Therapeutic Video Games for Attention Deficit Hyperactivity Disorder (ADHD)

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1.1 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].

1.2 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].

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1.3   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 videogame 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.

1.4 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 1).

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.

1.5 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.

Sources(s) of funding:

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Test each ANN's performance with the random sample of ten image files

Test performance of controlANN on test images

Thread[testimages → controlANN[testimages]]

{ *1* →1, *8* →8, *2* →2, *4* →4, *3* →3, *7* →7, *5* →5, *6* →6, *1* →1, *7* →7}

Test performance of adhdANN on test images

Thread[testimages → adhdANN[testimages]]

{ *1* →7, *8* →5, *2* →2, *4* →7, *3* →3, *7* →9, *5* →5, *6* →6, *1* →1, *7* →2}

Figure 1 -
Working Memory Deficit Preliminary Study Results