Disorder, OCD=Obsessive Compulsive Disorder). For a given structure, distinct subregions may be affected by each disorder. In the case of the basal ganglia, the affected subregion involves the nucleus accumbens for BPAD and the caudate for schizophrenia and ADHD.

Table 1

Neuroimaging studies in children and adolescents reporting medication effects on regional brain volumes

Study	Medication Type	Volumetric Effect of Psychopathology	Volumetric Effect of Medication
<i>Bipolar Affective Disorder</i>			
Arango et al. 2012	Antipsychotics	None in frontal, parietal, or temporal lobes	None
Ahn et al. 2007	Antipsychotics	Trend for increased right NAcc volume	None
Baloch et al. 2010	Mood stabilizers	Smaller left sgPFC volume in familial disorder	Greater right sgPFC volume in treated vs. untreated children
Baykara et al. 2012	Lithium	Illness duration negatively correlated with hippocampal volume	Greater right hippocampal volume in treated vs. untreated adolescents
Chang et al. 2005	Lithium or valproate	Decreased amygdala volume	Increased amygdala volume in treated vs. untreated children
Chiu et al. 2008	Mood stabilizers or atypical antipsychotics	Decreased left ACC volume	None
Frazier et al., 2008	Antipsychotics	Smaller cerebral volume and larger right NAcc volume	None
Geller et al. 2009	Stimulants	No difference in volumes of medial orbital frontal cortex, ACC, hippocampus, amygdala, or NAcc	Greater amygdala and NAcc volumes
Kalmar et al. 2009	Not specified	Decreased amygdala volume	None
Lopez-Larson et al. 2010	Antipsychotics	Decreased middle and posterior corpus callosum volume	None
Mitsunaga et al. 2011	Lithium or valproate	No difference in subgenual cingulate volume	Greater posterior subgenual cingulate volume in treated vs. untreated children and controls
Sanches et al. 2005	Lithium, valproate, or antipsychotics	No difference in sgPFC	None
<i>Schizophrenia</i>			
Arango et al. 2012	Antipsychotics	Greater loss of frontal and left parietal gray matter	None
Frazier et al. 1996	Clozapine	Larger caudate volume	No difference in caudate volume in treated subjects vs. controls
Frazier et al. 2008	Antipsychotics	Decreased thalamic volume and in males, left amygdala volume	None
Tang et al. 2012	Antipsychotics	Decreased left temporal gyrus volume	None
Jacobsen et al. 1998	Antipsychotics	Greater decreases in right temporal lobe subregions and left hippocampus	None
Rapoport et al. 1999	Antipsychotics	Greater gray matter loss in the frontal, parietal, and temporal lobes	None
Sporn et al. 2003	Antipsychotics	Greater gray matter loss in the frontal and temporal lobes and decreased frontal and parietal gray matter	None
<i>Attention Deficit Hyperactivity Disorder</i>			
Bledsoe et al. 2009	Stimulants	Decreased posterior inferior cerebellar vermis volume	Greater posterior inferior vermis volume in treated vs. untreated children and no difference in treated children vs. controls
Castellanos et al. 2001	Stimulants	Smaller total brain and posterior-inferior cerebellar vermis volumes	None

Study	Medication Type	Volumetric Effect of Psychopathology	Volumetric Effect of Medication
Castellanos et al. 2002	Stimulants	Smaller cerebral, cerebellar, and white matter volumes	Greater white matter volume in treated vs. untreated children
Frodl & Skokuskas 2012	Not specified	Decreased right globus pallidus, right putamen, and caudate volumes	Normalizing effect on caudate volume
Ivanov et al. 2010	Stimulants	Decreased thalamic volume	Greater thalamic volume, especially in pulvinar, in treated vs. untreated children
Nakao et al. 2011	Stimulants	Decreased volume of right lentiform nucleus and right caudate	Normalizing effect on right caudate volume
Semrud-Clikeman et al. 2006	Stimulants	Decreased caudate and right ACC volume	No difference in right ACC volume in treated children vs. controls
Semrud-Clikeman et al. 2012	Stimulants	Decreased caudate and right ACC volume and larger right prefrontal volumes	Greater right ACC volume in treated vs. untreated children
Valera et al. 2007	Stimulants	Decreased volumes in cerebellum, corpus callosum, cerebrum, and right caudate	None
<i>Obsessive Compulsive Disorder</i>			
Gilbert et al. 2000	Paroxetine	Increased thalamic volume	Decreased thalamic volume
Szeszko et al. 2004	Paroxetine	Larger left vs. right amygdala volume	Decreased left amygdala volume

NAcc=nucleus accumbens. sgPFC= subgenual prefrontal cortex. ACC=anterior cingulate cortex.