A Review of Executive Function Deficits and Pharmacological Management in Children and Adolescents

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Abstract

Objective: To review both the functions and dysfunction of the executive system (ES) focusing on the extent of executive function (EF) deficits in most psychiatric disorders in children and adolescents and the possibility of such deficits acting as markers for pharmacological management. **Method:** A literature review was conducted using MEDLINE, Psychinfo, CINAHL, PsychArticles and PubMed with the following keywords: executive function or dysfunction, pediatric or children or adolescents, psychopharmacology, psychotropic medications, attention deficit hyperactivity disorder (ADHD), depression, obsessive compulsive disorder, anxiety disorders, bipolar disorder, schizophrenia, autism spectrum disorders (ASD), fetal alcohol spectrum disorders (FASD). Due to the limited amount of specific information obtained for some childhood disorders, the search was broadened to include relevant adult literature where information was extrapolated. **Results:** Abundant literature was found on the nature of the ES and the executive dysfunctions in most psychiatric disorders in children and adolescents, but not so much on the use of medication. EF deficits were found to be more consistent in disorders such as ADHD, ASD and FASD than in the other disorders but were not specific enough for use as clinical markers for those disorders. For children with ADHD and ASD there was adequate information on the use of psychotropic medications and impact on some EF domains but information on the impact of medication on EF in the other disorders in children and adolescents was fairly limited. Medications acting on the dopaminergic system also showed positive effects on EF deficits and are commonly used in the treatment of EF disorders such as ADHD, ASD and FASD. **Conclusion:** Existing literature indicates that EF deficits underlie most psychiatric disorders in children and adolescents. However, there are so many executive functions linked to so many activities and circuits in the brain that it is hard to quantify them in a particular disorder for use as specific markers for that disorder. The ES uses dopamine as its main neurotransmitter and this has implications for clinical management. Dopamine agonists (e.g. stimulants) and antagonists (e.g. neuroleptics) are medications that have direct impact on the ES and are commonly used to treat EF disorders in children and adolescents while serotonergic medications e.g. selective serotonin reuptake inhibitors (SSRIs) have not been very successful in treating such disorders. Identifying EF deficits early could be useful in guiding management including the use of medication in those disorders.

Key words: *executive, function, deficits, children, adolescents, pharmacology*

Introduction

Children who do not have a visible disability are expected to function according to a set of norms and rules in today's society. Lately, there have been increasing concerns from parents, teachers and other professionals that many children are not responding to reasonable expectations or functioning adequately at home, school and in the community. They are referred to as lazy, unmotivated or forgetful and their behaviors are often regarded as deliberate. Their inability to start or complete a task, oppositional defiant behaviors, excessive anxiety, mood dysregulation, meltdowns, aggressive behaviors, suicidal threats/attempts and other disruptive behaviors lead to them being assessed and treated by a number of mental health professionals. When their symptoms fit the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, they are diagnosed and managed according to applicable practice guidelines. A core problem underlying many of these conditions is often a defective executive system (ES) (Parker, 2001). The DSM does not have a diagnostic category known as "Executive Function Disorders". As a result, these children's EF deficits are not assessed properly and they often go from professional to professional over a period of years without proper adaptations and management of these deficits. This review

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focuses on EF deficits described in the common psychiatric disorders of children and adolescents and their possible use as a guide in management including interventions with psychotropic medications.

The Executive System

To regulate and guide behavior through a constantly changing environment, the brain requires a central coordinating system. The ES is responsible for the simultaneous operation of a number of cognitive processes in charge of goal-directed, task-oriented behaviors, self-regulation and behavior inhibition as well as planning, working memory, mental flexibility, response inhibition, impulse control and monitoring of action (Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009). EF refers to the many skills required to prepare for and execute complex behaviors (Ozonoff et al., 2004). Any dysfunction of the ES affects the child's EF impairing his/her ability to analyze, plan, prioritize, schedule, initiate and complete an activity in a timely manner. Managing time and meeting deadlines then become a huge problem. These children need constant reminders because of problems with working memory. They are unable to change behaviors or plans according to environmental demands and have difficulties reconfiguring an alternate plan when presented with new situations or tasks. They live mainly in the here and now, do not deal with contradictions well and cannot adapt to changes or changing situations quickly. They do not shift easily, can get stuck on one routine, hyperfocus on one task and are rigid in their thinking. In their social interactions they expect their peers as well as parents to behave in predictable ways and when this does not happen they try to control the situation, react excessively or go to a shutdown mode.

Neurobiology

The ES is mediated by various networks in the frontal, parietal and occipital cortices, the thalamus and the cerebellum (Jurado & Roselli, 2007). It is linked through a series of circuits connecting every region of the central nervous system. The circuits originate in the dorsolateral prefrontal cortex (PFC) / orbitofrontal cortex (OFC), project through the striatum, synapse at the level of the globus pallidus, substrantia nigra and the thalamus and finaly return to the PFC forming closed loops (Narushima, Paradiso, Moser, Jorge, & Robinson, 2007). Each circuit regulates specific functions. The circuit that is most responsible for coordinating EF is located primarily in the frontal lobe. Functional imaging studies have implicated the PFC as the primary site of cortical activation during tasks involving EF (Elliott, 2003).

Neurochemistry

The PFC regulates attention and behavior through networks of interconnected pyramidal cells which are highly dependent on their neurochemical environment. Small changes in the catecholamines, norepinephrine or dopamine, can have marked effects on PFC function (chemical imbalance). Norepinephrine and dopamine are released in the PFC according to the child's arousal state; too little (during fatigue or boredom) or too much (during stress) will impair PFC function. Optimal amounts are released when the child is alert and interested (Arnsten, 2009). Dopamine, the main neurotransmitter of the ES, plays an essential role in the frontal cortex in mediating EF. Dopamine neurons participate in the in the modulation of expectation, reward, memory, activity, attention, drives and mood. Disturbances in the dopaminergic system form the basis of many psychiatric illnesses (Cohen & Carlezon, 2007).

Executive Dysfunction and Psychopathology

Damage to or dysfunction of the frontal lobe and disruption in fronto-subcortical pathways from chemical imbalances have been strongly associated with dysfunction of the ES as demonstrated through neuroimaging studies using PET and fMRI scanning (Elliott, 2003). Executive dysfunction indicates some malfunction in the circuits that connect the subcortical areas with the frontal lobes (Rosenblatt & Hopkins, 2006). Both genetic and environmental factors can interfere with ES efficacy.

EF impairments underlie the psychopathology seen in many psychiatric conditions and are strongly associated with functional outcomes, disability and specific problem behaviors (Royall et al., 2002). Executive dysfunction is hence implicated in the many symptoms that children may present with (Roberts, 2006) and has been linked to a number of disorders (Robinson et al., 2009).

Attention Deficit Hyperactivity Disorder (ADHD)

Children with ADHD have serious difficulties with EF in so many areas that some psychiatrists and psychologists have proposed renaming this disorder as EF disorder (Parker, 2011) or EF deficit disorder (Barkley, 2012). Many of the executive dysfunctions described earlier are found in children with ADHD including difficulties with priority and time management, planning and organization, initiating and completing tasks in a timely manner, difficulty shifting cognitive set, a high level of procrastination, forgetfulness and poor working memory.

In terms of pharmacotherapy most studies have associated stimulant medications, both methylphenidate (MPH) and dextroamphetamine (D-AMP), with improved EF performance, reducing and often normalizing cognitive and behavioral impairments in children with ADHD (Snyder, Maruff, Pietrzak, Cromer, & Snyder, 2008). EF was assessed in 30 children with ADHD; 15 were stimulant medication naïve and 15 were being treated with stimulant medication. These two groups were compared with 15 controls matched for age, sex and intelligence (IQ). The unmedicated children with ADHD displayed specific cognitive impairments on

several EF tasks while the medicated children with ADHD did not show impairments on any of the EF tasks except for deficits in spatial recognition memory (Kempton et al., 1999). A single MPH dose was associated with a robust improvement in prefrontal cognitive performance, including achievements in the Hearts and Flowers EF task and the visual continuous performance task when compared to placebo (Green et al., 2011). Such improvement in EF could be used as a marker for psychostimulant medication effect in children with ADHD, combined type (Efron et al., 2003).

The therapeutic effect of the stimulants in ADHD is associated with their effects on the catecholamine system. Impaired neurotransmission causing executive dysfunction occurs because of abnormalities of the dopamine transporter (Snyder et al., 2008). All currently approved pharmacotherapies for ADHD, both stimulants and non-stimulants, work by potentiating neurotransmission in the PFC (Arnsten, 2009). In ADHD subjects, single doses of the non-stimulant atomoxetine produced selective effects on response inhibition in the absence of effects on attention and memory (Marsh, Biglan, Gertenhaber, & Williams, 2009). Although a norepinephrine reuptake inhibitor, atomoxetine acts primarily via presynaptic norepinephrine transporter blockade and elevates dopamine in selective cerebral regions.

Autism Spectrum Disorders (ASD)

One of the most consistently replicated cognitive deficits in individuals diagnosed with autism is executive dysfunction. Recent structural and functional imaging work as well as neuropathology and neuropsychology studies provide strong empirical support for the involvement of the frontal cortex in autism (Ozonoff et al., 2004). Several studies comparing children with ASD (autism and Asperger syndrome) with age and IQ matched control groups have demonstrated EF deficits (Happe, Booth, Charlton, & Hughes, 2006). Behavioral similarities between patients with frontal lobe lesions and individuals with ASD led to the notion that some of the everyday social and non-social behaviors seen in individuals with ASD may reflect specific executive dysfunction (Robinson et al., 2009). A review of studies that had explicitly assessed EF skills such as planning ability, mental flexibility, inhibition, generativity and self-monitoring in people with ASD, as compared to a well matched controlled group or standardized test data, reported deficits in each of these domains (Hill, 2004).

There is strong evidence that abnormalities in the dopaminergic system are associated with the deficits in ASD (Denys, Zohar, & Westenberg, 2004; McCracken et al., 2002). Dopamine modulates motor activity, attentional skills, social behavior and perception of the outside world, all of which are abnormal in autism (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997). Antipsychotic medications, which act mostly as dopamine antagonists, including haloperidol and risperidone have been the most widely studied drugs for reducing symptoms of autism (Malone, Gratz, Delaney, & Hyman, 2005). The atypical antipsychotic risperidone was the first drug approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of irritability associated with autistic disorder, including symptoms of aggression, deliberate self-injury, temper tantrums, and quickly changing moods, in children and adolescents aged 5 to 16 years. Children treated with risperidone showed reductions in stereotypy, hyperactivity and aggressive symptoms compared to placebo (Parikh, Kolevzon, & Hollander, 2008). In 2009, aripiprazole was also granted approval by the FDA for this indication. Aripiprazole and risperidone each have a large effect size for the treatment of irritability, indirectly suggesting similar efficacy between the two compounds (Douglas-Hall, Curran, & Bird, 2011). Serotonin regulation has been implicated in the manifestations of repetitive behaviors (Kolevzon, Mathewson, & Hollander, 2006). Several randomized controlled trials studying the efficacy of SSRIs in the treatment of repetitive behaviors in children with ASD have reported uncertain effects but a meta-analysis of the published literature suggested a small but significant effect (Carrasco, Volkmar, & Bloch, 2012). Also, although not considered representative of the general population, a study of 60,641 US children receiving Medicaid reported that 56% were on at least one psychotropic medication and 20% were prescribed three or more medications concurrently. Neuroleptic drugs were the most commonly used (31%), followed by antidepressants (25%) and stimulants (22%) (Mendell et al., 2008).

Fetal Alcohol Spectrum Disorder (FASD)

EF has been implicated as a cardinal deficit in FASD, with prenatal alcohol exposure being a negative factor in the development of the frontal cortex (Rasmussen & Bisanz, 2009). In a study of 18 children (aged 8 to 15 years) the alcohol exposed children had more difficulties on EF measures of planning ability, selective inhibition, concept formation and reasoning (Mattson, Goodman, Caine, Delis, & Riley, 1999). Children with FASD also experience greater difficulty with complex adaptive behaviors that involve the integration of multiple domains including set-shifting, planning and strategy use, attention and spatial working memory, longer reaction and decision time which depend on the proper functioning of different parts of the brain, particularly the frontal lobes (Green et al., 2009).

No psychotropic medication is specific for the treatment of FASD. Prenatal alcohol exposure is associated with EF deficits in the frontal lobes. Given the link to dopamine and norepinephrine neurotransmitter disturbance in the frontal lobes (Frankel, Paley, Marquardt, & O'Connor, 2006) the negative behaviors are likely to respond to drugs that impact the dopaminergic system including the stimulants and the neuroleptics. Many of these children are often prescribed a combination of a stimulant and a second generation neuroleptic (atypical antipsychotic).

Depression

Major depressive disorder (MDD) has been associated with executive dysfunction (Fava, 2003) and related abnormal prefrontal ability (van Tol et al., 2011). Neuroimaging studies in humans support the hypothesis that MDD is associated with a state of reduced dopamine transmission (Dunlop & Nemeroff, 2007). Suicidal thinking has been seen as a maladaptive "executive decision" made by someone who exhibits cognitive rigidity and dichotomous thinking, i.e. a person who fails to see solutions to problems other than suicide. As the "executive decision center" of the brain, the frontal lobe may be dysfunctional in suicidal patients (Hartwell, 2001). No single treatment has been found to be uniformly effective in MDD as only 40% of patients achieve remission with an initial antidepressant trial. Although several studies have identified a range of cognitive deficits that can be used as markers for SSRI response, this has not been useful clinically to date as the essential neuropsychological profile related to SSRI non-response remains unknown. However, patients with more severe EF impairments are at risk for poorer treatment outcome (Gorlyn et al., 2008).

Bipolar Disorder

With regards to Bipolar Disorder (BD), cognitive deficits involving EF have been described across all phases of the disorder. Impairment in some cognitive domains such as visual memory, working memory and risk taking behavior, has been seen to remit during periods of euthymia but impairment in other areas such as selective attention, attentional shifting, verbal planning, verbal memory, perseveration, processing speed and other elements of EF such as inhibitory control, response inhibition and strategic thinking, is more likely to persist regardless of the current mood state (Goldberg & Chengappa, 2009). Also impairments in measures of executive dysfunction have been reported in adolescents prior to the manifestations of the disorder (Meyer et al., 2004). The cognitive deficits intrinsic to BD have been associated with problems of attentional processing, EF and verbal memory with relative preservation of other functions such as visuo-spatial memory, verbal fluency and vocabulary. A study of 44 stable euthymic bipolar outpatients compared with 46 matched controls suggested that impaired EF and loss of inhibition might be an important feature of BD regardless of the severity of the disease or the effects of medication (Mur, Portella, Martinez-Aran, Pfifarre, & Vieta, 2007).

Studies documenting the impact of specific medications on the EF of children and adolescents in any one phase of BD were not identified in this review. There is still disagreement among physicians on the appropriate course of action or medications in BD in children. Treatment options include mood stabilizers (e.g. lithium and valproic acid) and atypical antipsychotics (risperidone, quetiapine and aripiprazole as approved by the FDA). Aripiprazole was recently approved by Health Canada for use in adolescents 13–17 years old with BD (March 2012).

Schizophrenia

In schizophrenia, cognitive functioning is severely impaired in most patients. Deficits include impairment in attention, working memory and EF (Goetghebeur & Dias, 2009). The irrational thoughts, delusions and hallucinations (positive symptoms) relate to dopamine dysregulation and excessive dopamine in the brain. Improvement in some but not all domains of cognition during treatment with the atypical antipsychotic drugs clozapine, quetiapine, olanzapine and risperidone has been reported in some but not all studies (Harvey, Napolitano, Mao, & Gharabawi, 2003; Cuesta, Peralta, & Zarzuela, 2001). A randomized, controlled, double-blind, multi-center comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill patients with schizophrenia or schizoaffective disorder showed that treatment with either was associated with statistically significant improvements from baseline in attention, memory, working memory, motor speed and EF (Harvey, Siu, & Romano, 2004). No statistically significant differences between these medications were found in the magnitude of improvement from baseline in the extent of cognitive enhancement (Harvey et al., 2004). Thirty four patients with schizophrenia who were partial responders to typical antipsychotics were evaluated with a comprehensive neurocognitive battery including measures of EF: verbal and visual learning and memory, working memory, immediate, selective and sustained attention, perceptual/motor processing and motor skills, prior to and following treatment with the atypical olanzapine for six weeks and six months later. Olanzapine improved some but not all cognitive deficits in schizophrenia including verbal memory (McGurk, Lee, Jayathilake, & Meltzer, 2004). Responses did not seem consistent or specific enough to be useful as a marker for any particular medication.

Obsessive Compulsive Disorder (OCD)

OCD has been associated with executive dysfunction linked with neuropathology of the fronto-striatal pathways (Chang, McCracken, & Piancentini, 2007) but identification of common deficits has been inconsistent in various reports. A common deficit seems to be difficulties in inhibition and impaired set-shifting ability although planning ability appears unaffected. Few studies have identified such impairments in children with OCD and of those studies published the results are mixed (Ornstein, Arnold, Manassis, Mendlowitz, & Schachar, 2010). For example, findings on working memory and verbal fluency have been inconsistent. In one study, relative to controls, adolescents with OCD exhibited spatial-perceptual deficits similar to patients with frontal lobe lesions. A second study reported no impairments on an extensive neurocognitive battery that included several measures of EF (Chang et al., 2007). Another study

found no difference between children with OCD and controls (Andres et al., 2007). A more recent study (Ornstein et al., 2010) of 14 children with OCD and healthy controls showed that children with OCD demonstrated relative strengths in various executive control domains as well as intact memory functioning.

To date, SSRIs remain the most effective medication for treating OCD symptoms although their specific impact on the EF deficits is not clear. Some studies have suggested that serotonin plays an important part in the functioning of the frontal lobes by facilitating the communication of information from one neuron to the next (Huey, Putman, & Grafman, 2006) and through its interaction with dopamine (Dunlop & Nemeroff, 2007).

Anxiety Disorders

With regards to patients suffering from anxiety disorders, no major cognitive impairments were found when compared to healthy peers, and a lifetime history of anxiety disorders was not associated with cognitive impairment (Castaneda et al., 2011). The status of EF in anxiety disorders and in co-morbid depression and anxiety remain unclear (van Tol et al., 2011).

Discussion

This review has identified deficits in EF in most psychiatric conditions in children and adolescents and found them to occur most frequently and consistently in conditions such as ADHD, ASD and FASD. This "trio" seems to share common dysfunctions and behaviors, and at this point in time could be viewed as the "Executive Function Disorders". The deficits in these disorders arise from a frontal-subcortical disruption involving mainly the neurotransmitter dopamine. This has implications in clinical management especially in guiding the choice of medication. The first line treatment for ADHD remains stimulant medications (Hosenbocus & Chahal, 2009), while for autistic disorder the two medications that have FDA approval for use in ASD are risperidone and aripiprazole, and they both work to stabilize the dopaminergic system. Stimulants are dopamine agonists, risperidone is a dopamine antagonist, and aripiprazole is a dopamine partial agonist/antagonist. Both of these classes of medications are often used jointly in the management of ADHD, ASD and FASD. It is not rare to find a child with an EF disorder taking both a stimulant and risperidone concurrently. In the future, by considering distinct domains within EF, it may be possible to clarify the nature of the deficits in these disorders and map out distinct EF profiles (Happe et al., 2006) that could be clinically useful. This could change the way in which the children with EF disorders are managed. In other disorders such as OCD, MDD and BD the deficits are less consistent and are complicated by pre-morbid or co-morbid factors. The depression-executive dysfunction (DED) model which predicted that the presence of executive dysfunction is associated with a poorer response to antidepressant medication was not validated by the available evidence (McLennan & Mathias, 2010). This is unfortunate as the presence of certain EF deficits could have acted as a guide to medication use in depression. However, the SSRIs were the only antidepressants used in the study and to-date most SSRIs have fared poorly in treating childhood MDD, perhaps because depression may also be associated with strong deficits in the dopaminergic ES which SSRIs do not principally address.

No single medication has been identified as specific in fixing or improving all aspects of the ES in any one condition. Stimulants may help with attention and impulse control, atypical antipsychotics or anticonvulsants with mood stabilization, irritability, reactivity or aggression and SSRIs with excessive anxiety and repetitive behaviors but one medication cannot do it all. It is not infrequent to find all these symptoms co-existing in one child and medications are combined to control as many symptoms as possible leading to "poly-pharmacy." Psychotropic medication use in children and adolescents continues to be an area of controversy and the search for reliable biological markers, including whether specific EF deficits can play this role, to justify their use is ongoing.

Recommendations

EF deficits underlie most psychiatric disorders and should be identified early in the assessment process before setting up a management plan. Knowing which deficits do not respond to a particular medication or environmental measure would make the use of other resources or strategies essential to manage such deficits and, hopefully, lead to a better outcome. Besides, relying on the use of medication alone to make a difference places an unnecessary expectation on the medication and may lead to disappointment when the response is less than satisfactory or to "poly-pharmacy" in an attempt to cover all problematic symptoms. It is always important to combine medication with other management strategies and to also ensure that the medication or any combination of medications is not affecting cognitive functioning causing further impairment.

Formal assessment of EF is usually done by a psychologist or neuropsychologist using standardized testing such as the Behavior Rating Inventory of Executive Function (BRIEF), the Developmental Neuropsychological Battery (NEPSY II) or other neuropsychological test batteries. Unfortunately such professionals may not be readily accessible in many centers and children sit on long waiting lists to be assessed. However, a management plan needs to be set up as soon as the child is seen. Informally, useful information on a child's EF can be assembled from different sources including a one on one interview where various aspects of the child's functioning such as organizational skills, regulation of affect, information processing, planning ability, level of flexibility, ability to shift from task to task, task initiation/completion,

time management and child's problem solving ability can be observed and documented. His or her ability to perform the complex tasks of everyday living can also be informally assessed. Soft neurological signs can also be elicited and work samples reviewed. Standardized questionnaires, checklists or rating scales such as the Barkley Deficits in Executive Functioning Scale—Children and Adolescents (BDEFS-CA) can also be used whenever feasible. By organizing the information gathered, the child's EF profile can be pieced together and used in setting up a management plan while waiting for more formal testing.

EF deficits, once identified, should be discussed with the child (whenever practical), parents and other caregivers including teachers. In EF disorders, proper understanding of the deficits may lead to better acceptance and compliance for the adaptations or accommodations that are required in the home, at school and in the community to avoid complications or crisis situations. The use and impact of medication on certain deficits or target areas, when indicated, should be clarified together with their limitations and the need for concurrent therapies. In some disorders, it is important to set up a parent training program to teach management strategies such as consistent routines breaking down multi-step tasks to reduce frustration and use a collaborative problem solving approach between the child and the caregiver to avoid power struggles and explosive behaviors (Greene, 2005). The usual parenting techniques and behavior management that work for regular children, including rewards or consequences, have not had much success with children suffering from EF disorders. Also once per week counseling without efforts to insert accommodations at key "points of performance" in natural settings is unlikely to succeed for the patient with deficient EF (Barkley, 2012). Effective management needs to be multi-modal in approach with many agencies and professionals pulling their resources together and liaising cohesively with each other without any undermining or giving mixed messages to the child and parents. There is no cure for executive dysfunction and treatment must be continued for life (Jones, 2000). Children with EF disorders can achieve a sense of success and avoid getting into difficulties as long as they have support from another person, a parent, teacher, mentor or friend to act as a "surrogate frontal lobe" to guide them and keep them on track. Research focusing on how observable symptoms relate to specific EF deficits has important implications for future psychopharmacological interventions in this area by elucidating the neural substrates and pathways which underpin symptomatology (O'Grada & Dinan, 2007).

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