Published in final edited form as:

Child Adolesc Psychopharmacol News. 2011 October ; 16(5): 3–10. doi:10.1521/capn.2011.16.5.3.

Effects of Stimulants and SSRIs on Brain Function in Children: Emerging Clues from fMRI Studies

Michael S. Gaffrey, Ph.D.

Department of Psychiatry, Washington University School of Medicine

Rivka Shenoy [undergraduate student at Washington University]

Joan L Luby, M.D.

Department of Psychiatry, Washington University School of Medicine

A clinician's decision about whether or not to prescribe psychotropic medications to children has become an increasingly complex and difficult one. The clinician is faced with weighing the potential benefit of a given medication to ameliorate acute symptoms while remaining mindful of the potential long-term side effects. This decision is made even more difficult given the near absence of longitudinal studies of medication effects in children to inform these issues. Despite this, psychotropic prescriptions for the treatment of emotional and behavioral difficulties in children and adolescents have increased exponentially over the past few decades. Stimulants and antidepressants represent two of the main classes of psychotropic drugs most commonly prescribed to children (Valluri et al., 2010).

Despite limited data demonstrating the efficacy and/or safety of psychotropic medications in children, a rise in pharmacotherapy has been demonstrated at progressively earlier and earlier ages [e.g., 3 years of age (Zito et al., 2000)]. This has been particularly evident in studies suggesting that the use of antidepressants for children was one of the most increasingly utilized treatments prior to the more recent “black box” warning (Valluri et al., 2010). For example, Zito and colleagues (2000) noted that prescription rates in the United States for fluoxetine increased by 1.8-fold between 1991 and 1995 in elementary and preschool age children. Similarly, Minde (1998) reported that the use of selective serotonin reuptake inhibitors (SSRIs) increased ten-fold for Canadian children 5 and younger between 1993 and 1997. Increasing rates of antidepressant use in very young children within the United States has also been found with doubling rates in preschool age (0–5 years) girls and a similarly high (64%) increase in same age boys between 1998–2002 (Delate et al., 2004). Despite declines in overall use of SSRIs after the black box warning, prescription trends have remained largely unchanged for youth diagnosed with Major Depressive Disorder (Valluri et al., 2010).

Mirroring this trend, the use of stimulants in children and adolescents with attention difficulties has also notably increased over the last two decades, with 4 million children prescribed stimulants annually within the United States alone. While many children clearly benefit from their use (Connor, 2002) surprisingly little is understood about their mechanism of action and the long-term course of their early effects (Andersen, 2005; Molina et al., 2009).

While the use of these medications in children has proven effective and indicated in specific clinical situations, our growing knowledge of the developing brain requires that we develop

a clearer understanding of their mechanisms of action on brain systems. Based on increasing knowledge of early neuroplasticity and brain change, it has become clear that our understanding of the mechanisms of psychopharmacologic agents on brain function cannot simply be extrapolated from adults to children (Andersen & Navalta, 2011). While capturing the complex interplay between brain development and psychotropic medication use is beyond the purview of any one field of study and much less a single article, the practicing clinician may benefit from a brief review of where the field now stands in relation to this question.

Recent advances in neuroimaging methodology have begun to inform this issue in adults and to a lesser degree in children. Based on this available literature, we introduce the proposed mechanisms of neural action for two of the most frequently prescribed medications in children, stimulants and SSRIs, by reviewing what is currently known about the actions of these substances in the adult brain from treatment studies using functional magnetic resonance imaging (fMRI). We also examine the few available fMRI studies of children following treatment with these medications. Possible future directions for research in this important domain are also discussed.

Mechanisms of Action

Selective Serotonin Reuptake Inhibitors

Serotonin is a monoamine neurotransmitter in the brain. The neurons that synthesize serotonin largely reside in the brainstem raphe nucleus. Axons from the raphe nucleus extend to various locations within the brain, including the cerebral cortex. Neurons within this system are believed to play an important role in the modulation of a variety of psychobiological functions such as mood (projections to the frontal cortex), anxiety/panic (projections to the limbic areas), sleep (projections to the sleep centers), consumption behavior (projections to the hypothalamus), sexual activity (spinal cord projections), motor activity (projections to the basal ganglia), and gastrointestinal function (projections to the chemoreceptor trigger zone; peripheral gut receptors; Kandel et al., 2000). Generally, SSRIs are purported to exhibit their antidepressant effects by blocking the reuptake of serotonin once it is released, thus prolonging its activity within a given brain region(s) (Baudry et al., 2011). While the exact mechanism by which SSRIs convey their therapeutic effect remains unclear, its association with increased neuroplasticity is generally believed to play an important role. This has been evident in animal and post-mortem studies suggesting that SSRIs have a positive impact on neurogenesis (i.e., the creation of new neurons) within the hippocampus, a region frequently implicated in the pathogenesis of depressive disorders (Baudry et al., 2011).

Stimulants

The attention and impulsivity difficulties related to Attention-Deficit/Hyperactivity Disorder (ADHD) are primarily treated with psychostimulants. While the exact mechanism underlying their therapeutic effect is currently unknown, they are believed to induce behavioral change by increasing the level of extracellular dopamine in the brain (Volkow et al., 2005). Some support for this mechanism has come from preclinical studies of methylphenidate hydrochloride (MP). These studies demonstrated that both dopamine (DA) and norepinephrine transporters are blocked when MP is administered. Consistent with this, more recent neuroimaging studies in adults have also indicated an increase in extracellular DA following the oral administration of MP (Volkow et al., 1998; Volkow et al., 2001). Both dopamine and norepinephrine neurotransmitter systems are believed to be involved in the pathogenesis of ADHD (Solanto, 1998). More specifically, the noradrenergic system is implicated in self-regulatory functions such as mediating selective attention while

disruptions of the dopaminergic system are believed to be involved with the motivational difficulties characteristic of ADHD. Accordingly, recent research has suggested that the administration of psychostimulants helps "tune" these systems so that noise (i.e., inappropriate signaling) is reduced while salient signals from external events are amplified (Volkow et al., 2005).

Review of Brain Imaging Studies of Psychopharmacologic Effects in Adults

SSRIs

A growing body of literature has suggested that dysregulated functioning of subcortical limbic and dorsal "cognitive control" brain regions underlie depression and other associated mood disorders (e.g., anxiety; see Drevets et al., 2008 for a thorough review). In line with this work, functional neuroimaging studies examining the effects of SSRIs have suggested that atypical activity within these regions is ameliorated or reversed following a period of SSRI antidepressant treatment. For example, Sheline and colleagues (2001) recently demonstrated that heightened amygdala responses to fearful faces in depressed patients were attenuated following an 8-week course of sertraline. Functional brain imaging studies have also suggested that the effects of SSRIs are not necessarily limited to subcortical limbic regions and likely include dorsal cortical structures as well. For example, a study of unipolar depressed patients by Mayberg and colleagues (2000) recently demonstrated that reduced brain glucose in limbic areas (e.g., hippocampus) are coupled with increases in cortical control regions such as the dorsal lateral prefrontal cortex (DLPFC) following 6 weeks of fluoxetine treatment. Similarly, Fales and colleagues (2009) also recently demonstrated in depressed patients that the DLPFC shows a significant increase of functional activity following 8 weeks of SSRI treatment.

Consistent with the notion that SSRI treatment may increase the functional interactions between corticolimbic regions (i.e., connectivity), 6 weeks of treatment with sertraline has also been associated with increased connectivity between anterior cingulate and limbic regions (Anand et al., 2005). In an attempt to synthesize the treatment related functional neuroimaging literature, Fitzgerald and colleagues (2008) recently conducted a meta-analytic study of brain changes following SSRI treatment. The findings of their meta-analysis provided additional support for the pattern of results noted above. That is, frontal brain regions involved in the regulation of emotion show increased activity following treatment with SSRIs while regions related to emotion generation (e.g., limbic structures) generally exhibit reduced activity.

Stimulants

A converging body of research has begun to suggest that fronto-striatal network abnormalities are brain correlates of ADHD (See Bush et al., 2005 for a thorough review). Given the emergence of ADHD during childhood, there have been relatively few studies directly examining the effects of stimulants on these brain regions in adults. However, an early series of studies in healthy adults by Volkow and colleagues (1998; 2001) has established that MP acutely increases the amount of dopamine in the synaptic cleft and that these increases are highly associated with the performance of complex tasks or response to signals of possible reward. In a small study of adults with ADHD, Krause et al. (2003) reported that MP increased levels of dopamine in the brain through the possible reduction of dopamine transporter binding potential, generally believed to be increased in ADHD (Volkow et al., 2005). Studies using functional imaging techniques such as Positron Emission Tomography (PET) or fMRI in adults with ADHD number relatively few. However, Schweitzer and colleagues (2003) previously examined the effects of a 3-week trial of MP on blood flow in 10 adults with ADHD. They found that MP induced greater

blood flow within the cerebellar vermis as well as reduced blood flow within the precentral gyri, left caudate nucleus and right claustrum. A more recent study using fMRI in adults with ADHD by Bush and colleagues (2008) examined the effects of stimulant treatment on brain activation during a cognitively challenging interference task. Adults with ADHD who underwent a 6-week course of treatment with MP exhibited increased activity within the dorsal anterior cingulate when compared to patients in a placebo control group. In addition, the authors concluded that normalization of brain function within this region with clinical response might be a useful biomarker in future treatment studies.

Review of Brain imaging Studies in Children

SSRIs

Given that a large body of research suggests the neurobiological systems and brain regions involved in common mood and anxiety disorders are not fully developed until adulthood, there is a dearth of information available regarding the effects of SSRIs on brain function in children and adolescents. We were able to find only one functional neuroimaging study examining the effects of SSRI treatment on brain function in adolescents. In this study, Maslowsky and colleagues (2010) compared the pre- and post treatment fMRI scans of 14 adolescents with Generalized Anxiety Disorder (a number of whom were also diagnosed with MDD) who received either an 8-week course of cognitive behavioral therapy (CBT; $n = 7$) or fluoxetine ($n = 7$) to same age healthy peers ($n = 10$) during a task designed to assess the neural response to threat. Results indicated that both treatment groups demonstrated an increase of right ventrolateral prefrontal cortex (VLPFC) activity following treatment. However, while both groups showed a significant reduction in anxiety symptoms following treatment, a direct relationship between changes in clinical symptom level and VLPFC functional activity was not found for CBT or fluoxetine.

In addition to the study by Maslowsky et al. (2010), a few studies have also attempted to use pretreatment brain activity measured with fMRI to predict treatment outcome in children and adolescents with mood or anxiety disorders. This work builds on previous research in adults suggesting that functional activity in affect-related brain regions may serve as a biomarker to distinguish potential treatment responders and nonresponders. In the first of these studies, McClure and colleagues (2007) used fMRI to examine pretreatment functional brain activity in adolescents with DSM-IV anxiety disorders (primarily GAD) who underwent an 8-week course of CBT or fluoxetine. Focusing on the amygdala, the authors found a significant negative association between pretreatment activation and measures of post treatment symptom severity and clinical improvement for the group as a whole while viewing emotional faces. These findings suggest that patients with high levels of amygdala activity prior to treatment may show the most favorable responses. A more recent study by Forbes and colleagues (2010) also explored the potential use of pretreatment functional brain activity as a predictor of treatment response to CBT or combined CBT and SSRI treatment in adolescents with MDD. Using a monetary reward task, the authors found that the rate of anxiety symptom reduction during treatment was associated with greater pretreatment values of striatal reactivity as well as reduced reactivity within the medial prefrontal cortex (mPFC). More specifically, greater pretreatment reward-related striatal activity was associated with a faster rate of improvement in anxiety symptoms while increased mPFC activity was associated with slower improvement in anxiety symptoms.

In general, these studies indicate that the use of functional brain imaging may prove useful in identifying brain regions involved in the therapeutic action of SSRIs as well as predicting those children more likely to respond to their use. They further suggest that neuroimaging tasks “tapping into” disorder relevant characteristics (e.g., amotivation) may be most useful

for informing this issue. However, given the limited findings available in the small samples noted above, more research in these areas is needed.

Stimulants

The association between changes in functional brain activity and performance on attention/inhibitory tasks following the administration of stimulant medication in children and adolescents has been the focus of several studies. As with studies examining the effects of SSRIs in children, the inclusion of a small number of children and use of multiple designs has lead to a variable pattern of reported findings. In summary, these studies have generally reported changes in the functional activity of multiple brain regions including the cerebellar vermis (Epstein et al., 2007), the basal ganglia (Shafritz et al., 2004; Vaidya et al., 1998) and frontal (Epstein et al., 2007; Peterson et al., 2009; Sheridan et al., 2010; Vaidya et al., 1998) and posterior cortices (Peterson et al., 2009). In one of the largest studies to date, Peterson and colleagues (2009) used fMRI to compare brain activity in 16 children and adolescents with ADHD to their same age healthy peers ($N=20$) as well as to themselves while either on or off their medication. The authors found that relative to brain activity when not medicated, children and adolescents with ADHD demonstrated greater deactivation (i.e., reduced activity) within the ventral anterior (vACC) and posterior cingulate cortices than when medicated. Similarly, when compared to their healthy peers, the ADHD group did not differ in level of vACC activity when on medication but did exhibit significantly less deactivation within this region when not on stimulants. Interestingly, the authors also reported that connectivity between the vACC and a portion of left lateral prefrontal cortex increased to healthy control levels in ADHD following the use of stimulant medication. Similar to other research on stimulants in ADHD (e.g., Sheridan et al., 2010), this finding suggests that examining the interaction between brain regions may be as important for identifying treatment effects as functional change in any one brain area.

In general, studies examining changes in brain activity following the administration of stimulants to children and adolescents with ADHD suggest that their efficacy may be due to the remediation of inefficient function within multiple cortical (primarily frontal) and subcortical (e.g., basal ganglia) regions. They also point to the potentially important role of interactions between brain regions in treatment effects. However, future research with larger groups of children is needed to examine the potential role of symptom heterogeneity on treatment outcome as well as to identify which neuroimaging tasks will be the most sensitive indicators of therapeutic change.

Clinical Implications and Future Directions

Studies of functional brain imaging provide some initial and interesting clues about the mechanism of action for both SSRI antidepressants and stimulants in children. These studies suggest that "normalization" of brain activity can be detected in some circumstances associated with acute treatment response. While more studies are needed utilizing larger sample sizes and comparing populations at varying stages of development, these studies lend some further support for the appropriate use of these agents in specific clinical situations. These findings may also direct future studies of novel interventions both psychopharmacologic and psychosocial. The question of long-term side effects of these agents on brain development remains under-studied and is another critical issue that should become the focus of investigations using brain imaging.

References

- Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry*. 2005; 57:1079–1088. [PubMed: 15866546]
- Andersen SL. Stimulants and the developing brain. *Trends in Pharmacological Sciences*. 2005; 26:237–243. [PubMed: 15860370]
- Andersen SL, Navalta CP. Annual research review: New frontiers in developmental neuropharmacology: Can long-term therapeutic effects of drugs be optimized through carefully timed early intervention? *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2011; 52:476–503.
- Baudry A, Mouillet-Richard S, Launay JM, Kellermann O. New views on antidepressant action. *Current Opinion in Neurobiology*. 2011
- Bush G, Valera EM, Seidman LJ. Functional neuroimaging of attention-deficit/hyperactivity disorder: A review and suggested future directions. *Biological Psychiatry*. 2005; 57:1273–1284. [PubMed: 15949999]
- Bush G, Spencer TJ, Holmes J, Shin LM, Valera EM, Seidman LJ, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry*. 2008; 65:102–114. [PubMed: 18180434]
- Connor DF. Preschool attention deficit hyperactivity disorder: A review of prevalence, diagnosis, neurobiology, and stimulant treatment. *Journal of Developmental and Behavioral Pediatrics*. 2002; 23:S1–9. [PubMed: 11875284]
- Delate T, Gelenberg AJ, Simmons VA, Mothert BR. Trends in the use of antidepressants in a national sample of commercially insured pediatric patients, 1998 to 2002. *Psychiatric Services*. 2004; 55:387–391. [PubMed: 15067149]
- Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*. 2008; 213:93–118. [PubMed: 18704495]
- Epstein JN, Casey BJ, Tonev ST, Davidson MC, Reiss AL, Garrett A, et al. ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2007; 48:899–913.
- Fales CL, Barch DM, Rundle MM, Mintun MA, Mathews J, Snyder AZ, Sheline YI. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *Journal of Affective Disorders*. 2009; 112:206–211. [PubMed: 18559283]
- Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*. 2008; 29:683–695. [PubMed: 17598168]
- Forbes EE, Olino TM, Ryan ND, Birmaher B, Axelson D, Moyles DL, Dahl RE. Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cognitive, Affective, & Behavioral Neuroscience*. 2010; 10:107–118.
- Kandel ER, Schwartz JH, Jessel TM. *Principles of neuroscience*. McGraw-Hill; New York: 2000.
- Krause KH, Dresel SH, Krause J, la Fougere C, Ackenheil M. The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews*. 2003; 27:605–613. [PubMed: 14624805]
- Maslowsky J, Mogg K, Bradley BP, McClure-Tone E, Ernst M, Pine DS, Monk CS. A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. *Journal of Child and Adolescent Psychopharmacology*. 2010; 20:105–111. [PubMed: 20415605]
- Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA. Regional metabolic effects of fluoxetine in major depression: Serial changes and relationship to clinical response. *Biological Psychiatry*. 2000; 48:830–843. [PubMed: 11063978]
- McClure EB, Adler A, Monk CS, Cameron J, Smith S, Nelson EE, et al. fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology*. 2007; 191:97–105. [PubMed: 16972100]

- Minde K. The use of psychotropic medication in preschoolers: Some recent developments. *Canadian Journal of Psychiatry, Revue Canadienne de Psychiatrie*. 1998; 43:571–575. [PubMed: 9729682]
- Molina BS, Hinshaw SP, Swanson J. M. Arnold LE, Vitiello B, Jensen PS, et al. The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009; 48:484–500. [PubMed: 19318991]
- Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, et al. An fMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *American Journal of Psychiatry*. 2009; 166:1286–1294. [PubMed: 19755575]
- Schweitzer JB, Lee DO, Hanford RB, Tagamets MA, Hoffman JM, Grafron ST, Kilts CD. A positron emission tomography study of methylphenidate in adults with ADHD: Alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology*. 2003; 28:967–973. [PubMed: 12700698]
- Shafritz KM, Marchione KE, Gore JC, Shaywitz SE, Shaywitz BA. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 2004; 161:1990–1997. [PubMed: 15514398]
- Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biological Psychiatry*. 2001; 50:651–658. [PubMed: 11704071]
- Sheridan MA, Hinshaw S, D'Esposito M. Stimulant medication and prefrontal functional connectivity during working memory in ADHD: A preliminary report. *Journal of Attention Disorders*. 2010; 14:69–78. [PubMed: 20576647]
- Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: A review and integration. *Behavioural Brain Research*. 1998; 94:127–152. [PubMed: 9708845]
- Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JD. Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95:14494–14499. [PubMed: 9826728]
- Valluri S, Zito JM, Safer DJ, Zuckerman IH, Mullins CD, Korelitz JJ. Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. *Medical Care*. 2010; 48:947–954. [PubMed: 20856141]
- Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2005; 57:1410–1415. [PubMed: 15950015]
- Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *American Journal of Psychiatry*. 1998; 155:1325–1331. [PubMed: 9766762]
- Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *Journal of Neuroscience*. 2003; 21:RC121. [PubMed: 11160455]
- Zuo J, Safer D, dosReis S, Gardner J, Boles M, Lynch F. Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association*. 2000; 283:1025–1030. [PubMed: 10697062]