Testing ADHD, executive functioning, and stimulant medication as predictors of psychotic symptoms in children

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Thesis declaration form

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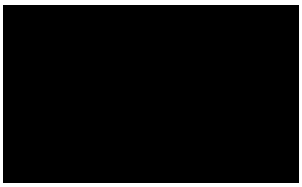

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Overview

Executive dysfunction has been associated with psychotic experiences. One of the syndromes most associated with executive dysfunction difficulties in childhood is ADHD. However, stimulant ADHD medications are known to increase psychotic-like symptoms in some circumstances. These interrelated factors make it difficult to tease apart which of these most predict psychotic experiences. Using cross sectional data analysis, this thesis looks into the extent of how executive dysfunction, ADHD, and stimulant medication each independently predict psychotic symptoms in 9-10-year-old children.

Part 1 is a conceptual paper based on a review of related literature. The primary aim was to understand the natures of ADHD, executive dysfunction, and stimulant medications. It further investigates their associations and potential mechanisms for psychotic experiences.

Part 2 is an empirical paper, which reports a study on predictors of psychotic experiences in children. The study aimed to examine to what extent a diagnosis of ADHD, stimulant medication, and executive dysfunction each independently predict psychotic symptoms in children after controlling for potential confounders. Findings indicate that ADHD was not associated with psychotic experiences. On the other hand, both stimulant medication and executive dysfunction showed a significant relationship with psychotic experiences, even after controlling for confounders. Stimulant medication did not moderate the relationship between executive dysfunction and psychotic experiences. Clinical implications and future recommendations are further discussed.

Part 3 is a critical appraisal of the study of the literature review and the empirical study. It includes personal reflections on the research processes from a clinical and research perspective.

Impact Statement

It is now known that the lifetime prevalence of psychotic experiences in the general population is 5.8% based on a large multinational study (McGrath et al., 2015). Besides how striking the persistence is, it is particularly relevant to note the occurrence in the younger population (Kelleher et al., In Press). Although psychotic symptoms tend to be transitory in nature in about 80% of individuals (Linscott & van Os, 2013) and only a small proportion (7.4%) develops into psychotic illnesses, it is important to emphasise that psychotic-like experiences can still increase the chances of one developing a psychotic disorder later on for those who continue to be affected by it. Thus, psychotic-like experiences in children and adolescents need to be given more attention by providing early intervention as this could potentially prevent poor mental health outcomes later on in life.

There may be various factors that contribute to the problem of understanding what really predicts psychotic-like symptoms, which make it hard to tease apart. Although various research papers show associations between psychosis and its known factors such as ADHD, stimulant medication, and executive functioning, no single study has examined the co-occurrence of their interactions to better understand the extent to which they predict psychotic experiences.

The review paper was the first to critically evaluate and synthesise fundamental theories, concepts, and literature findings on psychotic experiences of young people based on its associations with mental health problems such as ADHD and executive dysfunction, as well stimulant medications. The empirical study was also the first to conduct an in-depth quantitative analysis examining the extent to which diagnosis of ADHD, stimulant medication,

and executive dysfunction each independently predict psychotic symptoms in children after controlling for potential confounders. In addressing mixed findings in published literature, the study reveals associations between stimulant medication and psychotic experiences among children, providing further current evidence of the former as a predictor. In addition, the study found that executive dysfunction significantly contributes to psychotic experiences in children, even after controlling for potential confounders, adding to limited research in this area. Finally, the paper highlights the how large scale studies such as this are able to identify effect sizes that may be overlooked in small sample sizes investigating psychotic experiences in children.

It is hoped that the dissemination of the findings among colleagues, the academia and relevant professions in the field will lead be able to broaden its knowledge and answer more questions that have sprung from these initial findings. Further, raising an awareness of the in clinicians and commissioners involved in service design and will hopefully lead to improvements in service delivery and support available to this population, so that the needs of children and their families are met for the better. It is also hoped that increasing knowledge and awareness to society might be able to reduce the stigma associated with mental health disorders and psychopharmacological treatment among children and adolescents in order to prove the right scaffolding for optimal development. The results of this study provide important clinical and treatment implications with regards to child and adolescent development, particularly in the advancement of the field of brain health and development.

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Taos-pusong pasasalamat sa inyong lahat.

Para sa iyo ito, Pilipinas kong mahal.

Part 1: Literature Review

Testing ADHD, executive functioning, and stimulant medication as predictors of psychotic symptoms in children

Abstract

Aim: To investigate ADHD, executive functioning, and stimulant medication as potential predictors of psychotic symptoms across all studies.

Method: A conceptual review of relevant literature.

Results: Based on the literature review, various research papers show associations between psychosis and its known factors such as ADHD, stimulant medication, and executive functioning, However no single study has examined the co-occurrence of their interactions, along with other possible confounding variables (i.e., stimulant medication, age, gender, ethnicity, socioeconomic status, IQ,).

Conclusion: There is much to learn about predictors of psychotic experiences because of the interactions and the general pathways that are still unclear. Results have clinical implications for both professionals and families in and ensuring positive mental health outcomes for children during the crucial stages of their development.

Introduction

Psychosis is an important public health concern because of its lifetime prevalence in the general population (McGrath et al., 2015). Furthermore, psychotic experiences increase the risk of experiencing other mental health conditions. With psychotic experiences peaking in children in their adolescence (Kelleher et al., In Press), it is even more crucial to pay attention how this could potentially affect one's development and maturity.

Thus, the paper aims to understand to what extent certain factors might independently contribute to psychotic experiences in 9-10-year-old children. However, ADHD, executive functioning, and stimulant medication as predictors are also interrelated, a review of related literature of each variable aims to clarify their nature and the potential mechanisms that predict psychosis. In addition to interrelated factors making it difficult to tease apart which of these most predict psychotic experiences, a discussion of risk factors will also be conducted.

While the associations between psychotic like experiences and these risk factors have been studied independently, this paper likewise aims to expand on the knowledge base on their underlying mechanisms in a single study. Lastly, it will discuss how the ABCD dataset as an NIH initiative paved the way for an opportunity to conduct a large-scale study on psychotic experiences in children, which contributes to its goal of producing more research in the area of adolescent brain development.

Attention deficit–hyperactivity disorder

Attention deficit–hyperactivity disorder (ADHD) is characterized by behavioural symptoms of hyperactivity, impulsivity, and inattention, or by a combination of these, which may impair daily functioning (Feldman & Reiff, 2014). The Diagnostic and Statistical Manual of

Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) has divided this disorder into three subtypes namely: the predominantly inattentive (i.e., having six or more inattentive ADHD symptoms), predominantly hyperactive-impulsive (i.e., having six or more hyperactive-impulsive symptoms), and a combined type (i.e., having six or more of both inattentive and hyperactive symptoms (APA, 2013). To confirm a diagnosis of ADHD, these symptoms should be present before the age of 16.

ADHD can be diagnosed in individuals as young as the age of four (Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, 2011). Apart from the increasing prevalence of ADHD, children are getting diagnosed younger and younger . In the U.S., a recent prevalence study has reported that an estimated 6.1 million children between the ages 2–17 years (9.4%) had already received a diagnosis of ADHD (Danielson et al., 2018).

The role of executive function in theories of ADHD

It can be challenging to assess ADHD in merely one environment, as symptoms may not be apparent all the time. However, ADHD may be more observable in places, which might require more mental effort, social interaction, or a capacity for self-control such as the academic environment. This may be due to the fact that ADHD has been known to cause cognitive difficulties and an altered emotional level (recognition, regulation, and expression of emotions) (Sobanski et al., 2010), which have resulted to dysfunction in executive control processes (APA, 2013) that is important in the academic setting.

Pennington & Ozonoff (1996) proposed that the core deficits of ADHD were linked to the abnormal development of executive functions in childhood. Executive function refers to the

many skills required to prepare for and carry out complex behaviors (Ozonoff et al., 2004). This is also known as the higher order cognitive processes thought to comprise executive functions include impulse control, response inhibition, attention, working memory, cognitive flexibility, planning, judgment, and decision-making (Baddeley, 1998; Robbins, 1996; Stuss & Alexander, 2000). Thus, executive dysfunction or deficits in this area make it difficult for an individual to plan for and fulfil goals.

Although ADHD has often been described as a disorder associated by extensive executive functioning impairments, not all children with ADHD exhibit such deficits (Nigg et al., 2005). In fact, the association between executive functioning and ADHD only reveal a medium effect size, when using neuropsychological tests (Willcutt et al., 2005). It has also been argued that perhaps there is more than one type of executive functioning profile may well exist within the broader ADHD diagnosis (Nigg et al., 2005). Roberts et al. (2017) found that executive function deficits can be used to differentiate and describe subtypes of ADHD with three identifiable groups (1) lower ability to shift attention flexibly, (2) poor inhibitory control, or (3) unremarkable executive functioning.

Beyond this argument, researchers who support the executive functioning theory of ADHD have also stressed that ADHD arises wholly as a result of a reduction in executive control, which is caused by abnormalities in the structure, function and biochemical operation of the fronto-parietal and fronto-striatal neural networks (Willcutt et al., 2005). Executive functioning is known to be associated with several distributed networks (Chung et al., 2014), which include the frontal lobe region and subcortical areas of the brain (Collette et al., 2006; Bonelli & Cummings, 2007; Jurado & Rosselli, 2007; Marvel & Desmond, 2010). This theory focuses

mostly on symptoms related to impulsivity and inattention, and has less emphasis on hyperactive behaviour.

Treatment of ADHD

Given the complexity of ADHD, it is important to consider both the developmental stage and an individual's needs within the environment in treatment (Young & Myanthi Amarasinghe, 2010). With the right treatment and along with the help of experts in the field, this disorder can be managed. In addition, planning and monitoring progress is particularly relevant to address different types of concerns. There have been recommendations and guidelines provided by NICE (2018) on the diagnosis and management of ADHD for the youth and adults, which are covered in the next few sections.

Non-pharmacological treatments

Non-pharmacological treatments have been widely used and recommended on the basis of a growing body of research suggesting its efficacy in treating ADHD. The inclusion of psychological, behavioural and educational advice and other psychosocial interventions as part of a comprehensive treatment plan has also been highly encouraged by (2018). Psychological or non-medical treatments employing behavioural and cognitive techniques have been shown to be effective in the treatment of ADHD in children in empirical studies (Drechsler et al., 2007; Hechtman et al., 2004; Hoath & Sanders, 2002; Miranda, Jarque, & Rosel, 2006; Miranda, Presentacion, & Soriano, 2002).

One example of an evidence-based approach is *behavioural treatment,* which includes behavioural parent training, behavioural classroom management, and behavioural peer interventions, all of which are strongly recommended for children and adolescents of all ages

with ADHD, but especially for preschool-aged children (Compas et al., 2002; Kavale et al., 1999; Wolraich et al., 2011). These are taught directly and utilise reinforcement strategies to strengthen positive behaviours. However, consistency is crucial for these to be applied across different settings for it to be effective.

In the academic setting, *school-based psychological interventions* for ADHD integrate behaviour modification and cognitive-behaviour modification techniques, applying them in the classroom setting to assist teachers and students to gain control of behaviour at school (Miranda et al., 2002). Interventions are done in a real world setting, which provides the opportunity for a child to learn expected behaviour and to relate better with others. Further a reward and response cost system that can be applied in either academic or recreational settings in order to improve peer relationships, self-efficacy and academic performance (Pelham, Fabiano, et al., 2004; Pelham et al., 1998). Programs or teacher trainings are taken by educators who benefit from learning behaviour modification strategies. Parents and other people involved in the child's care are also encouraged to work closely with the school staff to properly monitor and support interventions.

Social skills training (SST), developed in the early 1970s, has also been known to address impulsivity in ADHD since its primary aim is improving patients social skills and teaching them to behave in a more socially acceptable manner (Young & Myanthi Amarasinghe, 2010). Research has shown that this form of group therapy are efficacious when implemented alongside parent management strategies school interventions, as well as reinforcement strategies (Kavale et al., 1997; Pfiffner & McBurnett, 1997).

Because parents are inevitably involved in the care and monitoring of patients, *parent-training* interventions are also done so that parents can be taught strategies to manage a child's behaviour (Hoath & Sanders, 2002). Similarly, it can also reinforce positive behaviour outside therapy sessions. Done at home or as an outpatient service, parents are taught strategies by trainers and guided by manuals so that they can manage parent-child interactions with the goal of empowering the caregiver. Routine and structure are also provided to the child, whilst providing him or her with prompts and feedback. Parent training programs have been found to be beneficial in the treatment of ADHD as this also helps the family unit because parents become more competent in addressing behavioural concerns (Young & Myanthi Amarasinghe, 2010).

Similar to this type of intervention is *coaching* (e.g., Brief Solution Focused Therapy) as it involves another person or a "mentor" who is able to provide structure, support and feedback to an individual (Young & Myanthi Amarasinghe, 2010). It involves having face-to-face contact, as well as check-ins via emails or telephone. Typically flexible in its approach, there is no particular method in terms of delivering this. Its main aim is to draw on unique personal strengths of a person. Coaching has been reported to be helpful for individuals who attend ADHD group programmes (Stevenson et al., 2002).

There are other interventions that aim to target specific difficulties as a result of ADHD to facilitate independent skill building in the process. One example is *working memory training* using a computerized task that increases in difficulty (Klingberg et al., 2005) to enhance attention, recall and retention of information. Another skill that facilitates independence over

time is *self-monitoring* as it involves regular completion of a checklist of the behaviours one has, or has not, engaged in over time. Similar to this is the concept of organisation skills training, which involves using daily planner and to-do lists, and breaking tasks into parts. An example of the application of this method is via a designed a digital game for children called Plan-it Commander (Bul et al., 2018). Along with psychostimulant treatment, a 65-minute session is done thrice a week for a duration of 10 weeks. Parent and teacher reports indicate that time management skills and working memory skills improved with this.

For most children, a combined approach may be the best way to address symptoms of ADHD. *Multimodal psychosocial* treatments integrate a number of individual psychological interventions such as those previously mentioned to target symptoms across multiple functional domains (Hechtman et al., 2004). This approach, which often includes elements of social skills training, has been found to be best suited for middle school/adolescent children (Young & Myanthi Amarasinghe, 2010).

There are likewise other treatments, which fall under the category of training interventions. One of which is *CBT*, a known evidence based approach for many of the comorbid problems associated with ADHD. CBT for ADHD, which relies on the principle that thoughts influence behaviour and emotions, is an adjunct form of treatment that is structured and goal-oriented (Safren, 2006). Treatments run from 8-12 sessions in either an individual or group format. The main objective of this form of therapy is managing symptoms and improving concerns caused by co-morbid issues such as anxiety and depression. However, CBT as a

treatment lacks strong evidence and evaluation in the treatment of ADHD and is still not currently recommended as an intervention (Young & Myanthi Amarasinghe, 2010).

A number of mind-body trainings, adding a more holistic approach to treatment, have come forth to address attention-related difficulties. These are typically composed of body and breath exercises, with a focus on movement and physical sensations. *Meditation*, which is more spiritual in its approach, has been recommended to help one focus on the present moment. Research has shown that meditative-based types of therapy can help enhance attention and focus. Similarly *Mindfulness training*, which has roots in Buddhism, has been recommended and is widely practiced form of meditation. Although emerging as a potentially effective training for children and adolescents with ADHD, this may also still need further studies to assess its benefits (Meppelink et al., 2016). *Yoga* has also been identified to provide physical, as well as mental benefits. A recent systematic review analysis (Evans et al., 2018) reveals that studies on child yoga and parent-child yoga indicate improvement in ADHD symptoms.

Other novel approaches include *neurofeedback,* which has been described as promising (Beauregard & Levesque, 2006; Kaduson & Finnerty, 1995), the individual is trained to control particular brainwave patterns using electroencephalographic technology, increasing beta activity while decreasing theta activity (Sonuga-Barke, 2013). Brain activity is typically measured by participating in a game, which provides points when positive changes are detected. As a result, individuals eventually learn to monitor their own brainwave patterns because of the immediate feedback that is provided to them.

Alternative approaches have been used by more than 50% of patients in the U.S. (Chan et al., 2003). Examples of these complementary and alternative therapies are biofeedback

therapy, dietary therapy, herbal therapy, attention training, massage, homeopathy, and acupuncture (Kemper et al., 2008).

Pharmacological treatments

Pharmacological therapy has been known to go hand in hand with other types of therapy or as a standalone approach in treating ADHD symptoms. Medications used to treat ADHD may be classified as stimulants and nonstimulants.

Nonstimulants (Cortese, 2020) are an option when an individual has a previous medical history of substance abuse or heart condition. These are also considered when a patient does not respond to treatment or when side effects are intolerable. Nonstimulants, such as atomoxetine, clonidine and guanfacine, though considered a newer class of drugs, have evidence as treatment and are widely utilised.

Stimulant medications, on the other hand, are usually the first choice due to its success rate in targeting ADHD (Cortese, 2020). There are several types approved under the Food and Drug Administration (FDA) such as amphetamines and methylphenidate (Cortese, 2020), which have generally been recommended as first-line pharmacologic treatment (Feldman & Reiff, 2014). In the UK, there are a range of stimulant medications that have been licenced to treat ADHD. Lisdexamfetamine mesilateor methyphenidate hydrochloride are recommended as first-line treatment for adults, while the latter is recommended for children (NICE, 2018). An amphetamine-based medication, lisdexamfetamine (Elvanse), is suggested as a second option if symptoms have not improved after six weeks. The approved brands of medications are known as Ritalin, Medkinet and Tranquilyn, Concerta XL, Medikinet XL, Equasym XL, Matoride XL,

Xaggitin XL, Xenidate XL or Delmosart. However, guanfacine and atomoxetine are not approved to treat ADHD in children younger than six.

Although these medications are not considered to permanently cure the disorder, these may help manage symptoms better. In fact, stimulants have been found to lessen ADHD symptoms in 70%-80% of those who have been prescribed with this (Kolar et al., 2008). There are a number of formulations available to treat ADHD symptoms, which can be taken as a pill or liquid. They can be categorised as short-acting, long-acting, or intermediate acting. Short acting medications are taken at least twice a day, which allows an individual more control over it. On the other hand, long acting medications are taken once in a day and stays in an individual's system much longer.

Stimulant medications act by blocking the reuptake of the dopamine and norepinephrine so that these remain in the synapse for a longer time (Stahl, 2008). Methyphenidate, dextroamphetamine and mixed amphetamine salts have been considered the safest and most studied types of stimulant medication. These generally work to enhance arousal in the prefrontal cortex, enhancing executive control. Consequently, it addresses problems related to inhibitory control and working memory reported of children diagnosed with ADHD (Barkley, 1997).

Mixed amphetamine salts or Aderrall promote the release of dopamine and norepinephrine, as well as serotonin, in the presynaptic neuron (Stahl, 2008). With more of these in the synapse there is more stimulation of receptors. Unlike methylphenidate though which does not promote dopamine release from synaptic vesicles, its counterpart Amphetamine is known to induce the release of dopamine that is four times the amount

produced by methylphenidate (Schiffer et al., 2006). Specifically in some regions of the brain, amphetamine has been found to increase dopamine levels in the synaptic cleft.

The dilemma with dopamine

Although the specific cause of ADHD has not been identified, the neurotransmitter dopamine has been identified as playing an important role and may indicate an additional link to executive dysfunction. Dopamine, a catecholamine neurotransmitter, which has been implicated in psychiatric disorders and is involved in many processes, is known to affect a person's mood, attention, motivation, and movement (Miller et al., 2013). This is synthesised in the substantia nigra and ventral tegmental area of the midbrain, and is released to the nucleus ambens and striatum, respectively Stahl (2008).

Based on the early dopamine theory of ADHD, low dopamine levels due to deficits in dopamine functioning that puts the brain hypo-dopaminergic state (Levy, 1991). In fact, research has also suggested links between low levels of dopamine and symptoms of ADHD (Swanson et al., 2007). Individuals with ADHD or those who have less dopamine levels may need to self-stimulate or find ways to cope with the environmental demands by seeking out more stimulation in low interest situations. Consequently, this kind of behaviour might be perceived as distractibility, impulsivity, risk-taking and inattentiveness, all of which are also indicative of deficits in higher order cognitive processes that make it arduous in accomplishing various undertakings that would necessitate mental effort (Baddeley, 1998; Robbins, 1996; Stuss & Alexander, 2000). In other words, the theory summarises that patients with ADHD are identified to have a dysfunctional dopamine release.

The dopamine hypothesis (Levy, 1991) may also explain why medications actually work and prove to be beneficial in managing symptoms. The hypothesis is based on the idea that stimulant medication plays the role of a dopamine agonist, which can lead to the build up of this neurotransmitter in the synapse that is said to be abnormally low in those with ADHD.

Yet, a more complex dopamine theory has also been put forth later on, as it was found that low dopamine levels simply did not account for the behavioural symptoms seen in ADHD and deficits in executive functioning. In fact, this amount in other areas on the brain varied, with some parts being characterised as hyper-dopaminergic (Castellanos, 1997) or having increased levels of dopamine. Castellanos (1997) argued that decreased dopamine functioning in the mesocortical pathway, which is related to the physiology of cognitive and executive functioning, affects attention, (i.e., selective attention). On the contrary, the same study suggests that increased dopamine functioning in the nigrostriatal pathway, related to the physiology of motor control, causes impulsivity and hyperactivity.

Other evidence suggests it is actually the concentration of dopamine transporters or re-uptake inhibitors responsible for removing these neurotransmitters that modulates symptoms of ADHD. However, findings around this notion appear to contradict each other. Dougherty (1999) found high concentrations of these were found adults with ADHD when compared to a control group. On the other hand, Volkow et al. (2007) found that there were in fact lower levels of dopamine transporters in the left caudate and nucleus ambens in participants with ADHD.

More recently these hypotheses have been further challenged, which also questions the primary role of dopamine as well as its mechanism. For example, researchers have

proposed that ADHD may be explained instead as a delay in brain development. Shaw et al. (2007) found that children with ADHD had a three-year delay in attaining peak thickness in the cerebrum and regions controlling attention affected. Taking into account this particular finding proves that the focus on dopamine solely obscures the forest for the trees. Although dopaminergic activity is consistent, the explanation may be multifactorial, which includes other factors such as genetic causes and brain circuitry. More importantly, this demonstrates that a more conclusive research is necessary to inform professionals about dopamine medication for psychiatric disorders.

The benefits and costs of stimulant medication

On average, the use of stimulant medication has been associated with good outcomes in a number of domains. A number of studies have been documented the beneficial effects among children and adolescents with ADHD prescribed with methylphenidate (Chan et al., 2016; Storebø, 2015). Therapeutic benefits have been found among those with impaired intellectual functioning. A meta-analysis conducted by Sun et al. (2019) suggests that children with borderline intellectual functioning or intellectual disability receiving methylphenidate experienced better improvements than those receiving placebo in overall ADHD severity. Moreover, most studies reported that methylphenidate was well tolerated without reports of severe adverse events, although this was largely dependent on the dose received by patients (Bodey, 2011; Correll, 2011). Most common side effects are known to be mild and have a short duration and despite these young people, who are the primary consumers, have even reported to have positive experiences taking stimulant medication. A qualitative study specifically found that a sample of young people felt medications were important for them and that it somewhat

helped with self-management with regards to their symptoms. They also generally did not feel anxious about taking medication and felt more positive about it compared to other interventions (Singh et al., 2010).

Stimulants as a cognitive enhancer

Stimulant medications have been also known to boost cognitive performance, with dopamine as a mediator. What underlies this mechanism of performance is that dopamine appears to be the primary neurotransmitter released in areas of the brain that are known as reward sites, which are the limbic system, the nucleus accumbens, and the globus pallidus (Koob & Bloom, 1988; Wise & Bozarth, 1984). What this neurotransmitter does in these parts of the brain is that it is involved in signalling and anticipating potential rewards (Stahl, 2008) dopamine agonism therefore increases functional in this system. This is because more reward stimulation for the individual with ADHD is needed to achieve the same amount of reward as a neurotypical brain (Levy, 1991). More recently, Westbrook et al. (2020) also found stimulants alter cognitive function by increasing dopamine in the striatum, which is associated with motivation, cognition and action. Specifically, dopamine is involved in striatal encoding of benefits, rather than the costs. In their experiment, it was shown that dopamine acts as a "motivation regulator" as those with lower levels were more sensitive to the potential costs of completing a difficult task, while those with higher levels focused more on what could be in store for them (Westbrook et al., 2020).

There have been findings that have shown how dopamine increases performance on cognitive tasks. A meta-analysis by Pietrzak et al. (2006) found that larger doses of methylphenidate provides better performance than the lower doses on various of

neuropsychological tasks measuring executive functioning skills of attention, vigilance, memory, and working memory. Similarly, amphetamine has been found to enhance one's performance when completing difficult tasks (Malenka, Nestler &Hyman, 2009). This finding was based on improvements on the performance of working memory tasks which were given therapeutic doses, which appear to improve all individuals' cortical network efficiency.

Taking these findings into account, it can be said that the elements of reward and motivation as a result of this chemical messenger may be key factors that maintain engagement on a task that may typically seem challenging or uninteresting. An individual who is thus stimulated in this manner may then enhance their overall cognitive performance (Westbrook et al., 2020) thereby increasing their attention and alertness, which likewise aids memory and enhance learning.

Psychotic symptoms as a side effect of stimulants

Medications, typically methylphenidate, are often prescribed and taken over long periods of time to patients with this developmental disorder as symptoms may persist until adulthood. In Taiwan, over a third of patients with ADHD have been taking stimulants (i.e., methyphenidate) for two years since being prescribed (Wang et al., 2016). In the US, a follow up study by Molina et al. (2009) found that prescribed medication, including methylphenidate was still being taken 8 years since the beginning of treatment by 32.5% of the sample. However, any medication taken for longer periods of time must be monitored and may put an individual at risk of side effects. Thus, it is important to likewise consider that there is a possibility that adverse effects might occur, leading to a deterioration of mental health.

A number of studies have generated evidence of symptoms related to psychotic-like symptoms in patients, indicating that stimulant medication may be a potential risk factor. What may explain the underlying reason for this may be the overproduction of dopamine due to amphetamine use. In addition, neurotoxicity of amphetamines can also occur when this substance interacts with the vesicular monoamine transporter 2 (VMAT2), contributing to higher levels of dopamine in the cytosol (Schiffer, et al., 2006). Thus, the increased surge in the amount of dopamine may be what contributes to adverse effect of stimulant-induced psychosis.

According to Snyder (1974), excess amounts of dopamine in specific receptor sites of the central nervous system produce stereotypic behaviour that is similar to the core schizophrenic behaviours. Higher doses of amphetamine can also interfere with one's executive functioning skills, particularly working memory and cognitive control (Malenka, Nestler &Hyman, 2009), which likewise can overlap with symptoms and difficulties occurring within the spectrum of psychosis. Similar behaviours that may be seen in patients with schizophrenia that have been observed in episodes of psychosis induced by amphetamine include difficulties concentrating, thought disorganisation, lack of insight, increase in motor activity, anxiety, and auditory hallucinations (Bell, 1973). Besides impairing one's cognitive functioning, high levels of amphetamine can also contribute to muscle breakdown (Schiffer, et al., 2006).

Shyu et al. (2015), who conducted large cohort study that specifically studied psychotic disorders as a potential adverse outcome of methylphenidate treatment, found an elevated risk associated with methylphenidate. Similar findings were also found in past studies, which concluded that psychosis may have resulted from methylphenidate treatment (Gross-Tsur et

al., 2004; Lee, 2016; Rashid & Mitelman, 2007; Young, 1981). Psychotic-like symptoms likewise were seen in both children and adults. A study by Morton & Stockton (2000) found that **t**he abuse of methylphenidate is also known to cause psychotic-like symptoms in adults. Research has shown that even therapeutic doses of stimulants can cause manic-like or psychotic-like symptoms in a small proportion of treated children (Ross, 2006).

Currently, studies demonstrate inconclusive and mixed findings regarding stimulant medications and its pros and cons. Krinzinger et al. (2019) has argued that more research is needed to look into stimulants as a risk factor for psychotic symptoms, as well the relationship between ADHD and psychotic symptoms. They also add that more research needs to be done among young people and the individual risk factors for methylphenidate-related psychosis.

Psychotic experiences in children and adolescents

It is now known that the lifetime prevalence of psychotic experiences, which are subtle subclinical symptoms, in the general population is 5.8% based on a large multinational study (McGrath et al., 2015). It is further reported that there are about 1-5 occurrences in 64% of individuals, with those having 2 or more psychotic symptoms experiencing more episodes later on. Besides how striking the persistence is, it is particularly relevant to note the occurrence in the younger population. According to Kelleher et al. (In Press), psychosis peaks during early adolescence. In addition, strong associations were also found between psychotic symptoms and psychopathology in middle adolescence. In children aged 9-11 years old, Laurens et al. (2012) found that about two thirds reported experiencing at least a psychotic-like experience, specifically auditory and visual hallucinations, as well as delusion-like ideas, suggesting a peak of this phenomenon at this age.

It has been shown though that psychotic symptoms tend to be transitory in nature in about 80% of individuals (Linscott & van Os, 2013) and only a small proportion (7.4%) develops into psychotic illnesses. It may even be said that psychotic-like experiences can be considered part of normative development in children because of the fact that it is possible for it to resolve without causing detrimental health issues. However, it is important to emphasise that psychotic-like experiences can still increase the chances of one developing a psychotic disorder later on for those who continue to be affected by it. According to the psychosis-proneness-persistence-model (Cougnard et al., 2007), psychotic experiences can even persist for vulnerable developing individuals exposed to environmental adversities. Moreover, psychotic experiences are considered part of the spectrum that includes ultra high-risk states, schizotypal symptoms, and psychotic disorders (Pedrero & Debbané, 2017), are associated with a multitude of mental health problems. For instance, evidence in an 8-year study was found showing clinical psychotic states have progressed from the more persistent subclinical psychotic experiences that started out between the ages of 14-17 years (Dominguez et al., 2011). Similar to this, it was found that the associations between psychotic symptoms and psychopathology is stronger in middle adolescence, despite the former occurring in early adolescence (Kelleher et al., In Press). Overtime, it appears that psychotic experiences can change its course by becoming more atypical in presentation and much more indicative of other issues. In another study, childhood psychotic symptoms starting at age 11 have been identified as a risk factor, which is not only associated with predictive of rates of research diagnoses of schizophrenia, but also post-traumatic stress disorder (PTSD) and suicide attempts by age 38 (Fisher et al., 2013). In fact, meta-analysis shows that psychotic experiences were even associated with a three-fold

increased risk of any mental disorder, beyond psychotic illnesses (Healy, 2019). These findings suggest that psychotic experiences, when they go unresolved, increase the risk in an individual. Thus, these major points and latest findings stress that psychotic-like experiences in children and adolescents need to be given more attention by providing early intervention as this could potentially prevent poor mental health outcomes later on in life.

ADHD as a risk factor of psychotic-like experiences

There may be various factors that contribute to the problem of understanding what really predicts psychotic-like symptoms, which make it hard to tease apart. ADHD is just one of the known risk factors that have been associated with psychotic experiences. For instance, Shyu et al. (2015) found that ADHD itself was a significant risk factor for psychosis in a sample of 74,009 children. The same associations appear to likewise occur later on in life. More specifically a childhood diagnosis of ADHD is associated with an increased risk of a subsequent psychotic disorder (***Dalsgaard, et al., 2013***; Nourredine, et al., 2021). Yet outside controlled environments, it can also be difficult to differentiate ADHD and psychotic symptoms shared also by other developmental disorders or cognitive deficits.

Executive functioning as a risk factor of psychotic-like experiences

The co-morbidity in mental health problems further complicates the issue at hand. One such example of this is executive functioning difficulties (i.e. inattention), which is known to often co-occur with ADHD, can appear to have similar features. If executive functioning difficulties were involved, it would make it hard to tease apart which of these factors independently predict psychosis.

Executive functioning, broadly described as cognitive processes involving control,

flexibility, inhibition, regulation, planning, and execution of goal-oriented behaviour (Zayat et al., 2011) have been associated with psychotic symptoms among individuals. Impaired executive functions have also served as a risk marker for subsequent onset in the at-risk mental state for psychosis (Riecher-Rössler et al., 2009). Significant neurocognitive dysfunction also tends to occur later on with early onset psychosis, which was revealed in a study involving typically developing adolescence from 10 to 17 year olds (Bohus et al., 2014). Both adolescent-onset and childhood-onset patients showed neurocognitive deficits, with the most severe deficits in executive functioning (Wozniak et al., 2008). It was found that neurocognitive performance correlated more with negative psychotic symptoms than positive ones. Moreover, adolescent patients in this study have also been shown to be impaired in the area of working memory and attention. Ueland et al. (2004) found impairment in pre-attentional processing, visual long-term memory, auditory short-term memory and working memory in adolescents. It is important to note that the abovementioned studies appear to focus on inattention, a skill deficit in executive functioning, as a central feature of those with psychotic presentations.

To add to further evidence regarding these associations, a systematic review indicated that providing training in cognitive function as an intervention increases cognitive improvement in patients diagnosed with a psychotic disorder (Rodríguez-Blanco, et al., 2017). Researchers also reported significant findings in studies that assessed structural brain changes and activated brain regions associated with executive functioning after giving cognitive interventions. This suggests that there are strong inextricable links in the relationship between executive functioning and psychotic-like symptoms.

There have been a number of studies suggesting strong associations between executive functioning and psychotic-like experiences. However, there is still a lack of understanding about what might explain the improvements in cognitive performance and executive functioning skills when stimulants are taken (Levy, 1991; Pietrzak et al., 2006; Westbrook et al., 2020) with the latter supposedly predicting psychotic-like symptoms (Gross-Tsur et al., 2004; Lee, 2016; Rashid & Mitelman, 2007; Young, 1981). Although research has indicated that executive functioning deficits and stimulant medication have both been claimed to predict psychotic-like symptoms, it is possible that their effects cancel out each other. The reason perhaps that some may continue to experience or develop psychotic-like experiences suggests that the underlying mechanism may not be a linear pathway. Thus, further clarifying whether executive functioning predicts psychotic-like experiences over and above the effects of stimulant medication could provide a step towards closing the knowledge gap on this issue. In a similar light, it may be important to consider other factors that contribute to the effect of psychotic-like experiences.

Other risk factors that increase vulnerability to psychotic-like experiences

It is also important to consider external risk factors that might be at play among ADHD, stimulant medication and executive functioning as potential predictors of psychotic-like experiences. A vulnerable individual may likewise be affected by other factors that may impact or even exacerbate cognitive functioning (i.e., psychotic-like symptoms, executive functioning) and impair typical development in young children. While a nurturing environment positively influences human development, a less than conducive environment can also negatively affect development in young children.

When it comes to executive functioning, social risk factors are strongly associated with impairments in preterm children (O'Meagher et al., 2017). In addition, there are also associations between low family socioeconomic status and poor performance on tasks of executive functioning in early childhood (Hackman et al., 2015). A study also found that children of mothers who smoked indicate that maternal nicotine use during pregnancy has a negative impact on various aspects of the child's executive functions (Daseking et al., 2015). The same study further emphasised that these children were likewise at higher risk of ADHD compared to children of non-smokers.

Besides the impact of parental physical health on children, having a parental mental health problem is another genetic risk. A recent longitudinal study that investigated 1,384 children and adolescents aged 11 to 17 years not only found that stronger parental mental health problems were associated with more ADHD symptoms in children and adolescents, but that an increase in parental mental health problems was associated with increasing ADHD symptoms over time (Wüstner et al., 2019). Examples of parental mental health problems that also increase the risk of ADHD risk may include alcohol/drug abuse (Roizen et al*.,* 1996; Wilens et al*.,* 2005). Consequently, substance use, which is linked to adversity, further compounds the problem of ADHD (Famularo et al., 1992). Although a substantial fraction of the aetiology of ADHD is due to genes, the studies reviewed in this article show that many environmental risk factors and potential gene–environment interactions also increase the risk for the disorder (Banerjee et al., 2007).

The effect of nature, particularly, environmental risk factors can contribute to mental health deterioration prior to onset of the illness. ADHD environmental risk factors that have

been proposed include prenatal substance exposures, heavy metal and chemical exposures, nutritional factors, and lifestyle/psychosocial factors. Psychosocial adversity (e.g., maternal stress during pregnancy, early traumatic experiences, and early institutional care) may increase ADHD risk (Froehlich et al., 2011). On the other hand, some of the environmental risk factors for schizophrenia are also similar (i.e. early hazards causing foetal growth retardation or hypoxia, and hazards nearer the onset of illness like drug abuse and migration) have been well documented (Dean & Murray, 2005). It is also interesting to note that with regards to psychosis, individuals experiencing psychosis-like experiences share demographic, etiological, and psychopathological risk factors with those experiencing psychotic disorders (Linscott & Van Os, 2013).

Individual risk factors may also have a part to play for mental health disorders. For example, a study suggests that the possibility that disruptions in sleep following or occurring alongside a traumatic experience may somehow contribute to, or exacerbate the presence of psychosis-like experiences or PLEs (Andorko et al., 2018). Since these factors contribute to impairments in functioning, consequently atypical developmental pathways inevitably occur. Thus, understanding and preventing these issues at an early age may prevent further deterioration of one's mental health. It is likewise crucial to take into account individuals' unique differences and external factors that may contribute or even exacerbate (Cougnard et al., 2007) psychotic-like experiences in the context of the individual's developmental stage.

Relevance of the study

Although various research papers show associations between psychosis and its known factors such as ADHD, stimulant medication, and executive functioning, no single study has

examined the occurrence of their interactions to better understand the extent to which they predict psychotic experiences. There is also a lack of understanding about what might explain the improvements in cognitive performance and executive functioning skills when stimulants are taken (Levy, 1991; Pietrzak et al., 2006; Westbrook et al., 2020) with the latter also predicting psychotic-like symptoms (Gross-Tsur et al., 2004; Lee, 2016; Rashid & Mitelman, 2007; Young, 1981).

To the best of our knowledge, the same associations have likewise not been investigated along with other possible confounding variables (age, gender, ethnicity, socioeconomic status, IQ). Additionally, the recruitment of children at this particular age can be difficult as sufficient numbers are necessary to be able to achieve an adequate statistical power. Large sample sizes can provide the opportunity to detect risk factors as well as mechanisms of diseases by detecting subtle effects that cannot be generally identified. Yet most studies in this area remain to be relatively low in numbers. There is certainly still much to learn about what really predicts psychosis with all these considerations held in mind as the general pathways when these interactions occur still appear unclear.

This project aims to shed light to the extent to which ADHD diagnosis, executive dysfunction and medication in 9-10 year old children. Because research analysing large sample sizes have been scant, the ABCD cohort study was used, making this the first large-scale study on ADHD, stimulant medication, and executive functioning as predictors of psychotic experiences. Approved by the institutional review board of the University of California, San Diego (IRB# 160091), the ABCD study is an ongoing NIH initiative that focuses on investigating adolescence, which is a critical period of development and profound changes.

Part of its objective is to track neuroimaging data on a periodical basis to be able to assess the impact of substance abuse, as well as other factors in the environment. While it initially aimed to investigate risk and resiliency factors and its associations with substance abuse, it now encompasses broader goals of providing information about child health and development. Data are likewise gathered on various social, psychological, cognitive, environmental and academic factors that may affect brain maturation at an early stage. Apart from substance abuse, other areas, which are to be investigated, are also on topics related to sleep, attention, and physical activity.

One of the most important future contributions of this study will be to provide results based on a longitudinal design, as it will be following individuals ages 9-10 years old, up until young adulthood. The investigators of this project aimed to develop a baseline sample reflecting a diverse population of children residing in the US from 21 study sites in terms of gender, ethnicity, socioeconomic status, and urbanicity. Part of the plan is to provide access to data via the NIH data archive, which will be updated on a yearly basis.

The ACBD is thus far the largest national longitudinal study that has been conducted on adolescent brain health. This will be able to provide promising and reliable results in understanding the development underlying many health issues in the field of psychology, biology and psychiatry. Consequently, it will also be able to answer questions around what mitigates risk and what serves as protective factors with regards to the onset of different pathologies. Researchers have taken on a “population neuroscience approach,” aimed to gather a representative sample of the US population (Garavan et al., 2018). This approach provides the opportunity to understand how various experiences and individual factors

uniquely possessed by participants influence brain functioning and child development at baseline.

With the help of the ABCD study's preliminary data, this project will thus increase our understanding of predictors of psychotic-like symptoms in children with ADHD and to what extent the combinations of these different factors increase the risk of psychotic-like symptoms.

Consequently, this study aims to investigate the following research questions:

- Research Question 1: Does ADHD diagnosis predict the total number of psychotic experiences?
- Research Question 2: Do stimulant medications predict the total number of psychotic experiences?
- Research Question 3: Does executive functioning predict the total number of psychotic experiences?
- Research Question 4: Does executive functioning predict the total number of psychotic experiences, over and above stimulant medication?
- Research Question 5: Do stimulant medication and executive functioning predict the total number of psychotic experiences after controlling for IQ, age, gender, ethnicity, and SES?

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Part 2: Empirical Paper

Testing ADHD, executive functioning, and stimulant medication as predictors of psychotic experiences in children

Abstract

Aims: The study aimed to examine to what extent a diagnosis of ADHD, stimulant medication, and executive dysfunction each independently predict psychotic experiences in children. A further aim was to understand whether the presence of potential confounders made an impact on these relationships.

Method: Using the NIMH ABCD dataset of 9-10-yer-old children (N=11,878), regression analyses was conducted to test the association between key hypothesized predictors and the presence of psychotic symptoms. In addition, adjusted regression analyses were conducted on relationships with statistically significant associations. Finally, IQ, age, gender, ethnicity, and SES were entered as control variables to assess how reliable the predicted associations are when controlling for potential confounders.

Results: ADHD was not associated with psychotic experiences. On the other hand, both stimulant medication and executive dysfunction showed a significant relationship with psychotic experiences, even after controlling for confounders. Stimulant medication did not moderate the relationship between executive dysfunction and psychotic experiences.

Conclusion: Stimulant medication and executive dysfunction were found to be significant predictors of psychotic experiences among children. Results shed light on potential interaction between risk factors and treatment for ADHD and psychotic experiences in children.

Introduction

Executive dysfunction has been associated with psychotic experiences. One of the syndromes most associated with executive dysfunction difficulties in childhood is ADHD. However, stimulant ADHD medications are known to increase psychotic-like symptoms in some circumstances. These interrelated factors make it difficult to tease apart to what extent each predicts psychotic experiences. In addition, potential confounders such as IQ, age, gender, ethnicity, and socioeconomic status could likewise affect the relationship among these associations.

The adolescent stage, a period of great emotional and physical change, is a crucial stage to examine. Using NIH's ABCD cohort data, investigating adolescent development in the context of unique differences may provide information about brain maturation and functioning during this period. Relevant information derived from a large sample of children likewise provides the opportunity to understand risk factors that may contribute to atypical development.

This thesis aims to examine the extent to which executive dysfunction, ADHD, and stimulant medication each independently predict psychotic symptoms in 9-10 year olds. By conducting a cross sectional data analysis, the study hopes to provide key findings on psychotic like experiences in children and preliminary data that influence future intervention strategies as it is said to peak at this stage (Kelleher et al., In Press).

For this research, the variables identified for analysis will be discussed in the next section to give the reader an overview. After this, the goals of the NIH's ABCD study will be indicated and consequently, how it is likewise relevant to the focus of understanding psychotic-like symptoms in children. The method of analysis will also be discussed. This will be followed

by the study's results and a discussion of findings, along with its clinical and research implications.

Attention deficit–hyperactivity disorder

Attention deficit–hyperactivity disorder, more commonly known as ADHD, has been described as behavioural symptoms of hyperactivity, impulsivity,and inattention (Feldman & Reiff, 2014). In fact these symptoms can present as a combination of hyperactivity, impulsivity, and inattention, which can impair one's daily function. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; 2013) states that a diagnosis may only be confirmed when symptoms are present before one turns 16. An individual may either be diagnosed as the predominantly inattentive (i.e., defined as six or more inattentive ADHD symptoms), predominantly hyperactive-impulsive (i.e., defined as six or more hyperactive-impulsive symptoms), or a combined type (i.e., defined as six or more of both inattentive and hyperactive symptoms (APA, 2013). In fact, ADHD can be diagnosed in individuals as young as age four .

Apart from the increasing prevalence of ADHD, children are getting diagnosed younger and younger. According to the Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management (2011), a child may even be diagnosed as early as four years of age. According to the most recent prevalence study in the US, there is an estimated 6.1 million U.S. children between the ages 2–17 years (9.4%) who have already received an ADHD diagnosis (Danielson et al., 2018).

With regards to assessing ADHD, it can be challenging as a diagnosis necessitates observed behaviour. However, not all symptoms present in one particular setting. Thus it is just as important to identify various settings where the child may need to exert more mental effort,

social interaction, or a capacity for self-control. Besides the home environment, symptoms also evidently manifest within an academic environment. School is where cognitive demands are much higher for one with ADHD because of the tasks, which are required to be accomplished. However, the core deficits of ADHD can cause cognitive difficulties and an altered emotional level (recognition, regulation, and expression of emotions; Sobanski et al., 2010). Inevitably, this likewise results in a dysfunction in executive control processes (APA, 2013) that is important for learning and task accomplishment in this type of environment.

Executive Functioning

It has been proposed that the core deficits of childhood ADHD are linked to the poor development of executive functions (Pennington & Ozonoff, 1996), which describes the skills that are needed to prepare and fulfil tasks related to our day-to-day functioning (Ozonoff et al., 2004). Also known as higher order cognitive thinking, these skills make up the capacity to demonstrate impulse control, response inhibition, attention, working memory, cognitive flexibility, planning, judgment, and decision-making (Baddeley, 1998; Robbins, 1996; Stuss & Alexander, 2000). Thus, if one has poor executive functioning or deficits creating goals and executing these it can be very difficult and frustrating to an individual, needing one to find compensatory ways to be able to fulfil his or her desired activity.

However, there is an ongoing debate that suggests that not all children with ADHD exhibit such deficits (Nigg et al., 2005) despite this disorder being used interchangeably and completely associating it with executive dysfunction. In addition, there also exists the idea that there is more than one type of executive functioning profile, which may exist within the spectrum of ADHD as a diagnosis (Nigg et al., 2005). More specifically, executive function

deficits can be used to differentiate and describe subtypes of ADHD with three identifiable groups: (1) lower ability to shift attention flexibly, (2) poor inhibitory control, or (3) unremarkable executive functioning (Roberts et al., 2017). In fact, it is also argued that it is ADHD that arises as a result of a reduction in executive control, which is caused by abnormalities in the structure, function and biochemical operation of the fronto-parietal and fronto-striatal neural networks (Willcutt et al., 2005). While there may be symptoms that overlap, it is still important to distinguish both terms. Doing so allows us better to identify the right type of intervention to address disorders and symptoms appropriately.

Stimulant Medication

With regards to the treatment for ADHD, providing pharmacological therapy alongside psychological therapies are indicated as the gold standard for symptoms of ADHD (NICE, 2018). Medications used to treat ADHD may be classified as stimulants and nonstimulants. Nonstimulants (Cortese, 2020) are an option when an individual has a previous medical history of substance abuse or heart condition. Stimulant medications, on the other hand, are usually the first choice due to its success rate in targeting ADHD. For instance, lisdexamfetamine-mesilate and methyphenidate hydrochloride are recommended as first-line treatments for adults, while the latter is recommended for children in the UK (NICE, 2018). An amphetamine-based medication is a second option when symptoms do not improve after six weeks. On the other hand, guanfacine and atomoxetine are not approved as treatment for ADHD in children younger than six.

Typically, the use of stimulant medication has been associated with good outcomes in a number of domains (Malenka, Nestler &Hyman, 2009; Pietrzak et al. 2006). Stimulants act as

dopamine agonists, which helps in those with ADHD who are said to have abnormally low levels of dopamine. A number of studies have documented the beneficial effects among children and adolescents with ADHD prescribed with methylphenidate (Chan et al., 2016; Storebø, 2015). However, any medication taken for longer periods of time must be monitored and may put an individual at risk of side effects. For instance, considerations regarding adverse effects might occur, which can also contribute to poor mental health outcomes. Evidence of deteriorating well-being can manifest as psychotic-like symptoms in patients as a result of overdosing from stimulants (Schiffer, et al., 2006; Snyder, 1974).

However, there are inconsistent findings regarding stimulant medications as a risk factor for psychotic symptoms or whether one gains more benefits from taking these. Researchers still argue that more research is needed to look into this, as well the relationship between ADHD and psychotic symptoms (Krinzinger et al., 2019).

Psychotic experiences

The lifetime prevalence of psychotic experiences manifesting as subtle subclinical symptoms in the general population is 5.8% based on a large multinational study (McGrath et al., 2015). Further, it is reported that there are about 1-5 occurrences in 64% of individuals. In addition, the same individual with 2 or more psychotic symptoms experience more episodes later on.

Apart from its persistence, the experience of psychosis has been found to occur in the younger population, with psychosis peaking as early the adolescent stage. Two thirds of children between 9-11 years old reported experiencing at least one psychotic-like experience (i.e., auditory and visual hallucinations, delusion-like ideas) (Laurens et al., 2012).

It has been argued though that psychotic experiences have a small chance of occurrence in the population and a transitory nature in about 80% of individuals (Linscott & van Os, 2013) posing less of a danger. Thus, it is deemed that it is likely to be resolved without causing negative health issues. However, this can still be a very traumatic experience for a young child. In the same light, it could increase the chances of one developing a psychotic disorder later on according to the psychosis-proneness-persistence-model (Cougnard et al., 2007). The model indicates that psychotic experiences can even persist for vulnerable developing individuals exposed to environmental adversities such as trauma.

It is just as important to emphasise that psychotic experiences are considered part of the spectrum that includes ultra high-risk states, schizotypal symptoms, and psychotic disorders (Pedrero, & Debbané, 2017), which have been associated with a multitude of mental health problems (Dominguez et al., 2011; Kelleher et al., In Press). Evidence also suggests that psychotic experiences has been found increase the risk of other mental issues beyond psychotic disorders occuring over time (Healy, 2019; Fisher et al., 2013).

ADHD is just one of the known risk factors that have been associated with psychotic experiences. This has been found to be a significant risk factor for psychosis in both children (Shyu et al., 2015) and adults (***Dalsgaard, et al., 2013***; Nourredine, et al., 2021). Unfortunately,the overlap in symptoms between ADHD and psychosis symptoms make it hard to tease apart. What further complicates the issue at hand is that symptoms such as inattention can also shared also by other developmental disorders or cognitive deficits. The co-morbidity in mental health problems requires more efficient assessment as there is a possibility of inaccurate diagnosis because of shared symptoms. Executive functioning difficulties (i.e.,

inattention), which can even co-occur with ADHD, can likewise be observed to have similar manifestations. If executive functioning difficulties were involved in the equation, it would also make it hard to tease apart whether ADHD or executive functioning independently predicts psychotic symptoms. Thus, this study can hopefully contribute to the knowledge gap in this particular area, as there have not been studies that have examined these associations together.

The NIH's ABCD study

With provided access to a large cross-sectional sample of 9-10 year olds, exploring the association between ADHD, executive function and stimulant medication as predictors of psychotic like experiences may be investigated by conducting a secondary analysis. Doing so adds to the ABCD study's primary research goal of examining overall individual development in the adolescent years. This investigation helps in contributing to understanding how different and unique experiences alongside individual differences can affect brain development at baseline.

Population diversity and confounding variables

Participants of this study aimed to represent a nationally diverse population. In other words, individual differences and characteristics exist among subjects who come from various backgrounds and environments may need to be controlled for. Also, given that social risk and individual factors (i.e. IQ, socioeconomic status) have been found to be associated with the predictors in this study, (Hackman et al., 2015; O'Meagher et al., 2017) and may have shared characteristics with each other, investigating confounding variables may provide an answer to what extent these predict psychosis. Identifying and testing these identified confounders are essential to see whether IQ score, gender, ethnicity, and one's socioeconomic status would

have a significant role and in the associations between ADHD, executive functioning, stimulant medications, and psychosis. Since these are unique attributes of the participants, which can vary, identifying its independent effect is of interest in this study. Thus participants' demographic information & IQ scores were used in the final model and included as potential confounders for this study to watch out for the bias it could possibly contribute.

For this study, the participants' demographic information was identified as a potential confounder. For every participant, one's age, gender (i.e. male, female) and race (i.e., white, black, Asian, Hispanic), were accounted for. Families' socio-economic status (SES), which focuses on one's household income, needs and spending capacity, was also examined. The study also made use of information from the WISC-V, which provided a participant's IQ score. The total scaled score was used for the analysis.

Aims and Hypotheses

The primary aim of this study is to investigate the impact of ADHD, stimulant medication, executive dysfunction, on psychosis among children aged 9-10 years old using secondary data analysis. This is an important step in terms of contributing to literature in this area as existing research have not investigated these interrelated predictors together across the lifespan, which make it impossible to tease apart their potential effects. Potential confounders, specifically participants' demographics and IQ will also be included in the analysis to control for individual differences that may impact certain outcomes.

Apart from fulfilling the goal the NIH initiative of understanding adolescent development, conducting this study helps in contributing to understanding how different and

unique experiences alongside individual differences can affect brain development at baseline. In particular, findings may help to further clarify questions we still have about what may be contributing to psychotic like experiences in children at a very young age. It may likewise contribute to initial hypotheses about what might be causing it to peak at this particular stage (Kelleher et al., In Press).

Findings from this study will thus increase our understanding of predictors of psychotic-like symptoms in children with ADHD and to what extent the combinations of these different factors increase the risk of psychotic-like symptoms. The study aims to investigate the following research questions:

Research Question 1: Does ADHD diagnosis predict the total number of psychotic experiences?

Research Question 2: Do stimulant medications predict the total number of psychotic experiences?

Research Question 3: Does executive functioning predict the total number of psychotic experiences?

Research Question 4: Do stimulant medication and executive functioning predict the total number of psychotic experiences after controlling for IQ, age, gender, ethnicity, and SES?

Research Question 5: Do stimulant medication and executive functioning predict the total number of psychotic experiences after controlling for IQ, age, gender, ethnicity, and SES?

Results could shed light on diagnosis, executive functioning difficulties, clinical help-seeking, and treatment, and how these have an impact on psychosis-like experience in children. Specifically, these figures should prompt awareness and inform daily decision-making between patients/family and prescribers, where a balance needs to be struck between safety and reported effectiveness of stimulants on ADHD symptoms.

Methods

Participant recruitment and inclusion

The on-going Adolescent Brain and Cognitive Development (ABCD) study data was used in the current study, to which 6 month and 1 year follow-up data was added in the Summer 2020. It is currently largest national longitudinal study that has been conducted on adolescent brain health. While it initially aimed to investigate risk and resiliency factors and its associations with substance abuse, it now encompasses broader goals of providing information about overall individual development. Researchers have taken on a "population neuroscience approach," aimed to gather a representative sample of the US population (Garavan et al., 2018). This approach provides the opportunity to understand how various experiences and individual factors uniquely possessed by participants influence brain functioning and child development at baseline.

The participants of this study consisted of a large sample of 11,867 children who are to be followed over the course of 10 years to better predict physical and mental health outcomes. The research focuses on adolescence, which is a critical period of development and profound changes. Thus, researchers identified 21 geographically distributed and diverse study sites

across the US to conduct a multi-stage probability sampling. This ensures local randomization and representativeness for the project through school based recruitment that have been widely used in longitudinal and adolescent research (Bachman et al., 2011; Chantala & Tabor, 2010; Conway et al., 2016; Ingels et al., 1990). An analysis of both the demographics of the youth within those catchment areas and students at each elementary school was completed. Schools were then coded based on its geographical location, racial, ethnic and gender composition, and their social economic status or, the percentage of students receiving free or subsidized meals. This allowed for a stratified sampling of private and public schools.

Maintaining a strong relationship with the school staff was an essential part of the recruitment process and retention efforts as it largely influenced the subjects' engagement and continuous participation in this longitudinal study (Feldstein Ewing et al., 2018). The researchers also needed to work with the school staff to begin inviting participants and in some cases, ask permission from principals in other sites before making initial contact. Part of the initial recruitment phase was to provide electronic and printed material to be distributed to the target age group, which includes information about the ABCD study. In addition, families of children were also contacted with via randomly selected public and private schools through their academic or extracurricular involvement. Another means of recruiting was via a snowball referral system, in which families were compensated for recommending another interested family. This allowed the participation of other subjects who were difficult to access or engage, as they preferred the recommendation of friends. In addition, commercial mailing lists were distributed to households in the catchment areas, affiliates of a research subject, and recruitment during the summer period via clubs, organisations (i.e. YMCA, summer meal

programs, etc.), and summer activities in the school allowed were also done to maximise the recruitment phase to achieve the goal of acquiring a large sample size.

Families who were interested in taking part were contacted by the research team and screened by phone. Participation was eligible for individuals who fit all of the inclusion criteria, specifically children between 9.00 to 10.99 at the time of assessment between 1 September 2016 and 31 August 2018, fluency in English, safe and valid completion of baseline measures, and finally an in-person baseline visit conducted by both child and the caregiver between October 2016 to October 2018 (Garavan et al., 2018). To supplement the latter, brief remote assessments after 6 months are conducted in between in-person visits.

Assessments took place at the research sites and were done either after school, during weekends, or during the school break with participants provided with research compensation and travel allowance each time. One of the procedures for data collection involve undergoing a bi-annual magnetic resonance imaging (MRI), behavioural assessments, performing neurocognitive tasks, and conducting yearly biospecimen collections and self-report interviews, focusing on various aspects of individual performance, health and development. Sociodemographic factors were also identified, such as age, gender, race, ethnicity, urbanicity and socioeconomic status. To summarise, the battery of tests provided can be categorised loosely into seven domains, namely: substance use, mental health, physical health and biospecimens, neurocognition, gender identity and sexual health, culture and environment, and brain imaging. Apart from the participants, information are also derived from teachers and caregivers based on their own observations and knowledge on the child.

Ethical Considerations

All participants have given their consent for their data to be used for any projects approved by the NIH committee. Informed consent was also obtained from all parents and informed assent was obtained from children. Data use certification has been applied for and confirmed by the NIH committee.

Consistent with the goals of the ABCD Study, curated data and detailed data dictionaries, are released yearly to the NIMH Data Archive (NDA; https://data-archive.nimh.nih.gov/) (for further data sharing details, see https://abcdstudy.org/scientists_data_sharing.html and the ABCD Study overview paper included in this special issue). Data can be accessed through registration with the ABCD study at https://nda.nih.gov/abcd and all analyses are carried out within their secure virtual environment. The researcher has received information governance training as part of access requirements, and has attended a 2-hour workshop on security arrangements to conduct a secondary data analysis.

Measures

The ABCD study has a wealth of data from a battery administered to participants. However, only specific variables and measurements that assess these will be discussed in detail. A description and brief reviews of each of these relevant instruments are indicated in the next section:

Attention Deficit Hyperactive Disorder (ADHD)

The Parent Diagnostic Interview for DSM-5 Full (KSADS-5) was used to establish a categorical diagnosis of ADHD for participants. The tool has a long history of use as a reliable and valid measure of psychopathology in children and adolescents (Orvaschel et al., 1982; Chambers et al., 1985; Kaufman et al., 1997). This study utilised a self-administered parent version (report on youth) repeated on a yearly basis assessing a range of diagnostic disorders, particularly ADHD in 6-18 years old.

Stimulant medications

Parents completed Medications Survey Inventory Modified from the PhenX toolkit (Hamilton et al., 2011) in which they listed the names and dosages of all medications taken by the child. Parents were asked to bring their child's prescription to ascertain their accuracy and to document medications that have been used in the past two weeks since the interview. Information provided has been updated at each follow up assessment.

A binary variable was created to identify whether participants were taking stimulant medications prescribed to treat ADHD (e.g., Adderall, Ritalin, amphetamine). Stimulant medications, such as Methylphenidate, and as well as their brand names (i.e., Adderall, Ritalin, Dexedrine) were searched and coded to be included in the data. The appendix contains a full list of medications that has been classified as a stimulant treatment for ADHD in this study.

Executive functioning

To assess executive functioning in children and adolescents, validated measures from the National Institutes of Health Toolbox Cognitive Battery (NIHTB-CB) was used (Gershon RC, et al., 2013). The NIHTB-CB is an iPad-based battery of brief memory, executive function (EF), processing speed, and language tests that was developed within the NIH Blueprint for

Neuroscience Research for individuals ages 3 to 85 years. The current study used participant's fluid composite scores of Flanker Inhibitory Control and Attention, List Sorting Working Memory, and the Dimensional Change Card Sort to examine an individual's executive functioning skills.

The NIH-TB Flanker Inhibitory Control and Attention Test evaluates cognitive control and attention. There are a total of 40 trials where the participant views a row of five arrows on each. Flankers or distractors, the outer four arrows, aim either to the left or right. On the other hand, the target, which is the middle arrow, aims in the same direction as the flankers on congruent trials, and the opposite direction of the flankers on incongruent trials. The task of participants is to indicate whether the center arrow points to the left or to the right. Scoring each trial depends on one's speed and accuracy in performing the task.

The NIH-TB List Sorting Working Memory Test measures working memory by instructing one to recall stimuli in various orders. For this task, participants are shown pictures and hear the names of animals and foods of different sizes. They are then asked to repeat back the items in order from smallest to largest. It is administered for about 7 minutes and its total scores consist of total items correct across all trials.

The NIH-TB Dimensional Change Card Sort Test was designed for children to assess cognitive flexibility. On each trial, participants are tasked to match an item in the middle of the screen with two objects that is visible on the bottom of the screen based on either its colour or shape. It first starts out by matching items based on the former, then the latter, and finally matching alternately on the dimensions of shape and colour in a pseudorandom order.

Performance scores are based on speed and accuracy. As with the flanker test, scores depend on accuracy and reaction times for the 40 trials.

Psychotic-like experiences

Psychotic-like experiences in participants were assessed in terms of its presence and distress associated with psychotic-like symptoms in using the Prodromal Questionnaire – Brief Child version (PQ-BC). It is a 21-item self-report measure that has been adapted for the use of children aged 9-10 years of age.

Items such as “When this happens, I feel frightened, concerned, or it causes problems for me” and “” aim to evaluate symptoms and experiences in those who meet may be at risk for psychosis. The presence or absence of each symptom is indicated with a “Yes/No” response in each item. For items with a “Yes” response, participants indicate the extent to which a symptom causes distress on a 5-point Likert scale (e.g., strongly disagree, disagree, neutral, agree, strongly agree). The measure provides two scores, which is the sum of the number of endorsed symptoms as the total score (ranging from 0 to 21) and the distress score (ranging from 0 to 126) as the mean of the coded distress ratings. For this study, the following selected items from the questionnaire were used in the study on the basis of measuring positive symptoms as psychotic-like experiences, where higher scores indicate higher risk:

1. “Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?” for auditory hallucinations
2. “Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?” for thought interference

3. "Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?" and "Did you feel that other people might want something bad to happen to you or that you could not trust other people" for paranoia
4. "Did you honestly believe in things that other people would say are unusual or weird?" for bizarre beliefs
5. "Have you seen things that other people can't see or don't seem to see" for visual hallucinations

Demographics

A demographics questionnaire was provided to the participant's parent/guardian to fill in. This determined the participants' demographic information that were used in the study, which include their age, gender (i.e. male, female), race (i.e., white, black, Asian, Hispanic), and socio-economic status (SES). For the purposes of this study, ethnicity was re-coded in to white/non-white. Information pertaining to the socioeconomic status of the participants' families were derived from the ABCD Parent Demographics Survey, which asked queried about one's household income, needs and spending capacity. For instance, "in the past 12 months has there been a time when you and your immediate family needed food but couldn't afford to buy it or couldn't afford to go out to get it?". Participants responded with either a yes or a no to each of the identified 7 and a total score was calculated, with higher scores on this indicating lower socioeconomic status, and vice-versa.

Intelligence quotient (IQ)

The study made use of information from the Wechsler Intelligence Scale for Children or WISC-V, which provided a participant's full IQ score. The total scaled score was used for the analysis. The WISC-V (Wechsler, Pearson Education, Inc., & Psychological Corporation, 2014) is a standardised clinical assessment tool, which can be administered to children 6 to 16 years of age. Typically completed between 60-90 minutes, it consists of several subtests that can measure domains identified as the Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Working Memory Index, and Processing Speed Index.

Overall, the goal for examining the effects of these variables allows the researchers to tease apart pathways that predict psychosis. Thus, controlling for these extraneous would be able to reliably predict the associations being tested, over and above identified confounders.

Data Analysis

Because the ABCD dataset is an existing dataset, no additional data was collected in addition to the 11,867 who gave consent to participate in the study. Using G*Power, the minimum effect size detectable was calculated using a dataset of this size. Using an alpha of 0.05 and a required power of 0.9, a logistic regression would be able to detect effects sizes of odds ratio 1.07 and greater, suggesting that the study will be sufficiently powered to detect effects of very small sizes and above - using the effect size classification criteria of Chen and Chen (2010) where odds ratios of less than 1.68 are considered in the small range.

To test the hypotheses of this study, statistical analyses were performed using *R* statistical software (RStudio Team, 2020). Unadjusted linear regression analyses were first used to estimate the following relationships for each research question:

Research Question 1: Does ADHD diagnosis predict the total number of psychotic experiences?

Research Question 2: Do stimulant medications predict the total number of psychotic experiences?

Research Question 3: Does executive functioning predict the total number of psychotic experiences?

Subsequently, adjusted regression analyses were used to examine:

Research Question 4: Does executive functioning predict the total number of psychotic experiences, over and above stimulant medication?

and subsequently:

Research Question 5: Do stimulant medication and executive functioning predict the total number of psychotic experiences after controlling for IQ, age, gender, ethnicity, and SES?

Unadjusted regression analyses were used to test the association between the exposure and outcome. If a reliable association was found, a subsequent analyses that included adjustment for potential confounders was completed.

The first three models tested ADHD, stimulant medications, and executive functioning as potential predictors of psychotic-like experiences. For the fourth model, stimulant

medication was added to evaluate how the relations between executive functioning and psychotic experiences would be affected. For the last model, IQ, age, gender, ethnicity, and SES were entered as control variables to assess how reliable the predicted associations are when controlling for potential confounders.

Variables with missing data include the following: executive functioning and intelligence quotient. However, the level of missing data was below 5%, which is below the threshold of 5% which is considered to bias estimates (Jakobsen, et al., 2017). Hence, cases with missing data for any relevant variables were excluded from the relevant regression analysis.

Results

Descriptive Results

This secondary data analysis involved 11,867 (*M* =118.98*, SD* =7.5) youth between the ages 9-10 at the time of interview. Of the total participants, a majority were males (52.15% male, 47.85% female). There were 57.07% who were of a white background, while 47.91% indicated having a non-white ethnicity.

Participants gave information to the ABCD research team about medications they were currently taking as a treatment for ADHD. Those have been prescribed with stimulants make up 95.38%, while 4.62% of the sample were not being treated.

Of 11,867, 61% of the respondents (*M* = 2.63*, SD* =3.56) experienced positive symptoms of psychosis, with majority of the participants (16.02%) reporting to have experienced at least one of this in their lifetime. 11,733 participants provided information about their social economic status (*M* = 0.47*, SD* =1.1). Data regarding cognitive ability was available from 11,621

participants (scaled score *M* = 9.86*, SD* =2.99).

Analysis

Table 1.
Descriptive statistics of count variables

Descriptive Statistics	**N = 11,867**	
Gender		
Male	6189	52.15%
Female	5678	47.85%
Ethnicity		
White	6179	5207%
Other	5685	47.91%
Taking Prescribed Stimulants		
Yes	548	95.38%
No	11,319	4.62%
Missing Data		
Executive Functioning	202	1.7%
Intelligence Quotient	360	3.0%

Table 2.
Descriptive statistics of continuous variables

Variables	N	*M*	Std. Deviation
Age	11,867	9.10 mo.	7.4
Socioeconomic status	11,733	0.47	1.1
IQ (scaled score)	11,621	9.86	2.99

Table 3.
Regression results

	Psychotic Experiences					
			Confidence Interval			
			2.5%	97.5%		
	β	*F*			*R2*	*p value*
Research Question 1		0.84			0.00	0.360
ADHD	0.00		-0.00	0.001		0.360
Research Question 2		32.07			0.003	<0.0001
Stimulants	0.88		0.57	1.19		<0.0001
Research Question 3		59.79			0.015	
Executive Functioning						<0.0001
Inhibition	0.004		-0.001	0.009		0.158
Working Memory	-0.025		-0.030	-0.021		<0.0001
Cognitive Flexibility	-0.012		-0.016	-0.007		<0.0001
Research Question 4		52.187			0.018	<0.0001
Executive Functioning						
Inhibition	0.004		-0.001	0.010		0.110
Working Memory	-0.025		-0.029	-0.020		<0.0001
Cognitive Flexibility	-0.012		-0.017	-0.007		<0.0001
Stimulants	0.840		0.53	1.15		<0.0001
Research Question 5		46.142			0.035	<0.0001
Executive Functioning						
Inhibition	0.004		-0.001	0.009		0.156
Working Memory	-0.018		-0.023	-0.013		<0.0001
Cognitive Flexibility	-0.007		-0.011	-0.002		0.008
Stimulants	0.84		0.53	1.15		<0.0001
Overall IQ score	-0.035		-0.059	-0.011		0.004
Age	-0.020		-0.029	-0.011		<0.0001
Gender	0.27		0.14	0.40		<0.0001
Socioeconomic status	0.22		0.15	0.28		<0.0001
Ethnicity	0.57		0.42	0.71		<0.0001

Research Question 1: Does ADHD diagnosis predict the total number of psychosis-like experiences?

The regression analysis revealed a non-significant relationship between ADHD and psychosis-like experiences (β = 0.00 [-0.00 – 0.001], p = 0.360). Therefore, ADHD does not

predict the total number of psychosis-like experiences. Hence, it was not necessary to include this variable in the final model in which confounders were included.

Research Question 2: Do stimulant medications predict the total number of psychosis-like experiences?

The regression analysis revealed that stimulant medications (β = 0.88, [0.57 – 1.19], p = 0.000) significantly and positively predicted the total number of psychosis-like experiences. Stimulant medication accounted for 0.30% of the variance in the total number of psychosis-like experiences and the change in R was significant, $F(1,11865) = 32.069$, p = <0.0001

Research Question 3: Does executive functioning predict the total number of psychosis-like experiences?

Taking into account executive functioning as a predictor of psychosis, calculated scores from three cognitive tasks of 11,665 participants were analysed. Results showed that inhibition (β = 0.004, [-0.001 – 0.009], p = 0.16) did not yield significant associations with the outcome. On the other hand, working memory (β = -0.025, [0.030 – -0.021], p<.01) and cognitive flexibility (β = -0.012, [-0.016 – -0.007], p<.01) also were found to have significant and negative association with psychotic experiences. Executive functioning skills accounted for 0.15% of the variance in the total number of psychotic experiences.

Research Question 4: Does executive functioning predict the total number of psychotic experiences after controlling for stimulant medication?

Similarly, data from 11,665 participants were studied and stimulant medication was added to the model. Taking into account executive functioning as a predictor of psychosis, calculated scores from three cognitive tasks of 11,665 participants were analysed. Linear model

results showed inhibition (*β* = 0.004, [-0.001 – 0.010], p = 0.110) did not yield significant associations with the outcome. Working memory (*β* = -0.025, [-0.029 – -0.020], p = <0.0001) and cognitive flexibility (*β* = -0.012, [-0.017 – -0.007], p = <0.0001) also were found to have significant and negative association with psychotic-like experiences. Stimulant medications (*β* = 0.84, [0.53 – 1.15], p = <0.0001) significantly and positively predicted the total number of psychotic experiences. In comparison to the unadjusted model, the variance increased slightly to 1.8% when accounting for the total number of psychotic experiences.

In sum, predictors retained their pattern of significant association. Inhibition did not show significant associations with the outcome. On the other hand, working memory, cognitive flexibility, and stimulant medication were significantly associated with psychotic-like experiences. Table 3 may be referred to regarding the significant associations of all predictors.

Research Question 5: Do stimulant medication and executive functioning predict the total number of psychotic experiences after controlling for IQ, age, gender, ethnicity, and SES?

Results showed that inhibition (*β* = 0.004, [-0.001 – 0.009], p = 0.11) did not yield significant associations with the outcome. Working Memory (*β* = -0.018, [-0.023 – -0.013], p = <0.0001) and cognitive flexibility (*β* = -0.007, [-0.011 – -0.002], p = 0.008) also were found to have significant and negative association with psychotic experiences. Stimulant medications (*β* = 0.84, [0.53 – 1.15], p = <0.0001) significantly and positively predicted the total number of psychotic experiences.

Finally, potential confounders were added. Results revealed that IQ (*β* = -0.035, [-0.059 – -0.011], p = 0.004), age (*β* = -0.020, [-0.029 – -0.011], p<.01), gender (*β* = 0.027, [0.14 – 0.40], p = 0.000), socioeconomic status (*β* = 0.22, [0.15 – 0.28], p = <0.0001), and ethnicity (*β* = 0.57,

[0.42 – 0.71], p = <0.0001) significantly contributed to the adjusted model for psychotic experiences. All variables accounted for an increase of 3.5% in the variance explained in psychotic experiences, $F(9,11295) = 46.142$, p = <0.0001.

In sum, all predictors retained their pattern of significant association after controlling for confounders. Inhibition remained non significant in its association with the outcome. On the other hand, all others (working memory, cognitive flexibility, and stimulant medication) remained significantly associated with psychotic-like experiences. As with research question 4, Table 3 may be referred to regarding the significant associations of all predictors.

Discussion

The objective of this study was to determine whether ADHD, executive functioning, and stimulant medication are reliable predictors of psychosis in children. The study also investigated whether executive functioning predicted psychosis, over and above stimulant medication. Lastly, it aimed to test whether any significant effects held after controlling for IQ, gender, ethnicity and social status as confounders

Summary of the main findings and its clinical implications

Consistent with past research (Laurens et al., 2012; McGrath et al., 2015), a majority of children in the study indicated the presence of psychotic-like experiences. A high number of children have reporting psychotic experiences (Dominguez et al., 2011) is a risk factor in the later development of clinical psychotic conditions, which can be very problematic. Consequently, long-term outcomes of this could lead to poor mental health outcomes and

other co-morbidities (Fisher et al., 2013), which could result to even more complex consequences.

Preventive approaches should be prioritised as an effort towards ensuring an overall positive well-being. At the same time, findings suggest the need to increase an awareness regarding child development and mental health in the community. The adolescent years are a crucial stage that should be attended to due to the brain's vulnerable nature with the aim of preventing comorbidities. Specifically, a high number of cases related to psychotic-like experiences identified at this age (Dominguez et al., 2011) perhaps may suggest the importance of consistent monitoring and screening of children's mental health. Besides parents and health professionals, educators likewise have important roles to play at this stage of development. Involving those centered around the child's care and psychologically informed members of the community may facilitate early referral. This provides the opportunity for children to receive an assessment, and if necessary, a follow up and reassessment after a period of time. Providing services early, creating a potential treatment plan, on and being informed may likewise decrease the emotional and psychological distress in children and families. Further, data from this research may help key decision makers in revaluating current practices and guidelines in terms of addressing ADHD, executive functioning and psychosis.

The regression analysis revealed that both stimulant medication and executive dysfunction are significant predictors of psychotic experiences among children. Although regarded as a risk factor, ADHD did not prove to be associated with psychotic experiences.

It is important to emphasize that these significant associations had expectedly detected a small effect size in a large research sample. Conducting a large-scale research made it possible

to detect the subtle effects of identified risk factors as well as mechanisms of psychotic experiences. Although it may not necessarily be meaningful on an individual level, viewing this from a population perspective makes this finding especially relevant.

At a service and policy level, findings from the results of the study can serve as useful data in terms of ironing out the right care pathway for children and adolescents. This may likewise help child mental health services (CAMHS) in the UK in tailoring a better stepped care approach, which will allow children to access the right services based on their developmental needs. Consequently, this could influence organisation and access to services, which can enable better triaging. Lastly, an awareness of these findings may push policy makers to create a more collaborative approach with all individuals involved in the child's care across social services, education and health. The identified risk factors from this study may serve as early markers for psychosis that can inform the intensity of an intervention and may likewise serve as a guide for helping professionals and educators in terms of providing the appropriate scaffolding.

ADHD did not predict psychotic experiences

Although ADHD has been acknowledged as a potential risk factor in past research (***Dalsgaard, et al., 2013***; Nourredine, et al., 2021; Shyu et al., 2015), there was no evidence that this contributed to psychotic experiences among children. Although ADHD and psychosis tend to share similar features and may co-occur, findings based on the ABCD data indicate that ADHD is not associated with psychotic-like experiences. This finding adds to the growing body of research that challenges the notion of ADHD as a predictor of psychotic experiences (Shyu et al., 2015). Perhaps future research can continue to look into other factors, together with ADHD at play, to further investigate what may have contributed to previous findings supporting this as

a predictor.

For example, one reason for this might be due to age and the onset of psychosis as potential confounding variables. It has been suggested that psychosis tends to occur at a later age for those who have had a childhood diagnosis of ADHD (Dalsgaard, et al., 2013; Nourredine, et al., 2021). Since the ABCD study is still in the process of acquiring longitudinal data, it would not be possible to predict this. Hence, it can be justified that associations do not exist in this age group, until further investigation can be made. Thus, clinical assessments may need to be more detailed by considering one's age when taking into consideration the risk for psychosis and to avoid pathologising normal developing behaviour. Also, it may be more practical to watch out for other known risk factors such for the development of psychosis, including on-going substance/cannabis abuse and a family history of psychosis (Moran et al., 2019). Finally, it might be helpful to test ADHD as a potential confounder, rather than it being identified as a predictor. It is possible that perhaps ADHD may possibly influence the outcome of psychotic-like experiences in the context of risk factors at play.

Stimulant medication is associated with psychotic experiences

Results indicated a reliable association between stimulant medications and psychotic experiences as with previous literature (Gross-Tsur et al., 2004; Lee, 2016; Rashid & Mitelman, 2007; Ross, 2006; Shyu et al., 2015; Young, 1981). This finding further strengthens the notion of what we know about this relationship.

The same relationship was found over and above potential confounders. Although research has mentioned that it cannot ascertain whether psychosis may be due to stimulants or

is due to vulnerability factors (Cortese et al., 2018), the results of this study provides evidence of stimulant medications as a predictor. In addition, the findings also contribute to ongoing debates about how gender, ethnicity and SES may impact brain development. Specifically in this area, results add to the evidence suggesting that psychotic-like experiences are not influenced by one's unique difference and background despite taking stimulants.

Contrary to research that indicates that there is no immediate and increased risk of psychosis with methylphenidate-use (Hollis et al., 2019), the results imply that perhaps dosages may not be appropriate and other formulations of stimulants may be at play. First, side effects are still known to occur, despite reports of adverse events being low (Bodey, 2011; Correll, 2011). Methylphenidate, when taken at high doses, have been known to cause, delirium, aggressiveness, panic states, and hallucinations (Rappley, 1997; Wender, 1998). Long term use and abuse may also explain psychotic experiences as an outcome (Morton & Stockton, 2000). This has been documented to last for months or even years, despite no longer using methamphetamine, stress has also been shown to increase vulnerability of a spontaneous recurrence of methamphetamine psychosis (Glasner-Edwards & Mooney, 2014).

It has also been suggested that although amphetamines were the found to be the most efficacious stimulant in all age groups, younger people have had difficulty tolerating its side effects (Cortese et al., 2018). Moreover, there is much higher incidence of psychosis in patients on amphetamines versus methylphenidate (Moran et al., 2019). In other words, other stimulant drugs such as Adderall, may pose more of a risk than others as a result of a condition known as MA-induced psychosis (Marshall & Werb, 2010).

MA-induced psychosis induces acute psychotic symptoms (i.e., hallucinations and persecutory delusions) caused by amphetamine intake as a result of the surge in dopamine in the brain (Snyder, 1974). The use of amphetamine also has very serious implications and consequences as it also has the potential to induce neurotoxicity, which is also associated with substance abuse (Schiffer, et al., 2006). Because this can happen during the critical period of the brain, psychotic-like symptoms in to being predisposed to substance abuse, could result to altered neural pathways that deviate from healthy development lasting until adulthood. Hence, one's development may not be able to occur in the most optimal manner and may lead to unhealthy trajectories due to exposure of these risk factors. This unhealthy development could predispose one to psychosis and drug abuse later on in life, which can contribute to further comorbidities and negative consequences. In other words, stimulant medication increases the risk that the child may later become vulnerable to poor mental health outcomes as reflected in previous studies (Fisher et al., 2013).

In summary, methylphenidate at an appropriate and clinically supervised dose may be considered as first-line treatment for ADHD for children. While it may be difficult to completely prevent psychosis, a careful approach such as considering this first over amphetamine might be a better option for younger people. Since stimulant medications are considered the first line of defense for treating ADHD, with amphetamines proven as the more effective drug, it becomes even more important for prescribing professionals, particularly psychiatrists and pediatricians, to educate their patients about its potential risks. Health care professionals could adopt a more conservative approach, especially if the child's day to day functioning is not severely affected. Since prescribed ADHD medications are on the rise (Molina et al., 2009), adopting this manner

and limiting access to stimulant medication to those who are most in need could also decrease the problem of potential abuse of such drugs.

It may be important to reassess whether non-stimulant medications might be the better choice, if the former prove to be a precarious step. Depending on the child's need and the targets for treatment in the context of co-morbid conditions, it is crucial to determine if the costs outweighs the gains. At the moment, there are specific recommendations and guidelines provided by NICE (2018) in terms of managing ADHD. Because of this finding, perhaps reemphasising patient choice and collaboration with health care professionals can inform better treatment planning and progress.

With these considerations in mind, it may allow families to make clinically informed decisions for children needing treatment for ADHD. In addition to psychoeducation, both parties should prioritise regular follow up and careful monitoring as part of the treatment plan.

Executive dysfunction is associated with psychotic experiences

The study also found that executive dysfunction significantly contributes to psychotic experiences in children, even after controlling for potential confounders. This finding is consistent with other studies adds to limited research in this area (Riecher-Rössler et al., 2009; van Amelsvoort et al., 2004; Weinberger et al., 2016).

More importantly, the study found that there are specific executive function domains, specifically working memory and cognitive flexibility, which may increase the risk for psychotic symptoms. This is in line with the finding that indicates the association between poor working memory and psychotic presentations (Ueland et al., 2004). Given the predictive utility of the measures used in the study, these may be used to identify high-risk children and may be further

analysed to see whether there might be a potential pattern or executive functioning profiles that predicts psychotic experiences. This also suggests that targeting executive dysfunction may be a worthwhile intervention in order to reduce the likelihood of psychotic experiences.

Findings also reveal that stimulant medications, also a predictor of psychotic symptoms, do not affect the relationship previously mentioned. In other words, stimulant medication did not moderate the association with executive function and psychotic experiences. Therefore, psychosis may be triggered by both risk factors independently.

Since the brain circuitry is not clear-cut, various sites might operate differently from one another. In fact, different parts of the brain can both be in hyperdopaminergic (Castellanos, 1997) and hypodopaminergic (Levy, 1991) states, not necessarily influencing one another because of the different dopaminergic pathways. This hypothesis may be supported by Castellanos' (1997), whose work suggests that dopamine levels vary in different brain sites, which can cause imbalance in its activity due to pathways being disrupted. Results imply that the dopamine theory (Levy, 1991) may not just be simply about the whole brain having low dopamine levels nor do patients with ADHD merely have a dysfunctional dopamine release in explaining the associations with psychotic experiences.

Although early theories provided the foundation of what we now know, what underlies psychotic experiences might be more than the hypothesised interactions of dopamine and executive functioning, which may open up the path to future research directions. A biological framework, for instance brain maturation (Shaw et al., 2007) could play a part as well in terms of understanding the associations between executive functioning and psychosis, separate from stimulant medications. In a similar light, the psychosis-proneness-persistence-model (Cougnard

et al., 2007) may also need to be tested whether there are variables in the environment that cause the deterioration of executive functioning, leading to this outcome. There may be social factors (Linscott & Van Os, 2013; O'Meagher et al., 2017) that also underlie or potentially trigger the association between executive functioning and psychotic-like symptoms.

This finding also highlights how important it is to differentiate and clearly define both ADHD and executive dysfunction. Although both have similarities with regards symptoms and disorder presentation, the former does not predict psychotic symptoms. A misdiagnosis of either ADHD or psychotic symptoms can be worrying as it could result to either a type 1 or type 2 errors when considering the risk for psychosis. Further, it may be helpful to investigate three ADHD subtypes that has already been proposed (Nigg et al., 2005) as the results of this study supports the idea that there may be other pathways that can more accurately predict psychosis. Identifying distinguishable terms allows for a more universal understanding of what these disorders are. Doing so will make it easier to communicate to others and can facilitate better discussions among professionals with regards to diagnosis and treatment. Lastly, this provides a rationale to develop evidence-based treatment plans to prevent psychotic experiences by incorporating alternative methods (i.e. psychological, social, pharmacological interventions) to decrease vulnerability.

Limitations of the study and future directions

Although the study has a number of strengths, it is not without limitations that can possibly be improved on in future research. First, it is important to emphasize that this study was purely based on cross-sectional observational data. This means that a causal relationship cannot be established, but only hypothesized. Second, averaging outcome over a range of

psychotic symptoms may miss some of the diversity and individual association with specific psychotic symptoms. A longitudinal analysis to examine long-term effects using the same secondary data set could also not be accomplished, as the ABCD study is currently still ongoing. Furthermore, having a large sample size, which detect small effect sizes, may also pose as a challenge in determining how meaningful these are. Thus, caution must be taken in generalizing the results to children of a different ethnicity.

There are several areas that future investigators could look into. While this study only focused on a few confounders, this does not guarantee causal relationships of significant findings as there may be other factors that trigger one's vulnerability to psychotic experiences, such as on-going substance abuse or using cannabis, or family history of psychosis (Moran et al., 2019). A replication of this study using a cross-cultural approach may also be useful, so that findings can be verified across different contexts and environments. This can reveal as well how variables operate and whether findings can be considered universal phenomena.

Future studies can support these initial findings through an approach called deep phenotyping, another way of gathering information and balancing findings vis-à-vis large scale studies (Robinson, 2012). This procedure can only be done with a small sample size, as it requires a huge amount of resources to successfully define very specific phenotypes. Doing so would help advance our knowledge in tailoring the right interventions for individuals through precision medicine efforts. With regards to the significant finding in the associations between stimulant medications and ADHD, this study was unable to narrow down or specifically analyse which type of stimulant (i.e. amphetamines, methylphenidate) increased the risk for psychotic symptoms. Future studies might be able to verify if there were specific brands or ingredients

that produced such side effects. It might also be beneficial to find out the length of time stimulants are taken as long-term use usually increases the chances of side effects.

Since the study focused on understanding potential risk factors in this age group, it would likewise be helpful to assess the protective factors that mitigate psychotic-experiences. Identifying what buffers the relationship can likewise allow the improvement of treatment and preventive strategies against poor mental health outcomes. Researchers can also look into gathering and understanding data that may provide information around differences or similarities in terms of risk factors by considering other developmental periods as its baseline for longitudinal studies (i.e., adolescents, infants).

Conclusion

This is the first large-scale study to examine to what extent a diagnosis of ADHD, stimulant medication, and executive functioning each independently predict psychotic like experiences in 9-10 year old children using the NIMH ABCD dataset. Results from the regression analysis revealed that ADHD did not prove to be associated with psychotic experiences. On the other hand, both stimulant medication and executive dysfunction are significant predictors of psychotic like experiences among children.

The study also found that executive functioning predicted psychotic like experiences, over and above stimulant medication. Lastly, stimulant medication and executive functioning remained as predictors of psychotic like experiences after controlling for IQ, gender, ethnicity and social status as confounders

This study contributes to understanding the predictive factors surrounding psychotic experiences among a sample of children. The findings shed light into other ways we can now

prevent the onset of psychosis in childhood, as well as long-term health consequences, through appropriate assessment, treatment and preventive strategies.

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Part 3: Critical Appraisal

Introduction

The intention of this this critical appraisal is to provide an opportunity for the reflective process of this project in order to consider conceptual matters and significant progressions and practices that arose upon the completion of this research. Further, it will explore in more detail key implications and recommendations based on the findings of the study.

The experience of conducting a secondary data analysis

The review paper highlights how little we know about the mechanisms in relation to the impact of ADHD, stimulant medication and executive dysfunction. More so, there are no large-scale studies investigating this phenomenon, creating a huge gap in this area.
From a clinical point of view, this likewise limits the progress of preventive strategies with regards to psychotic experiences, as well as other mental health disorders.

The empirical paper was the first paper to rigorously assess the extent to which a diagnosis of ADHD, stimulant medication, and executive dysfunction each independently predict psychotic experiences in children. It also investigated the presence of potential confounders made an impact on these relationships. Although many have studied and have written information about the variables of the study, there are still a number of mixed findings that presented as inconsistent or were unclear during the process of the review literature. In addition, these interrelated factors make it difficult to tease apart to what extent each predicts psychotic experiences. To clarify the latter point with an example, it has been has indicated that executive functioning deficits and stimulant medication both predict psychotic-like symptoms (Gross-Tsur et al., 2004; Lee, 2016; Levy, 1991; Pietrzak et al, 2006; Rashid & Mitelman, 2007;

Young, 1981; Westbrook et al., 2020). However, given this idea, it would suggest that interactions might just simply cancel each other out assuming that both work in the same way. Certainly, the brain is a complex organ and there have been a number of theories that suggest how it operates in the context of cognitive deficits. For this reason, it was important to have investigated the relations of the predictors with psychotic experiences individually, which was followed by the adjustments of the regressions after on the basis of their level of significance.

Contributions in all shapes and sizes

As an international trainee, especially coming from a country where addressing mental health problems is deemed to be a luxury, it brings me great pride to be able to collaborate with other researchers in contributing to the work through an NIH initiative. I likewise feel grateful to have been given the opportunity to gain access to the ABCD study's data set, which allowed me to contribute to the advancement of in the field of adolescent brain development. Despite a steep learning curve, I feel that I have gained a lot both from a professional and personal standpoint. For one, it reminded me of the **i**mportance of paying attention. Too often, we fail to notice what might be considered subtle signs before us in favor of the more obvious ones. It is easy to fall into this trap because most of the time gauging mental health may be subjective vis-à-vis physical health. In addition clinicians will need to rely on clinical intuition, especially those with a more psychodynamic or humanistic background. Another issue is that mental health most of the time is also just managed in the best way possible. However, the results of this study and the significant findings on psychotic experiences feels like a wake up call, a reminder to take notice of the little things despite the fact that it may be considered part of normative development due to its transitory or even rare nature (Linscott and van Os, 2013).

Doing so might be able to prevent inevitable developmental challenges in the future, and could even go as far as paving the way for optimal growth in an individual.

The huge impact of a small effect

It is hoped that increasing knowledge and awareness in the area of psychotic experiences and its associations with other mental health concerns might be able to reduce the stigma around this experience or condition. One of the most important contributions of this study, although it may seem ironic, was finding significant associations that detected a small effect size in a large research sample. Undoubtedly, this felt a bit worrying initially as it may seem potentially meaningless based on first impressions. Yet, without a large-scale study such as this, there might not have been any opportunity to detect the study's identified risk factors, as well as the mechanisms that underlie psychotic experiences. Because of this rare occurrence, the effects might have been so subtle that it could not have been generally identified. However, the data set provided the possibility of recognizing psychotic experiences. Although this may not seem to be important on an individual level, the result of this could still become relevant on a population level. In other words, the small effect that psychotic experiences have on children may not necessarily affect the lives of many, yet it is still important to consider the profound effect it might have in increasing an individuals risk for other mental health problems later on that could have been avoided.

Implications and further research

I believe that this study brings forth many an opportunity for other similar research opportunities that can answer more questions that this project has been limited to. With regards to the significant finding in the associations between stimulant medications and ADHD,

this study was unable to narrow down or specifically analyse which type of stimulant (i.e. amphetamines, methylphenidate) increased the risk for psychotic symptoms. Based on reviewed literature, studies have consistently shown that much there is a much higher incidence of psychosis in patients on amphetamines versus methylphenidate (Marshall & Werb, 2010; Moran et al., 2019). Future studies might be able to further validate this with a large sample size and to further scrutinize whether specific brands and certain ingredients were more prone to inducing psychotic experiences. Although we may be at the initial stages in terms of understanding stimulants as a potential predictor of psychotic experiences, this suggests how crucial it is to involve service users in clinical decision-making and in providing psychoeducation in order to weigh the risks and benefits that a child might be exposed to. This also implies how important it is to seek out safer alternatives when the costs are too high and prioritizing the innovation of types of treatment that prevent psychotic experiences when addressing executive functioning deficits and ADHD. While known confounding variables were also assessed in this study, it will also still be helpful to include other risk factors such for the development of psychosis, including on-going substance/cannabis abuse and a family history of psychosis (Moran et al., 2019), extending our understanding in this complex area.

Since this project was able to conduct a study on a large sample size, future research can now verify the consistency of the results to further validate its findings. Further, longitudinal designs can further prove its significant results by assessing the impact of time and development in children. For example, it can examine whether it is the use of stimulants in the long term profoundly increases the chances of side effects such as psychotic experiences. Also because it has been suggested that psychosis tends to occur at a later age for those who have

had a childhood diagnosis of ADHD (Dalsgaard, et al., 2013; Nourredine, et al., 2021) perhaps this can be further verified.

The approach of deep phenotyping is likewise another way for future researchers to gather information and balance findings vis-à-vis large scale studies such as this (Robinson, 2012). However, this process can only be done with a small sample, which would define very specific phenotypes. Doing so would help advance our knowledge in tailoring the right interventions for individuals through precision medicine efforts.

Because of my background as an international trainee, I cannot help but wonder how much culture comes into play with psychotic experiences. Having the eyes of someone who grew up in a country where the influence of myths and folklore are strong in the local belief system, it is likewise curious to note how this might be separate or even similar to the notion of psychotic experiences in young Asian or Filipino children. Perhaps conducting a cross-cultural study with a broader representative sample might present interesting findings for future projects as well. Doing so might be able to increase generalizability in terms of results to children of a different ethnicity. Lastly, it would be largely beneficial to also look into protective factors that mitigate psychotic-experiences. The interaction of risk and protective factors, variables that may shift developmental pathways, may play key roles in the cultivation of resilience (Johnson et al., 2010). Prioritizing an assessment process that involves these would make a large contribution in the area of psychotic experiences. Identifying what buffers the relationship can likewise allow the improvement of treatment and preventive strategies against poor mental health outcomes.

Conclusion

The issues considered here demonstrate the importance of investigating how ADHD, stimulant medication and executive dysfunction are associated with psychotic experiences. Psychotic experiences, though only considered to be on the milder end of the spectrum constituting more severe psychotic disorders, proves to be a relevant area of investigation because of its associations to a multitude of potentially preventable mental health disorders. More so, it is important that pay attention how this impacts young people at a critical stage of brain development. Further research and longitudinal studies required in order to continue to broaden our understanding of the experiences of psychotic experiences in children and how we can reverse this impact for future generations to come to help raise resilient individuals who are able to maximize their potentials.

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Appendices

Appendix 1: Selected items from the PQ-BC

1. “Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?” for auditory hallucinations
2. “Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?” for thought interference
3. “Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?” and “Did you feel that other people might want something bad to happen to you or that you could not trust other people” for paranoia
4. “Did you honestly believe in things that other people would say are unusual or weird?” for bizarre beliefs
5. “Have you seen things that other people can’t see or don’t seem to see” for visual hallucinations