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THERAPEUTIC VIDEO GAMES AND THE SIMULATION OF EXECUTIVE FUNCTION DEFICITS IN ADHD

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THERAPEUTIC VIDEO GAMES
AND THE SIMULATION OF EXECUTIVE FUNCTION DEFICITS IN ADHD

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Pharmacy
at the University of Kentucky

By
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ABSTRACT OF DISSERTATION

THERAPEUTIC VIDEO GAMES AND THE SIMULATION OF EXECUTIVE FUNCTION DEFICITS IN ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by difficulty paying attention, impulsivity, and hyperactivity. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012. In 2011, 3.5 million children were treated with drugs. Optimizing therapy can take a year, and may not be completely effective.

A clinical trial is currently being conducted of a device/drug combination using the computer game Minecraft, to determine how certain activities affect executive function, working memory, and restraint in patients diagnosed with ADHD. The human subjects' responses are being modeled using artificial neural networks (ANNs), an artificial intelligence method that can be utilized to interpret highly complex data. We propose using ANNs to optimize drug and Minecraft therapy for individual patients based on the initial NICHQ Vanderbilt assessment scores. We are applying ANNs in the development of computational models for executive function deficiencies in ADHD. These models will then be used to develop a therapeutic video game as a drug/device combination with stimulants for the treatment of ADHD symptoms in Fragile X Syndrome.

As a first step towards the design of virtual subjects with executive function deficits, computational models of the core executive functions working memory and fluid intelligence were constructed. These models were combined to create healthy control and executive function-deficient virtual subjects, who performed a Time Management task simulation that required the use of their executive functions to complete. The preliminary working memory model utilized a convolutional neural network to identify handwritten digits from the MNIST dataset, and the fluid intelligence model utilized a basic recurrent neural network to produce sequences of integers in the range 1-9 that can be multiplied together to produce the number 12. A simplified Impulsivity function was also included in the virtual subject as a first step towards the future inclusion of the core executive function inhibition.

KEYWORDS: Video games, executive functions, attention deficit hyperactivity disorder, artificial neural networks

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CHAPTER 1. BACKGROUND

1.1 Executive Functions

Executive functions are a set of effortful, top-down mental processes that govern attention and regulate behavior[1]. Executive functions enable both visualization of the future and remembrance of the past, allowing for control of one's behavior over time to accomplish long-term goals and self-reflection to recognize past mistakes so that they are not repeated. In addition to the consideration of behavior across time, executive functions also enable conscious manipulation of thoughts and ideas, which includes the use of creativity to combine conflicting ideas in novel ways.

A set of core executive functions has been proposed to serve as a foundation for higher order executive functions and the general application of executive functioning in life activities[1]. These core executive functions include working memory, inhibitory control, and cognitive flexibility. Fluid intelligence is a higher order executive function that requires the use of the core executive functions for its execution. Application of the executive functions allows for the development and use of important skills such as time management, organization, planning, self-regulation, sustained attention, and metacognition.

Working memory and inhibition are described as distinct core executive functions, but work together very closely[1]. Working memory is the ability to hold a piece of information in consciousness (short-term memory) and then manipulate it in some way[2]. Inhibitory control includes the ability to ignore environmental distractions (attentional control[3] as well as the ability to prevent automatic or impulsive thoughts and behaviors when they may not be appropriate. The inhibitory control of automatic thoughts, particularly thoughts resulting from previous experiences that may interfere with appropriate responses to present circumstances[4] is of interest in this project. When working memory is active, attention focuses on the information present in short-term memory, which precludes the capture of this attention by unproductive thoughts and supports their inhibition. Likewise, when inhibition is actively preventing the intrusion of distracting thoughts, a greater degree of attention remains free for the use of working memory.

Cognitive flexibility[5] includes the ability to change perspectives and adjust accordingly when situational changes arise, and may be conceptualized as the combined use of working memory and inhibition[1]. For example, when one attempts to change perspectives the old perspective may continue to intrude as the individual effortfully focuses their attention on the consideration of the new perspective. Thus, cognitive flexibility in this case requires the use of inhibition to prevent the focus of attention on the old perspective while the use of working memory shifts these attentional resources towards the consideration of a new perspective.

Fluid intelligence is the use of adaptive reasoning in novel situations[6]. For the purposes of this project fluid intelligence is considered as a problem solving ability consisting of the mental processes analysis and synthesis[7]. Analysis is the deconstruction of a complex idea into simpler pieces, whereas synthesis is the combining of simpler ideas

in various ways to construct larger, complex ideas. A pertinent example of the use of fluid intelligence is in the practice of time management. When considering how to complete a complex task most efficiently, one may first analyze the task carefully to determine the individual steps needed for its completion. There will be a finite number of ways to organize these steps, and the best sequence of steps will be the one that produces the best outcome in the shortest amount of time. Working memory and the synthesis process of fluid intelligence can be used to mentally rehearse the completion of varying combinations of these steps and determine the time required to complete them. Some combinations of steps may overlap better in time than others when they are completed sequentially, and some steps may be found to provide minimal contributions to the overall goal. The order of the overlapping steps may then be preserved in the final sequence, and the marginally important steps may be left at the end of the sequence to be completed after the more highly prioritized steps should time permit. In this way, fluid intelligence can work together with the core executive function working memory in a time management activity.

As will be explained in detail later, a central component of this project is the construction of computational models that simulate the use of executive functions in virtual tasks designed to resemble real-life activities that train executive functions. In the initial computational model described here, simplified representations of working memory and the synthesis component of fluid intelligence were combined to create a virtual time management activity. In lieu of behaviors being chosen and combined to complete a goal in the most efficient manner as described above, integers between 1 and 10 were chosen and combined to produce the larger integer 12. Working memory is represented here by the identification of integers that are contained in image files of handwritten digits in the MNIST dataset[8]. As a first step towards building a representation of inhibitory control, an impulsivity function that interferes with the use of the working memory handwritten digit identification function is included. Finally, the synthesis process of fluid intelligence is represented by the combining of integers into sequences to produce the number 12.

The construction of a set of virtual executive function activities that represent real-life executive function training activities in human subjects could enable the rapid computational simulation of different schedules of these activities. If a virtual set of activities can be designed to resemble the use of human executive functions closely enough, the simulations could potentially provide insight into how variations in the selection and scheduling of these activities affect the outcomes of executive function training in humans. Combinations of these activities the selection of an optimal schedule of activities to improve executive function deficits in humans. In this way, an effective virtual simulation model of executive function training activities could provide considerable time and cost savings compared to clinical studies for the optimization of training activity schedules in humans.

1.2 Artificial Neural Networks

Artificial neural networks (ANNs) are a group of computational models that are inspired by the structure and function of biological neural networks[9]. ANNs are composed of individual units that receive inputs, process these inputs, and produce an output, similar

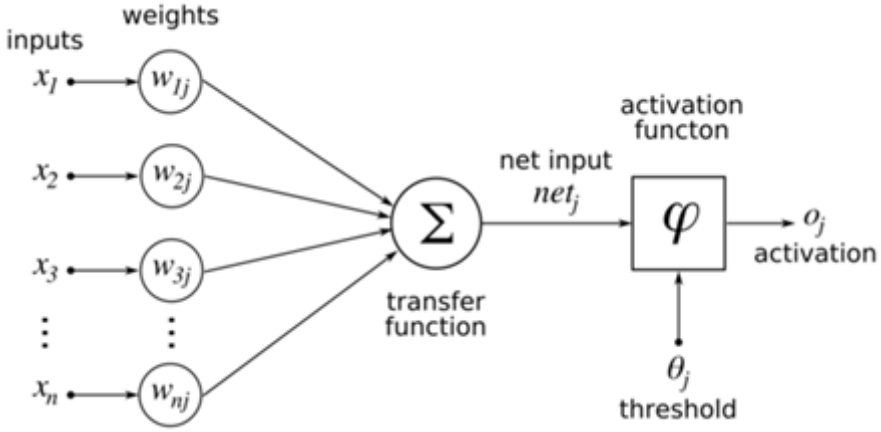
to the way that individual neurons in biological neural networks receive, process, and produce electrical signals. Multiple units are combined into layers, and these layers are combined to form the full network. Each unit in a given layer receives multiple inputs produced by units in the previous layer, and produces a single output that is used as an input for multiple units in the next layer. The design of the units, layers, and their connectivity pattern is known as the network architecture.

A single unit in an ANN consists of a set of parameters called weights and biases, a transfer function, and an activation function (Figure 1)[9]. Each unit possesses multiple weights (one for each input it receives), and a single bias value. The transfer function uses the unit's weights and biases to combine a unit's multiple inputs into a single net input value. The weights may be thought of as values that assign an importance to each input a unit receives, similar to the way that the strength of a neural synapse determines the influence that the outputs of a presynaptic neuron exert on a postsynaptic neuron. The bias parameter is included to allow a unit to produce an output in the absence of any inputs. A common transfer function uses an operation called the dot product to multiply each input by its corresponding weight parameter, and then sum these weighted inputs together. The bias value is then added to this sum to produce a single net input value for the unit, which is processed by the activation function to determine the output of the unit.

ANNs have attracted interest as a computational model in drug development and healthcare because of their ability to learn how to accomplish tasks that involve the processing of complex input data. For example, ANNs have been used to predict the quantitative structure-activity relationships of potential drug candidates[10], predict the occurrence of cardiovascular disease[11], and screen for skin cancer[12], diabetic retinopathy[13], and other retinal diseases.[14] This automation of complex tasks requiring specialized knowledge offers a significant potential advantage in time and cost savings.

Before an ANN is able to perform a task effectively, it must first learn how to perform the task by completing a training procedure[9]. ANNs are part of a broader collection of computational techniques called machine learning algorithms, which are a set of computational models that learn how to complete tasks more accurately by performing the tasks on their own without explicit guidance from a human[15]. Machine learning methods are advantageous in that they allow for the automation of complex procedures where a model can learn how to perform a task on its own without explicit instructions for how to do so. There are three categories of training procedures: reinforcement learning, unsupervised learning, and supervised learning. While unsupervised and supervised learning involve the performance of a task on only a single example of training data at a given time, reinforcement learning involves the performance of multiple sequential actions within a complex environment to maximize total rewards. In reinforcement learning, the environment consists of a series of different states presented to the model (or "agent") as inputs, where the agent makes a decision at each unique state and each decision is associated with a unique reward value[16]. After the initial step, each new state depends on the actions taken in the previous states, and each state may have a unique set of rewards associated with the possible decisions in the state. In this context, the agent is trained to make the best series of decisions as it proceeds through each state of the environment to maximize the total reward value received. A simple application of reinforcement learning is training an ANN to navigate a maze, and reinforcement learning techniques are of

Figure 1 – Structure of a computational unit in an Artificial Neural Network[17]



interest for developing navigation systems for autonomous vehicles[18].

In contrast to learning how to make multiple decisions in response to a series of related states with reinforcement learning, the models for unsupervised learning and supervised learning learn how to make single unrelated decisions in response to distinct, but possibly similar, inputs. Unsupervised and supervised learning differ in the quantity of information available with the training examples. In unsupervised learning, the training examples are presented without any information describing the correct response associated with them[19]. Clustering algorithms are an example of a computational technique using unsupervised learning. In clustering algorithms, data points are grouped into categories based on similarities in their features. The relevant features of the data points are not known in advance, and therefore the clustering algorithm must group the data points without any guidance for how to do so.

In contrast, supervised learning training procedures include information about the correct response for a training example during its presentation to the ANN[20] (Figure 2). In this case, the correct response (or training label) associated with a training example acts as a feedback mechanism to adjust the ANN's performance on the task. The accuracy of an ANN's response to a training example is determined by the ANN's loss function, which measures the deviation between the ANN's output and the correct response. The output of the loss function passes through each layer of the ANN in reverse order by the calculation of partial derivatives in a technique called backpropagation[21]. Eventually, backpropagation calculates the effect that all the weights and biases in the ANN exert on the loss function, and this result is used to adjust the values of each weight and bias in a manner that nudges the ANN's response to a training example closer to the correct response indicated in the training label.

A relatively simple variety of ANNs is a fully-connected feedforward network[22] (Figure 3). As its name implies, the fully-connected feedforward network possesses a full set of connections between each layer of units. In other words, each unit in a given layer receives an input from every unit in the preceding layer, and its output is passed on to every unit in the next layer. The term "feedforward" refers to the unidirectional forward flow of information through the ANN.

An autoassociative memory network is a fully-connected feedforward network that is trained to reproduce the input data it receives as an output[23-24]. These networks are trained by supervised Hebbian learning, which is a variety of synaptic connection between two neurons when both neurons are activated in close succession[25]. Since it is able to produce a representation of an input that may be retained after the input is removed, the autoassociative memory network can potentially perform the short-term memory function of working memory within the scope of this project.

Figure 2 – The Supervised Learning Process for Artificial Neural Networks[26]

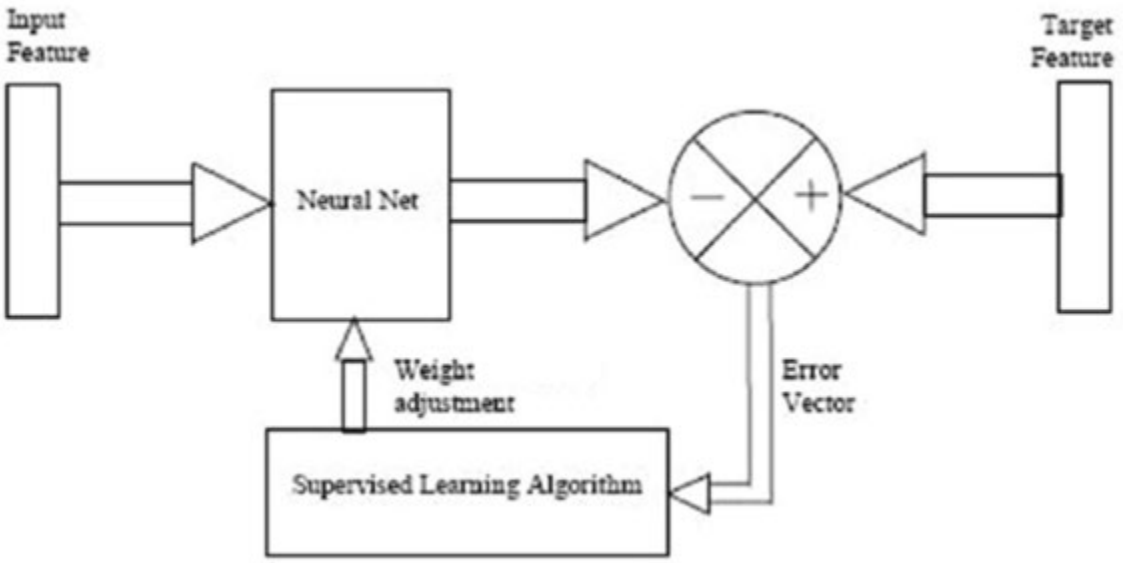
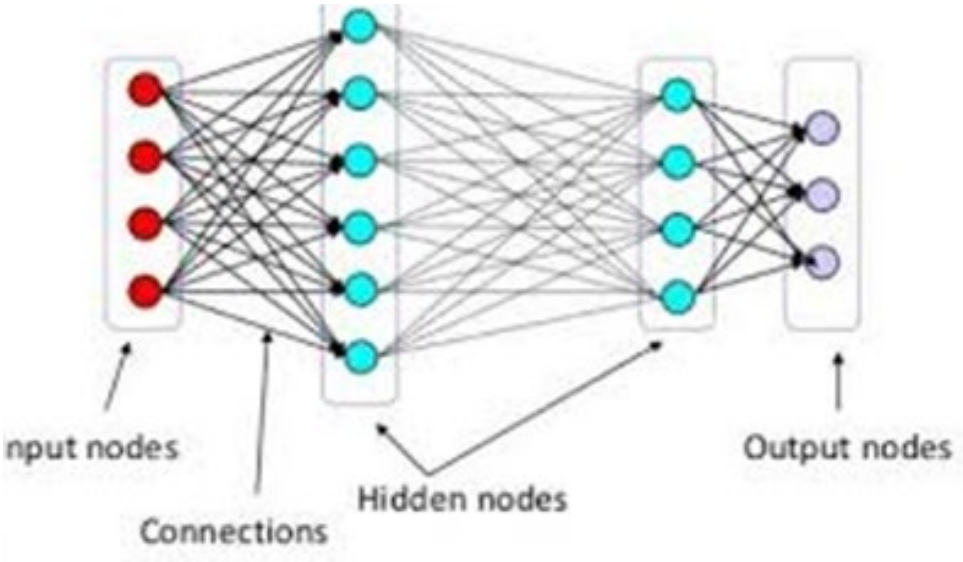


Figure 3 – Structure of a Fully-Connected Artificial Neural Network[27]



Another variety of feedforward network that does not possess a fully-connected structure is the convolutional neural network (CNN)[28]. A CNN is constructed from alternating convolutional and pooling layers. The convolutional layers consist of a set of sliding filters that learn how to detect relevant features in that layer's input data. Each unit in a convolutional layer uses a filter to detect a feature in a sub-region of the input data, and therefore is not fully connected to the outputs of the previous layer. Each unit in a pooling layer in turn connects to a sub-region of the output of its preceding convolutional layer, and compresses all the values contained in this sub-region into a single value. The design of CNNs is inspired by the structure and function of the visual cortex, making them particularly useful for analyzing visual information. In this project, CNNs are utilized to serve as a representation for the information manipulation function of working memory.

The varieties of ANNs discussed thus far are only capable of processing a single input at a time. A recurrent neural network (RNN)[29], on the other hand, is capable of processing multiple inputs (or sequences) at one time. While an RNN uses a feedforward network structure to process the individual inputs in the sequence, it possesses a unique set of weight and bias values that define a distinct internal layer for each input in the sequence. A basic RNN determines the values of each internal layer from the values of the previous internal layer by a process called matrix multiplication. This procedure is limited in its usefulness for longer sequences of inputs, however, so an RNN called a Long Short-Term Memory network (LSTM)[30] includes a set of gates between internal layers that allows for the "forgetting" of irrelevant information and improved performance.

Due to their similarity to biological neural networks, ANNs could potentially be used as a computational model for neurological activity. This premise inspired the selection of ANNs as a computational tool to simulate the training of executive functions in this project. Importantly, the neurological activities of interest in this project are the neural adaptations that occur during learning processes, rather than the actual function of neurons during mental processes. It is hypothesized that ANNs can be trained to perform virtual tasks that resemble activities in humans that require the use of executive functions, and that this training process can provide insight into the optimal way to train the use of executive functions in humans.

1.3 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity[31]. The onset of ADHD typically occurs by 3 years of age, and must occur by 12 years of age for a diagnosis. While symptom severity decreases with age, ADHD may persist into adulthood[32], when the hyperactive-impulsive symptoms typically subside but the inattentive symptoms persist[33]. The American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) has identified three ADHD subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and combined type. Diagnosis of the predominantly inattentive and predominantly hyperactive/impulsive subtypes requires the presence of at least six of their respective symptoms (listed below) for at least six months. These symptoms must be

present in at least two settings, and cause clinically significant distress or impairment in social, academic, or occupational functioning[34]. The combined subtype requires the presence of at least six symptoms from both the predominantly inattentive and predominantly hyperactive/impulsive subtypes for at least six months.

Inattentive Symptoms:

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
- Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
- Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
- Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
- Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
- Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

Hyperactive/Impulsive Symptoms:

- Often fidgets with or taps hands or feet or squirms in seat.
- Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
- Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
- Often unable to play or engage in leisure activities quietly.
- Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).

- Often talks excessively.
- Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
- Often has difficulty waiting his or her turn (e.g., while waiting in line).
- Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

Both the number of children diagnosed with ADHD and the use of stimulant medications for its treatment has been rising in recent years. The overall prevalence of ADHD increased from 6.1% in 1997-1998 to 10.2% in 2015-2016. The prevalence in boys increased from 9.0% to 14.0%, while the prevalence in girls more than doubled from 3.1% to 6.3%. However, it is unknown at this time whether these increases reflect the actual number of ADHD cases, or are instead a result of factors leading to increased diagnosis of ADHD, such as increased physician awareness, changes in diagnostic criteria, or increased access to medical care[35]. In 2011, 3.5 million children were being treated with stimulants according to parents[36]. In addition, prescriptions for ADHD meds in women of child-bearing age increased by 344% from 2003 to 2015, which included a 700% increase in women of ages 25-29 years and a 560% increase in women of age 30-34 years[37].

The causes of ADHD remain largely unknown, although environmental factors and genetic risk factors are known to be involved. Potential environmental risk factors for the development of ADHD include fetal development, diet, and family interactions[38]. The risk factors related to fetal development include prenatal smoking[39], premature birth[40], and low birth weight[41]. However, the increased risk due to prenatal smoking may be due to other environmental confounders[38], and the increased risk observed from premature birth may actually be due to the low birth weight of children who are born preterm[41]. Dietary risk factors include deficiencies in fatty acids[42], zinc[43], and iron[44], as well as the intake of artificial food colorings[45]. The observed nutritional deficiencies may be due to altered nutrient metabolism in children with ADHD rather than dietary intake, however[46]. Finally, risk factors related to family interactions include parenting behaviors and early deprivation and neglect[38]. Although difficult family environments and adverse parenting behaviors have been associated with ADHD[47-49], it remains uncertain whether these risk factors are actually a causative factor of ADHD, or whether they result from the behavior of children with ADHD[38]. However, early deprivation and neglect[50] has shown stronger evidence of a causative role.

Factors that protect against negative outcomes in children with ADHD have also been identified, although this area of research is relatively recent so the scope of findings is limited (for review, see Ref. 51). These factors are psychosocial, and can be classified as personal factors, family factors, and social factors. Coping self-efficacy[52], a sense of competence[51], and a sense of optimism and control[53] are personal factors that protect against negative outcomes in ADHD. Family factors include family cohesion[54], parenting style[55-56], parenting skill[57], and parental affection[58-59]. Social factors include friendship presence[60], friendship intimacy[61], and peer acceptance[51,62]. The effects of these factors have

been discovered in cross sectional studies and longitudinal studies of limited duration[51], so the long-term persistence of the protective effects over time has not yet been established.

With an estimated heritability rate of 0.7[63], genetic influences also play a considerable role in the development of ADHD. Investigations into genetic factors of ADHD have so far revealed modest associations for the dopamine transporter (DAT1), dopamine receptors D4 & D5 (DRD4, DRD4), and the serotonin transporter (5HTT)[64]. Therefore, many other unknown genetic variants likely interact with these genes to produce the observed large heritability rate[65].

Pharmacologic therapies are widely used to treat ADHD and have proven effective in controlling ADHD symptoms. The most commonly used pharmacologic treatments include stimulants (methylphenidate and amphetamine salts), a norepinephrine reuptake inhibitor (atomoxetine), and alpha-2 adrenergic agonists (clonidine and guanfacine)[66]. Of these, stimulants are the most efficacious and are recommended for use as the first-line treatment option[66]. Stimulants increase release of the neurotransmitters norepinephrine and dopamine release into neuronal synapses, primarily from binding to the dopamine transporter (DAT1)[67]. DAT1 is a membrane protein located in the presynaptic terminal of dopaminergic neurons, and terminates the action of dopamine and norepinephrine on postsynaptic neurons by transferring them from the neural synapse back into presynaptic nerve terminals[68]. While methylphenidate binding inhibits DAT1's reuptake activity, amphetamine reverses the direction of DAT1's neurotransmitter transport function. In other words, methylphenidate prevents removal of dopamine and norepinephrine from the synapse, while amphetamine both prevents the removal of dopamine and norepinephrine and increases its release from the presynaptic neuron via reversed function of DAT1. In addition, amphetamine displaces dopamine and norepinephrine from synaptic vesicles to increase their available cytosolic concentration for reverse transport by DAT1 into the synapse. The overall effect of stimulants is to increase synaptic levels of dopamine and norepinephrine, and increase their availability for signaling to post-synaptic neurons.

Atomoxetine binds to and inhibits the function of the norepinephrine transporter protein, which removes norepinephrine from neuronal synapses in a manner similar to DAT1's uptake of dopamine[67]. Alpha-2 adrenergic agonists enhance the action of the alpha-2 G-protein coupled receptor located in the presynaptic terminals of sympathetic neurons[67]. The alpha-2 receptor binds to the inhibitory Gi-protein; the stimulation of this receptor decreases neurotransmitter release from sympathetic neurons, resulting in a reduction in the overall level of sympathetic neurotransmission.

Despite the variety of pharmacologic treatment options available and their widespread use, there still remains a strong need to develop additional therapies[69]. While a general consensus exists for the efficacy of stimulants, a recent systematic review of methylphenidate concluded that the evidence supporting its use is of very low-quality, and more caution should be exercised in its use[70]. However, the benefits that do result from stimulant use do not persist after discontinuation and patients with ADHD still suffer from adverse long-term outcomes such as poor academic performance, drug addiction, and criminal behavior to a much greater degree than non-ADHD subjects despite optimal therapy[71]. Despite their tolerability in a majority of ADHD patients, the side effect profile of stimulants (anxiety, irritability, insomnia, gastrointestinal distress, loss of appetite, and

growth suppression) still precludes their use in a significant number of patients due to the widespread need for their use. An additional safety concern of stimulants are their long-term effects, for which there is a paucity of research in humans. However, two recent studies have shown altered cerebral blood flow responses after discontinuation of stimulant use[72] and reduced GABA levels in the pre-frontal cortex of ADHD patients who were treated with stimulants at a young age[73]. Drug treatments also suffer from further under-utilization due to parents' concerns about their safety and preference for the use of non-drug treatments[69]. Finally, the widespread use of stimulants has also led to their misuse and abuse for non-medical purposes, which may be obviated by a greater availability of other effective treatments for ADHD.

An alternative treatment strategy for ADHD attracting wide interest is the targeting of neuropsychological functioning, such as executive function impairments. Russell A. Barkley proposed an executive function theory for ADHD in 1997, which states that an impairment in the core executive function inhibition is the central causative factor in the development of ADHD[7]. Since the hyperactive behavior of children with ADHD reflects a lack of behavioral inhibition and the use of inhibition keeps attentional resources available for the use of other executive functions, Barkley reasoned that a deficit in inhibition leads to a cascade of impairments in other executive functions culminating in the characteristic behavior of ADHD.

As discussed in Chapter 2, computerized training programs (including video games) have drawn interest as a tool to train executive function deficits. Our lab is currently conducting a pilot study of the online game Minecraft as a therapeutic video game (TVG) to train executive function deficits in children with ADHD (Chapter 3). The effects of the TVG intervention in combination with stimulants is being investigated to develop a combination therapy that can address both the dopaminergic dysfunction and executive function deficits in ADHD. Although the results of this study will be used to guide the clinical development process, additional guidance for the optimization of the executive function training activities will be provided by the computational model of executive functions currently under development. This model is using ANNs to complete virtual tasks that resemble the tasks that subjects with ADHD complete in the Minecraft world, and the schedule of virtual tasks that result in maximum improvements in ANN function will determine the selection of training regimens in future clinical studies.

An orphan drug indication for a drug/device combination of stimulants with the therapeutic video game will be pursued for the treatment of ADHD-like symptoms in Fragile X Syndrome (FXS)[74]. FXS is a rare genetic disorder and is the most common form of inheritable mental retardation. Most commonly, FXS is caused by an excess quantity of CGG-nucleotide repeats (>200) in the 5'-untranslated region of the fragile X mental retardation 1 (FMR1) gene located on the X-chromosome. The expanded set of CGG-nucleotide repeats leads to hypermethylation and silencing of the FMR1 gene, and decreased production of the fragile X mental retardation 1 protein (FMRP).

The estimated prevalence of FXS is 1 in 4,000[75], which qualifies this disorder for the FDA's Orphan Drug Designation Program that promotes accelerated drug development for rare diseases[76]. ADHD symptoms are present in 80% of FXS patients, which can be treated with stimulants and alpha-2 adrenergic agonists[77-78]. However, stimulants show

efficacy in approximately 60% of FXS patient[79], so drug therapy could potentially be improved by the combination of stimulants with a therapeutic video game.

This intervention will utilize a novel personalized medicine approach where an individualized treatment regimen consisting of an initial stimulant dose recommendation and schedule of therapeutic video game activities will be determined from the initial ADHD assessment results of new patients. We hypothesize that the training of ANNs can serve as a computational model for the adaptations that biological neural networks undergo in response to practicing of activities requiring the use of executive functions. In the model, a set of ANNs will first be trained to resemble the pattern of executive function deficits reflected in a new patient's assessment responses. A large set of virtual tasks resembling the therapeutic video game activities will be tested in the model, and the set of virtual tasks that produces the maximum improvements in the ANNs of the virtual "subject" will predict the analogous set of therapeutic video game tasks most beneficial for the human patient. A future clinical study will test this hypothesis by including an experimental group with a personalized executive function activity training schedule guided by the computational model that will be compared with a control group completing an executive function activity training intervention that is not guided by the computational model.

CHAPTER 2. ADHD, PHARMACEUTICALS, AND VIDEO GAMES

2.1 Attention Deficit Hyperactivity Disorder

Diagnosis rates of ADHD in children range from 3-11% compared to 4% in adults[80-82]. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012[81]. In 2011, 3.5 million children were being treated with therapeutics as reported by their parents[81]. Stimulant medications such as amphetamines and methylphenidate are currently the first-line treatment for ADHD[66], although there are significant problems associated with their use. They are often misused, abused, and diverted for nonmedical purposes. Stimulant use is associated with, and, in many cases, limited by, side effects such as insomnia, gastrointestinal distress, irritability, loss of appetite, and growth suppression[66]. Parents also have poor perceptions of their safety[69,85-86], and thus they remain underutilized as a treatment option in children[69,85-86]. Although these medications are effective in controlling symptoms in the short term in many patients, their efficacy does not persist after discontinuation[71], many patients may experience only a partial response or no response at all[87-88], and, even with treatment, children with ADHD still suffer from greater rates of adverse long-term outcomes such as drug abuse and criminal behavior than healthy children[71].

2.2 Pharmacotherapy

Pharmaceutical therapy with stimulants is the most effective monotherapy for most patients with ADHD, with the exception of the very young[89]. The advantages of combining pharmaceutical therapy with behavioral therapy include lower cost, as personnel time with patients is reduced, and reduced doses of pharmaceuticals (50-75%)[90]. Additionally, the benefits of behavior therapy are more likely to carry forward once treatment has stopped[90]. Behavior therapy for ADHD patients includes repetitively reducing negative behaviors with consequences and increasing positive behaviors with rewards[89]. However, behavior therapy is not widely available to all patients, and its benefits are limited to the targeted behaviors only[71].

2.3 Video Games

A potential alternative approach to address these issues is to improve the cognitive processes that underlie the observed symptoms[71]. One potential intervention target to do so is executive function, which is a set of top-down mental processes that regulate distracting influences and automatic, unproductive behaviors to enable self-control[1]. Training of the core executive function working memory has previously been shown to increase cortical D1 receptor density[91]. As dopaminergic function is compromised in ADHD[92], these alterations could provide additional benefits in improving the function of patients with ADHD. To this end, computer-based programs with repeated cognitive

exercises without video game elements have been used as a treatment intervention in ADHD[93]. However, it is thought that delivery of these interventions in a video game format can help improve their effects by promoting a state of optimal cognitive performance and increasing the participant's focus and motivation to complete them[93]. Indeed, children with ADHD have shown reduced impairments in inhibition (but not working memory) while playing video games[94], and the addition of video game elements to executive function training tasks have resulted in improvement of working memory[95-96] as well as improved working memory performance over time[96].

In addition, training methods used to enhance learning have traditionally shown effects only in the specific areas targeted by the training[97]. However, healthy action video game players have outperformed non-players in a broad variety of cognitive performance measures, including some executive functions such as flexibility and top-down attention, suggesting their potential usefulness as a cognitive training tool[97]. Notably, improvements in these areas have been seen in randomized, controlled trials of non-players trained with either an action video game or a non-action video game (as an active control group) in the action video game group only, suggesting that action video games have a causative role on this improved performance[97]. Furthermore, video gaming may be able to increase motivation and one's ability to learn[98]. This effect is thought to be mediated by games producing increased striatal dopamine levels[99-100] that enhance long-term potentiation of neural connections in the striatum[101]. The potential of using a video game as a therapeutic tool was further evidenced in a recent article in the journal *Nature* that described a video game training multitasking ability that was capable of improving measures of the neurological functions that underlie cognitive control in elderly subjects[102]. Thus, by using a video-game based cognitive training intervention as part of a drug/device combination with stimulants, it could be possible to increase the efficacy of currently available treatments and/or reduce the dose of stimulants needed to control symptoms.

However, video game play has also been associated with several adverse effects. Like pharmaceuticals, the effect seen seems to be related to the amount and style of video games to which humans are exposed. First-person shooter games with violence have been associated with anxiety and fear[103]. However, these associations have been found in subjects with excessive video game use or internet gaming addiction,[104-112] (but see Ref. 113) and it is thought that the excessive gaming could be used as a form of escape from negative emotions rather than a causative factor for them[107-108,111] (but see Ref. 109). The negative outcomes of video game play include obesity, aggressiveness, antisocial behavior, and addiction[103]. Although video games could potentially be advantageous as a learning aid, increased time spent playing video games has been associated with worse academic performance[114]. Despite these concerns, there have not been any significant safety concerns reported in studies using video games for executive function training. Thus, we suspect that video game play using a schedule similar to the training interventions that have resulted in improved executive function will still have a favorable safety profile compared to pharmaceutical treatments.

Recognizing the therapeutic potential of video games, the FDA has issued a guidance for therapeutic video app developers. Pfizer and Shire Pharmaceuticals are funding research in video games, and companies like CogCubed and Akili are developing video games for approval as FDA-regulated devices. Although drug companies are

currently seeking prescription video games, they must eventually move toward drug/device combinations to increase efficacy.

Most studies investigating executive function training in children with ADHD have targeting single executive function only, mostly working memory. Visuospatial working memory is considered the most important neuropsychological deficit in children with ADHD[115] and training of working memory has been shown to alter cortical dopamine D1 receptor density[91]. A recent meta-analysis concluded that the use of cognitive training interventions targeting working memory or attention alone have resulted in substantial improvement in these executive functions, with some studies also showing improvements in parent ratings of ADHD symptoms[88]. The improvements in working memory have been shown to persist at 6 months[116-117] and 8 months[118] after completion of training. However, far transfer effects to functional areas beyond the targeted executive functions (such as improvements in academic measures) and teacher ratings of ADHD symptoms have remained largely unaffected[119-121]. These inconsistencies could potentially be due to practice effects resulting from repeated assessments affecting the executive function measures and insufficient blinding procedures affecting parents' ratings[88].

The scope of research involving cognitive training interventions targeting multiple executive functions is more limited than for those targeting a single executive function. However, studies investigating interventions targeting multiple executive functions have shown a greater magnitude in improvement of ADHD symptoms assessed by parents compared to those targeting a single executive function[88,115,122-125]. Although these improved effects could be due to an increased duration of training, it is possible that training strategies targeting a broader set of executive functions may be required to effectively address both the full spectrum of neuropsychological deficits present in ADHD as well as the inter-individual variation of deficits among children with ADHD[88].

With regard to ADHD symptom assessments by blinded raters, two recent studies investigating an intervention with added video game elements to simultaneously train multiple executive functions showed effects in teacher-rated outcomes. One intervention training working memory, inhibition, and flexibility was able to produce moderate-to-large improvements in ADHD symptoms ratings by teachers, but these effects were also obtained with the placebo intervention, suggesting that the improvements were due to general features of the intervention not related to the executive function training itself[98]. Another intervention training time management, organization/planning, and cooperation resulted in small-to-moderate improvements of parent-reported daily functioning in the areas of working memory, time management, and responsibility[126]. Improvements in time management were also reported by teachers in this study, suggesting that training interventions targeting skills that are directly applicable in daily life could potentially improve far transfer effects across multiple settings[126].

Therefore, there is still a need to further explore the potential of using video gaming interventions to train multiple executive functions, including those that are directly utilized in daily life, as a treatment for ADHD. Our laboratory is currently conducting a pilot clinical study investigating the use of the popular online game known as Minecraft in combination with stimulant medications in subjects with ADHD. Minecraft is an online video game containing a "virtual land where users can create their own worlds and

experiences, using building blocks, resources discovered on the site and their own creativity" that requires its users to apply problem solving, planning, and organizational skills for creative building and exploration[127]. It has many levels of difficulty, which allows for adaptation to users with a wide range of cognitive abilities as well as potential for incremental progressions in difficulty as the user's performance improves. Minecraft is widely available across a variety of commonly used devices, its recommended age range and content is appropriate for children, and its online world allows considerable flexibility for designing a variety of activities that challenge executive functions. In Survival Mode, Minecraft becomes an action game that should carry action game benefits.

One possible mechanism of action associated with the effects of Minecraft on ADHD is the opportunity for reinforcement of positive behavior and punishment for negative behaviors provided by Minecraft. Minecraft is an online medium with several built-in components similar to behavior therapy exercises but enjoyable so that children want to play. High performance in several major executive functions noted to be lacking in ADHD children is positively reinforced by gameplay, in that success yields completion of a specific task, acquisition of a rare in-game item, or even character survival in a given situation. Furthermore, Minecraft allows players to re-attempt failed challenges as characters re-spawn after death, though with certain disadvantages. This both gives players the impetus to improve in those executive functions (to prevent character death or hassle) and the ability to continue improving.

In contrast to the behavioral training components of Minecraft, the training of executive function is expected to yield more generalizable benefits across multiple environments, because executive function processes underlie all cognitive processes while training to modify behaviors can only affect the specific behaviors targeted[69]. In order to direct the practice of executive functions, during this trial players are required to work from an activity list with additional reinforcement for practicing behavior therapy type activities. The activity list includes two tasks of increasing difficulty for each of the following executive function skills: planning, time management, self-regulation, sustained attention, organization, response inhibition, working memory, goal-directed persistence, flexibility, and metacognition. A self-assessment component of the trial provides an additional opportunity to encourage subjects to develop metacognition. Thus, the training activities address both the underlying core executive functions (working memory, inhibition, and cognitive flexibility), as well as executive function skills utilized in school and work settings (planning, time management, self-regulation, sustained attention, organization, goal-directed persistence, and metacognition).

The primary objective of this trial is to derive a functional relationship between NICHQ scores (an assessment that measures ADHD symptoms as well as the patient's function in everyday life), game aspects of Minecraft, and executive function. All patients in this study are required to be on stimulant drugs, so the effects of varying stimulant doses on the changes in executive function can also be explored. The development of this functional relationship could ultimately enable a personalized medicine approach to the treatment of ADHD by identifying the executive functions where an individual is most deficient and predicting the stimulant drug dosage and nature and schedule of the Minecraft activities that would be most effective for treating these deficits. This strategy could potentially improve the efficacy of treatment by targeting each patient's unique deficits, as

well as reduce the time to achieve optimal treatment effects by using artificial neural networks to simulate the patients' Minecraft therapy (Neural networks can be programmed to perform tasks in Minecraft faster than humans).

The executive function deficits are assessed by a patient's pattern of responses on the NICHQ assessment, and the nature and schedule of the Minecraft activities used to correct these deficits predicted by a computational model utilizing artificial neural networks (ANNs). Artificial neural networks are a computational technique inspired by the structure and function of biological neural networks and categorized under the headings of artificial intelligence and machine learning. Due to their similarity to biological neural structures, it is possible that the learning processes that occur during the training of an ANN could be used to simulate the learning processes that occur in human subjects from the completion of cognitively demanding tasks. An abbreviated "NICHQ" which assesses behavior that can be appropriately observed in the context of the computational model will be used to measure changes of executive functioning within the model that result from the application of computational tasks that are similar to the Minecraft activities that the human subjects perform. Separate models will be developed with ANNs that show poor performance (ADHD-ANNs) and relatively good performance (control-ANNs) on these tasks. Modifications of these tasks will also be tested in this manner to determine how optimal performance improvements in the ADHD-ANNs can be produced. Finally, these modified tasks will be tested in a future clinical study to determine the external validity of the model.

The structure of these computational models will be based on three of the core executive functions: inhibitory control, working memory, and cognitive flexibility[1]. Inhibitory control refers to the ability to suppress the influence of internal or external forces that distract one from accomplishing a goal.[3-4] Inhibitory control works closely together with working memory[1], which is the ability to hold information in mind after it is no longer perceptually present and effectively manipulate it as desired[2]. For example, using working memory to focus attention on accomplishing a goal helps to remove attention from distracting impulses. Similarly, using inhibitory control to focus attention away from distracting impulses supports the use of working memory by leaving more mental "working space" available to be directed towards accomplishing a goal. Cognitive flexibility[5] involves the ability to change perspectives, which requires the simultaneous use of both inhibitory control and working memory, where inhibitory control is used to resist the influence of one's current perspective on their actions and working memory is used to hold a new perspective in attention to change one's actions accordingly[1].

The first of the core executive functions, inhibitory control, is represented by an "Impulsivity" function, the value of which will increase over time and result in the activation of a distracting activity once its value increases above a given threshold. An ANN will be able to modify the parameters of this Impulsivity function, and a repeatedly executed training procedure will be implemented where the ANN will learn to modify these parameters more effectively to prevent the distraction function from activating as training proceeds.

Secondly, working memory will utilize this inhibitory control structure, but with the inclusion of a "Goal Activation" function and a working memory mental space. This

function will work similar to the Impulsivity function, but if its value crosses a given threshold, then a goal activity function will be activated (as opposed to the distractor activity function). The working memory mental space will be represented by immediate computer memory, where function instructions (for either the goal or distracting activity) and the values of their associated parameters can be efficiently accessed and manipulated by the CPU. In this case, the implemented training procedure will be designed such that the ANN will learn to simultaneously modify the parameters of both the Impulsivity and the Goal Activation function to more effectively devote computational resources towards the completion of the goal activity and consequently complete the appropriate task function more efficiently.

Finally, cognitive flexibility will utilize the described interaction between inhibitory control and working memory, but at a given time point, the conditions of the task shall be changed such that activities other than the goal activity are to be performed for a given time period. Eventually, the conditions will be switched back so that the goal activity is to be completed once again, and this pattern will then be repeated in a cyclical manner. When computational resources are to be focused on the goal activity, the training of the ANN will involve diminishing the value of the Impulsivity function while increasing the value of the Goal Activator function as described above. However, when the conditions of the task change such that the goal activity is not to be pursued, the training of the ANN will be altered to instead increase the value of the Impulsivity function while diminishing the value of the Goal Activator function. An effectively trained ANN for cognitive flexibility will be able to more rapidly perform these transitions, and devote computational power towards the goal only when appropriate based on the given conditions.

2.4 Preliminary Feasibility Study

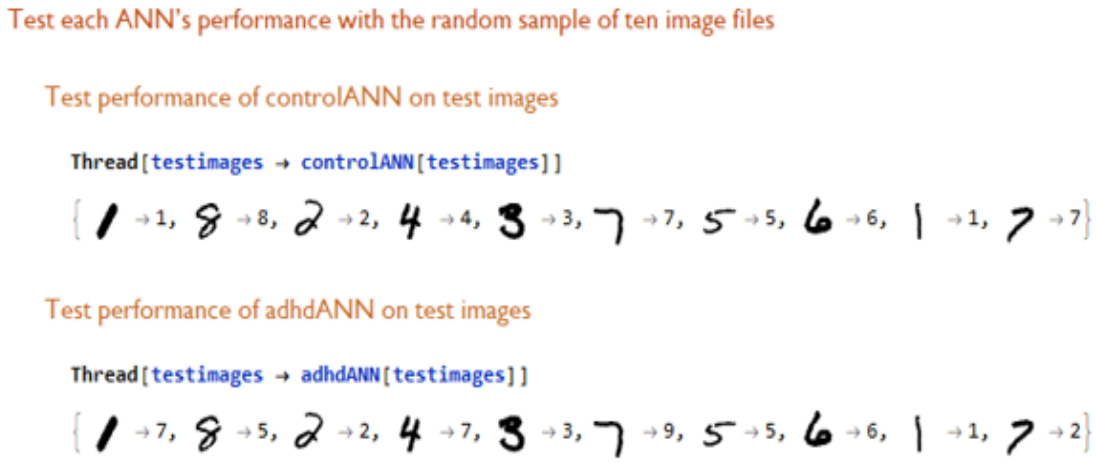
A preliminary study was conducted to determine the feasibility of performing a basic simulation of a working memory deficit in an ANN. For this experiment, a convolutional neural network (commonly used in image recognition applications) was utilized to identify images of handwritten digits from the MNIST database. The MNIST database is a publicly available database that contains a training set of 60,000 image files and a test set of 10,000 image files of handwritten numbers, each with a label identifying the correct number contained in the image[8]. The training set is used to present the ANNs with examples from which to "learn" how to identify handwritten digits, while the test set is used to measure the performance of the ANN in identify the digits after training has been completed. This dataset is a commonly used tool to benchmark the performance of ANNs in image recognition applications.

Wolfram Mathematica v11.1 was used for all calculations. Two ANNs of identical convolutional structure, but differing in training procedures, were used in this study. The first ANN was trained with the full MNIST training set and represented a "healthy" control condition, while the second ANN was trained with a truncated form of the MNIST training set and represented an experimental "ADHD" condition with a working memory deficiency. The test set consisted of randomly selected images that were not included in the training sets, and the performance of the trained ANNs was tested on six different test

sets consisting of ten images each. The control ANN achieved 100% (SD 0%) correct recognition of handwritten digits in sample images taken from the MNIST test set, while the working memory-deficient ADHD-ANN achieved only 50% (SD 8.9%) correct recognition of sample images taken from the MNIST test set (Figure 4).

Two examples of working memory (the ability to hold information in one's attention and manipulate it) include mentally relating information to derive a general principle or to see relations between items or ideas, and incorporating new information into one's thinking or action plans[1]. The truncated training procedure represented a lack of attention in the ADHD-ANN that led to its failure to derive the general principles and see the proper relations between the images of handwritten digits and the number that they contain. This deficiency was reflected in the ADHD-ANN's inability to correctly identify digits in the test set, which represented a failure to properly incorporate new information into one's thinking. Furthermore, since the ANNs were of identical structure, and differed only in the training procedure, any differences in their performance would be interpreted as being due to an environmental (rather than genetic) effect.

Figure 4 - Working Memory Deficit Preliminary Study Results



2.5 Conclusion

This work is an extensively simplified model of working memory, but future work will focus on increasing its complexity. First, the modeling of working memory can be improved by requiring the ANNs to make more complex manipulations of their input images. For example, the ANNs can be trained to receive two image files with handwritten numbers as an input, and then output the sum of these numbers. Alternatively, they could be presented with image files containing handwritten words as inputs, and trained to output these words spelled backwards.

Next, an additional task will be included (distractor activity) to model the interaction of working memory plus inhibition, as well as cognitive flexibility. This task will be a similar simple image identification task at first, such as identifying objects contained in photographs, rather than handwritten numbers. To model the interaction of working memory with inhibition, these models will first include the Impulsivity function discussed earlier that is promoting the second distractor activity task. Then, to model cognitive flexibility the ANNs will be required to switch their focus between the goal & distractor functions at a given time interval. Finally, the complexity of the model will be increased by using multiple ANNs in larger algorithms to model the more complex executive function skills, such as planning or time management.

The use of this variety of ANN as a working memory model is not ideal from a neurobiological perspective since working memory function has been linked to dorsolateral prefrontal cortex activity[4], which possesses a distinct structure and connectivity pattern from the visual cortex. Despite the structural dissimilarities of CNNs with the prefrontal cortex, working memory also relies on the cerebellum[128] where supervised learning processes are active[129], and therefore CNNs may nonetheless be useful for modeling adaptations of working memory function even if they are not capable of accurately representing working memory function itself.

It will likely not be possible to capture the full complexity of executive function processes with this approach. Nevertheless, it could be possible to develop this model to the extent that it would provide some degree of utility for gaining insights into how modifications of training tasks can affect performance of their targeted executive functions. This utilization of ANNs to optimize a therapeutic intervention in the drug development process would be a novel application that could result in considerable savings in time and resources over the trial-and-error process for optimizing therapy that is now the standard approach.

CHAPTER 3. A PILOT STUDY OF A DEVICE AND DRUG THERAPY FOR ADHD

3.1 Introduction & Background

3.1.1 Background Information

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by difficulty paying attention, impulsivity, and hyperactivity. The medical community has been largely unable to standardize an accepted definition of ADHD as indicated by the medical community′s differing definitions according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[130] and the International Classification of Mental and Behavioural Disorders 10th revision (ICD-10)[131]. ICD-10 refers to disorders in this area as hyperkinetic disorders rather than attention deficit and relies upon hyperactivity to distinguish ADHD from other disorders. The DSM-5 separates patient phenotypes into three differing presentations: predominantly inattentive-type, predominantly hyperactive-impulsive type, and combined inattentive hyperactive-impulsive. Diagnosis of ADHD is predominantly based upon patient, teacher and parent responses to standardized questionnaires containing questions based on a list of criteria for diagnosing ADHD. People with ADHD are expected to have experienced at least six symptoms of inattention (predominantly inattentive-type), or hyperactivity (predominantly hyperactive-impulsive type), or both (combined) within the six months previous to the time of the assessment.

In this study, we will use specially designed training activities performed within the environment of the popular computer game Minecraft to determine if they affect executive function, working memory, and restraint in patients diagnosed with ADHD. Various cognitive training interventions are currently under investigation for their effects on improving deficits in executive function in ADHD, and the addition of gaming elements to the cognitive training may help improve outcomes (for review, see Ref 93 P. 5-9). For example, utilization of a video game format to train biofeedback skills (reduction of heart rate through slowed breathing) in children with ADHD resulted in improved scores on the ADHD Questionnaire and the Strengths and Difficulties Questionnaire[132]. Gamification of the Conners Continuous Performance Test II, used to measure sustained attention, resulted in significant improvements in performance compared to the regular test in children with ADHD[133]. The addition of gaming elements to standardized working memory training tasks resulted in significantly improved motivation, training performance, and working memory of children with ADHD[95] and the use of a gaming task also normalized task persistence in ADHD children in a visuospatial working memory task[96]. Finally, a multiple domain executive function training game resulted in improvements in the specific domains trained (inhibition, visuospatial short-term memory, and visuospatial working memory) in children with ADHD, although no benefits were seen in overall behavior ratings[98].

3.1.2 Rationale

3.1.2.1 Rationale for use of stimulant-type medications to treat ADHD

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known, but amphetamines increase extracellular dopamine and norepinephrine. These alterations in extracellular neurotransmitters are a result of amphetamine's inhibition of the Dopamine Transporter (DAT), Norepinephrine Transporter (NET), Vesicular Monoamine Transporter-2 (VMAT- 2), and Monoamine Oxidase (MAO).

DAT and NET are located in the presynaptic terminal cell membrane, where they function to clear dopamine and norepinephrine, respectively, from the synaptic cleft into the presynaptic neuron. This clearance is necessary to end the response of the postsynaptic neuron and recycle the neurotransmitters in the presynaptic neuron for subsequent repackaging and release. Thus, competitive inhibition of DAT by amphetamine prolongs the presence of dopamine in the synapse, which results in a greater degree of dopamine signaling to the postsynaptic cell. In addition to competitive inhibition of DAT function, amphetamine can reverse the direction in which dopamine is transported. This effect can further increase synaptic dopamine levels beyond the level resulting from transport inhibition alone. Although NET primarily uses norepinephrine as a substrate, it is also capable of transporting dopamine and its inhibition can increase synaptic dopamine levels[134].

While DAT and NET are located in the presynaptic cell membrane, VMAT2 and MAO are located within the presynaptic nerve terminal. VMAT2 is responsible for transporting monoamine neurotransmitters into vesicles within the nerve terminal, after which they can be released into the synaptic cleft. When VMAT2 is inhibited by amphetamine, cytosolic dopamine levels will increase. The increased cytosolic dopamine can then be acted on by the "reversed" DAT and transported into the synaptic cleft. However, while in the cytosol, dopamine is also susceptible to oxidative degradation by MAO. By inhibiting MAO function, amphetamine prevents this degradation and leaves increased cytosolic dopamine available for transport into the synaptic cleft[67]. In contrast, methylphenidate inhibits DAT and NET and has weaker inhibition of MAO than amphetamine[67]. Thus, methylphenidate increases extracellular dopamine levels by blocking its reuptake only, rather than also increasing its release as amphetamine does[135].

3.1.2.2 Rationale for use of Minecraft as add-on therapy to stimulant type ADHD medications

Diagnosis rates of ADHD in children range from 5-11% compared to 2.5% in adults[80-82]. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012[81]. In 2011, 3.5 million children were being treated with therapeutics as reported by their parents[81]. One of the issues with continued reliance upon therapeutics to treat ADHD is that increased availability tends to increase nonmedical use of amphetamine-type ADHD drugs by adolescents and young adults. In addition, parents prefer non-drug treatment options for ADHD[83], and thus medical treatments for ADHD remain underutilized[85]. Finally, the beneficial effects of currently available drug and behavioral therapies do not persist after discontinuation[71,138], thus making alternative treatments with benefits that continue long-term highly desirable.

Some new companies make video games designed to treat ADHD, and FDA has issued a guidance for therapeutic game designers. Lexington is becoming a hotbed of

videogame development[137-138]. Pfizer and Shire Pharmaceuticals are funding research in videogames. Drug companies will head toward drug/device combinations, even though they currently seek prescription video games. Companies like CogCubed and Akili are developing videogames for approval as FDA regulated devices, but not drug device combinations. There is some evidence of efficacy of games, but the efficacy could be improved. The ultimate goal is to increase overall treatment efficacy and create the first FDA-approved device/drug combination for ADHD treatment.

To that end, this clinical trial will be conducted as an exploratory study to investigate the functional relationship between NICHQ scores, game aspects of Minecraft, and executive function. Two study groups will be included: a videogame group (ADHD drug regimen + Minecraft a minimum of 30 minutes per day, 5 times per week x 4 weeks) and a control group (ADHD drug regimen only x 4 weeks). By using a no Minecraft control group who will continue their usual ADHD medication regimen, we expect to be able to determine the effect on executive function from adding Minecraft to the usual standard of care for ADHD. (All subjects enrolled in the study will be free to play any video games or computer games that they want to play during the course of the study. However, the Minecraft group will be the only group of subjects playing in the private Minecraft Realm and doing the activities described there.) Furthermore, subjects in the control group will be taking varying doses of stimulant medications as well as different types of stimulant medications prior to enrolling in the study. This will allow for easier recruitment and, more importantly, allow for additional data to be collected. A dose response effect across dose parameters will be examined, and the introduced variance will be managed with factor analysis[139]. However, one potential problem in this study design is the effects of other medications used to treat ADHD (such as atypical antipsychotics or alpha-2 receptor agonists) that may have negative effects on cognitive function, and therefore confound the results. We expect that such effects will be negated by requiring that the study subjects are being treated with a stimulant medication, which would counteract the negative effects of these medications on cognitive function.

Previous studies which found effects of gaming interventions on executive function have used study durations ranging from 2-16 weeks, with 2-5 training sessions per week[93]. However, a less intense schedule of 5 x 30 minute (minimum) game sessions per week for 4 weeks was chosen for this study because of concerns related to lowered compliance to study procedures. These concerns are due to the study's taking place during the school year, when increased time demands for the study subjects could limit adherence to a more intensive intervention schedule.

Our hypothesis is that subjects in the videogame group (usual ADHD drug + Minecraft) will show improvements in NICHQ scores and executive function at the end of the 4 week game playing period compared to the control group.

Pharmaceutical therapy is the most effective monotherapy for most patients with ADHD, with the exception of the very young[89]. The advantages of a combining pharmaceutical therapy with behavioral therapy include lower cost, as personnel time with patients is reduced, and reduced doses of pharmaceutics (50-75%)[90]. Additionally, the benefits of behavior therapy are more likely to carry forward once treatment has stopped[90]. Behavior therapy for ADHD patients includes repetitively reducing negative behaviors

with consequences and increasing positive behaviors with rewards[89]. One possible mechanism of action associated with the effects of Minecraft on ADHD is the opportunity for reinforcement of positive behavior and punishment for negative behaviors provided by Minecraft. Minecraft is an online medium with several built-in components similar to behavior therapy exercises but enjoyable so that children are likely to want to play. High performance in several major executive functions noted to be lacking in autistic children is positively reinforced by gameplay, in that success yields completion of a specific task, acquisition of a rare in-game item, or even character survival in a given situation. Furthermore, Minecraft allows players to re-attempt failed challenges as characters re-spawn after death, though with certain disadvantages. This both gives players the impetus to improve in those executive functions (to prevent character death or hassle) and the ability to continue improving.

Application of executive functions in gameplay is exemplified in the following:

1) Executive Functions Exemplified in Construction - A great deal of time and focus are required to acquire the necessary resources and build a desired project, particularly in Survival mode (a mode of gameplay which requires players to harvest resources while harassed by cartoon monsters); a great amount of time and self-direction are required to build an ideal structure in Creative mode as well (a mode of gameplay in which players have free, unlimited access to all resources, unlimited mobility, and no danger of character death). The construction of complex structures requires inhibition as players must work exclusively on one project to complete it in a timely fashion, working memory as players must mentally construct the project in their minds in order to place building blocks on the proper squares of the game grid, planning as players choose how much of the resources they wish to acquire and design their structures, and self-monitoring as players balance their time and the amount of risk associated with the acquisition of resources.

2) Executive Function Exemplified in Mobility - Manual dexterity is required for proper placement of blocks, navigation of obstacles, and combat with cartoon monsters. All of these can be difficult, and the failure to execute these maneuvers correctly results in character death (and loss of experience and items) and/or in the frustration of traveling back to the location, often over difficult terrain.

3) Executive Function Exemplified in Fluidity - Maintaining and changing mental set and emotional regulation is applicable to overcoming challenges presented in survival mode in particular, though challenges also arise in the building process in any mode, and players often have to modify their strategies in order to succeed.

4) Executive Function Exemplified in General Gameplay - Focus and concentration skills are practiced as players must monitor their health and surroundings in the game to stay alive. Due to the fact that Minecraft is borderless, subjects can become lost if attention is not paid to their surroundings. While other games may also require monitoring of health, there is an element of required organizational skills that may be missing in other video games popular with this demographic. While subjects will likely have an exhaustive inventory of general supplies after having played for awhile, survival may mean the ability to find needed supplies quickly

and acquisition of specialized resources is still a lengthy and sometimes difficult process (when play is conducted in Survival mode).

In contrast to the behavioral training components of Minecraft, the training of executive function is expected to yield more generalizable benefits across multiple environments, because executive function processes underlie all cognitive processes while training to modify behaviors can only affect the specific behaviors targeted[69]. Moreover, training of working memory has previously been shown to increase cortical D1 receptor density[91]. As dopaminergic function is compromised in ADHD[92], these alterations could provide additional benefits in improving the function of patients with ADHD. In order to direct the practice of these executive functions, during this trial players will be required to work from an activity list with additional reinforcement for practicing behavior therapy type activities. A self-assessment component of the trial will encourage subjects to develop self-cognition, or metacognition.

In addition to its effects on behavior and executive function, Minecraft could beneficially affect neurological functions underlying cognitive control. A previous study assessing the effects of a therapeutic video game designed to train multitasking ability in elderly subjects found that improvements in multitasking were associated with increases in midline frontal theta power and long-range theta coherence between the frontal and posterior brain regions as determined by two electroencephalography methods used to assess cognitive control. These improvements persisted for six months following the completion of training and reached a level comparable to that of younger adults[102].

Furthermore, utilizing cognitive training activities in a gaming format is suggested to increase motivation and one's ability to learn[98]. This effect is thought to be mediated by games producing increased striatal dopamine levels[99-100] that enhance long-term potentiation of neural connections in the striatum[101,140].

3.1.3 Potential Risks and Benefits

3.1.3.1 Known Potential Risks of Video Games, Specifically Minecraft

The immediate risks of this study appear to be few. Although there is little research on the effect of Minecraft in humans, there is considerable research on the effects of other video games. Like pharmaceuticals, the effect seen seems to be often related to the amount and style of video games to which humans are exposed. One person shooter games with violence are associated with anxiety[141]. The negative outcomes of video play include obesity[142], aggressiveness[143], and addiction[144]. The risk of obesity is complicated by some studies that suggest high school students who exceeded the recommended screen time (TV and computers) were also more likely to consume fast food and sugary drinks and less likely to consume fruits and vegetables[145]. Additional potential risk might include eye strain[146], repetitive motion injuries[147], seizures[148], and vertigo/motion sickness[149].

Diagnosis rates of ADHD in children range from 5-11% compared to 2.5% in adults[80-82]. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012[81]. In 2011, 3.5 million children were being treated with therapeutics as reported by their parents[81]. Unfortunately, increased availability of stimulants tends to increase nonmedical use of amphetamine-type ADHD drugs by adolescents and young adults. An estimated 97% of

adolescents play video games[150]. On average, American children play video games at least one hour per day[151]. Additional nonpharmaceutical therapies are needed for ADHD because stimulant diversion is associated with increased availability of amphetamines. The prevalence of ADHD along with the total amount of time American children spend playing video games would provide a rationale for the study of both.

The video game chosen, Minecraft, is considered to be nonviolent. One of the only violent aspects is cartoon skeletons that have the ability to shoot arrows. Thus, care has been taken to select a nonviolent game. Secondly, time spent playing Minecraft was limited to 30 minutes/day, far less than the normal amount of time most American children spend playing video games. Risks have also been minimized with purchase of private Minecraft Realms for the participants. Children playing Minecraft during the trial will only interact with investigators and other subjects while playing and their play will be monitored periodically by investigators to ensure appropriate play by all.

3.1.3.2 Known Potential Risks of Video Games with CNS Stimulant Treatment

Little is known about potential risks of videogame play with a background of CNS stimulant treatment. Sudden death has been reported in association with CNS stimulant treatment alone at usual doses in children and adolescents with structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may predispose increased vulnerability to the sympathomimetic effects of a stimulant drug.

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder. Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic episode in such patients.

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses.

Other adverse effects of amphetamines include growth suppression, loss of appetite, weight loss, stomach ache, insomnia, headache, rebound symptoms, and irritability/jitteriness[66].

3.1.3.3 Known Potential Benefits of Video Games

Action video games are associated with increased multiple tracking tasks (improved attention)[152], increased basic cognitive skills such as tracking objects moving at greater speeds, better ability to detect changes to objects stored in visual short-term memory, to change tasks more rapidly, and mentally rotate objects more efficiently[153].

3.2 Objectives and Purpose

3.2.1 Primary Objective

To derive a functional[154] relationship between NICHQ scores, game aspects of Minecraft, and executive function.

3.2.2 Secondary Objectives

Using EDA and factor analysis, we will examine specific clinical symptoms of ADHD, including deficits in inhibition, working memory, planning, self-monitoring, verbal regulation, motor control, maintaining and changing mental set and emotional regulation as revealed by the NICHQ questionnaire and other assessments, that are affected by putative therapeutic features of the game Minecraft to determine which features to enhance to increase effectiveness of the intervention.

3.3 Study Design and Endpoints

3.3.1 Description of the Study Design

This clinical trial will be conducted as an exploratory, randomized parallel open label pilot study to investigate the functional relationship between NICHQ scores, game aspects of Minecraft, and executive function in ADHD patients receiving stimulant type medications as standard of care.

The study has two arms and is conducted at a single center using multiple physicians. The study agent/intervention is the video game Minecraft. Subjects will be randomized by sex and age to the video game group or the combination group. The two study groups include a study group (ADHD drug regimen + Minecraft played for a minimum of 30 minutes per day, 5 times per week for 4 weeks) and a control group (ADHD drug regimen only followed for 4 weeks). There are no schedule changes, stratifications, or dose escalations.

3.3.2 Study Endpoints

3.3.2.1 Primary Endpoint

The primary endpoint of this pilot study will be change in ADHD symptoms as measured by the NICHQ questionnaire after 4 weeks of therapeutic gaming. No statistical hypothesis is being tested. Post hoc exploratory data analysis (EDA) techniques will be applied to compare drugs used and their doses along with game features to the NICHQ results.

3.3.2.2 Secondary Endpoint

Using EDA and factor analysis, we will examine specific clinical symptoms of ADHD, including deficits in inhibition, working memory, planning, self-monitoring, verbal regulation, motor control, maintaining and changing mental set and emotional regulation as revealed by the NICHQ questionnaire and other assessments, that are affected by putative therapeutic features of the game Minecraft to determine which features to enhance to increase effectiveness of the intervention.

3.3.2.3 Exploratory Endpoints

Not Applicable.

3.4 Study Enrollment and Withdrawal

3.4.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Primary diagnosis of ADHD in accordance with DSM-5.

2. On a current regimen of a stimulant type ADHD medication, such as Vyvanse.

3. Sex: males and females.

4. Age: between 10 and 15 years of age.

5. Stated willingness to comply with all study procedures and availability for the duration of the study, including adherence to medication and play regimen.

6. Are capable, as determined by the investigator, to perform the following:

a. complete the study log.

b. are able to comply with the required study visits.

7. Have given written informed assent along with parents/legal guardians to participate in this study in accordance to local regulations before any trial related activities (other than initial screening) are carried out.

8. Are Minecraft players and have access to a full version of PC/Mac (Java) Minecraft, Xbox Minecraft, or pocket Minecraft version (Android, Kindle) that supports play on Realms.

9. Subjects' parents and subjects both currently have Google accounts and electronic devices to access Google accounts online.

10. Must have an NICHQ Vanderbilt Assessment scored by parents and teacher(s) within the last month, or get an assessment scored by parents and teacher(s) within one week of enrollment and before beginning to play the video game if the subject is in the video game arm).

11. At least one parent and the subject must be proficient in spoken and written English.

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3.4.2 Participant Exclusion Criteria

Any of the following would render a person ineligible to participate in the study:

1. Current or past history of substance abuse.

2. Patients who for whatever reason are deemed by the investigator inadequate for participation in this trial (e.g., patients with incapacitating mental illness).

3. Have previously completed or withdrawn from this study after having signed the informed consent/assent document.

4. Lack of proficiency in spoken and written English

3.4.3 Strategies for Recruitment and Retention

As the study is a pediatric study, the pediatric population is the only one being studied. ADHD disproportionately affects children and therefore, children are the subjects being recruited. Recruitment will include females and minority groups as appropriate. The ADHD population is predominantly male, so our study population will reflect the patient population. The medical investigators contacted for this trial have indicated they predominantly treat Medicaid patients, thus lower economic status patients should also be adequately represented.

Compensation ($100/subject) will be provided to children and parents in a 60/40 split to compensate for their playing time, travel time, and expenses to the site. Children will be given $60 gift cards for participation and one parent/legal guardian will be paid $40 via check.

As the study duration is only 4 weeks, study retention is not likely to be a problem. Additionally, study personnel will contact subjects periodically if subjects do not appear to be logging on and playing Minecraft or if data is not being shared with researchers. Subjects will be asked to unshare their data with us after the trial has been completed.

UK CCTS will be the only clinical site. Thirty-two patients (32) will be screened in order to enroll 16 subjects (8 female 8 male), to ensure 12 complete the study. The study will enroll 16 participants (8 female, 8 male) with a previous medically confirmed diagnosis of ADHD at the CCTS in order to have at least 12 complete the study. All of the 16 subjects enrolled will currently be on a stimulant type ADHD drug regimen with active prescriptions.

An i2b2 survey conducted in July 2016 identified 257 potential subjects which are currently on a standard of care including a stimulant type ADHD drug. It is expected that all investigators will go through their medical files and will review existing patient records to screen these patients for inclusion and exclusion criteria. Similarly, additional study candidates will be referred by other physicians or will respond to advertisements or web announcements made by CCTS if recruitment falls short of goals.

3.4.4 Participant Withdrawal or Termination

3.4.4.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

3.4.4.2 Handling of Participant Withdrawals or Termination

In case any participant drops-out from the study at any given point during the study period, every effort will be made to contact the subject by phone, mail, and email to investigate the reason for the subject stopping participation in the trial. Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible and collect study products (NICHQ assessments, Minecraft Realms, self-assessments). Additional subjects initially screened but not enrolled may be added if the investigators feel this is warranted.

3.4.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the Investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

Determination of unexpected, significant, or unacceptable risk to participants

Demonstration of efficacy that would warrant stopping

Insufficient compliance to protocol requirements

Data that are not sufficiently complete and/or evaluable

Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and IRB.

3.5 Study Agent

3.5.1 Study Agents(s) and Control Description

3.5.1.1 Acquisition

The study agent in this study is the video game Minecraft. The subjects will already be Minecraft players and will already have Gmail accounts. The subjects will receive instructions for Minecraft play via their Google Mail accounts. Study subjects will already be on a regimen of prescription drugs as standard of care from their physicians.

3.5.1.2 Formulation, Appearance, Packaging and Labeling

The Minecraft game is available for download on the Internet and has no packaging, labeling or appearance.

Minecraft Study participants in this protocol will already be on a regimen of various FDA approved stimulant-type ADHD medication therapies in various doses. Those drugs are standard of care agents and it is not practical to discuss the formulation, appearance, packaging or labeling of all the different types of possible pharmaceuticals.

3.5.1.3 Product Storage and Stability

Minecraft can be stored on a hard drive or removable media (such as a USB memory stick). Downloaded Realm worlds will be saved with a user's single player worlds. Downloaded worlds are accessible offline and are available for upload to another Realm or world on your Realm.

3.5.1.4 Preparation

Subjects will be asked to play the desktop computer version of Minecraft.

3.5.1.5 Dosing and Administration

Subjects will be asked to play Minecraft for a minimum of 30 minutes per day five times per week.

3.5.1.6 Route of Administration

Not applicable.

3.5.1.7 Starting Dose and Dose Escalation Schedule

Subjects will be asked to play Minecraft for a minimum of 30 minutes per day five times per week. There will be no escalation.

Subjects will maintain their prescribed doses of ADHD medication that were determined by their physician prior to enrollment in the study.

3.5.1.8 Dose Adjustments/Modifications/Delays

Not applicable.

3.5.1.9 Duration of Therapy

The videogame trial is scheduled to last for four weeks. Subjects will maintain current standard of care during and after the trial.

3.5.1.10 Tracking of Dose

Subjects will log their own video game play on their existing online accounts.

Parents will track children's medication compliance on their existing online accounts. They will be asked to share the data periodically with investigators.

3.5.1.11 Device Specific Considerations

Not applicable.

3.6 Study Procedures and Schedule

3.6.1 Study Procedures/Evaluations

3.6.1.1 Study Specific Procedures

Medical history will be obtained by interview by CCTS. Most recruited individuals will be the patients of the initial medical investigators and the investigators will also have their patients' histories. Investigators will be added if recruitment falls short of goals.

Questions to be asked of subjects include:

1. Do you have any current medical problems or issues other than ADHD?
2. What illnesses have you been diagnosed with in the past? Age at diagnosis?
3. What surgeries have you had in the last five years?
4. How often do you normally play computer and video games? What hardware platforms do you use (desktop, pad, phone, console?) How long is an average session of playing on each? What video games have you previously played on each? What are the dates you played these games (i.e., approximately when did you start, and if you no longer play, when did you stop?)

Medicinal history will be obtained by interview. CCTS personnel will use this information to ascertain whether subjects are eligible for enrollment as all participants are required to be currently taking a stimulant type ADHD medication.

Questions will include:

1. What prescription medications are you taking for ADHD? What are the doses and schedule?
2. What prescription medications are you taking for other indications? What are the doses and schedule?
3. What OTC medications, or herbal supplements are you currently taking? What are the doses? How often do you take them?

Physical examination will include height and weight at both exams.

Discussion Points:

1. No results will be shared with trial subjects.
2. Assessment of study agent adherence

3. Administration of questionnaires or other instruments for subject-reported outcomes, such as the NICHQ, self-assessment questions, parent reported study compliance for medications, video gaming log, and completed activity list.

3.6.1.2 Standard of care study procedures

A Psychiatrist will serve as the medical director and a site PI. The PI as well as the other physicians (Medical Investigators) are responsible for standard of care and NICHQ assessments from parents and teachers.

Standard of care for children 6-11 years of age is FDA-approved medications for ADHD and/or evidence based parent and or teacher-administered behavior therapy as treatment, preferably both[89]. Stimulant based medication is strongly recommended. Adolescents, aged 12-18, should be administered FDA-approved ADHD medication with the patient's accent. Behavior therapy may also be added to the prescription regimen. The dose of the medication should be titrated to achieve the maximum benefit of the drug with the fewest side effects.

3.6.2 Laboratory Procedures/Evaluations

3.6.2.1 Clinical Laboratory Evaluations

Not applicable.

3.6.2.2 Other Assays of Procedures

Not applicable.

3.6.2.3 Specimen Preparation, Handling, and Storage

Not applicable.

3.6.2.4 Specimen Shipments

Not applicable.

3.6.3 Study Schedule

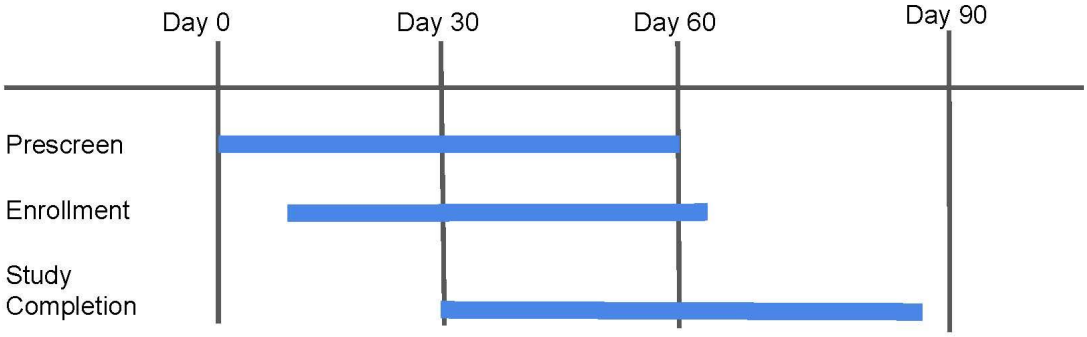
3.6.3.1 Screening

This is a rolling enrollment trial. Enrollment is expected to be open for a maximum of 62 days. Final visit will occur within 7 days of completing 42 days of video therapy.

Prescreening Visit (Day 0 to 60)

- Obtain informed consent/assent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Review history of computer and video game play (which games, start date, end date, minutes per day

Figure 5 - Therapeutic Video Games Pilot Study Timeline



Prescreening Visit (Day 0 to 60, cont.)

- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Provide participants with instructions, such as, we will evaluate your tests and contact you within 4 weeks to tell you whether you have been chosen to participate in the study. Do not do anything regarding this trial until we contact you. If you are chosen you should follow the instructions in the subject instructions (hand potential subjects' and parents a copy of these instructions). Review important parts of the trial protocol in the instructions including the difference in the trial groups, the IT requirements, and the data to which the investigators will expect to be given access.

3.6.3.2 Enrollment/Baseline

Enrollment (Day 1-44)

- Ascertain that potential participants have NICHQ scores (no older than 1 month old) from parents, collected on visit 1, and teachers, submitted by medical investigators, before subjects can be enrolled in trial. After eligibility has been determined, attempt to enroll eligible subjects, with priority given to 10-12 years old, but open up to 15 year olds if 16 subjects are not available in the 10-12 year-old range, with randomization based upon age and sex. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data. However, the initial assessment must be available for enrollment. Enrollment will be conducted by electronic means (telephone and/or email).
- Contact eligible participants via phone to reconfirm current eligibility and enrollment, provide groups assignment, and review study instructions, including continuing with ADHD medication. If potential participants can not be reached after 3 phone call or 2 emails, they will be excluded from the study and another participant enrolled. Ask subjects to verbally confirm what their activities will be during the trial to confirm their understanding. Gather Google emails addresses from parents and children, if available. Determine which version of Minecraft the subjects randomized to the Minecraft group will play (i.e. do subject wish to play via a PC or a gaming console or mobile device) Details to discuss with participants: See phone script. Remind subjects that study instructions will also be shared with them via Google Drive.
- Schedule final study visits for participants who are enrolled in the study.

3.6.3.3 Follow-up

Not applicable.

3.6.3.4 Final Study Visit

Final Study Visit (Visit 2, Day 29-86, including + 7 day window to have final visit after last completer of 28 days of video therapy)

- Record adverse events as reported by participant or observed by investigator. Subjects will be told to report AEs to their physician.
- Record weight and results of post- NICHQ questionnaire. The post study NICHQ data will allow us to assess the primary endpoint, change in NICHQ scores. The secondary endpoints can be assess through the electronic data made available to the investigative team periodically by the subjects and their parents throughout the study.
- Record participant's adherence to regimen.
- Provide final instructions: Continue your standard of care routine from your physician.
- Inform patients and parents that data will not be available to them. Since this is an exploratory study neither efficiency nor safety is being assessed. Thus, it is unlikely to present any meaningful information to the subjects. It will likely consist of only patterns and be used to guide further research.

3.6.3.5 Early Termination Visit

If an early termination visit occurs, all final study visit procedures should be performed.

3.6.3.6 Unscheduled Visit

Since this trial is only 4 weeks long, it is doubtful that any unexpected visits will occur. If an unscheduled visit should occur data concerning AEs will be documented.

3.6.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and nonprescription medications.

3.6.4.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

3.6.4.2 Prohibited Medications, Treatments, and Procedures

Not applicable.

3.6.4.3 Prophylactic Medications, Treatments, and Procedures

Not applicable.

3.6.4.4 Rescue Medications, Treatments, and Procedures

Not applicable.

3.6.4.5 Participant Access to Study Agent at Study Closure

Although Minecraft is commercially available to play for free the Minecraft Realms used in this study will be closed and not available for additional play by participants.

Table 1 - Schedule of Events in Therapeutic Video Games Pilot Study

Event	Visit 1 Screening	Enrollment	Final Visit
Registration	x		
Schedule Visit (Terminal)		x	
Informed Consent/Assent	x		
Medical History	x		
Demographics	x		
Previous & Concomitant Medication interview	x	x	x
Review Inclusion/Exclusion criteria	x	x	
Dispense questionnaire tests (ADHD assessment)	x		x
Education materials-collect questionnaires	x		x
Randomize participants		x	
CRF enter and Transmit	x	x	x

3.7 Assessment of Safety

3.7.1 Specification of Safety Parameters

3.7.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

3.7.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

3.7.1.3 Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

> Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
>
> Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
>
> Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

3.7.2 Classification of an Adverse Event

3.7.2.1 Severity of Event

All AEs will be assessed by the clinician using a protocol defined grading system. For this trial, AEs related/not related will be those associated with playing the video game. Stimulant related AE's, which are standard of care, will be reported to Medwatch at physician's discretion. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

3.7.2.2 Relationship to Study Agent

All AEs will have their relationship to study agent or study participation assessed with a level of specificity appropriate to the study design.

The clinician's assessment of an AE's relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship

between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

3.7.2.3 Expectedness

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol, as amended.

Medical Investigators (i.e., the subject's physician) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for Minecraft.

3.7.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the

last day of study participation. At the study visit, the investigator will inquire about the occurrence of AE/SAEs since the initial visit. Events will be followed for outcome information until resolution or stabilization.

3.7.4 Reporting Procedures

3.7.4.1 Adverse Event Reporting

Responsible Parties

Sponsor/Investigator/ Safety Officer- Robert Lodder

Other Investigators - Medical Investigators (site PIs), Adriane Grumbein, and Kyra Hunting

The Sponsor-Investigator/Safety Officer will inform the IRB of any events of which he becomes aware of.

3.7.4.2 Serious Adverse Event Reporting

Safety reports will be made of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 14 calendar days after the sponsor determines that the information qualifies for reporting.

The PI will report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the therapeutic agent and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

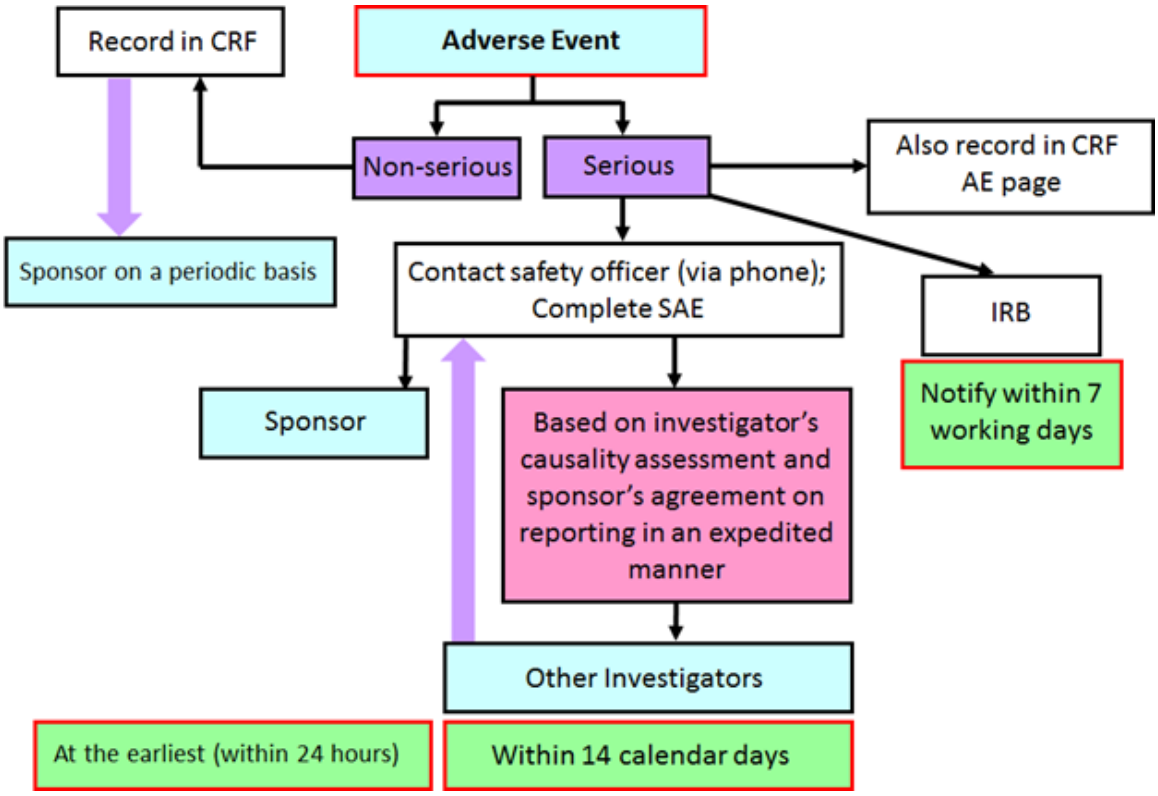
(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical.

Life-threatening suspected adverse reaction as soon as possible but in no case later than 7 days after sponsor determines that the information.

The study clinician will complete a SAE Form within the following timelines:

Figure 6 - Adverse Events Reporting in Therapeutic Video Games Pilot Study



All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness.

Other SAEs regardless of relationship, will be submitted to the study sponsor within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying IRB of any unexpected fatal or life- threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

3.7.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

A detailed description of the event, incident, experience, or outcome;

An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs that are SAEs will be reported to the IRB within 7 days of the investigator and to the sponsor within 24 hours of the investigator becoming aware of the event.

Any other UP will be reported to the IRB and to the study sponsor within 14 days of the investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by UK per Serious or Continuing Noncompliance or Unanticipated Problems Involving Risks:IRB Reporting to Federal Agencies using the UK IRB reporting form within the timeline in accordance with the SOP for Unanticipated/Anticipated Problem/Adverse Event Reporting (UK) of the IRB's receipt of the report of the problem from the investigator.

3.7.4.4 Events of Special Interest

Not applicable.

3.7.4.5 Reporting of Pregnancy

Report as a non-treatment related AE to the IRB. Physicians will ultimately make the decision as to whether to continue the drugs they have prescribed. If subjects are removed from their ADHD pharmaceutical regimen then participants will be discontinued from study. Subjects that remain on the ADHD pharmaceutical regimen will continue in the study.

3.7.5 Study Halting Rules

Administration of study agent will be halted when three severe AEs determined to be "probably related" are reported to the Study Coordinator. The Study Coordinator will notify the study sponsor and investigators immediately when the third severe event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the IRB within 24 hours of this occurrence and will provide the IRB with AE listing reports. The Investigative team, medical investigators, and CCTS will convene an ad hoc meeting by teleconference or in writing as soon as possible.

3.7.6 Safety Oversight

As overall risk of this study is extremely low due to use of subjects' normal standard of care FDA approved pharmaceutical and a non-rated, fairly innocuous video game (No language concerns, limited violence (i.e. cartoon skeletons shooting arrows and scary cave noises), as well as portals to the Nether). Therefore, a data safety management board will not be used. Safety oversight will be under the direction of the Monitor, with prior expertise in clinical monitoring. The Monitor will inspect the CCTS site at least once to assess data in the study. The Study Monitor will provide its input to the study sponsor.

3.8 Clinical Monitoring

Our designated monitor will conduct the monitoring. The monitor has experience monitoring other human trials. Monitoring will include an on-site initiation visit and close

down visit. Additional remote monitoring will be conducted to verify data by our auditor. Data verification will be comprehensive (100%) of the primary endpoint. Secondary endpoint verification of data will be more random with at least 10% of data verified. The monitor will also distribute monitoring reports to the Sponsor/Investigator and our research coordinator at CCTS.

Independent audits will not be conducted to ensure monitoring practices are performed consistently across all participating sites.

CCTS will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

3.9 Statistical Considerations

3.9.1 Statistical and Analytical Plans

This is a pilot study to investigate video game use as an add-on to stimulant type ADHD medications.

3.9.2 Statistical Hypotheses

None. This is an exploratory data analysis to look for relationships between game design factors and NICHQ scores and executive functions.

3.9.3 Analysis Datasets

Safety Population - All subjects who play at least one day on the trial Minecraft realm will be included in the safety analyses. All adverse events reported in this study will be listed and tabulated using descriptive statistics, frequencies, and proportions.

Intent-to-Treat (ITT) Analysis Dataset will include all randomized subjects.

Per-Protocol (PP) Analysis Dataset: All subjects with a pre- and post-trial NICHQ questionnaire scores and completed at least 80% of each of the components of the study.

3.9.4 Description of Statistical Methods

3.9.4.1 General Approach

This is a pilot study with a parallel design in which one group plays Minecraft and the other group does not. Both groups will already be receiving the ADHD standard of care stimulant drugs. No preliminary data are available and there are no expectations regarding the results. This pilot study will enable us to propose further studies with testable statistical hypotheses.

Exploratory data analysis (EDA) techniques will be used for analysis. EDA is an approach to analyzing data sets to summarize their main characteristics, often with visual methods. A statistical model may or may not be used, because the purpose of EDA is primarily to see what the data can tell us beyond a formal modeling or hypothesis testing task. Typical EDA modeling techniques include: box plot, histogram, Multi-vari chart, run chart, pareto chart, scatter plot, stem-and-leaf plot, parallel coordinates, odds ratio, multidimensional scaling, targeted projection pursuit, principal component analysis (PCA), multilinear PCA, projection methods such as grand tour, guided tour, and manual tour, interactive versions of the plots, single linkage cluster analysis, and other forms of hierarchical clustering methods. Quantitative techniques that may be applied include median polish, trimean, and ordination to distinguish related patterns. Post hoc tests of significance may be performed. In addition, exploratory data analysis enables checks of assumptions (e.g., normality) underlying statistical procedures.

3.9.4.2 Analysis of the Primary Efficacy Endpoint(s)

For the primary endpoint, due to the small sample size and the fact that this is a pilot study, exploratory data analysis will be used. Data to be collected includes pre-play and post-play NICHQ questionnaire scores, drugs and doses, and executive functions played out in Minecraft. We will be looking for correlation trends and goodness of fit of linear and nonlinear models as well as the presence of covariates and factors in the predictive model for NICHQ scores.

All attempts will be made to prevent any missing values. Data imputation may be done as part of EDA. For the analysis of the primary endpoint (NICHQ values), the Last Observation Carried Forward (LOCF) concept will be used for subjects who discontinue prematurely from the study. These results will be compared with those obtained by the use of data splines. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data and continue with only the assessments from the parents.

Data points that appear to be erroneous or inexplicable based on clinical judgment will be investigated and considered outliers. If a data point is identified as an outlier, two analyses will be performed, one with the outlier data point and one without the outlier. All data points will be reported in the listings, including any data point that may have been identified as an outlier. No data points will be excluded from the listings.

3.9.4.3 Analysis of the Secondary Endpoint(s)

Secondary Endpoint exploratory data analysis will include subject reflection data, number of Minecraft assigned activities completed, subject-reported compliance rate of game play and pharmaceutical use, Minecraft Realm history, sex, age, and drugs and dose

levels as the factors of interest. For missing data, models will be built with and without data imputation and the results compared .

3.9.4.4 Safety Analyses

All subjects who play at least one day in the trial Minecraft realm will be included in the safety analyses. All adverse events reported in this study will be listed and tabulated using descriptive statistics, frequencies, and proportions.

Safety data will be analyzed for all subjects in the safety population. The safety population is defined as all subjects who have signed the study Informed Assent Document and have played at least one day in the Minecraft Realm. The safety variables that will be analyzed, at the minimum, include all reported adverse events.

All adverse events (AEs) as defined by the Common Terminology Criteria for Adverse Events[155] (CTCAE) will be analyzed for safety and tolerability. All study emergent adverse events (TEAEs) will be coded using the latest version of the MedDRA dictionary.

The number and proportion of subjects who report any TEAE will be tabulated by study group. All reported TEAEs will be summarized using descriptive statistics (n, mean, median, range, SD, or number and percentage of subjects) per study group. Study-emergent adverse events are defined as those events occurring or worsening upon or after receiving the first exposure to the randomized study agent (Minecraft). Adverse events will be listed by study group and subject. For any inferential statistics, appropriate statistical tests [Chi-square or Fisher's exact tests for categorical variables and Analysis of Variance (ANOVA) or Analysis of Covariance (ANCOVA) with the baseline value as the covariate for continuous variables] will be used. These models along with their parameters will be detailed in the SAP.

The Intent-to-Treat (ITT) population, safety population, and efficacy evaluable population will be defined and described in detail as part of the Statistical Analysis Plan (SAP). The SAP will be developed and finalized before the database is locked. This is a pilot study of a videogame and it is not clear what kind of safety information will be collected if any during the course of the trial. Information gathered during the interim analysis may help in the design of the SAP.

3.9.4.5 Adherence and Retention Analyses

Minecraft Realms provides user statistics to allow some subject adherence analysis. Additionally, users will be required to provide some user completion data of Minecraft associated activities. All subjects will keep a log of video gaming play (all games, including

Minecraft). The log will include dates, times, and specific video games played, which will be analyzed for adherence and possible confounders.

3.9.4.6 Baseline Descriptive Statistics

Baseline demographic data will include age, sex, and race Baseline intervention data will include NICHQ pre-study questionnaire scores, gaming history, and medical and drug history.

3.9.4.7 Planned Interim Analyses

An interim analysis will be conducted by the PI two weeks after the study begins to ensure the software is working properly and that all relevant data are being collected in the CRF. Conducting an interim analysis will allow investigators to determine any issues associated with subjects' use of technology and/or missing data and resolve these issues before database lock. There is no risk in conducting an interim analysis because the study is not blinded

3.9.4.8 Additional Sub-Group Analyses

Both the primary and secondary endpoints will be analyzed based on age, sex, and race.

3.9.4.9 Multiple Comparison/Multiplicity

Not applicable.

3.9.4.10 Tabulation of Individual Response Data

Individual participant data will be listed by measure and time point.

3.9.4.11 Exploratory Analyses

Exploratory analysis will be performed on the NICHQ scores, including:

Self-reflective scores, video gaming logs, drug use, and Minecraft Realm play by subjects digitally saved during the trial will be analyzed post hoc. Exploratory data analysis (EDA) is an approach to analyzing data sets to summarize their main characteristics, often with visual methods. A statistical model may or may not be used, because the purpose of EDA is primarily to see what the data can tell us beyond a formal modeling or hypothesis testing task. EDA will be conducted to identify outliers, trends and patterns in data that merit further study.

Types of exploratory procedure will include: box plot, histogram, multi-vari chart, run chart, pareto chart, scatter plot, stem-and-leaf plot, parallel coordinates, odds ratio, multidimensional scaling, targeted projection pursuit, principal component analysis, principal curve analysis, multilinear PCA, projection methods such as grand tour, guided tour and manual tour, interactive versions of these plots, single linkage cluster analysis, or

other hierarchical clustering methods. Typical quantitative techniques that may be used include median polish, trimean, and ordination.

3.9.5 Sample Size

The study will enroll 16 subjects (8 female, 8 male) at the UK Center for Clinical and Translational Science (CCTS) with a previous medically confirmed diagnosis of ADHD in order to have at least 12 complete the study. As this study is primarily exploratory, no sample size calculations were performed. Having 6 subjects per group allows a standard deviation to be calculated as well as a mean for each group, and also minimizes the number of subjects exposed to the intervention in this preliminary pilot study.

If a participant is lost to follow-up at any point during the trial the subject outcome will be assessed in the intent to treat analysis under the principle of the last observation carried forward (LOCF).

Statistical software used will include R and Matlab.

3.9.6 Measures to Minimize Bias

3.9.6.1 Enrollment/Randomization/Masking Procedures

The population of subjects with ADHD is predominantly male. The enrollment of sexes between the two study arms will be equalized as much as possible. The enrollment of different races and ages will also be equalized between the two arms as much as possible within the constraints of the small sample size. Participants who discontinue early will not be replaced.

The exploratory pilot study is open label and blinding procedures will not be employed.

3.9.6.2 Evaluation of Success of Blinding

Not applicable.

3.9.6.3 Breaking the Study Blind/Participant Code

Not applicable.

3.10 Source Documents and Access to Source Documents

Appropriate medical and research records will be kept for this trial for a minimum of 6 years. FDA and IRB personnel will be given access to source data as needed.

Source Documents and Data

Participant files included in trial: CRFs, study compliance logs (gaming and medication), self reflection questions, pre- and post-study completed NICHQ questionnaires, and memoranda.

Software as a Service Vendor (SaaS) Models[156]

This project will use the multi-tenant infrastructure cloud provided by Google. The inclusion criteria will limit subjects to those who are already using Google services. The security and privacy controls are basically the same for everyone, with a few variations such as two factor authentication which can be enabled or disabled by the subjects. (The therapeutic video game (TVG) project can only be accessed with two-factor authentication on, but individual subjects have the option of using two-factor authentication or leaving it turned off for their own data). 21 CFR part 11 compliance is gained by a business associate agreement with Google, by designing our security controls to interface with those specified by the agreement with Google, and by following our SOP's (built around 21 CFR part 11 compliance). Google also employs version control making the trial documents, even those completed by subjects, completely traceable. Version control, a standard feature of Google Drive, allows researchers to monitor the date, ownership, and exact change made to any source document, including assessments. Minecraft Realm administrator privileges also allow the research team to access the individual playing time metrics to analyze for discrepancies between actual time played versus the self reported playing time.

Platform as a Service (PaaS) vs. SaaS[157]

NIST defines PaaS as the capability provided to the user to deploy onto the cloud infrastructure programs created by the user or acquired by the user. Acquired applications are created using programming languages, libraries, services, and tools supported by the provider. The purpose of PaaS is to provide a programming platform to create a software application solution without the overhead of hosting and maintaining the underlying technology stack.

Figure 7 - Software as a Service (SaaS) Vendor Model

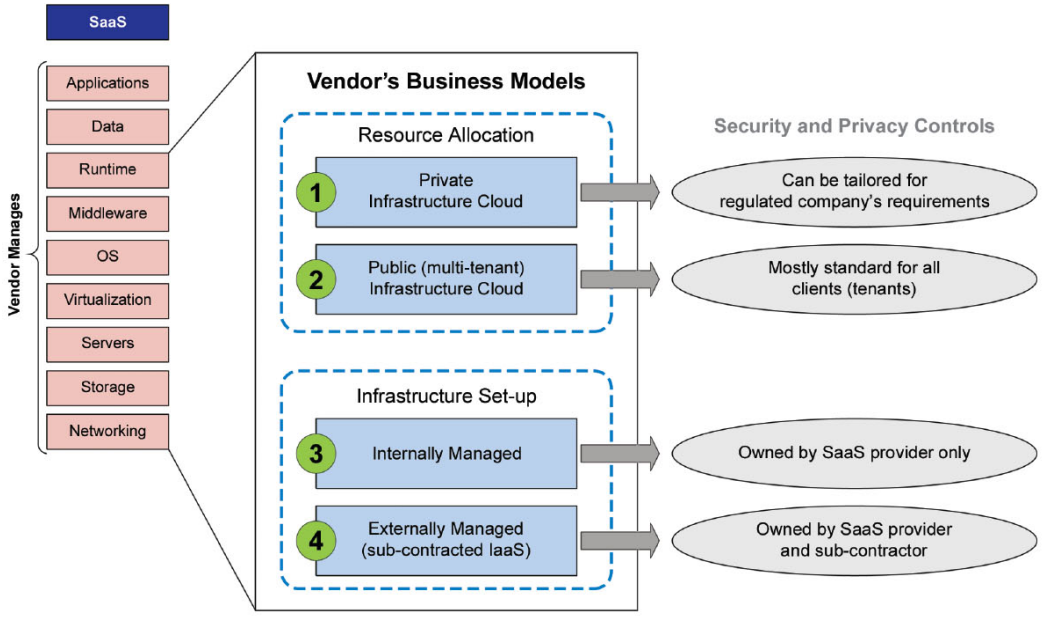
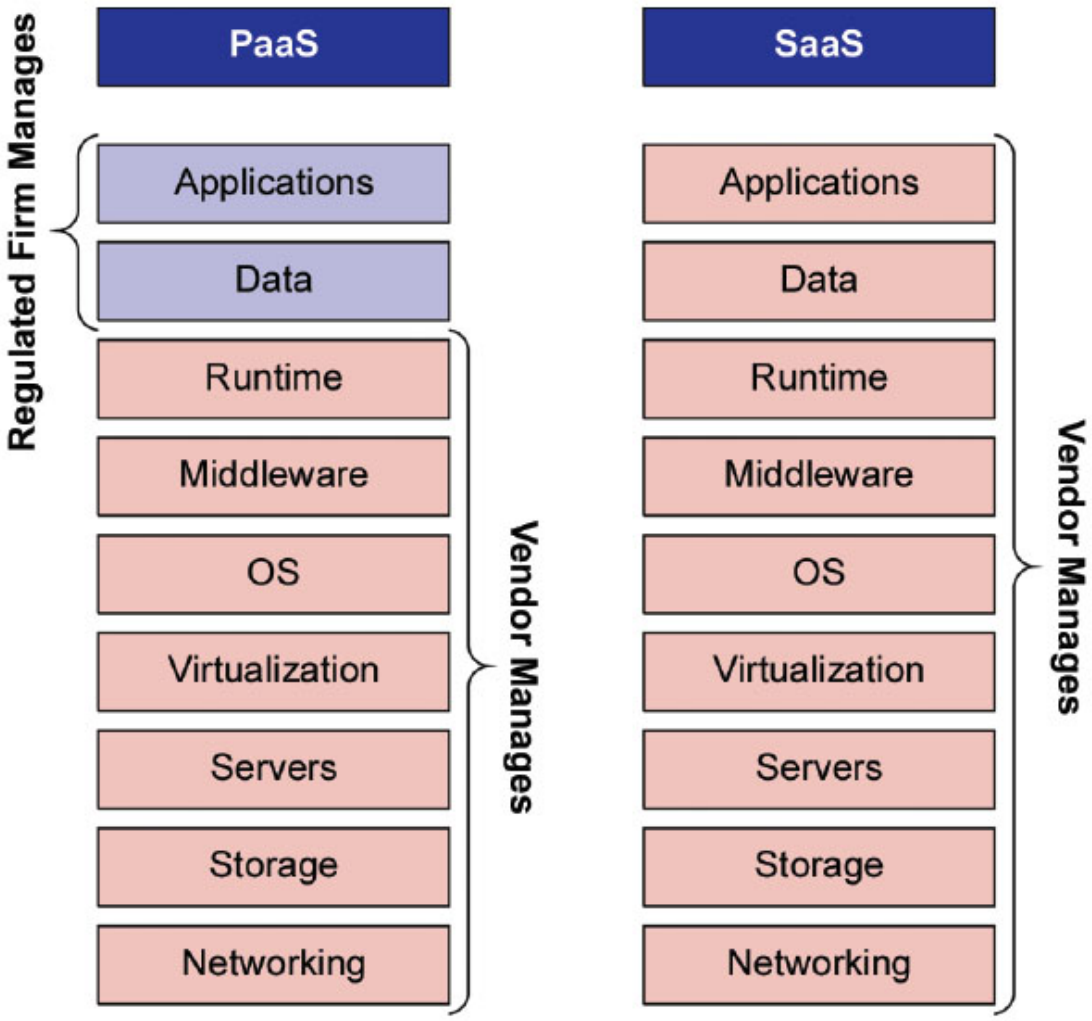


Figure 8 - Platform as a Service (Paas) Vs. Software as a Service (Saas) Vendor Model



NIST defines SaaS as the capability provided to the user to run the provider's applications executing on a cloud infrastructure. The applications are accessible from various client devices through either a thin client interface, such as a web browser, or a program interface. The user does not manage or control the underlying cloud infrastructure including network, servers, operating systems, storage, or even individual application capabilities, with the possible exception of limited user specific application configuration settings.

Using both SaaS and PaaS enables the encryption of subject-provided data from a SaaS system in a PaaS system (the Therapeutic Video Games or TVG Google PaaS).

Data stored will be encrypted using the OpenPGP standard as defined by RFC4880. Data transmitted on networks will be encrypted by Transport Layer Security or Secure Sockets Layer.

The list of subjects and ID numbers will be encrypted with a different key than the key used to encrypt all of the other data.

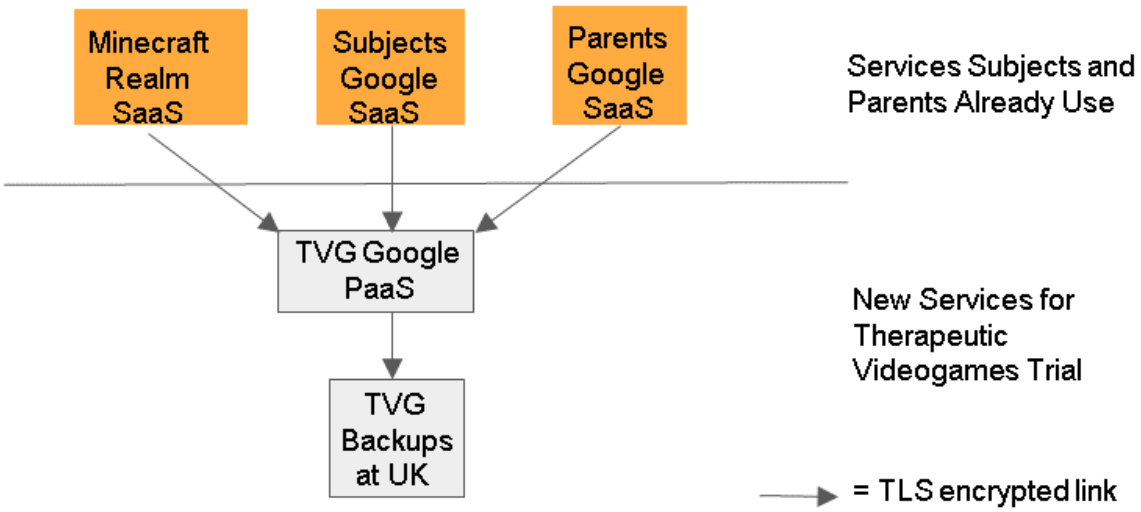
Cloud services the subjects and their parents already use include Minecraft and Google by the inclusion and exclusion criteria. These are all SaaS. The data aggregator to collect the subjects information from Minecraft in Google must have access to Google (PaaS) in order to create the backup at UK.

CCTS personnel, PI, the trial Monitor, and the trial Auditor will have access to CRFs. CRF data will be recorded electronically because most of the data (which include the Minecraft Realm evolution over 4 weeks as recorded for backup purposes in save-sets, as well as subject reflections on gameplay for Minecraft, and logging of other video game play are in large data sets and only available in electronic form. Other CRF data include medical problems/issues, past illnesses as well as age at diagnosis, surgeries, amount of time subjects spend playing video games, gaming platform, typical length of playing session, video games previously played, age at which subject started playing, list/doses of current prescription, otc, and herbal supplements being taken, and height/weight.

The de-identified CRF data listed above will be copied to a compact disk for archiving. The de-identified data will also be available in the UK repository. The data will be de- identified during the download process by removing fields tagged as identifiers as part of the download process.

The CCTS study coordinator, will input the baseline NICHQ teacher scores into the eCRF from paper records if a teacher test record exists in participants' files that is no

Figure 9 - Service Models for Therapeutic Video Games Pilot Study



more than 1 month old, once subjects' parents/legal guardians have given consent for the information to be accessed.

Study and drug compliance records subjects make on their own Google Drives (Google is an inclusion criterion), as well as study reflection questions, will be shared by the subjects with the PI) online via Google, ensuring protection for data with personal identifying information (PII) or personal health information (PHI). The PI will automatically collect the shared data, which will be de-identified while still on Google and downloaded for backup to a password-protected single-user computer behind a firewall. Periodically and at the end of the study, the data will be downloaded to a password-protected compact disk.

3.11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks for the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data. However, the initial assessment must be available for enrollment.

The monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, and GCP.

The investigational site will provide direct access to all trial related materials, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

3.12 Ethics/Protection of Human Subjects

3.12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

3.12.2 Institutional Review Board

The protocol, informed consent/assent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent and assent forms must be obtained before any participant

is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

3.12.3 Informed Consent Process

3.12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: Informed Consent, Assent, web advertisement, activity list, video gaming log, drug compliance log, example self-assessment question list.

There are two ways in which subjects may enter this trial. In the first way, subjects will be referred by their physician. In this case, the physician will obtain informed consent and assent. The second way is through advertisements. When a subject responds to an advertisement, the subject will have first contact with the research coordinator in the CCTS, and will be taken through the informed consent and assent process by the clinical research coordinator in the CCTS. The medical investigator or clinical research coordinator will explain the research study to the participant and answer any questions that may arise. The participant of legal age will sign the informed consent document prior to any procedures being done specifically for the study. A participant of less than legal age must sign an assent form, while that person's parent or guardian must sign the consent document. The participants (i.e., the subject or the subject's parent) may withdraw consent or assent at any time throughout the course of the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the

study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

3.12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent and Assent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent / assent document prior to any procedures being done specifically for the study. The participants may withdraw consent or assent at any time throughout the course of the trial. A copy of the informed consent / assent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

3.12.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UK Data Repository and on password protected CD. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical personnel and CCTS research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the UK Data Repository.

3.12.4.1 Research Use of Stored Human Samples, Specimens, or Data

The investigator will assure that subject's anonymity will be maintained. On CRFs or other documents submitted for analysis, subjects will not be identified by their names, but by an identification code. The investigator will keep a separate log of subjects' codes and names.

The data from this study may be used for additional analysis, but it will be coded or blinded data. Data collected for this study will be analyzed and stored by Investigator. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Investigator/Sponsor's lab, under the supervision of PI, for use by other researchers including those outside of the study. Permission to transmit de-identified raw data to the designated UK data repository will be included in the informed consent.

3.12.5 Future Use of Stored Specimens

Not applicable.

3.13 Data Handling and Record Keeping

3.13.1 Data Collection and Management Responsibilities

All data will be entered on CRFs at each examination, reviewed and verified. To ensure accurate, complete, and reliable data, Investigator/Sponsor will do the following:

Provide instructional material to study sites, as appropriate

Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, how to complete the CRFs, and study procedures.

Periodic visits will be made to the study site

Be available for consultation and stay in contact with study site personnel by mail, telephone, and/or fax

Review and evaluate CRF data using standard computer algorithms to detect errors in data collection

Conduct a quality review of the data base

To ensure the safety of participants in the study, and to ensure accurate complete, and reliable data, the investigator will keep records including clinical notes, and subject medical records in the subject fields as original source documents for the study. If requested the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB with direct access to original source documents.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a file on Google Drive, a data capture system. Clinical data will be entered directly from the source documents, if necessary.

This project will also use the multi-tenant infrastructure cloud provided by Google. The inclusion criteria will limit subjects to those who are already using Google services. Data, such as drug and study compliance logs and subject evaluation questions, will be uploaded to a secured Google Drive web page which uses Secure Sockets Layer for transmission and shared with Dr. Robert Lodder by the subject. The security and privacy controls are basically the same for everyone, with a few variations like two factor authentication. (The TVG project can only be accessed with two factor authentication on, but individual subjects have the option of using two factor authentication or leaving it turned off for their own data). 21 CFR part 11 compliance is gained by a business associate agreement with Google, by designing our security controls to interface with those specified

by the agreement with Google, and by following our SOP's (built around 21 CFR part 11 compliance).

3.13.2 Study Records Retention

In order to comply with HIPAA requirements, IRBs generally require investigators to retain research records for six years after completion of the study[158]. However, most FDA regulations require records be kept at least 2 years post-marketing approval, which could be as long as 10-15 years in this particular case. Therefore, records will be kept minimally 6 years but possibly up to 15 years by the Sponsor/Investigator. Records, which are expected to be only electronic, will be maintained in a secure fashion with limited access, including additional controls to ensure password protection, authenticity, integrity, confidentiality of electronic records.

3.13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

Quality Assurance and Quality Control, section 5.1.1

Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to PI. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

3.13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

3.14 Study Administration

3.14.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study PI, Co-Investigators, and Medical Investigators. The Steering Committee will meet in person as needed.

3.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership as well as the University of Kentucky has established policies and procedures for all study group members to disclose all conflicts of

interest and will establish a mechanism for the management of all reported dualities of interest. However, there are currently no conflicts of interest to disclose at this time among study leadership members.

CHAPTER 4. COMPUTATIONAL MODEL

4.1 The Virtual "Subject" as a Computational Model

To enable the computational simulation of tasks requiring the use of executive functions in humans, computational models representing the executive functions working memory and fluid intelligence were constructed. An impulsivity function was also built as a first step towards the construction of a model for the behavioral inhibition executive function. These virtual executive function models and the impulsivity function were then combined in a virtual Time Management activity requiring their combined use for its completion. In this context, the virtual "subject" is defined as the combination of the executive function models within the Time Management activity (Figure 10).

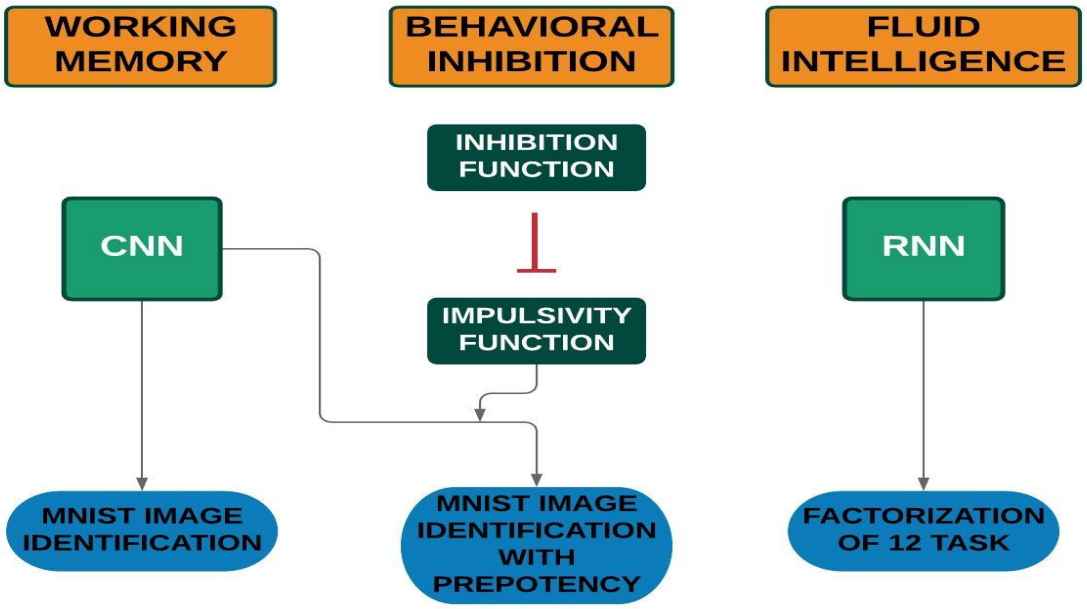
Unique virtual "subjects" can be designed by varying the parameters of the executive function and impulsivity models. The working memory and fluid intelligence models contain ANNs, but the impulsivity function does not. As a result, the performance of the working memory and fluid intelligence models can be modified by varying the training parameters for their respective ANNs, but modification of the impulsivity function requires manual manipulation of its parameters.

In this first implementation of the model, different groups of virtual "subjects" are created by varying the training procedures of ANNs to form groups that differ in the level of performance in the tasks that these ANNs are trained to perform. The training variations introduced here include the number of training examples presented to the ANNs during their learning and the duration of their training. When the efforts of multiple ANNs trained to perform single tasks are combined to work together on a larger, more complicated task, there will be a complex relationship between the set of training parameters for all the ANNs and performance on the larger task. If this relationship is defined as a function that receives the ANN training parameters as independent variables and transforms them into performance on the larger task as the dependent variable, an optimization problem can be created to maximize the improvement in performance that occurs with minimum variations in training. If this model can be developed to possess a sufficient amount of translational applicability to human subjects with executive function deficits, then the results of the optimization could provide guidance for designing interventions to treat these executive function deficits in humans.

4.2 Generating Working Memory Deficiencies (Colab Notebook)

As a first step towards the creation of a computational model of working memory deficiencies, convolutional neural networks (CNNs) were trained to identify handwritten digits in the MNIST dataset. The Keras Machine Learning library[159] was used to create and train the CNNs and the experiment was run in a Google Colaboratory Notebook. In this implementation, the input of an MNIST image file into the first layer of the network is proposed to represent the holding of information in consciousness

Figure 10 – Building the Virtual "Subject"



component of working memory. The subsequent processing of this image pixel data by the internal network layers is proposed to represent the information manipulation component of working memory. Two groups of CNNs were created by varying the number of MNIST images (the size of the training set) used in their learning process. A "healthy" control working memory group consisted of CNNs trained to achieve high accuracy in the handwritten digit recognition task, while a "deficient" working memory group consisted of CNNs trained to achieve approximately half the accuracy of the "healthy" control group.

All of the CNNs in both groups possessed an identical architecture, or structure of layers and connectivity between individual units. The architecture chosen was a modified version of the original historical CNN called lenet that was developed to identify handwritten digits in MNIST to automate zip code recognition for postal service[28,160]. The CNN architecture used here consist of two sets of convolutional and pooling layers, followed by two fully-connected layers, and a softmax classifier. As discussed in Chapter 1, each unit in a convolutional layer is only connected to a limited set of the inputs provided by the previous layer. The first convolutional layer in a CNN receives the input data to the network (the image files themselves) as its input. The units in a convolutional layer are arranged in a three dimensional rectangular shape, and the units in each two dimensional "slice" of this rectangle shares the same set of weights and biases. The shared set of weights & biases for the units in each slice is called the kernel, and can be thought of as a filter that slides across the layer's input to detect features that are used for determining the final output of the CNN. Each convolutional layer is followed by a pooling layer that reduces the number of parameters of the network by reducing the size of the convolutional layer's output before it is used as an input for subsequent layers. Similar to the units in a convolutional layer, each unit in a pooling layer is also connected to a limited set of inputs and simply saves the maximum value of the inputs it receives. The two fully-connected layers reduce the quantity of outputs from the convolutional and pooling layers to the number of classes that the model predicts. In the case of the MNIST dataset, which contains images of the numbers 0-9, there are ten different classes. Finally, the softmax classifier[162-163] normalizes the output of the final fully-connected layer so that the sum of the outputs is equal to 1. This modification allows the interpretation of the final outputs of the network as a set of probabilities that the input to the network falls into each prediction class. For example, the CNN's output for a given MNIST image consist of a set of 10 values, each of which represents the probability that the image contains a handwritten digit of one of the numbers 0-9.

The structure of the CNN was modified by including a batch normalization layer[163] with each convolutional layer and using the rectified linear unit (ReLU) activation function[164]. The batch normalization layers reduce the magnitude of the variability in their inputs by subtracting each input by the mean of all inputs and then dividing each mean-centered input by the standard deviation of all inputs. These layers are located after each convolutional layer and after the first fully connected layer of the network. They receive the net inputs calculated by the preceding layer, and the normalized outputs they calculate are passed on as inputs for the ReLU activation function. The ReLU activation function returns an output of zero for all input values < 0, and returns the original input value for all input values > 0. Batch normalization layers help reduce overfitting of a neural network to training data, and the use of the ReLU activation function hastens the training time for

neural networks by avoiding the vanishing gradient problem[161] associated with the use of other activation functions.

To generate deficiencies in this working memory representation, the relationship between the quantity of training examples and handwritten digit recognition performance of CNNs was first investigated. Five groups of identically structured CNNs (n = 10 x CNNS per group) were trained with sets of MNIST images with sizes in the range of 25 – 50000 MNIST images per set. The MNIST images used for training were randomly selected from the training subset of the MNIST dataset, and randomly selected sets containing less than 100 MNIST images were checked to ensure that they contained at least one example image of each handwritten digit 0-9. Updates of the CNN parameters (weights & biases) were performed after training on batches of 25 MNIST images. The categorical cross-entropy loss function[161] was used to measure the handwritten digit recognition performance of the CNNs during training and calculate the gradients of its weights and biases. The ADAM optimizer[165] was then used to calculate the magnitude of the parameter updates from these gradients.

After training, the percent accuracy of handwritten digit recognition performance of each CNN was evaluated on the 10,000 MNIST images of the MNIST test set, and the mean accuracy of each group of CNNs was determined. As expected, the group mean handwritten digit recognition accuracy increased with increasing number of MNIST images presented during training (Figure 11). The minimum group accuracy achieved was 44.3% (SD 4.1%) with 25 MNIST training images, and the maximum group accuracy achieved was 98.2% (SD 0.5%) with 50,000 MNIST training images. The observed relationship between group accuracy and the number of MNIST training images was logarithmic, and the rate of increase in performance was relatively minimal in groups trained with set sizes larger than 2,500 MNIST images (mean group accuracy = 95.7% (SD 0.5%)).

Training procedures for the CNNs representing working memory in the virtual Time Management Task were selected to create a sizeable difference in performance between the “healthy” working memory control group with high handwritten digit recognition performance and the “deficient” working memory group with poor handwritten digit recognition performance in a minimal amount of computational time. Computational efficiency was prioritized over marginal improvements in accuracy in the selection of a training procedure for the “healthy” working memory control group. While a 2.5% improvement in group accuracy was observed from increasing the training set size from 2,500 to 50,000 MNIST images, this improvement was achieved at a significant cost of increased computational time. Thus, a training set size of 2,500 MNIST images was selected to efficiently train CNNs in the “healthy” working memory control group to achieve a sufficiently high handwritten digit recognition performance.

The selection of a training procedure for the “deficient” working memory group was based on a similar consideration of weighing the level of performance achieved with the training time required to achieve the performance. A large performance decrement compared to the “healthy” working memory group was desirable in this case. The minimum accuracy achieved in this experiment was 44.3% (SD 41%) in the group trained with 25 MNIST images. While this level of accuracy could be decreased further by

Figure 11 – Effect of MNIST Training Set Size on MNIST TestSet Handwritten Digit Recognition of CNNs (n = 10 x CNNs per Group)

reducing the size of the training set, this decrease was achieved at a cost of significantly increased computational time to randomly select smaller training sets with at least one MNIST image containing each handwritten digit. Thus, a training set size of 25 MNIST images was selected to efficiently train CNNs in the "deficient" working memory group to achieve a sizable reduction in handwritten digit recognition performance compared to the "healthy" working memory control group.

To summarize, this investigation was performed to select training procedures for MNIST handwritten digit recognition by CNNs as a computational representation for working memory in humans. In this context, a "healthy" working memory was defined as high handwritten digit recognition performance by CNNs and a "deficient' working memory was defined as poor handwritten digit recognition performance by CNNs. Differences in performance were created by varying the number of MNIST images used to train the CNNs. A training set size of 2,500 MNIST images was selected to generate CNNs with high handwritten digit recognition performance representing "healthy" working memory, while a training set size of 25 MNIST images was selected to generate CNNs with poor handwritten digit recognition performance representing "deficient" working memory.

4.3 Prepotent Impulsivity

As a first step towards the construction of a computational model for the behavioral inhibition executive function, the prepotent impulsivity function was created to generate impulsive behavior that may be inhibited. Prepotent responses are defined as unproductive behaviors that have been overlearned in a given circumstance, and are then used indiscriminately in other circumstances where they may no longer be appropriate[7]. This function was designed to be an addition to the MNIST handwritten digit recognition representation of working memory and activates unproductive behaviors resembling prepotent responses in this context.

When the CNNs representing working memory were evaluated for their performance, their handwritten digit recognition accuracy was determined on an ordered test set. In other words, the CNNs were first presented with all the images containing a handwritten zero, then all the images containing a handwritten one, all the images containing a handwritten two, and so on. In contrast, this experiment was conducted with shuffled test sets where the images containing the various handwritten digits were presented to the CNNs in a random order. A shuffled test set will contain sub-sequences of different images containing the same handwritten digit. When these sub-sequences with consecutive images containing the same handwritten digit are presented to a CNN, a prepotent impulse is created. This prepotent impulse grows in strength as the number of consecutive digit repeats grows larger and promotes an automatic response with the identity of the repeated digit from the virtual "subject". The automatic prepotent response is produced without the presentation of an MNIST image to the CNN, and is more likely to be incorrect than a non-impulsive response produced with the presentation of an MNIST image to the CNN. Thus, the prepotent impulsivity function can be considered a method to

produce erratic behaviors without the benefit of reasoning with executive functions (working memory) in this model.

In addition to the prepotent impulse, the prepotent impulsivity function also includes a competing executive function-activating component. The executive function-activating component supports the activation of a response determined by executive functions, specifically the presentation of an MNIST image to the CNN. The probability of carrying out an impulsive prepotent response is determined by subtracting the strength of this executive function-activating component from the strength of the prepotent impulse (Figure 12).

Both the prepotent impulse and the executive function-activating component of the prepotent impulsivity function are Gaussian curves constructed with a strength parameter, an efficiency parameter, and a delay parameter. These curves are calculated with normalized time as the independent variable; this variable is considered an abstract representation of computational processing time and not a real time related to the computational task. The maximum values at the curves' peaks are used to calculate the prepotent response probability. The strength parameter determines the magnitude of the curve's peak, the efficiency parameter determines the rate at which the curve reaches its peak, and the delay parameter determines the location where the curve begins to grow. While the values of the parameters for the executive function-activating curve stay constant as the evaluation of the shuffled test set proceeds, the magnitude of the strength parameter for the prepotent impulse curve increases at a constant rate as MNIST images containing the same handwritten digit are encountered consecutively.

The purpose of the prepotent impulsivity experiment was to determine whether this model could produce a significant difference in the performance of the working memory function. All calculations were performed with Wolfram Mathematica v11.1. In this experiment two groups of CNNs (n = 6 x CNNs per group) were generated with the training procedures described in Section 4.2 to produce a working memory deficient group and a "healthy" working memory group and their baseline handwritten digit recognition accuracy was evaluated on the MNIST test set. Both groups were then evaluated on six trials of shuffled test sets with the addition of the prepotent impulsivity function (all group "subjects" were evaluated with the same shuffled test set in each trial). The prepotent response was simply a repeat of the response given for the previously encountered image without giving the current MNIST image as an input to a CNN, while a non-impulsive response was generated by the CNN after presentation with the current MNIST image as an input. Both the difference in handwritten digit recognition performance between groups and the differences in handwritten digit recognition within each group with the addition of the prepotent impulsivity function were tested for significance with the Mann-Whitney U test.

Results of this experiment are shown in Figure 13. After training for MNIST handwritten digit recognition, the "healthy" working memory group achieved a mean accuracy of 98.8% (SD 0.1%) while the "deficient" working memory group achieved a mean accuracy of 56.6% (SD 3.7%) on the MNIST test set. With the addition of the prepotent impulsivity function the "healthy" working memory group achieved a group

Figure 12 – Effects of Repeated Handwritten Digits on Prepotent Impulsivity Function

(PI = Prepotent Impulse; EF = Executive Function-Activating Component; PR = Prepotent Response Probability)

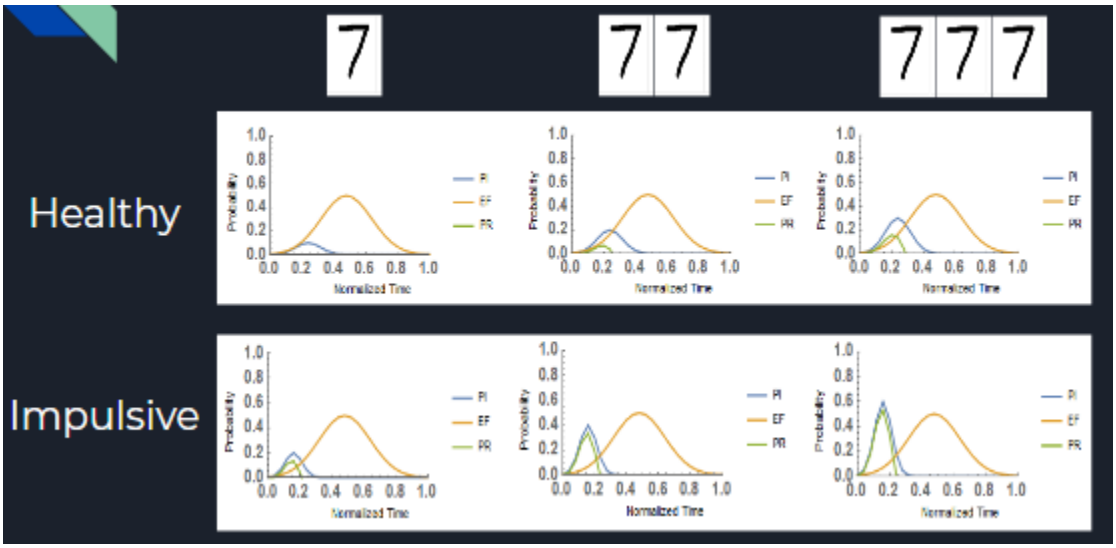
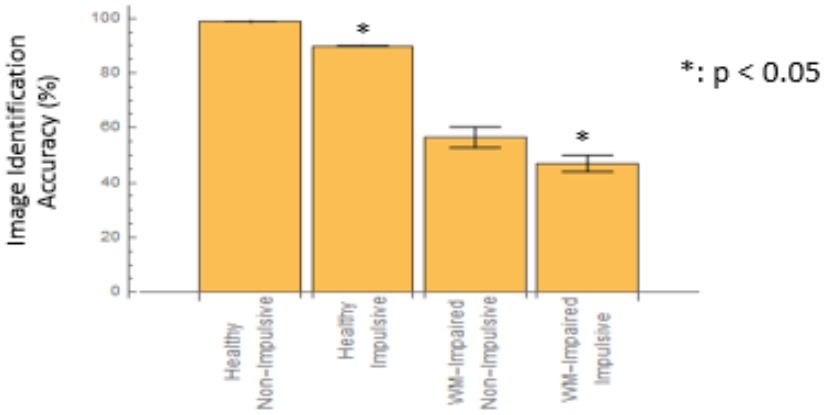


Figure 13 – Effects of Prepotent Impulsivity Function on Group Mean Handwritten Digit Recognition Accuracy of CNNs on MNIST TestSet (n = 6 x CNNs per Working Memory Group)



mean accuracy of 89.9% (SD 0.2%) while the "deficient" working memory group achieved a group mean accuracy of 47.1% (SD 3.0%). Both the baseline difference in performance between the two working memory groups, and the differences in performance within each group resulting from the addition of the prepotent impulsivity function were significant. These results indicate that a statistically significant difference in handwritten digit recognition performance could be produced in both the "healthy" and "deficient" working memory groups with the addition of the prepotent impulsivity function.

4.4 Generating Fluid Intelligence Deficiencies (Colaboratory Notebook)

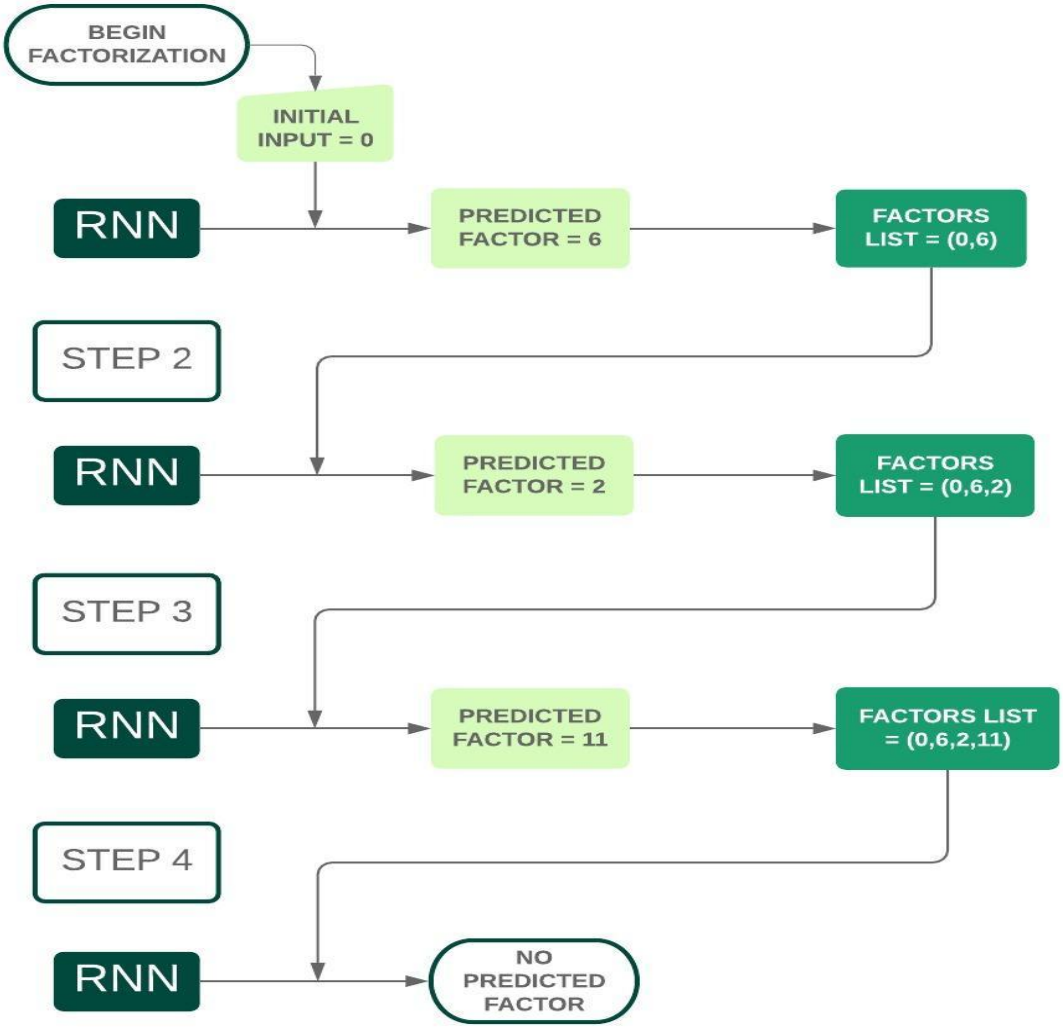
The higher order executive function fluid intelligence has been described in terms of the mental processes of analysis and synthesis[7]. The process of analysis involves the decomposition of complex information into smaller, simpler parts, while the process of synthesis involves the combination of simple pieces of information into more complex, novel combinations. The generation of sets of factors of the number 12 by basic recurrent neural networks (RNNs) is used as a representation of the synthesis component of fluid intelligence in this experiment, as the simple integers 1-10 are combined in varying ways until the more complex number 12 is produced.

While CNNs are only capable of processing a single input at a time, RNNs are capable of processing sequences consisting of multiple inputs[29]. Although the architectures of RNNs can vary considerably in complexity, the simplest form of RNN possesses a single internal layer that changes its state as the sequence is processed and three sets of weight parameters. One set of weights processes the input to the network, another set of weights modifies the state of the internal layer of the network, and the third set of weights converts the inner state of the network into an output. The inner state of the network changes as each individual element of the input sequence is processed in a series of steps; this inner state is affected by the current element being processed as well as all the previously processed elements and determines the output that the network produces at each step. As a result, the output of the network at each step depends on both of the previously processed elements of the sequence and the currently processed element.

To produce a list of integers that are factors of the number 12, the RNN produces a single predicted factor at each step, this predicted factor is recorded in a list containing all the previously predicted factors, and this set of previously predicted factors can then be used as an input for the RNN in the next step (Figure 14**)**. This process repeats until the RNN produces an output indicating the output sequence is complete.

All calculations for this experiment were performed with Python v3 in a Google Colaboratory Notebook. A basic RNN model modified from a RNN designed for language modeling and the generation of reddit comments[166] was implemented. This RNN contained a single inner layer of 100 units, used the tanh activation function (a non-linear function with outputs ranging from -1 to 1) to calculate the inner layer, and a softmax activation function to generate a list of normalized probabilities for integers in the range 1-11 as an output. The number 0 was used as a "start token", or initial

Figure 14 – Factor Prediction for the Number 12 by a Recurrent Neural Network



input to signal the start of a factorization prediction, while the number 11 was used as an "end token" to indicate the end of a sequence of predicted outputs.

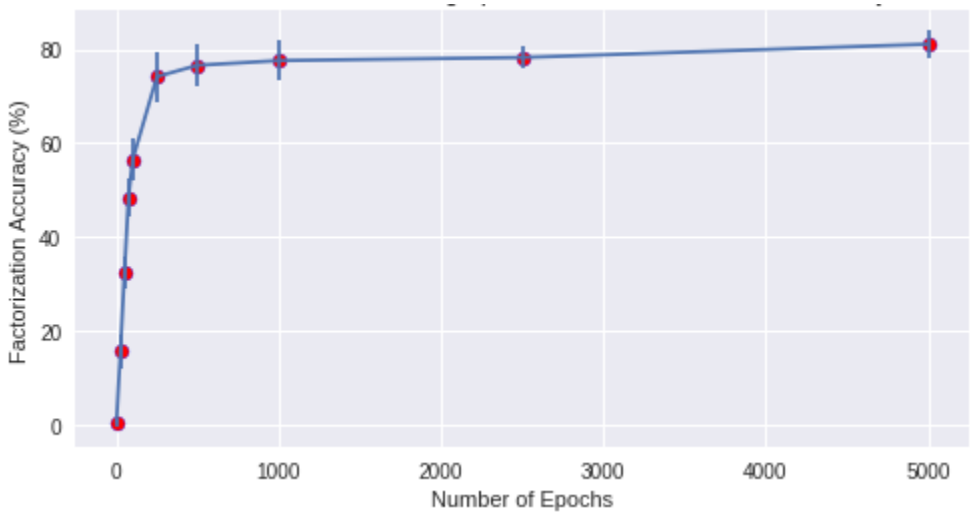
A training set composed of 29 training examples with features (inputs) and labels (correct outputs) were generated by hand. The set of training features consisted of lists of integers between 0 and 10, and the list for each training feature began with the integer 0. Lists of integers that could be multiplied together to produce the number 12 and lists of integers that that could not be multiplied together to produce the number 12 were both included. The set of training features lists that produced the number 12 included all the permutations of each set of factors, while the training features lists that did not produce the number 12 simply consisted of the start token 0 followed by the incorrect factor. A matching training label was created for each training feature. The training label for each example contained the same list of integers contained in the features for the example, but the start token 0 was removed and the end token 11 was added to the end of the list.

Similar to the working memory function, modifications in a supervised learning training procedure were investigated to produce different categories of performance for the factorization of 12 in RNNs. In this case, the data available for training was limited (29 training examples vs. 50,000 MNIST training examples) so the differences in performance were created by varying the number of training cycles (or epochs) as the independent variable rather than the number of training examples presented. All of the training examples are presented to a neural network in one training epoch, so the number of times a neural network sees each training example is equivalent to the number of training epochs. Ten groups of 12 x RNNs per group were assigned unique durations for their training ranging from 1 training epoch to 5,000 training epochs. The categorical cross-entropy loss function was used to measure the deviation between RNN outputs and correct predictions and calculate gradients to adjust parameter values. Stochastic gradient descent with a learning rate of 0.005 was used for the optimization method to adjust parameter values.

After training, the performance of each RNN was evaluated by calculating its percent accuracy on 100 factorization of 12 predictions. As expected, the mean percent accuracy for the RNNs in each group increased with the number of training epochs in a logarithmic relationship **(**Figure 15**).** The minimum group mean accuracy was 0.5 % (SD 0.9%) for the RNN group trained for 1 epoch while the maximum group mean accuracy achieved was 81.1% (SD 2.9%) for the RNN group trained for 5,000 epochs. The rate of improvement in performance began to level off at a group mean accuracy of 74.2% (SD 5.4%) with 250 training epochs, although significant improvements in performance were still observed as the number of training epochs was increased further.

The training procedure for "deficient" fluid intelligence RNNs was selected to achieve a goal of approximately 50% mean factorization of 12 accuracy, while the training procedure for "healthy" fluid intelligence RNNs was selected with a consideration of performance and computational efficiency. The goal performance level for "deficient" fluid intelligence was achieved in RNNs trained for 75 epochs (group mean accuracy = 48.3% (SD 4.1%). Training for 1000 epochs was selected as the learning procedure for "healthy" fluid intelligence RNNs to achieve a mean group accuracy of 77.6 % (SD 4.2%) with a sacrifice of 3.5% accuracy in exchange for significantly improved computational efficiency compared to training for 5000 epochs.

Figure 15 – Effect of Number of Training Epochs on Mean Group Accuracy of Factorization of 12 in Recurrent Neural Networks (n = 12 x RNNs Per Group)



In summary, a computational representation for the synthesis function of the higher order executive function fluid intelligence in humans was developed in this experiment. This model includes basic RNNs to predict integers between 1 and 10 that can be multiplied together to produce the number 12, where a "healthy" fluid intelligence is represented by RNNs with high factorization of 12 accuracy and a "deficient" fluid intelligence is represented by RNNs with poor factorization of 12 accuracy. This factorization of 12 fluid intelligence function was then integrated together with the MNIST handwritten digit recognition function representation for working memory and the prepotent impulsivity function to create the first implementation of virtual "subjects" who perform a virtual Time Management task.

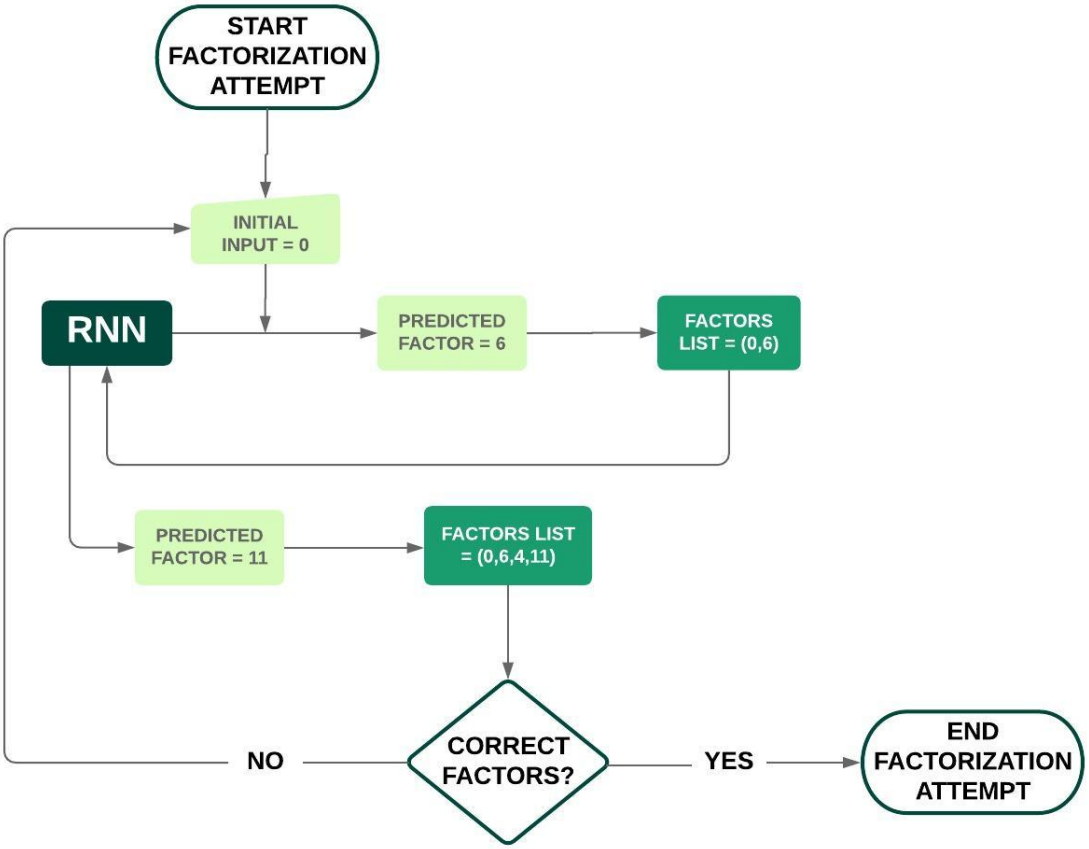
4.5 Time Management Task (Colaboratory Notebook)

Similar to the fluid intelligence task described in Section 4.4, the goal of the Time Management task is to create a list of integers between 1 and 10 that can be multiplied together to produce the number 12. However, the process required to achieve this goal is modified in three important ways. Firstly, the Time Management task is not complete after a single factorization of 12 attempt, but rather continues until a successful factorization of 12 is completed (Figure 16**)**. Secondly, the Time Management task requires the use of the working memory function impeded by the prepotent impulsivity function for its completion. The working memory function with prepotent impulsivity is used after the prediction of a single factor to locate and correctly identify an MNIST image that contains the predicted factor as its handwritten digit in the MNIST test set. Finally, the performance of the Time Management task is measured by the total number of MNIST test set images searched through to complete a successful factorization of 12 rather than the percentage of successful factorizations.

The procedure to create virtual "subjects" who complete the virtual Time Management task is simply a combination of the neural network training procedures developed in the preceding sections of this chapter. Each virtual "subject" consists of a working memory function consisting of a CNN trained for handwritten digit recognition in the MNIST test set, a set of parameters for the prepotent impulsivity function that impedes the performance of the working memory function, and a fluid intelligence function consisting of an RNN trained to factorize the number 12. Two groups of virtual "subjects" with n = 6 x virtual "subjects" per group are created: a control group with "healthy" working memory and fluid intelligence and an "ADHD" group with "deficient" working memory and fluid intelligence. Prepotent impulsivity was included in all "subjects" in both groups with the control group possessing a set of parameters that leads to lower impulsivity than the "subjects" in the "ADHD" group.

All computations for the Time Management task were performed with Python 3 in a Google Colaboratory Notebook, and the creation and training of CNNs were performed with the Keras Machine Learning Library. Data visualizations were created in Wolfram Mathematica v11.1. ANNs for the virtual "subjects" in the control group were trained with

Figure 16 – Recurrent Neural Networks (Fluid Intelligence) in the Time Management Task



the learning procedures that produced 6x "healthy" working memory and 6x "healthy" fluid intelligence representations, while ANNs for the virtual "subjects" in the ADHD group were trained with the learning procedures that produced 6x "deficient" working memory and 6x "deficient" fluid intelligence representations. All ANNs (CNNs and RNNs) for each executive function representation possessed an identical architecture across both groups as described for CNNs in Section 4.2 and for RNNs in Section 4.3. "Healthy" working memory representations for six virtual control "subjects" were produced by training each of six CNNs with 2,500 handwritten digit images randomly selected from the MNIST training set and "deficient" working memories for six virtual "ADHD subjects" were produced by training each of six CNNs with 25 randomly selected MNIST training set images. Similarly, "healthy" fluid intelligence representations for six virtual control "subjects" were produced by training each of six basic RNNs for 1,000 epochs to factorize the number 12 and "deficient" fluid intelligence representations for six virtual "ADHD subjects" were produced by training each of six basic RNNs for 75 training epochs. Baseline accuracies of the working memory representations were measured by handwritten digit recognition by CNNs on the MNIST test set while baseline accuracies of the fluid intelligence representations were determined on 100x factorization of 12 attempts by RNNs. The Mann-Whitney U test was used to test for significant differences between group means in baseline performance for each executive function representation.

After training and evaluation of baseline performance of all ANNs, the Time Management task was performed by the virtual "subjects" (Figure 17). In the first step of the task, the virtual "subject's" fluid intelligence representation uses a basic RNN to perform a single factor prediction. The identity of this factor is then provided to the virtual "subject's" working memory representation with prepotent impulsivity, and the virtual "subject" begins to identify handwritten digits in randomly selected images from the MNIST test set. The virtual "subject's" prepotent impulsivity function is operational with each identification, and may activate an automatic impulsive response where the virtual "subject" simply responds with its previous handwritten digit recognition output rather than using its working memory representation to identify the handwritten digit with a CNN. As described in Section 4.3, the automatic impulsive response becomes more likely as multiple MNIST images containing the same handwritten digit are encountered in succession. This search continues until the predicted factor is located AND correctly identified in the MNIST test set. Once the search is successfully completed, another factor prediction is performed and this sequence of steps continues until a complete factor list is predicted and all of its elements are correctly identified in the MNIST test set. If a correct factor list is predicted one trial of the task is complete. Otherwise, this procedure is repeated until a correct factor list is produced. Each virtual "subject" completed 25 successful factorizations of 12 trials, and a mean MNIST test set images searched count for all the trials was calculated for each "subject". The Mann-Whitney U Test was then used to test the group mean images searched counts for significant differences.

Without prepotent impulsivity, virtual "subjects" in the "healthy" control group achieved a baseline group mean handwritten digit recognition accuracy of 95.9% (SD 0.9%) while virtual "subjects" in the "ADHD" group achieved a baseline group mean handwritten digit recognition accuracy of 39.2% (SD 5.1%) on the MNIST test set (Figure 18).

Figure 17 – Time Management Task Flowchart

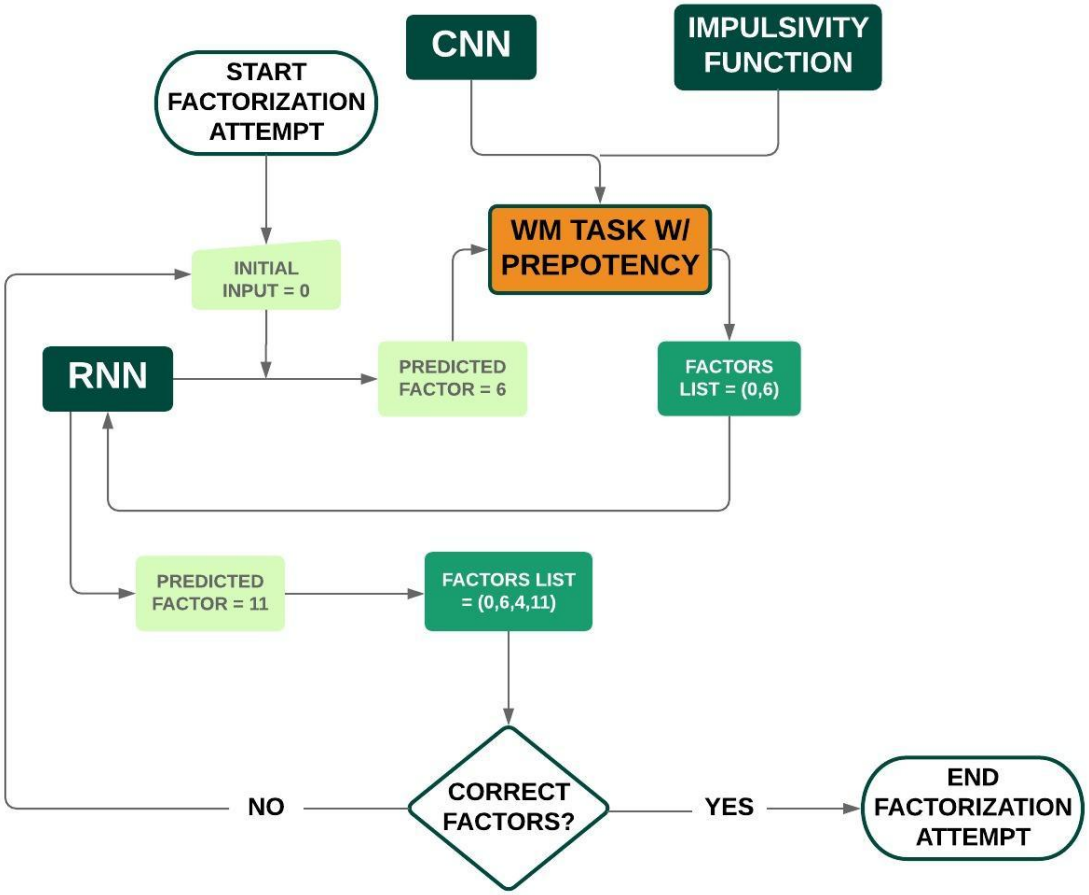
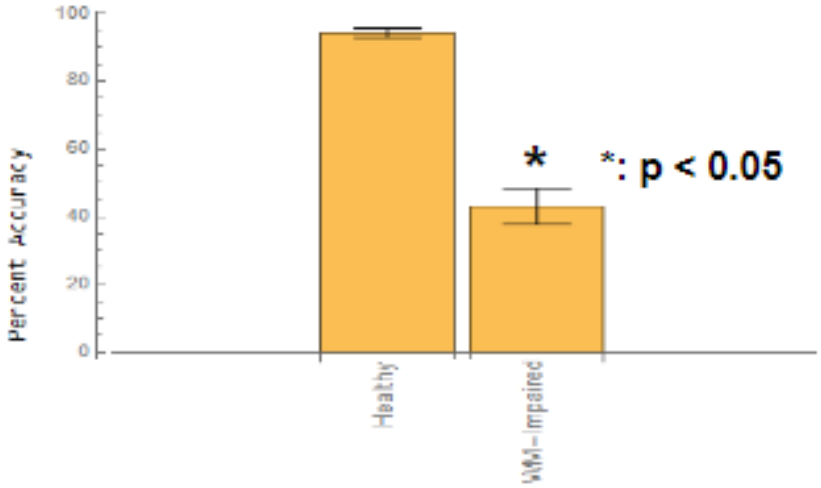


Figure 18 – Baseline Difference in Mean Group Accuracy of Handwritten Digit Recognition on MNIST TestSet by Convolutional Neural Networks of Virtual "Subjects" in the Time Management Task (n = 6 x CNNs Per Group)



A Mann-Whitney U Test showed a significant difference between the groups ($p = 0.025$). For comparison, in the Generating Working Memory Deficiencies experiment (Section 4.2) the CNN-group trained with a random set of 2,500 MNIST images achieved a mean group accuracy of 95.7% (SD 0.5%), while the CNN-group trained with a random set of 25 MNIST images achieved a mean group accuracy of 44.3% (SD 4.1%) in handwritten digit recognition on the MNIST test set. A Mann-Whitney U test comparing the results of each group between different experiments resulted in non-significant differences for both groups ($p = 0.704$ and $p = 0.0577$ for the "healthy" and "deficient" groups, respectively). Taken together, these data indicate that a significant difference in performance of the working memory function was successfully produced between the virtual "subjects" in the "healthy" control and "ADHD" groups, and the working memory deficiency results in this experiment were consistent with the results of the previous experiment.

Virtual "subjects" in the "healthy" control group achieved a baseline group mean factorization of 12 accuracy of 79.5% (SD 4.0%) while virtual "subjects" in the "ADHD" group achieved a baseline group mean factorization of 12 accuracy of 47.3% (SD 4.7%) (Figure 19**)**. A Mann-Whitney U Test revealed a significant difference between groups ($p = 0.025$). For comparison, in the Generating Fluid Intelligence Deficiencies experiment (Section 4.3) the RNN-group trained for 1,000 epochs achieved a mean group accuracy of 77.6% (SD 4.2%), while the RNN-group trained for 75 epochs achieved a mean group accuracy of 48.3% (SD 4.1%) on the factorization of 12 activity. A Mann-Whitney U test comparing the results of each group between different experiments showed non-significant differences for both groups ($p = 0.479$ and $p = 0.707$ for the "healthy" and "deficient" groups, respectively). Taken together, these data indicate that a significant difference in performance of the fluid intelligence function was successfully produced between the virtual "subjects" in the "healthy" control and "ADHD" groups, and the fluid intelligence deficiency results in this experiment were consistent with the results of the previous experiment.

Finally, virtual "subjects" in the "healthy" control group required a group mean of 37.4 (SD 2.5) MNIST test set images searched through, while virtual "subjects" in the "ADHD" group required a group mean of 579.1 (SD 352.3) MNIST test set images searched through to complete the virtual Time Management task (Figure 20). A Mann-Whitney U Test showed a significant difference between groups ($p = 0.0025$). These results indicated that this model composed of virtual "subjects" built from executive function representations of working memory and fluid intelligence with impulsivity that complete a virtual Time Management task that requires the use of these executive function representations was able to produce two groups of "subjects" with distinct levels of performance in the virtual task.

Figure 19 – Baseline Difference in Mean Group Accuracy of Factorization of 12 by Recurrent Neural Networks of Virtual "Subjects" in the Time Management Task (n = 6 x RNNs Per Group)

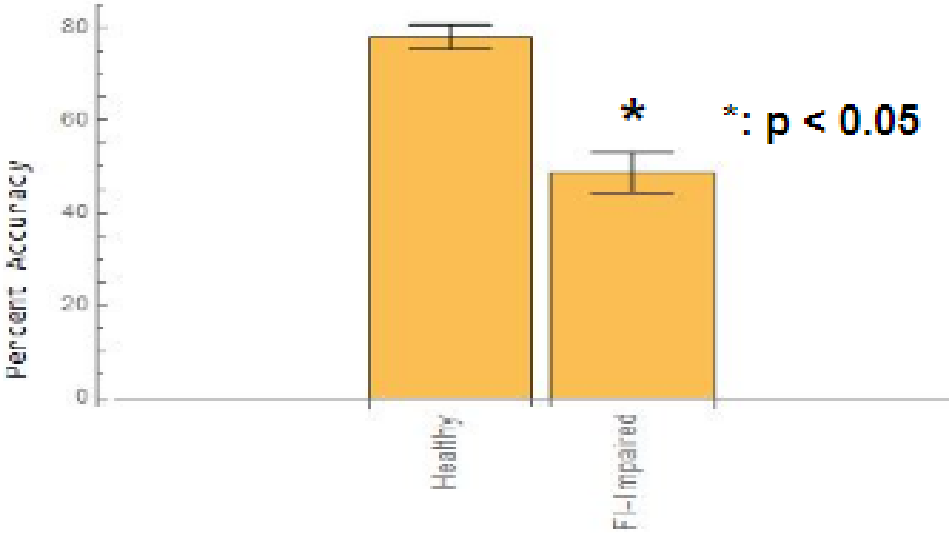
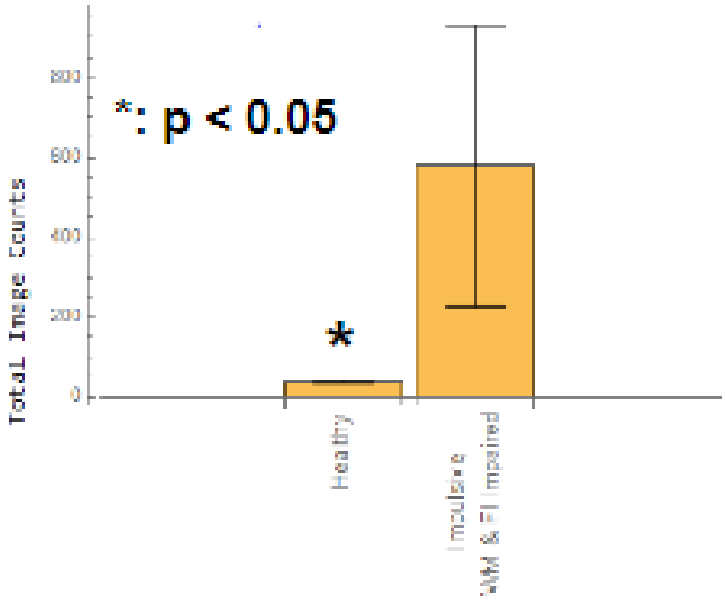


Figure 20 – Performance of Virtual “Subjects” in the Time Management Task (n = 6 x Virtual “Subjects” Per Group)



CHAPTER 5. DISCUSSION

In summary, a virtual Time Management task utilizing convolutional neural networks, recurrent neural networks, and the MNIST dataset was designed as a first step towards the development of a virtual subject. This virtual subject will be used as a computational model to guide the selection of personalized treatment regimens for the training of executive functions in children with ADHD. The virtual Time Management task requires the use of a working memory function composed of a convolutional neural network trained to identify handwritten digits in the MNIST dataset, as well as an impulsivity function that produces impulsive responses. Recurrent neural networks trained to output sequences of integers that are factors of the number 12 are used to represent a simplified fluid intelligence function. Thus, the virtual Time Management task that was developed required this first version of a virtual subject to use both a working memory function, hindered by an impulsivity function that produces impulsive responses, and a fluid intelligence function for its successful completion. The remainder of this chapter will first address general limitations of the computational models, then describe the development of each executive function model in more detail, and conclude with a discussion of approaches to improve the translational applicability of the computational model to human subjects and the progress of the TVG pilot study.

The overall design of this project is limited in two important ways. First, it is unlikely that a therapeutic video game intervention will be sufficient for addressing the full scope of impairments present in ADHD. The executive function theory for ADHD has not proven to be a complete description of the neuropsychological impairments present in this disease. A meta-analysis investigating the likelihood of executive function deficits being the primary cause of ADHD found that these deficits were not present in all the study's subjects, and their presence only exerted a moderate effect size on ADHD symptoms[167]. Executive function deficits in ADHD have also proven to be heterogeneous in nature, and inhibition deficits are not present in every patient[168]. Notably, this latter finding is contrary to Barkley's proposal of a central deficit in inhibition being responsible for the development of ADHD[7]. Taken together, these results indicate that executive function deficits are neither necessary nor sufficient to cause the development of ADHD. Furthermore, new multiple pathways theories have emerged that incorporate executive function deficits as a single pathway together with an excessive motivation to avoid delays[169] and temporal processing deficits[170]. Therefore, the targeting of executive function impairments alone will not be an effective approach for the treatment of ADHD.

Even if the targeting of executive function deficits does not prove to be a method to correct the full scope of impairments in ADHD, this strategy may nonetheless be of use to improve the functioning of children with ADHD. In addition, the personalized treatment strategy of the therapeutic video games intervention remains an advantageous approach to address a heterogeneous set of impairments such as those in ADHD due to the highly individualized treatment recommendations it may prove to offer. The flexibility of the Minecraft environment would also permit the development of additional tasks to target neuropsychological deficits in non-executive function domains.

Secondly, while the artificial neural networks used in the computational model of executive function deficits bear some similarity to biological neural networks, they nonetheless remain a profoundly simplified approximation. A complete discussion of these simplifications is beyond the scope of this work, but a few illustrative limitations are worth pointing out here.

The most significant limitation of artificial neural networks as a model for neurological activity may be their simplified representation of the structure and function of biological neural networks. Although the design of a single feed-forward network with multiple layers may resemble the structure of a biological network composed of multiple neurons working in tandem, this kind of network might more closely resemble the structural complexity of an individual branch of a dendritic tree in a single neuron[171]. As a result, even the largest artificial neural network models in use would not be capable of achieving computational complexity that a single neuron is capable of producing.

An important functional simplification in artificial neural networks is the exclusion of spatial and temporal information from their design[172]. Whereas the spatial distribution of input signals to the dendritic tree of a biological neuron is an important factor for the processing of these inputs, this factor is not accounted for in commonly used artificial neural networks. Furthermore, the functioning of the current generation of artificial neural networks relies on the rate code approximation, which means that all the inputs and outputs in a network model are represented as average firing rates of electrical impulses in synapses. In contrast, biological neurons interpret the patterns of input signals they receive and convey important information in the patterns of the output signals they produce.

New generations of artificial neural networks currently under development hold promise for the amelioration of the functional limitations in the current generation of network models. For example, spiking neural networks are designed to more accurately model the temporal function of real neurons, and are currently under development as a computational tool for widespread use[173]. Spiking neural networks utilize differential equations to incorporate temporal input information as biological neural networks do, but their use is currently limited by difficulties in their training procedures. These, and other neural networks systems under development, may increase the computational power of artificial neural networks over time to improve their capability to model the function of biological neural networks more accurately.

5.1 Working Memory

Working memory is defined as the ability to hold information in consciousness (short-term memory) and manipulate it[2]. This definition leads to the rationalization for the use of image identification by convolutional neural networks as a model for working memory. In the current implementation, the input of an MNIST image file into the first layer of the network is proposed to represent the holding of information in consciousness component of working memory, and the subsequent processing of this input data by the internal network layers is proposed to represent the manipulation component of working memory.

The input of data into the network as the short-term memory component of working memory admittedly is not a strong representation of this mental ability for two reasons. First, the data provided as input to the convolutional neural network is the actual MNIST example data itself, so there is no recall mechanism to produce an internal representation of this MNIST example data in its absence. Second, there is no holding mechanism to maintain this internal representation of the data over time to allow its manipulation. Thus, the working memory function could be improved through the addition of data recall and holding mechanisms to the convolutional neural network. The recall mechanism would operate prior to the input of data to the convolutional neural network, while the holding mechanism would operate simultaneously with the processing of the input data in each hidden layer of the convolutional neural network. These modifications could potentially improve the resemblance of this working memory function to the function of working memory in biological neural networks by including a simplified representation of the biological short-term memory component while maintaining a manageable level of computational complexity.

Although several neural network models have been proposed to represent the short-term memory component of working memory[174], a degree of redundancy may exist in the actual biological neural networks that are responsible for this executive function so no single computational process is responsible for biological working memory in all cases[175]. Two examples of artificial neural network models for modeling biological working memory include cell assemblies and synfire chains. Cell assemblies[176] consist of strongly interconnected groups of neurons in a Hopfield model that maintain a persistent excitation pattern over time through their mutual activation. Here, the outputs of a given group of neurons at one instance in time is used as the input for this same group of neurons in the next instance to produce a recurrent firing pattern. The excitation pattern maintained by cell assemblies is a representation of a piece of information held in short-term memory, and this model relies on the use of the leaky-integrator differential equation to model the temporal dynamics of input currents and firing rates of individual neurons. Synfire chains[177] also rely on the leaky-integrator differential equation to model their temporal dynamics, but use a feedforward neural network model rather than a recurrent Hopfield model. While the standard feedforward neural networks have the individual neurons in each layer firing at varying rates, individual groups of neurons/layers in synfire chains all fire simultaneously in time, and produce a persistent chain of spikes across multiple layers that represent the piece of information held in short-term memory. These models have been developed from the biophysical properties of individual neurons' dynamic function, and therefore attempt to capture a level of complexity that is too great for the purposes of this project at this time. Nevertheless, much of this complexity may be obviated with the selection and design of simpler models that ignore these temporal dynamics of neural function while still representing similar functions.

To represent the recall mechanism of short-term memory, an autoassociative memory linear associator network trained by supervised Hebbian Learning[9] could be utilized. This type of network could potentially be trained to produce an MNIST image as an output when similar MNIST images are presented as inputs. With proper training, the output of such networks would provide accurate representations of MNIST images, even when provided with a corrupted version of a given image as its input. Hence, a properly

trained network with an effective recall would reproduce high-quality MNIST images as outputs when provided with altered MNIST images as inputs, whereas a poorly trained network with an ineffective recall would produce poor-quality MNIST images as outputs. These reproduced versions of MNIST images would then be provided as inputs to the manipulation function represented by convolutional neural networks in the current implementation of the working memory model. The high-quality MNIST images produced by well-trained linear associator networks with effective recall would enable more effective performance of the manipulation function represented by convolutional neural networks and result in a higher probability of a correct handwritten digit identification and more effective use of working memory as a whole. In contrast, the low-quality MNIST images produced by poorly-trained linear associator networks with ineffective recall would impede the performance of the manipulation function represented by convolutional neural networks and result in a lower probability of a correct handwritten digit identification and less effective use of working memory as a whole.

One potential approach to represent the holding mechanism of short-term memory is to interfere with the passage of information between individual layers of the convolutional neural network during the operation of the manipulation function. Although the original input data is transformed with each passage from layer to layer, it can still be considered a modified representation of the original information and therefore the act of transferring the output from one layer as an input to the next layer could be considered analogous to holding the information being manipulated. Within this context, a dysfunctional holding mechanism could be represented with an ineffective transfer of information between layers (by randomly corrupting the data values before they are input into a layer, for example) and an effective holding mechanism could be represented by an unimpeded transfer of information between layers.

5.2 Impulsivity & Inhibition

The design of the impulsivity function was influenced by both the race model and the passive-dissipation hypothesis for the control of impulsive behavior. These theories have been used to explain the results observed in the stop-signal task, which is a behavioral task requiring the use of inhibitory control. Both of these theories describe impulsive responses and their inhibition in terms of mental processes that grow in strength over time and compete to reach a threshold value that activates a behavioral response. These theories differ in the mechanism of impulsive behavior prevention, as the passive-dissipation hypothesis includes an active role for inhibitory control (described below). The impulsivity function in the current project was designed to represent the mental processes that compete to produce behavioral responses as described in these theories. However, the role of the impulsivity function at this time is the generation of impulsive behaviors rather than their inhibition, although the design of an inhibitory control component that works as described in the passive-dissipation hypothesis remains to be addressed in future work.

The race model has been used to describe the mental processing of prepotent responses and their inhibition in the stop signal task[177]. Prepotent responses are a category of behavioral responses to stimuli for which immediate reinforcement is presently available

or has been available in the past, and were identified as a target for the behavioral inhibition executive function in Barkley's influential executive function theory for ADHD[7]. Prepotent responses can be overlearned behaviors, occur impulsively without reflection, and can oftentimes conflict with long-term goals. All individual trials in the stop signal task contain a "go" signal that requires the experimental subject to select a response. A subset of these trials also include the presentation of a "stop" signal at varying time intervals after the "go" signal has been presented, and require the experimental subject to withhold the selection of a response. The presentation of the "stop" signal after the "go" signal is significant in that the mental processing for responding to the "go" signal is already active when the "stop" signal is presented. The race model proposes that these processes are independent and compete to produce a behavioral response, and the resulting behavioral response is activated by the process that reaches a given threshold more rapidly in time.

The passive-dissipation hypothesis[178] builds on the race model by allowing the prepotent response to be overcome by the use of the executive function of inhibition to create a delay in the decision to respond. This delay allows the slower correct response to continue growing in strength to reach the response threshold as the prepotent response dissipates. While the use of the executive function inhibition is not included in this project, the impulsivity function was designed to allow for the use of inhibition to create a delay in the decision to respond. When this delay occurs the slower mental process for an appropriate response grows in strength and exerts a greater influence on the decision-making process.

The impulsivity function was developed to produce prepotent responses during the operation of the working memory function as the convolutional neural network identifies handwritten digits in the shuffled MNIST test set. The prepotent responses are generated by the impulsivity function when multiple examples of MNIST images are encountered in a row during the operation of the working memory function. Every time a subsequent image containing the same digit as the previously encountered image is presented as an input to the convolutional neural network, positive reinforcement is provided for a correct response to that digit and the strength of the prepotency for this response grows. Then, when an image containing a different handwritten digit is encountered, this previously reinforced prepotent response may be activated and lead to an incorrect response. The likelihood of activation of the prepotent response may be reduced by an executive function response, however, and the prevailing behavioral response is determined by the relative strength of these two competing responses.

The impulsivity function attempts to model the mental processes that compete to produce either impulsive behaviors or more carefully considered productive behaviors. This initial implementation of the impulsivity function is limited to a prepotent response (PR) process curve and an executive function (EF) process curve. These mental process curves are generated from a strength parameter, efficiency parameter, and delay parameter. The strength parameter determines the size of the curve's peak, the efficiency parameter determines how rapidly the curve reaches its peak, and the delay parameter indicates the time delay from presentation of the stimulus to when the mental process curve initiates. A behavioral response is determined by subtracting the value of the EF process curve from the value of the PR process curve at the decision point to produce a prepotent response

probability (PRP). The PRP is then compared to a randomly generated value between 0 & 1 (RV). If the PRP is greater than RV a prepotent response is initiated, otherwise a non-impulsive response is initiated.

Importantly, the EF process curve described above represents the application of a set of executive function processes that are distinct from the behavioral inhibition executive function. The EF process curves are dedicated towards the creation of productive behaviors, whereas the behavioral inhibition executive function is dedicated towards the delay of the decision point to allow these EF process curves to overcome the opposition of the PR process curve that activates unproductive, impulsive behavior. In this example, the EF process curve represents the strength of the mental process that activates the use of working memory through a trained convolutional neural network to identify a handwritten digit, while the PR process curve represents the strength of the mental process that bypasses the use of working memory in the formation of a response that is less likely to be correct. The addition of a behavioral inhibition executive function in future implementations of the impulsivity function would delay the decision point and thus allow for the EF process curve to grow in strength while the PR process curve weakens. As a result, the PRP would decrease and the likelihood of the initiation of a productive behavior would increase.

Similar to the impulsivity function, both the race model and passive-dissipation hypothesis describe impulsive behaviors and their inhibition in terms of competing mental processes. However, while the race model and passive-dissipation hypothesis define this competition as a race in time between mental processes to reach a given threshold value, the impulsivity function defines this competition in terms of the relative magnitudes of the outputs of the mental processes. In other words, the race model and passive-dissipation hypothesis describe the resulting behavioral response as an outcome of only one of the mental processes, while the impulsivity function defines the behavioral response as an outcome of an interaction between both mental processes. In the race model the winning process is simply the process which reaches the threshold first, while in the passive-dissipation hypothesis the winning process is the one which reaches the threshold when the decision to act is made. In contrast, the impulsivity function implements the resulting behavioral response as the outcome of an interaction between both of the mental processes by subtracting the strengths of the outputs of the mental processes.

This initial implementation of the impulsivity function was designed to create impulsive responses to interfere with the operation of the working memory function in the absence of any influence from behavioral inhibition. Thus, the current version of the impulsivity function simply defines the decision point as the time when the PR process curve reaches its peak value, which is when the PR process exerts its maximum effect on the behavioral response and the EF process exerts a relatively minor effect. However, a behavioral inhibition delay parameter may be added in future implementations of the impulsivity function to create a delay of the decision point to allow for the PR process to weaken as the EF process strengthens, leading to a greater opportunity for the application of a productive behavioral response as reflected in a decreased PRP value.

Two alternative computational methods that have been used for modeling inhibition are the negative bias weight learning mechanism and the drift-diffusion model. The negative bias weight learning mechanism[179] was applied within the context of a dynamic

gating neural network model for a task-switching activity similar to the Wisconsin card sorting task, which is a psychological test used to measure cognitive flexibility[180]. The dynamic gating model utilizes a feedforward network with a single hidden layer that is connected to another layer representing the pre-frontal cortex. This pre-frontal cortex layer learns representations of the various rules governing appropriate responding in the task. As the task proceeds, the active rule changes and the neural network's pattern of responding must also change accordingly to avoid making erroneous responses resulting from the previously active rule. The negative bias weight learning mechanism inhibits responses from the previous rule by rapidly decreasing the values of the weights for the units representing this previous rule to a large negative value, making these units inactive. These weights are then allowed to gradually return to increase to zero as the task continues to lift the inhibition. The negative bias weight learning mechanism operates within the context of the continuous training of a neural network as it performs a given task. In contrast, the impulsivity function operates as an external precursor to the CNNs in this model, and therefore the negative bias weight learning mechanism would not be compatible with this current approach.

A potential alternative method for the computational modeling of behavioral inhibition processes is the drift diffusion model[181]. The drift diffusion model has garnered interest in computational psychiatry to model decision-making processes[182], and the parameters of this model have been linked to neural functions[183-186]. It has been utilized for the modeling of decision-making processes in two-choice decision tests[181], including tests measuring inhibitory control, such as the go/no-go task[183] and the stop-signal task[187]. In the case of the go/no-go task, the drift-diffusion model was used to analyze reaction time data in subjects with ADHD to compare predictions between theories of ADHD[188-189], while the capability of the model to represent the results of a rational decision-making process involving Bayesian inference was investigated in the case of the stop-signal task[187].

The drift diffusion model has been useful for modeling simple one- or two-choice decisions[183], where the selection of a decision is determined by one or more stochastic drift processes that move towards boundaries representing the available decisions. The stochasticity in the model is incorporated through the addition of random noise to the movement of the drift processes as they travel towards a boundary. When the movement of the drift process reaches one of the boundaries, a decision to complete the action represented by that boundary is made.

The drift diffusion model consists of the following parameters: a start point (z), the boundary separation (a), the drift rate (v), and non-decision process time (ter). After a time delay representing the encoding of a stimulus, the start point z is reached. The start point z may be located closer to one or the other of the boundaries, depending on an individual's expectations of the correct response in the decision making task. The distance between the boundaries representing each decision is represented by the boundary separation a, which is determined the amount of information required by an individual to make a decision and the individual's decision-making strategy, such as a speed-accuracy trade-off. For example, an individual with a greater concern for accuracy than speed would require a greater amount of information before making a decision, and a greater boundary separation would result. In contrast, an individual with a greater concern for speed than accuracy would require less information to make a decision and possess a smaller separation between

the boundaries representing their decisions in this model. The drift rate v represents the rate at which the sensory information required for an individual to make a decision accumulates, and is affected by the individual's level of arousal. In the case of an individual with low arousal, such as a subject with ADHD for example, this information would accumulate more slowly and a longer time would be required for this individual to make a decision than an individual with higher arousal. Finally, the non-decision process time ter represents the times required for the encoding of the stimulus before the drift process initiates and for the motor processing of the behavior representing the decision after the drift process is completed.

In the case of the Go/No-Go task where the inhibition of a prepotent response is considered, there would be two possible decisions (go and no-go) represented by two boundaries and a single drift process that ends when one of these boundaries is reached. However, in the case of the stop-signal task where the inhibition of an ongoing response is considered, there are two drift processes that occur. The first of these is similar to the single drift process of the Go/No-Go task that proceeds towards one of two decision boundaries, while the second represents the additional inhibition process that must be initiated to prevent the ongoing response. This second drift process begins later in time than the initial drift process representing the mental processing of the decision that must be inhibited; the drift process that is completed sooner in time activates the decision to respond or not to respond, as described in the race model.

In contrast to the negative bias weight learning mechanism described earlier in this section, the drift-diffusion model offers a viable alternative for the representation of impulsive behaviors and their inhibition currently offered by the impulsivity function. While the drift-diffusion model has a stronger record of evidence for its use, to our knowledge its application has been limited to the modeling of decision-making in simple one- or two-choice decision-making tasks. A complex gaming environment such as Minecraft, however, presents dynamic decision-making scenarios where more choices may be available at any given moment and choices are continuously removed or added as circumstances change. It is foreseeable that higher complexity environments could present decision-making scenarios that require alternative criteria for inhibitory decision-making that extend beyond the time-based processing of alternatives by the drift-diffusion model. Therefore, the use of multiple inhibitory decision-making models may be advantageous in this project to determine whether different models may work more effectively in different varieties of decision-making scenarios.

5.3 Fluid Intelligence

The Factorization of 12 task using basic RNNs to output factor sets of the number 12 was used as a representation for the synthesis component of fluid intelligence in this experiment. This task can be improved by the inclusion of a representation for the process of analysis to create a more comprehensive model of fluid intelligence and by adopting a different variety of RNN to increase the complexity of the task. Consider the process of analysis (breaking down complex ideas) as the inverse of the process of synthesis (building up complex ideas). When the process of synthesis is then represented as the building up of

the "complex" number 12 from its simpler component factors, the process of analysis may be represented as the breaking down of the number 12 into its simpler component factors. Thus, the fluid intelligence operation that currently consists of the process of synthesis will be expanded to include an RNN task to break down the number 12 as a representation for the process of analysis.

In the current version of the task, the RNN begins by producing a factor of the number 12, which is then used as an input in the next loop of the task for the RNN to output another factor. This process continues until the RNN produces an output to indicate the end of the sequence of factors and then concludes with an evaluation of the accuracy of the sequence. The reverse process can be implemented through the modification of the RNN's training set. The training set will be differentiated into two separate categories, where one category consists of factor sequences with factors ordered from smallest to largest in size and vice-versa for the other category. The training set with examples ordered by increasing size of their factors will train RNNs for the process of synthesis (where the larger number is assembled), while the training set with examples ordered by decreasing size will train RNNs for the process of analysis (where the larger number is broken down).

An additional improvement is the substitution of the basic RNNs with Long-Short Term Memory networks (LSTMs). While basic RNNs indiscriminately update every parameter of their internal layer with each step of the sequence they produce, LSTMs include additional "forget" gates in this updating process that screen for and exclude the passage of extraneous information to the internal layer between steps in the sequence. This increased efficiency of updating permits the processing of larger sequences in LSTMs, and thus LSTMs would be beneficial to permit the analysis and synthesis of larger numbers in this project. The capability to process larger numbers in this way would allow the creation of multiple difficulty levels for the task to more accurately capture the properties of the therapeutic video games tasks which have multiple difficulty levels.

A comparison of this work to alternative modeling approaches is difficult due to a paucity of research related to the neural functions that produce fluid intelligence. The function of a network of brain regions known collectively as the Multiple-Demand System has been proposed to play a general role across multiple complex problem solving tasks in primates[190]. Detailed functional neural network theories are lacking however. While a recent theory has proposed that fluid intelligence results from a widespread, randomly connected network structure of groups of neurons[6], to our knowledge there does not seem to be any research available that examines the computations that these types of networks conduct.

5.4 Translation to Human Subjects

The translational applicability of this model to the treatment of executive function deficits in humans with ADHD could be improved with the development of an assessment tool, similar to the NICHQ assessment used in the clinical pilot study, to measure simplified ADHD-like behaviors in the virtual "subjects". The NICHQ is completed by parents and teachers who observe a child with ADHD, so the assessment tool for the

computational model will also be completed by trained observers who will monitor the actions of the virtual "subjects". With the inclusion of this virtual "NICHQ" tool, the changes in performance resulting from modifications in the training procedures of the ANNs would be determined not only by their final performance on a complex virtual activity, but also their "behavior" as they complete the activity.

To increase the translational applicability of the virtual "NICHQ", its assessment questions will be designed to be as similar as possible to the questions of the actual NICHQ in humans. Many of the behaviors measured by the NICHQ involve the interaction of a child with their peers and environment. To simulate these interactive behaviors, it will be necessary to develop an interactive environment for the ANNs. One potential method to do so would be to program the ANNs to function within the Minecraft environment itself that is used as the platform for the therapeutic video game executive function training activities. In fact, CNNs have been trained with reinforcement learning to function in Minecraft[191]. However, a simpler approach to implement would be to continue using the supervised learning approach in this model, but create an environment with multiple virtual "subjects" working side-by-side by parallelizing the computations to run across multiple processors simultaneously in a cloud environment. This way, the current implementation of the model could still be used to produce an interactive environment with the creation of additional functions to enable interactions between the ANNs of multiple virtual "subjects".

5.5 Clinical Pilot Study

At the present moment, the progress of the clinical pilot study of the TVG intervention has been slower than expected due to difficulties with patient recruitment. To accelerate the progress of recruitment, a contract research organization (CRO) was hired to manage the operations of the clinical study. However, further consideration of the nature of the patient recruitment difficulties may be instructive as a source of guidance for the improvement of the therapeutic video game intervention for future clinical studies.

One potential reason for these recruitment difficulties is the complexity of the study intervention. The study group completing the video game intervention requires an investment of 150 minutes of Minecraft game play per week (Section 3.1.2.2), which may require a larger commitment than ADHD patients and their parents are willing to agree to. In addition to recruitment difficulties, a complicated treatment intervention could also lead to problems with compliance and high subject dropout rates. While the development of a computational optimization method to streamline the TVG training schedule could ameliorate some of the intervention's complexity, this treatment intervention will still require a greater investment of effort to complete than a pharmacological intervention.

To ameliorate potential problems with compliance even further, a parental involvement component could be added to the intervention. This component could encourage the participation of parents in a supportive coaching role, and include parent training to improve the quality of the interactions with their child. The inclusion of psychosocial interventions targeting parents is an effective treatment for children with ADHD[193], and has been found to enhance the effects of working memory training[193].

Furthermore, positive parental and family interactions have shown protective effects against the development of ADHD in cross-sectional and longitudinal studies[54-59]. Thus, modifying the therapeutic video game intervention to increase parental involvement could prove to be an effective strategy to increase treatment compliance and efficacy.

5.6 Conclusion

An orphan drug indication for a drug/device combination of stimulants with the online game Minecraft to train executive function deficits is being pursued for the treatment of ADHD-like symptoms in Fragile X Syndrome. This intervention will utilize a novel personalized medicine approach where an individualized treatment regimen consisting of an initial stimulant dose recommendation and schedule of therapeutic video game activities will be determined from the initial ADHD assessment results of new patients. In the model, a set of ANNs will first be trained to resemble the pattern of executive function deficits reflected in a new patient's assessment responses. A large set of virtual tasks resembling the therapeutic video game activities will be tested in the model, and the set of virtual tasks that produces the maximum improvements in the ANNs of the virtual "subject" will predict the analogous set of therapeutic video game tasks most beneficial for the human patient. The translational efficacy of this computational optimization method to human subjects will then be determined in a future clinical study where an experimental group completing a computationally optimized executive function activity training schedule is compared to a control group that completes a generic, non-optimized executive function activity training schedule. This application of ANNs as a guide for optimization of clinical study interventions and individualized therapy recommendations is a novel use of computational approaches to save time and expense in a clinical development process and improve the medical treatment of patients with ADHD.

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Education

2009 - 2013	**Palm Beach Atlantic University** Lloyd L. Gregory School of Pharmacy West Palm Beach, FL 33401	Pharm.D. Magna Cum Laude May 2013
2008 – 2009	**Duquesne University** Pittsburgh, PA 15282	Pre-Pharmacy
1999 – 2006	**Pennsylvania State University** University Park, PA 16802	B.S., Biochemistry & Molecular Biology May 2006

Work Experience

2015 – 2018	**Teaching Assistant and Exam Proctor** University of Kentucky College of Pharmacy, Lexington, KY
2014 - 2015	**Lab Technician** University of Kentucky College of Pharmacy, Lexington, KY
2014	**Pharmacist-in-Charge** Liberty for all Pharmacy, Sunrise, FL
2010 – 2012	**Student Tutoring** Palm Beach Atlantic University, West Palm Beach, FL
2010, 2011	**Student Research Assistant** Palm Beach Atlantic University, West Palm Beach, FL
2007 – 2009	**Pharmacy/Compounding Technician** Prescription Center Plus, South Park, PA
2008	**Student Research Assistant** Duquesne University, Pittsburgh, PA
2005, 2006	**Lab Co-op Student** Walter Reed Army Institute of Research, Silver Spring, MD

Publications

Tiitto M, Lodder R. Therapeutic Video Games for Attention Deficit Hyperactivity Disorder (ADHD). WebmedCentral PAEDIATRICS 2017;8(11):WMC005330

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Publications (cont.)

Tiitto MV, Chang Y, Nornoo AO. CYP3A4 activity of paclitaxel and vinorelbine in microemulsions. *Diepharmazie*. 2013 (In preparation).

Honors and Awards

2016	**Omega Delta Kappa Honor Society Membership** University of Kentucky, Lexington, KY
2016	**Tied 1st Place in Elevator Speech Competition** Ashland Inc Symposium on Drug Discovery & Development, Lexington, KY
2013	**Kappa Psi Grand Council Scholarship Key** Kappa Psi Central Office, Richardson, TX
2013	**Mylan Institute of Pharmacy 2013 Excellence in Pharmacy Award** Palm Beach Atlantic University, West Palm Beach, FL
2012	**ACCP Clinical Pharmacy Challenge Online Rounds** Advanced to 2nd round in the nationwide online competition
2012	**1st Place – Gregory School of Pharmacy: ACCP Clinical Pharmacy Challenge** Palm Beach Atlantic University, West Palm Beach, FL
2012	**Kappa Psi Asklepios Key Award for Academics and Service** Delta Upsilon Chapter, Palm Beach Atlantic University, West Palm Beach, FL
2009 – 2012	**100th percentile nationwide on PCOA (Pharmacy Curriculum Outcomes Assessment) Exam** Palm Beach Atlantic University, West Palm Beach, FL
2009 – 2012	**Dean's List for Academic Excellence** Palm Beach Atlantic University, West Palm Beach, FL
2012	**Mr. Pharmacy 2012 Competition – Runner-up** Palm Beach Atlantic University, West Palm Beach, FL
2011	**REMS Medications You-Tube Superlatives Award – Best Actor** Palm Beach Atlantic University, West Palm Beach, FL
2011	**2nd Place – Gregory School of Pharmacy: ACCP Clinical Pharmacy Challenge** Palm Beach Atlantic University, West Palm Beach, FL
2011	**Rho Chi Honors Society** Palm Beach Atlantic University, West Palm Beach, FL