Time Effects of Attention Deficit Hyperactive Disorder

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Abstract

This project proposes a method for analyzing the change over time in symptoms of attention deficit hyperactive disorder (ADHD). ADHD is a disorder often diagnosed in young children which includes symptoms of inattention and hyperactivity. Most available research focuses on the immediately observable behavioral characteristics of the ADHD, but recent advancements in neuroscience allow a more detailed look at the biology of the disorder. Low levels of dopamine and norepinephrine have been associated with the characteristics of attention deficit hyperactive disorder. It is proposed that the levels of these neurotransmitters, and thus the symptoms of ADHD, will worsen over time without the introduction of stimulant medication to treat the disorder. The results of this study will give doctors and patients an expectation of the progression of ADHD throughout a patient's life.

Introduction

This project addresses the underlying physiology of attention deficit hyperactive disorder. This is a cognitive disorder characterized by bodily hyperactivity and a poor ability to sustain attention. ADHD is primarily diagnosed in early childhood when performance in school is substandard. Cases of ADHD range in a broad spectrum with some individuals experiencing more severe symptoms than others. Some will show primarily inattentive symptoms, while others will prominently show hyperactive symptoms. Still others will be both inattentive and hyperactive (Barkley). Because of this, the disorder may go undiagnosed into early adulthood. The prevalence for ADHD diagnoses in the general population is about 3-7%, and males are three times more likely to have ADHD than females. (Barkley).

A good deal of research focuses on the immediately observable behavioral characteristics of those with attention deficit hyperactive disorder. People with ADHD cannot by demand hold their attention on a task for extended lengths of time. These people also tend to fidget their body or exhibit abnormally high levels of energy. This project proposes an experiment to quantify the change in severity of ADHD symptoms over time by analyzing the specific neurotransmitters modulating them. Comparing neurotransmitter levels between ADHD and control groups of both children and adults will allow a good analysis to be made. I hypothesize that most clinically diagnosed children with unmedicated ADHD will see neurotransmitter levels decrease over time.

This project will provide insight into the change in ADHD symptoms over time. Doctors prescribe stimulant medications for a number of years for this disorder, and these drugs have their own side effects and are often discontinued at some point (citation needed). This research will give doctors and patients an expectation of how ADHD symptoms will improve, stagnate, or worsen over time. This allows for better planning for the future to determine if additional physician visits or drug therapy is needed. This paper will begin by providing an overview of the current literature concerning attention deficit hyperactive disorder. Next, an experiment will be suggested to improve the current research concerning ADHD.

Background

The available research concerning attention deficit hyperactive disorder has been growing fast over the past few decades. ADHD was first described by a doctor Sir Alexander Crichton in 1798 (Lange). The most widely used criteria for diagnosing ADHD is contained in the Diagnostic and Statistical Manual of Mental Disorders. The DSM-V gives several criteria for diagnosis of ADHD which must be present and impair functioning for six consecutive months. The first is inattention, an inability to orient attention properly and to sustain focused attention on one task. The second is bodily hyperactivity, which often gives way to impulsivity (Lange). The early descriptions of ADHD as well as these diagnostic criteria are based on behavioral observation, but current research is focusing on the neurological characteristics of ADHD.

The dysfunction of attention in ADHD is matched by a dysfunction of the prefrontal cortex, the area of the brain responsible for high level cognitive tasks and executive functioning. Positron emission tomography studies show low levels of the neurotransmitters dopamine and norepinephrine in the prefrontal cortex in adults with ADHD (Arnsten). Norepinephrine is a neurotransmitter associated with the arousal level of an animal. It has been implicated in sustaining attention on a particular task (Sergeant). Very high levels of norepinephrine have been shown to increase alertness so much that working memory and attention are impaired. Low levels of norepinephrine have also been shown to impair working memory and attention. Drugs increasing the levels of norepinephrine in subjects has been shown to reduce symptoms of ADHD, so it can be inferred those with ADHD have too little norepinephrine (Arnsten).

Dopamine is associated with reward seeking behavior and psychomotor activity. The dopamine transporter is largely responsible for transporting dopamine to and from the synapse where it activates neurons. There is a study which finds adults with ADHD to have 70% higher dopamine transporter density compared to controls (Dougherty). However, there is also a study which finds no difference in dopamine transporter density compared to healthy adults (Dyck). This research is conflicting, but the transporter is only one portion of the dopamine system. Another study shows decreased activation of the ventral-striatal reward system, a system largely regulated by dopamine, in response to rewarding stimuli (Plichta). Although the availability of dopamine transporters may not have much impact, there is definitely a deficiency of dopamine neural activation in those with ADHD as evidenced by Plichta's study. It is postulated this deficiency is responsible for relatively low motivation to achieve rewards in those with ADHD (Volkow).

This project seeks to examine the impact of attention deficit hyperactive disorder on these neurotransmitters, dopamine and norepinephrine. The existing literature shows decreased levels of dopamine and norepinephrine in ADHD compared to healthy control groups. The existing neurological literature also focuses mostly on adults with ADHD as they are easier to recruit for studies. The majority of those with ADHD receive medication which alter neurotransmitter levels and impact the results of such studies. Dougherty's study included four medicated adults with ADHD and two unmedicated adults. Dyck's study included eight medicated participants and one unmedicated participant.

The levels of neurotransmitters will change over time if medication is provided to those with ADHD. However, it can also be the case that neurotransmitter levels will change over time without medication. It is often seen that symptoms of ADHD improve into adulthood, but

adults with ADHD still persist to this day (Lange). For those adults, it is reasonable that symptoms could become progressively worse as time progresses. This project will analyze the impact of attention deficit hyperactive disorder on neurotransmitter levels over time by analyzing groups of unmedicated children and adults.

Technical Approach

This project proposes an analysis of both children and adults with attention deficit hyperactive disorder. I hypothesize that without treatment, symptoms of ADHD will become progressively worse. It is not completely fair to compare children to adults; adults have many more cells and neurotransmitters in their bodies than children. A small child might weigh about forty pounds while an adult might weight easily four times as much. Neurotransmitter levels could be analyzed in unmedicated children as they progress through life, but the dysfunction experienced without medication raises ethical concerns, so participants for a study such as this are unlikely to arise.

To examine the impact of time, four groups of participants must be recruited: unmedicated children with ADHD, healthy children, unmedicated adults with ADHD, and healthy adults. For statistical significance, I propose at least thirty individuals to be recruited for each of the four categories of the experiment. Each of the sixty adults must be the same age, ideally age twenty-five, when the growth of humans tends to level off. In addition, each of the sixty children must be the same age of ideally five years old, when ADHD symptoms are typically noticed. The similarities in age are necessary to make a fair comparison of the effects of ADHD over time. These participants with ADHD must be naïve to stimulant medication used to treat ADHD, as many people with ADHD do not show symptoms into adulthood after treatment. It is estimated only 30-50% of ADHD cases persist into adulthood (Barkley). Participants in this experiment may be difficult to recruit because ADHD is often noticed early in childhood and treated with stimulant medication.

Adults are likely to show differences in neurotransmitter levels because their bodies have developed for many more years and contain more cells. As such, neurotransmitter levels in children and adults must first be compared with their healthy counterparts, the control groups. This will gather an idea of how ADHD children compare to healthy children as well as how ADHD adults compare to healthy adults.

Positron emission tomography can be used to measure dopamine and norepinephrine levels in all four groups of participants. This can be done by using a radioactive molecule which binds to these receptor sites. However, this will simply count the number of receptor sites made available for these neurotransmitters in the body. To measure the amount of dopamine available in a participant, a drug acting as a dopamine releasing agent can be introduced into the participant's system. This will flood the receptors with dopamine. At a time ensuring concurrency, the radioactive molecule binding to dopamine sites will be introduced. Some receptor sites will be occupied by the participant's dopamine, while the rest will be occupied by the radioactive tracer molecule. The difference in the amount of radioactive tracer molecules before and after the introduction of the dopamine releasing agent will give a good indicator of

how much dopamine the participant has in his or her body. This very same process can be used to measure the amount of norepinephrine in a participant's body, using a radioactive molecule which binds to norepinephrine sites as well as a norepinephrine releasing agent. Because neurotransmitters impact each other in a system, these measurements must be taken on different days.

Because these are all different individuals, the levels of dopamine can be summed for each of the thirty individuals within each group, creating a group dopamine level for adults and a group dopamine level for children. A group norepinephrine level for adults and a group norepinephrine level for children can also be obtained. With the overall levels of dopamine and norepinephrine gathered in the four groups of participants, two ratios can be made. There will be ratios of the neurotransmitters dopamine and norepinephrine comparing the two groups of children and a separate ratio for comparing the adults. These ratios will be D(children) and D(adults) for dopamine and N(children) and N(adults) for norepinephrine. Two further ratios can be made for dopamine and norepinephrine as shown below.

$$\text{Dopamine Change} = \frac{\text{D(adults)}}{\text{D(children)}} \qquad \text{Norepinephrine Change} = \frac{\text{N(adults)}}{\text{N(children)}}$$

A value less than one indicates worsening ADHD symptoms as the dopamine in ADHD adults compared to healthy adults will be smaller than the dopamine in ADHD children relative to healthy children. A value of one indicates constant ADHD symptoms because the levels of dopamine in ADHD adults compared to healthy adults will be the same as the dopamine in ADHD children relative to healthy children. Finally, a value greater than one shows improving ADHD symptoms because the levels of dopamine in ADHD adults compared to healthy adults will be greater than the dopamine in ADHD children relative to healthy children. The same judgements can be made about the change over time of norepinephrine levels using the ratio given above.

There are thirty individuals in each of the four groups, so thirty different comparisons were averaged to create the ratios above. In statistics, the central limit theorem implies that sample sizes of at least thirty are enough to approximate a normal distribution within a population. The levels of dopamine and norepinephrine in individuals follow some distribution that likely approximates a normal curve, and thus it can be assumed by the central limit theorem that the samples acquired in each of the four groups approximates the true population of individuals in each group. Thus, it can be reasoned that the ratios calculated are valid and will extend to the general population as well.

Conclusions

Designing this experiment forced me to learn more about experimental aspects I never considered. Positron emission tomography is a powerful tool for learning more about the human body and mind. During the design of the technical approach, it was easy to make a mistake in the experimental design that would nullify any conclusions about the results. I was

forced to modify aspects of the experiment such as increasing the sample size and holding constant the age characteristics of each group to ensure validity of the experiment.

The results of the proposed experiment would enable doctors and patients to understand more about ADHD and give an idea of the future effects and needs of the disorder. Doctors and patients would have a better expectation of when stimulant medication would be necessary to treat the disorder. Patients would have a better expectation of how their symptoms will change over time. Whether my hypothesis that symptoms will worsen over time is correct or incorrect, I recommend additional research in this area to validate the results of this experiment. If possible, a study of changing neurotransmitter levels over time in the thirty unmedicated children is a different experimental method that would yield the same conclusions. This experimental method would hold more validity because the differences of unique individual neurotransmitter levels found in this experiment would be ruled out. However, it is more difficult to track unmedicated individuals over time because medication is often given to alleviate the symptoms of attention deficit hyperactive disorder.

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