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graduating in May, 2006

Running Head: EVOLUTION AND ADHD

Evolution and Attention Deficit Hyperactivity Disorder (ADHD)

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Introduction

This thesis reports multiple, interdisciplinary research projects that investigate Attention Deficit Hyperactivity Disorder (ADHD), attempting to place the etiology and the epidemiology of the mental disorder in an evolutionary context. The methods employed in the two completed and two ongoing studies reported here are recruited from a variety of fields, with an emphasis on an interdisciplinary approach in generating research questions, creating experiments, data analysis, and interpreting results. Though this thesis is an example how an evolutionary vantage can inform ADHD research specifically, the broader goal is illustrate the potential usefulness of using adaptationist logic in the investigation of most mental disorders.

Most mental disorders that are believed to have genetic components are associated with genes that exist in the general population at rates are that are above the rate of random genetic mutation. This is a strong indication that these genes were therefore selected for and maintained in the population through adaptation. This suggests that the genes of interest code for behavioral or cognitive phenotypes that were once adaptive, to at least a significant portion of the population. Currently, however, these genes appear to be predisposing some of the individuals who carry them to developing complex mental disorders. This raises the following questions: what cognitive or behavioral components of these genes were once adaptive, and what about the modern mental environment is different from our past environments, such that it interacts with these genes phenotypes to create predispositions to the development of maladaptive mental disorders?

These questions assume that mental disorders are genuine phenomenon of *maladaptive mental functioning*, and that the increasing rates of mental disorder are not simply due to a greater awareness of mental disorder by the biomedical community (though that is a factor), but rather also by novel gene-environment interactions in which the mental environment is dramatically changing. Our modern culture has changed the mental environment at a rate too fast to allow certain brain-related genes to adapt. For example (a fictitious one), genes that once benefited the young hunter in hunter-gatherer societies may now create antisocial behaviors in the cramped and disciplined classroom. If it is the case that once adaptive cognitive and behavioral genes are now the underlying bases of predispositions to mental disorders, then evolutionary logic – by placing all current clinical knowledge and research into an adaptionist framework – is an essential approach if we are to understand the causes and treatment of mental disorders. Hopefully, such logic could also aid in the development of ways to prevent those genetically predisposed to disorder from developing that disorder by providing coping mechanisms as they grow throughout childhood and perhaps into adulthood.

The Research Projects Reported in This Thesis

The two articles presented – and the other active, ongoing research that is presented after – were completed for undergraduate independent research credit, course credit and honors credits at the University of Pennsylvania. When necessary, study protocol was approved by the university's Institutional Review Board.

"On the Road to a Diathesis-Stress Model of ADHD"

This paper provides draws from psychiatry for its title – in a diathesis-stress model of mental illness, the environment and genes must interact to result in disorder.

This paper outlines the considerations and questions that must be addressed if one is to inquire about the evolutionary and environmental implications in the etiology of ADHD. The paper describes the state of the current knowledge regarding ADHD – from such diverse fields as population genetics and modern psychiatry – and attempts to provide a conceptual framework that might be used in the integration of these approaches using an evolutionary vantage.

"Attention-Deficit/Hyperactivity Disorder (ADHD) and the Media – An Evolutionary Perspective"

This paper reports a meta-analytic cross-cultural investigation of ADHD and the media with the hypothesis that one of the important contemporary environmental factors that is interacting with ADHD-predisposing genes to produce ADHD is the level of media-related environmental stimuli. The prediction was that countries with higher levels of "media saturation" should positively correlate with ADHD prevalence in those countries. Correlations, regression and factor analysis were conducted using national ADHD prevalence rates from various studies as a proxy for the level of ADHD in a country and national telecommunications statistics as proxies for the general level of media saturation in the environment. The analysis produced mixed, though interesting results.

Ongoing Research Efforts

There are currently three areas of research related to ADHD and evolution. For more in depth descriptions, please refer to the "Ongoing Research" section.

1) The first of these efforts consists of a questionnaire that is designed to further test the hypothesis that media is a predisposing environmental factor to the development of ADHD.

2) The second effort is designed to look at specific features of attentional cognition using a working-memory distract task on normal subjects who also complete the Conners' Adult ADHD Rating Scale (CAARS), to serve as a proxy for ADHD-like cognitions among normal populations. The task is designed to measure two things, the ability to remember item in serial order, and the effects of adding novel features that can either facilitate or hinder this memory process.

3) The third project is a large project using actual ADHD subjects, and may take up to two more years to complete. The study consists of running the ADHD subjects through a battery of attention and working memory tasks and genotyping these subjects for the DRD4 dopamine receptor gene. Then the data will be analyzed to investigate whether specific attentional-cognitive profiles can be correlated with either the diagnostic subgroups, their genotypes or both.

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On the Road to a Diathesis-Stress Model of ADHD

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD), a common childhood mental disorder affecting approximately 5% of American youth, is currently understood primarily as a behavioral disorder, characterized by inattention, hyperactivity and impulsivity (Wolraich, Hannah et al. 1998). Though ADHD is a complex developmental disorder, there is considerable evidence for the presence of underlying biological differences in the brains of people with the disorder (Swanson, Castellanos et al. 1998). Specifically, a blunted or irregular response to the neurotransmitter dopamine appears to contribute to the disorder. Furthermore, specific genetic contributors to dopamine regulation have been implicated, though there is no single-gene model. The most widely implicated genes are polymorphisms of the DRD4 dopamine receptor gene. This heritable biological predisposition implies that DRD4-associated ADHD is best characterized by a diathesis-stress model, in which a predisposition for a disorder must react to certain environmental stressors (and possibly other genes), in order for pathology to occur. Evolutionary theory, by focusing on gene-environment interactions, offers two important insights into the mechanics of this diathesis-stress model: first, adaptionist logic helps us better understand the nature of the DRD4 biological predisposition as being a functional behavioral adaptation to certain environments; second, we can then analyze that behavioral adaptation in the context of the contemporary environment to identify those stressors that may contribute to the development of the maladaptive disorder. The present paper outlines the current understanding of how the 2-repeat (2R) and 7-repeat (7R) polymorphisms of the DRD4 gene may have evolved as frequency-

dependent (defined below) behavioral adaptations and then suggests how those adaptations may now serve as predispositions for distinct developmental pathways leading to the manifestation of diagnosable ADHD. Specifically, the author suggests that hypersensitive reactivity to environmental stimuli in 7R and 2R individuals, though previously adaptive, is now the source of a predisposition to ADHD, because the current environmental demands on selective attention combined with an excess of environmental stimuli appear to stress this evolved attentional type.

DOPAMINE AND ATTENTION

Dopamine, a central neurotransmitter, has long been associated with attentional capacities. Evidence of this association first came from the observation that amphetamines improve attention (and indeed most pharmacological treatments for ADHD are psychomotor stimulants that operate as dopamine agonists.) Amphetamines stimulate the presynaptic dopamine neurons to release more cytoplasmic dopamine into the synaptic cleft, thereby increasing the firing rate of the postsynaptic neurons. Other psychomotor stimulants that are used to treat attention problems such as methylphenidate (Ritalin) operate in a similar manner, increasing the firing rate of dopaminergic neurons by altering the levels of dopamine in the synaptic cleft.

The dopamine system is an evolutionarily ancient neuronal system that serves to regulate some of the most fundamental behaviors and cognitions. Some of the same genes that regulate our dopaminergic system are found in all mammals, such as laboratory rats who have the DRD4 gene, indicating both that the dopaminergic system evolved long before homo sapiens, and that it has been consistently adaptive throughout

our evolution, as well as the evolution of all mammals. In laboratory experiments with rats, dopamine has proven to regulate a variety of functions that are crucial for motor and limbic functions (hyperactivity, arousal, novelty seeking) as well as directed behaviors and their associated cognitions, such as learning and reinforcements, decision-making, attention, and other cognitive functions that are collectively referred to as Executive Functioning (EF) (Nieoullon 2002).

The cognitive deficits that are associated with attention and EF appear to be the result of disordered functioning in those dopaminergic pathways that extend from subcortical regions such as the basal ganglia and the caudate nucleus (parts of the brain associated with basic regulatory function) to the frontal cortex (the part of the brain responsible for higher-level cognition) (Swanson, Castellanos et al. 1998). For the purposes of this paper, the exact specifics of the entire complex dopaminergic system need not be reviewed because our knowledge of the role the DRD4 polymorphisms plays in altering the dopaminergic system's functioning is limited, and our knowledge of how these alterations effect attentional behavior is more limited.

To investigate the evolution of a behavior that predisposes one for a mental disorder, knowing the exact chemical substrates of that behavior is not a prerequisite; instead, we only need have evidence that a particular predisposing behavior was selected for by the environment. At present, we know only that the relatively rare 7R and 2R polymorphisms (as opposed to the "common" 4R allele) of the DRD4 gene are associated with an increased prevalence in ADHD individuals (Swanson, Oosterlaan et al. 2000), and that these polymorphisms appear to have been selected for by the environment in a frequency-dependent manner (Wang, Ding et al. 2004), meaning that these alleles have

been adaptive to certain percentages of the population, but were everyone to have these alleles, they would no longer be adaptive. Another example of frequency-dependent selection would be sickle cell disease as an adaptation to malaria.

EVOLUTIONARY THOERIES OF ADHD

There are a various hypotheses regarding the evolutionary history of ADHD. The generally fall into one of two groups. First, researchers have begun to focus their attention on the evolution of just the DRD4 polymorphisms. Second, many hypotheses operate irrespective of specific genes, instead focusing on the potential adaptive purposes of those behaviors that clinicians have identified in ADHD individuals. The present paper will review both, as they overlap, and both have direct relevance to the investigation of the DRD4 gene's role in our evolutionary history and the development of ADHD.

The DRD4-specific hypotheses are important because they directly target the distinct predisposition to the development of ADHD that we are investigating. From this back-to-front approach, we can begin to look at ADHD as being a maladaptive behavioral state that can be broken into individual predisposing behavioral components (one of which is that of the DRD4 gene), giving us a more dynamic understanding of the complex etiology of the disorder. Further, these gene-specific models can potentially give us direct insight into the neurochemical basis of different attentional behaviors. Finally, because of the relatively recent selection operating on the DRD4 polymorphisms (Ding, Chi et al. 2002), the DRD4-specific models may offer important clues about

human history in the past 100,000 years, a period during which Homo sapiens underwent extraordinary changes such as population migration.

The gene-general models are important because we cannot know whether the behaviors that are currently considered part of the disorder by clinical science are the same behaviors that were selected for in our evolutionary past; instead, they may be new manifestations of older behaviors that are encountering a novel environment in a maladaptive manner. This front-to-back approach allows us to look at the entirety of ADHD as a complex developmental disorder, giving us a better idea of the maladaptive behaviors involved. Most importantly, because we do not yet know the *specific* behavioral contributions of the DRD4 gene, these gene-general models may hold valuable clues as to the selection history and the functional purpose of the DRD4 polymorphisms.

DRD4 POLYMORHPHISM MODELS

The DRD4 is a polymorphic gene, meaning that there are multiple forms of the alleles. The common variant is the 4-repeat (4R) allele, and in most populations (except some American ethnic populations) it is the dominant variant, followed by the 7R and then the 2R, with the remaining polymorphisms existing at extremely low rates (Chang, Kidd et al. 1996).

In multiple studies, the 7R polymorphism of the DRD4 has been associated with increased prevalence in ADHD (Faraone, Doyle et al. 2001) and with the personality trait of novelty seeking (Rogers, Joyce et al. 2004); however, the mechanisms that may account for these associations are unclear. Worldwide allele frequencies vary

ADHD individuals from other studies (Leung, Lee et al. 2005). These results taken together clearly indicate that the 2R is functionally similar enough to the 7R to call into question Harpending's explanation of the frequency data, which ignores the 2R frequency data; however, further evidence regarding the relationship between the selection of the 7R and the 2R is needed.

The most recent model has been proposed by Wang, Ding et al. (2004), who have used complex population genetics methods to model the selection operating on the 4R, the 7R and the 2R alleles. The authors accept Harpending's suggestion that the frequencies are most likely explained by a frequency-dependent model; however, they acknowledge that the 2R may be functionally equivalent to the 7R, and suggest that a variety of selective pressures may have been operating on these alleles.

According to this model, the 7R allele arose about 40-50,000 years ago, perhaps as a rare mutational event or series of events, prior to the major out-of-Africa migrations. Shortly thereafter, the 2R allele arose from recombination of the 7R and the 4R. The authors explain the unusually high 7R frequencies found in the Americas by citing the population bottleneck that occurred with migration to these areas. In general the authors remain conservative in their suggestions as to exactly what forces have selected these alleles. They suggest that sexual selection, determined by local cultural norms may have selected these alleles. However, they also point out the potential benefits of a "response ready" behavioral pattern that could have been selected for in the initial population migrations that occurred prior to local selection. This suggestion that is supported by two studies that found faster reaction times in ADHD individuals with the 7R allele as compared to those without (Swanson, Oosterlaan et al. 2000; Langley, Marshall et al.

2004). They also do not exclude the possibility that the 2R and the 7R may be in competition for similar, yet distinct niches. In short, this model does not provide an answer to the question of the alleles selection; however, it does outline the considerations that must be taken into account as research progresses. Namely, that frequency-dependent selection is operating at the local level and that the respective behavioral contributions of *both* the 7R and the 2R alleles must be considered.

GENE-GENERAL MODELS AND THEIR RELEVANCE TO THE DRD4 POLYMORPHISMS

The gene-general models focus on the behavioral traits found in the clinical diagnosis. This is advantageous because there is no single-gene model for the disorder and we do not know the exact behavioral adaptations of the DRD4 predisposition. Such a method gives us a broader perspective on the behaviors involved in the disorder and thus allows us to compare the various possible adaptive functions may have been selected for in the DRD4, and that have become maladaptive in today's environment. In effect, this approach generates hypothetical adaptive roles that we can then apply to the DRD4 selection model we have outlined above, determining which if any can fit the frequency-dependent model. It should be noted that the following comparisons of the gene-general models to the DRD4 selection requirements are speculation at this point.

One general model is the "hunter" model, originally proposed by Hartmann (Shelley-Tremblay and Rosen 1996), in which he proposes that pre-agricultural hunters would have benefited from the behavior traits we see in the clinical disorder. "He suggested that the traits of distractibility, impulsiveness and even aggression would have

been directly useful to a hunter." (Shelley-Tremblay and Rosen 1996) The problem with Hartmann's model is that he suggests that all hunter societies would have selected these behaviors for all members of those societies, and therefore the current ADHD prevalence of approximately 5% would be far too *low*, having needed serious deleterious selection. Hartman suggest that agriculture would be this negative selecting force; however this does not account for those populations in which agriculture has not been a selective force. We can modify his hypothesis to consider a frequency-dependent scenario, in which "hunter types" would only be beneficial to a certain low percentage of the population. This could have been one of the local selection processes demanded by Wang's model, as his model does not exclude the possibility of multiple adaptive niches.

Various authors have suggested that ADHD behaviors would have benefited "fighters" (Shelley-Tremblay and Rosen 1996). Some propose that humans were in direct competition with Neanderthals, and that aggressive behavior as seen in ADHD would have been selected for. Though this particular scenario may be true, it cannot explain the selection of the DRD4 because it again operates in a directional manner inconsistent with a balanced polymorphism. However, from this hypothesis we can take the notion that aggressive behavior may have played a role in local selection. This hypothesis, similar to Harpending's, seems like a feasible hypothesis if we reconceptualize the aggression as being within-group fighting. It is aggressive behavior that is cited in the famous "hawk and dove" scenario, proposed by Dawkins as an archetypal frequency-dependent scenario, in which being aggressive is beneficial to some members of a group, but not all because of the cost of constant confrontation. It is important to remember that Harpending's explanation is not necessarily incorrect because

we do not fully understand the interaction between the 7R and the 2R – male-to-male competition could well have played a role in local, frequency-dependent selection; however, it is unlikely that Harpending's "cad-society" model can account for the 2R, due to its prevalence in large, agricultural societies such as the Chinese.

Finally, Jensen et al. (1997) have constructed a dynamic continuum of ADHD related behavior dimensions and environtypes, in which he contrasts "problem-solving" with "response ready" environments (in which ADHD types would be adaptive.) In "response ready" environments: unsafe, rapidly changing or novel conditions would select for "hypervigilant, high-scan" behaviors; time-critical conditions would select for "impulsive" behaviors; resource-depleted conditions would select for "high motor activity" behaviors. Respectively, in "problem-solving" environments: safe, little changing conditions would select for "focused attention" behaviors; time-optimal conditions would select for "non-impulsive" behaviors; resource-rich conditions would select for "low motor activity" behaviors.

Jensen's "response ready" model is advantageous to the development of a DRD4 selection model, as Wang et al themselves suggested. First, it might help explain the initial population spread of the 7R and 2R alleles. Once local frequency-dependent selection took over, "response ready" environments would have discontinued as selecting factors; *however*, the response ready behavioral traits (hypervigilance, impulsivity, and high motor activity) would have continued to play a role in local selection. It is possible that these "response ready" traits could factor into a frequency-dependent model akin to the "hawk and dove" scenario. It is also possible that such behaviors could play a role in

sexual selection, which would support Wang's suggestion; however, more research is needed.

CURRENT ENVIRONMENTAL INTERACTIONS IN THE DEVELOPMENT OF DRD4-RELATED ADHD

In order to speculate as to what about the current environment is causing DRD4 polymorphisms to become a predisposition, we must combine what we know about the potential adaptive behaviors in the selection history of the DRD4 with what we know about the attentional differences of ADHD individuals with the 7R allele as compared to those without the allele to suggest a dynamic description of the DRD4's behavioral profile. Simultaneously, we must assess how ADHD individuals appear to be interacting with the environment in maladaptive or unusual ways. In this manner, we can hope to suggest a preliminary outline of a diathesis-stress model for DRD4-related ADHD.

Two studies have been done on the attentional performance of ADHD individuals with the 7R allele as compared to those without. Swanson et al. (2000) found that those ADHD individuals with the 7R allele did not show the slowed cognitive responses typical of non-7R ADHD. Rather, they appeared to be free of many of the common deficits assumed to be part of ADHD. Langley et al. (2004), using different tasks, further elaborated. Though she did find some deficits in accurate decision-making, she confirmed that 7R ADHD individuals are characterized by faster reaction times than non-7R ADHD individuals, and in her study, to controls as well. Together these studies are consistent with aspects of the "response ready" model. Specifically, it appears that 7R individuals give speed priority over accuracy. This could indicate that they have a

"scanning attention" that is designed to quickly process environmental stimuli, perhaps in order to integrate as many aspects of their environment as possible in high-pressure situations, at the cost of slow, but accurate decision-making. Essentially, this would allow the 7R individual to "multitask", paying attention to multiple things at once (as mentioned above, this could factor into a frequency-dependent model.)

There is some evidence to support the notion of multitasking. In one study (Landau, Lorch et al. 1992), ADHD children were compared to controls in their attention to television. After watching television with distractor toys present, the ADHD children showed significant problems compared to controls in recalling the content of the show they had watched when asked to simply report the shows content. Interestingly, when investigators elicited cued recall (asking specific questions about the shows content), ADHD children showed no deficit, indicating that they were paying attention to multiple things at once, though at a less conscious level.

Given this evidence I suggest the following diathesis-stress model. The 7R and 2R alleles of the DRD4 gene code for an attentional cognition that is characterized by quick, uncontrolled shifts of attention that give the individual the ability to pay attention to multiple stimuli in their environment. This hypothesis is consistent with the genetic evidence outlined above, and though I cannot provide a concrete frequency-dependent selection model, I suggest that such a cognition could have been adaptive in a variety of situations, and that the current evidence suggests that there may be multiple adaptive niches. This hypothesis does not contradict the available data regarding the selection of the DRD4, and it is consistent with our current understanding of 7R attentional cognition.

This suggested cognition should currently be maladaptive in the form of a predisposition to develop ADHD because our current environment demands a high degree of selective and sustained attention, while simultaneously presents a degree of environmental stimuli that is higher than at any point in our evolutionary history. A child with 7R will have a difficult time attempting to sustain his attention in the classroom, or a businessman will have a difficult time keeping staying on one task long enough to finish it because he is distracted by the many other demands of the office place. Similarly, television – presenting a constant stream of stimuli, should act as an environmental stressor. And indeed, there is evidence that TV exposure can lead to attentional problems (Christakis, Zimmerman et al. 2004).

Though there are no concrete answers to the questions investigated in this paper, the various lines of evidence are beginning to yield clues as to the evolutionary history and current manifestation of DRD4-related ADHD. With further neurological studies (of the neurophysiological and neurochemical substrates of ADHD), genetic studies (of the DRD4 as well as other candidate genes), cognitive studies (of the attetional components of the various forms of ADHD), and evolutionary studies (of the populations for which we have frequency data), we can begin to formulate a comprehensive and dynamic picture of ADHD as a product of our evolutionary past, and a representation of our current environment – a diathesis-stress model.

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Evolution and ADHD
HONORS THESIS IN BIOLOGICAL ANTHROPOLOGY

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Abstract

Objective: In this paper, I report the results of one preliminary, cross-cultural statistical analysis in which I examine the effect of media-saturation in society on the development of Attention-Deficit/Hyperactivity Disorder (ADHD,) as a pilot study into an evolutionary model of the disorder. ADHD is marked by hyperactivity/impulsivity and/or inattentive behavior, and is the most common childhood mental disorder at about 5%. Research has pointed to both genetic and environmental contributions, but there has been little research into developing a comprehensive evolutionary model of ADHD. ADHD is associated with genetic components maintained at high rates in the population, indicating that aspects of cognition relating to the disorder were at one time adaptive, selected by the environment. I propose that many ADHD individuals have an evolved form or forms of attention and memory processes that becomes maladaptive when the amount of information and stimuli in the environment increases far enough beyond that of the environment in which our cognitions evolved. The most obvious societal correlate of information complexity and the degree of access to stimuli is the level of media saturation; therefore, media was chosen as a proxy for the amount of information and stimuli in the environment. If the degree of information and stimuli available in the environment is a significant predictor of ADHD, then in a given society, as the level of media in the environment increases the prevalence of ADHD should also increase. One recent study has shown that exposure to television at a young age is correlated with later attentional problems, indicating the importance of television as an environmental factor in the development of ADHD, and supporting my prediction. **Methods:** I directly tested my hypothesis using indicators of media saturation, as indexed by the International Telecommunication Union's Telecomm database of telecommunications indicators, and worldwide prevalence rates from multiple independent studies compiled by Faraone (2003). Simple and partial correlations, principle component analysis, and multiple regressions were performed on the combined data set. **Results:** Analysis yielded near significant results, supporting the prediction that television is associated with ADHD; however, every other indicator of media, showed weak to moderate negative associations with ADHD. Also negatively correlated with ADHD was Gross Domestic Product (GDP). **Discussion:** These results appear to rule out a simple a model of media's effect on ADHD that excludes a consideration of different cultures' selection pressures on ADHD-like behavior. I propose three explanations that may be valid: 1) There is a distinction between interactive media, such as the internet and passive, non-interactive media, such as television, 2) Media and information in the environment do causally influence the development of ADHD, as a disorder; however, cultures in which there is less media may also happen to be cultures that, independently, do not demand the same level of attentive behavior as those cultures in which there is more media. This might occur because in these low-media cultures there has been less of a need to adapt to an excess of stimuli, and thus the ADHD-like behavior (which encouraged attention to many disparate details) flourishes. Therefore, when American diagnostic criteria are applied to these poorer, less media-saturated cultures, the more prevalent, yet benign ADHD-like behavior would *falsely* appear as an increased prevalence of the disorder. This demands a distinction between ADHD as a disorder specific to high-stimuli environments, and as an evolved, underlying behavior. We cannot apply diagnostic criteria from stimuli rich environments to stimuli poor environments because the behavior is not as maladaptive in stimuli poor environments; and, though the underlying behavior will be more prevalent, those with the behavior cannot necessarily be considered as having a disorder on the basis of the DSM criteria. 3) Television, as the only media variable found in every country, may be the only variable that should be considered currently. **Conclusion:** I propose a theoretical framework in which to illustrate the various gene/environment interactions surrounding ADHD as a dynamic process, and explain the issues that must be taken into consideration when looking at ADHD across cultures. **Future directions:** Finally, a platform for the development of an evolutionary model of ADHD is outlined to conclude the paper, taking into consideration the results of this statistical analysis and proposing future directions for research.

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Attention-Deficit/Hyperactivity Disorder (ADHD) and the Media – An Evolutionary Perspective

Understanding the evolutionary basis of a mental disorder is a process that yields knowledge of what specific cultural and social factors of the environment are responsible for the maladaptive behavior. A behavior is considered a disorder if it is both sufficiently different from the norm and affects an individual's ability to function in society (DSM-IV). Mental disorders that appear to have a genetic basis must have underlying behaviors that were at one time both functional and adaptive to a portion of the population, else those genes would never have become widespread in population. Attention-Deficit / Hyperactivity Disorder (ADHD,) like many mental disorders, is heritable (Swanson et al., 2000), and as such must have an evolutionary history. The evolution of a heritable disorder must be marked by two phases: 1) one during which the behavior must have been adaptive for a long period of time to a certain percentage of the population an the environment of evolutionary adaptiveness, and 2) the contemporary phase, in which something in the environment has changed such that the evolved behavior has become maladaptive in the form of a mental disorder. This paper is concerned with the contemporary phase, addressing the issue of what environmental factors are at play in the pathogenesis of ADHD, and discussing the possible role of known genetic contributions in that pathogenesis.

One recent study has found that exposure to television at a young age can lead to attentional problems (Christakis et al., 2004). I examine the relationship between ADHD and media in the current environment, predicting a casual association consistent with

Christakis et al. (2004)'s findings. This statistical investigation is a pilot study, in which I try to provide evidence to support a hypothetical evolutionary model of ADHD that centers on the individual's ability to attend to and integrate informational stimuli. I suggest that it would have been adaptive to have an impulse to integrate as much information (or stimuli) as possible in any one moment (a "scanning" attention,) in order to integrate and process more information about the environment in certain high-stimuli situations in contrast. This is envisioned to be in contrast to the contemporary environment in which high levels of stimuli are accompanied by societal demands for selective focus (a "screening" attention.) In this paper I delay the question as to what specific situations such cognition would have been adaptive in our evolutionary past. Though this is an interesting question in its own right, it is enough for the present purposes to recognize that current environments must be different such that certain evolved genetic influences on cognition are now maladaptive. The focus of this paper will be on the potential mechanisms at work in the cotemporary environment that are currently placing selective pressures against those genetically predisposed to ADHD, and those who display ADHD behavior.

The adaptive benefit of a "scanning attention" should disappear if the amount of information increases and the demand for *selective* focus simultaneously increases. Today, it is adaptive to screen out as much extraneous information as possible – such as in the classroom or the workplace (Jensen et al., 1997) – so an impulse to attend to extraneous information should be maladaptive and socially dysfunctional. I specifically examine what I believe to be the current selective environments in which available informational stimuli is associated with ADHD. Evidence of this association provides a

platform for future research in which the current environmental forces at play in the development of ADHD can be better understood, lending in turn to a future investigation into the evolutionary history of those environmental interactions.

Currently, ADHD is clinically understood solely as a behavioral disorder. ADHD is the most common mental disorder in the United States among children, and the disorder often carries into adulthood. The primary behavioral symptoms used in the clinical diagnosis of disorder are inattentiveness, overactivity and impulsiveness (Sagvolden, et al., 2004).

Self report, teacher report and parent report are all methods employed by clinicians in their diagnosis. Rating scales are often used – these focus on the behavior of the patient in certain situations, such as the classroom or at home. The studies from which we acquired the prevalence rates for the present statistical analysis employed any or all of these methods. Such methods are designed to evaluate behavior in reference to the standardized American criteria.

The current instrument most employed in the diagnosis of ADHD is the American Psychological Association's Diagnostic and Statistical Manual IV (DSM-IV.) The DSM-IV specifies three subgroups of ADHD: Inattentive, Hyperactive/Impulsive, and Combined types. Attention deficit disorder is multifactorial in both its pathogenesis and symptomology; however it is currently a disease defined by behavioral features, and there has been little investigation into the underlying cognitive features of the disorder, and hence no effort to redefine ADHD subgroups by cognitive or genetic features. To define ADHD subgroups, it is necessary to understand how the environment affects the pathogenesis of the disorder, and how neurological variation contributes.

The neurological evidence for ADHD centers around the function of the neurotransmitter/neuromodulator dopamine. Investigation into dopamine function began because of a history of success using psychomotor stimulants to treat ADHD symptoms. Psychomotor stimulants are dopamine agonists, increasing the amount of dopamine involved in neurotransmission. Functional Magnetic Resonance Imaging and Electro Studies support the idea that dopamine systems are hypofunctional in patients with ADHD. Dopamine – both through direct regulation or modulation of other neurotransmitter systems – is known to regulate important prefrontal activities such as attention and memory, as well as motivation and response inhibition (Sagvolden, et al., 2004). Though "it is undoubtedly too simplistic to assume that the genetic etiology of ADHD is caused by abnormal dopamine transmission alone," (Kirley et al, 2002), it is clear that certain dopamine-related genes are associated with ADHD.

Because of the obvious role of dopamine in the neurobiology of ADHD, the studies investigating possible genetic factors have revolved around genes involved in dopaminergic functions. Various genes have been studied. The DAT1 and the DRD4 genes show the most evidence of an association with ADHD (Swanson et al., 2000). The DAT1 gene codes for the dopamine transporter (Barr et al., 2001), but there is little evidence of a direct functional significance (Tannock, 1998). The DRD4 is one of the genes that code for dopamine receptors.

The 7-repeat allele of the DRD4 gene has a well documented association with ADHD (Faraone et al., 1999), (Kirley et al, 2002), (Swanson et al., 2000). There is an increased frequency of the allele in ADHD populations relative to the general population,

and studies have linked the allele to specific cognitive features of the disorder (Swanson et al., 2000)(Langley et al., 2004), as well a novelty seeking (Rogers et al., 2003).

The DRD4 gene may play a specific role in the attention of some of those with ADHD, specifying a distinct subgroup (Swanson et al, 2000). Ultimately, it will be necessary to determine what the exact cognitive contributions of these two genes are (and possibly other genes), in order to develop a comprehensive analysis of gene/environment interactions that can lead to the clinical manifestation of the disorder. As will be discussed, the gene that most likely contributes to a scanning attention (as opposed to a screening attention) is the DRD4, though this requires more research.

Besides a well-documented general association with ADHD, the 7-repeat allele of the DRD4gene has been associated with certain specific behaviors and cognitive features. The primary behavioral association, other than with ADHD, is with the personality trait of novelty seeking. A few studies (Swanson et al., 2000)(Langley et al., 2004) have attempted to examine the cognitive performance of those ADHD individuals with the allele compared those without the allele. Swanson took a sample of combined-type ADHD children with identical clinical symptomology, genotyped the sample, and subjected the children to a suite of neuropsychological tests of attention. Interestingly, though the 7-repeat children displayed the exact same symptoms of those without the allele, they performed equally well as controls on these attention tests. Langley, using a different set of tests, indicated that those ADHD children with the allele showed abnormally inaccurate and impulsive response that exceeded the non-7-repeat children. Though this test showed inaccuracy, it is important to note that the 7-repeat children had very rapid response times, which is consistent with Swanson's study, in which speed was

the primary cognitive feature assessed. In Swanson's study, those ADHD children without the allele showed the slowed cognition that was expected from ADHD children, based on current theory that attributes slowed executive functioning to ADHD. The 7-repeat ADHD children did not display these response time deficits.

These findings are preliminary support for my hypothesis. In this model, individuals with the 7-repeat allele represent those who have a hyperactive, scanning attention that compels them to attend to multiple stimuli and react quickly. If this is true, it would imply that those with the allele both have a measurably different manner of attending to stimuli as well as integrating information. I suggest that the 7-repeat allele may code for a cognition that allows individuals to have 1) better attention to multiple stimuli at once, 2) worse to one stimuli in the presence of distractors, 3) and similar attention to controls when attending to one stimuli without distractors present. If these suggestions are true, it would explain why the 7-repeat allele of the DRD4 gene confers risk for ADHD because it implies that those with the allele will have trouble focusing on one thing in the presence of environmental distractors. This would be consistent of the model I have set forth and attempted to test in this paper.

Thus, it appears that part of ADHD's onset stems from differences in evolved attentional cognition, though the specific genetic contributions may vary between individuals. I suggest that it is also possible for an individual to display ADHD-like behavior without a distinct genetic contribution; however, the prevalence of such individuals should quickly diminish as the demand for selective attention in a given society increases. What these types of individuals share is reactivity to a common environmental pressure – here hypothesized to be available stimuli. Regardless of

genotype, if the cognitive ability to selectively attend is poor enough while the demand for selective attention is great, an individual could be clinically diagnosed as ADHD.

Research has shown that the developmental path of children is affected by stimuli in the environment (Christakis at al., 2004), and that ADHD children attend to stimuli in a different manner than normal children. Specifically, Christakis et al. show that pre-school exposure to television is associated with later attention problems. In addition, Landau et al. (1992) showed that ADHD children appear may attend to television less well when distractor toys are present if gauged on a free-recall criteria, in which children are requested to simply recount what happened. However, when asked specific questions regarding the television show's content (cued-recall,) ADHD children performed equally well as controls. Thus, it is not that ADHD children do not pay attention to details in their environment; by contrast, some appear to pay close attention, though in a manner distinct from normal children. Swanson et al. (2000) showed that ADHD children with the 7-repeat allele of the DRD4 gene performed equally well as controls on certain tests of attention, despite showing all outward clinical symptoms.

Evidence, therefore, shows that all individuals with ADHD have trouble processing stimuli (the focus of this paper,) yet there may be discrete underlying cognitive predispositions to the development of the disorder that have an evolutionary basis. This could eventually lead to ADHD subgroups defined by genotype associated with specific cognitions. Regardless of genotype and the underlying cognition of ADHD individuals, I argue that all ADHD individuals are affected by the same environmental pressure of excess stimuli, resulting in similar problems with selective attention, even though clinical symptomology may not show differences between these hypothetical

subgroups. I will argue below that an evolutionary perspective could lead to a better understanding of the various manifestations of ADHD and help resolve the debate over diagnosis.

The prevalence of ADHD is disputed (Faraone et al., 2003). In this investigation, the prevalence data for each nation is often hard to determine conclusively, because two studies may report very divergent rates, though they use the same DSM criteria (such as the DSM-IV prevalence data for Brazil, in which Guardiola et al. (2000) reported 18% and Rhode et al. (1999) reported 5.8%.) Furthermore, prevalence rates in countries other than the US employ the American DSM criteria, which is not necessarily cross-culturally sensitive. This raises the most important issue pertinent to this statistical analysis – not only is the prevalence disputed within the countries, but the application of the DSM across cultures demands reevaluation because national studies, such as those analyzed here, have used American diagnostic criteria in nations with distinctly different cultures. I hope to use an evolutionary perspective to explain the fallibility of these cross-cultural DSM studies, and in doing so, shed new light on our concept of ADHD as a behavior and a disorder.

This paper will first report my statistical investigation pertinent to the proposal that the most important current selective force on ADHD is the amount of available information in the environment – in which I correlate levels of media saturation with prevalence of ADHD. Prevalence rate studies were representative of individual nations and were grouped into three categories, each based on one of the three relevant versions of the Diagnostic and Statistical Manual, designed in the United States. These three sets were combined to maximize statistical power. It is unlikely that differences between

ADHD criteria in different DSM versions had a significant impact on prevalence rates. If the effect of media is large, we should see some positive associations.

Issues that must be raised include cultural factors such as attitudes toward ADHD behavior, the cross-cultural applicability of the DSM criteria, the manner in which other forms of media may differ from television in their effect on ADHD and their degree of presence in individual cultures, and the difficult question as to what distinguishes a behavior from a disorder and how this distinction holds across cultures. A discussion of culture and the genetic contributions to ADHD will help clarify the state of these issues and direct future research efforts into ADHD as a behavior and a disorder across cultures.

In the conclusion I will summarize my findings and suggest the implications of the present research. Following the conclusion, I will suggest a platform from which an evolutionary model of ADHD should be investigated, discussing the current state of knowledge, and the implications of the present analysis. I will outline the directions that future research should take, emphasizing the importance of evolutionary thinking in the development of genetic subgroups of ADHD.

Method

The data on prevalence rates were taken from a variety of ADHD international population studies – compiled by Fareone (2003) – covering a twenty year period from 1981 to 2002. These studies are representative of the three versions of diagnostic criteria that have been used by the American Psychological Association's "Diagnostic and Statistical Manual" (DSM) since ADHD was added as a disorder. In chronological order, these three sets of diagnostic criteria are found in the following editions of the DSM: DSM-III, DSM-III-R, and DSM-IV. For each DSM set, there was multiple prevalence

rates reported, both within and between studies. Some studies reported one prevalence rate whereas others reported multiple. Those that reported multiple rates, did so according to either the instrument or the method of diagnosis used (i.e. "teacher", "parent", "functional impairment").

A discussion regarding the controversy over prevalence rates is not addressed in this article, and in the absence of an existing resolution to this debate, I felt that it was appropriate to average prevalence rates both within and among studies to attain a single datum point for as many nations as possible. For the studies with multiple reported rates, I averaged the prevalence rates using weighted means to generate a single prevalence rate for each study. When multiple studies were available for a single country, I attained a weighted mean in a similar manner. Thus I generated a single national statistic for each nation for each DSM set.

For each DSM set, population studies from a variety of nations were available and analyses were performed for each DSM set. The weighted-mean prevalence rates for each set of studies were not consistent, nor were the ranges of prevalence: the DSM-III reported a mean of 8.51% with a range of 5.2% to 16.6%, the DSM-III-R reported a mean rate of 5.49% with a range of 3% to 14.4%, the DSM-IV reported a rate of 10.67% with a range of 3.7% to 16.43%. This suggests that the set of diagnostic criteria used does not have a significant affect on the prevalence reported, and that combining the sets is a the most appropriate technique given the paucity of datum points within each DSM set.

Though interesting results were found individually for each set, the number of nations was too few to make firm assertions. Thus I combined these sets. When a

particular nation appeared in more than one set, I again generated a weighted average. This combined set was used for the final analysis. (see table 1)

Country	ADHD prevalence (% pop)
Australia*	7.1
Brazil*	9.7
Columbia*	16.4
Iceland	5.2
Ukraine	19.8
Finland	3.6
Israel	3.9
Italy	3.9
Japan	7.7
New Zealand	2.9
Spain*	7.1
China	5.8
Hong Kong	6.1
United Kingdom	16.6
SWEDEN**	4.0
CANADA**	5.8
GERMANY**	10.8
NETHERLANDS**	2.6
US**	7.7

(Mean: 7.831 95% CI: 5.56-10.10)
*weighted average from multiple studies within a DSM set
**weighted average from multiple studies across DSM sets

TABLE 1: Summary - ADHD prevalence by Country

Media and relevant population statistics were taken from ITU. These statistics cover a variety of national media indicators, such as numbers of TVs and personal computers in a nation. Important demographic indicators, such a gross national product and population, were also compiled from ITU in order to assess any confounding variables. Media and demographic data were compiled for each country for which ADHD prevalence rates were available, for the year prior to an individual ADHD study (to address publication lag time.) The same weighting system described earlier was applied to media data, first creating weighted averages for single studies, then for each

nation both within and among DSM sets. For each DSM set and for the compiled set, per capita data were generated for each media variable.

All data were logarithmically transformationed.

There was a significant degree of variation in both ADHD prevalence data and media data. We performed a battery of statistical tests to determine whether the variation of any one or more media variables explained any of the variation in ADHD prevalence across countries.

Correlations between log-transformed media variables with ADHD prevalence were calculated. Principle component analysis was also performed to determine whether the media variables could be reduced to a smaller number of dimensions. In addition, similar analyses were performed after controlling for Gross Domestic Product (GDP), allowing inference without the influence of monetary capital.

To control for GDP, I used the residuals from linear regressions of each variable n log GDP. By correlating these residuals, partial correlations were thereby generated for both media and ADHD prevalence data for which the effects of GDP were removed.

Pairwise correlations were first performed to assess any single variable effects. Principle component analysis was then performed with and without prevalence, in order to identify multiple variable dimensional effects. Finally, multiple regressions were performed to assess any multiple variable effects.

Results

Simple Pearson correlations between log-transformed prevalence, media, and GDP variables, before controlling for GDP, showed a negative correlation between Gross Domestic Product and ADHD prevalence, $r = -.4166$, $p<.0676$ $N=19$. When an outlier,

China, was removed because of the country's relatively extremely low GDP, the strength of this correlation increased significantly, r = -.5804, p<.01 N=18. (see figure. 1)

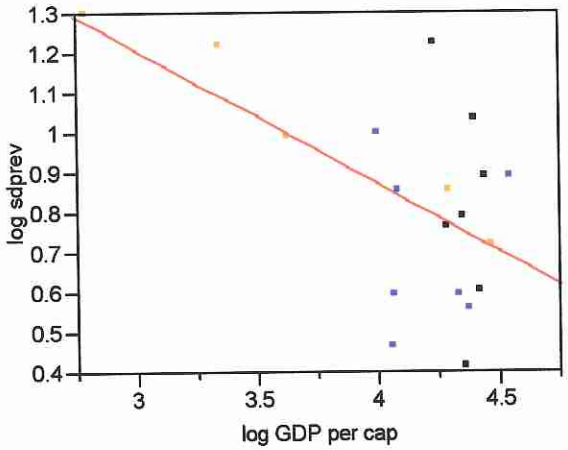

FIGURE 1: Prevalence by Gross Domestic Product.

Except for TVs per capita and TV equipped households per capita, which showed no correlation, all media variables showed negative correlations with ADHD prevalence. Many showed weak significance, except cable TV subscribers per capita, which had a negative correlation, r = -.5381, p<.05 N=13. Moderate negative correlations were found with telecommunications equipment per capita, r = -.46198, p<.1 N=15, and personal computers per capita, r = -.4158, p<.1 N=18. (see table 2)

Variable	by Variable	Correlation	Count	Signif Prob	Plot Corr
log sdprev	Log GDP per cap	-0.4166	20	0.0676	
log sdprev	log cable tv subscribers per cap	-0.5381	14	0.0471	
log sdprev	log home satellite antennas per cap	-0.3083	11	0.3563	
log sdprev	Log internet hosts per cap	-0.3718	19	0.1170	
log sdprev	Log internet users per cap	-0.2348	19	0.3333	
log sdprev	log mobile comm. rev. per cap	-0.2872	12	0.3655	
log sdprev	log ISDN subscribers per cap	-0.4684	12	0.1245	
log sdprev	log personal computers per cap	-0.4158	19	0.0766	
log sdprev	log telecom. equip. export per cap	-0.4618	16	0.0718	
log sdprev	log TV equipped households per cap	-0.0569	19	0.8169	
log sdprev	Log tvs per cap	-0.0461	20	0.8471	

TABLE 2: Pairwise Correlations - Media Variables to ADHD Prevalence.

Factor analysis of the media variables and GDP showed that the first principle component explained 67.31% of the total variance. There were relatively similar loadings across all variables, indicating that this third component represents a general media and GDP dimension. This component showed a moderate negative correlation with ADHD, r = -.589, p<.1 N=8. (see table 3)

	1st Principle t
Eigenvalue	7.8812
Percent	65.6766
Cum Percent	65.6766
Eigenvectors	
log GDP per cap	0.22774
log cable tv subscribers per cap	0.34404
log home satellite antennas per cap	0.19957
log internet hosts per cap	0.29889
log internet users per cap	0.32544
log ISDN channels per cap	0.33727
log mobile comm. rev. per cap	0.33727
log ISDN subscribers per cap	0.32242
log personal computers per cap	0.29542
log telecom. equip. export per cap	0.23473
log TV equipped households per cap	0.29819
log tvs per cap	0.17870

TABLE 3: First Principle Component summary statistics and components, showing a general "media / GDP" dimension.

Partial correlations between ADHD prevalence and media after controlling for GDP are shown in table 4. These Pearson correlations indicated once again that media variables are negatively correlated with ADHD prevalence, except TVs per capita, r= .4239, p<.07 N=19, and TV equipped households per capita, r = .3658, p<.13 N=18, both of which are correlated positively with ADHD, consistent with the general hypothesis. All other media variables were weakly correlated except cable TV subscribers per capita, which showed a moderate negative correlation, r = -.3865, p<0.18 N=13.

Regarding the TVs per capita correlation, two outliers at the extremes ends of prevalence and TVs per capita (China and the Ukraine) heavily affect the correlation; however, these

two outliers are not validly excluded because they confirm the positive trend that weakly exists without them. Without them the correlation is less significant, but does not disappear. (see figure. 2, 3)

Variable	by Variable	Correlation	Count	Signif Prob	Plot Corr
Residuals log sdprev	Residuals log cable tv subscribers per cap	-0.3865	14	0.1722	
Residuals log sdprev	Residuals log home satellite antennas per cap	0.0393	11	0.9088	
Residuals log sdprev	Residuals log internet hosts per cap	-0.2112	19	0.3853	
Residuals log sdprev	Residuals log internet users per cap	-0.0652	19	0.7910	
Residuals log sdprev	Residuals log mobile comm. rev. per cap	-0.1780	12	0.5800	
Residuals log sdprev	Residuals log ISDN subscribers per cap	-0.3207	12	0.3095	
Residuals log sdprev	Residuals log personal computers per cap	-0.0453	19	0.8539	
Residuals log sdprev	Residuals log telecom. equip. export per cap	-0.1668	16	0.5369	
Residuals log sdprev	Residuals log TV equipped households per cap	0.3658	19	0.1235	
Residuals log sdprev	Residuals log tvs per cap	0.4239	20	0.0625	

TABLE 4: Pairwise Correlations: Media Variables to ADHD Prevalence after controlling for GDP.

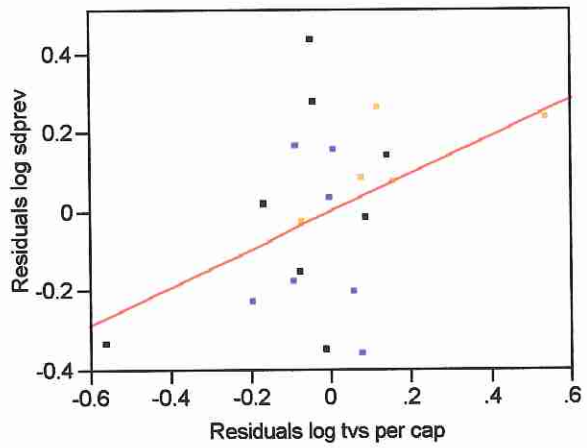

FIGURE 2: TVs per capita to ADHD prevalence with outliers

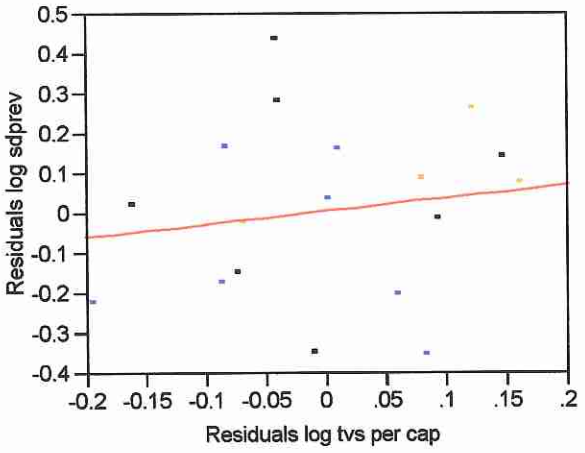

FIGURE 3: TVs per capita to ADHD prevalence without outliers

Factor analysis of the media variables showed no principle components with significant correlation with ADHD prevalence, however including ADHD prevalence into the factor analysis with the media variables did produce a sixth principle component for which ADHD prevalence loaded highly, along with internet hosts per capita and, negatively, mobile communications revenue per capita. While not conclusive, this suggested that there might be an important association between these three variables. A multiple regression was therefore performed correlating internet hosts per capita and mobile communications revenue per capita with ADHD prevalence, producing a near significant prediction, $r^2=.47$, $F(2,11) = 3.94$, $p<.06$, adjusted $r^2=.349$. Individually, internet hosts per capita in a stepwise regression contributed. $t=-2.71$, $p<.03$, and contributed 36% in shared variability with the ADHD prevalence.

Discussion

Though the results of this analysis indicate a negative correlation of ADHD prevalence with media indicators, I will argue that the results support the hypothesis that media should affect the prevalence of ADHD, though my predictions were based on too

simple a model. I will propose three possible explanations of the data. The first is based on the idea that there are two categories of media – interactive and non-interactive – that have opposite effects on the prevalence of ADHD. The second is based on a critical distinction that must be made between ADHD-like behavior and ADHD as a disorder, and that prevalence rates generated by the DSM criteria may falsely diagnose ADHD as a disorder in nations where ADHD-like behavior is not maladaptive due to a paucity of media and stimuli. In these nations, ADHD-like behavior is allowed to flourish and should be more prevalent, though classification as a disorder may be inappropriate. The third assumes that television (being the only variable that is found in every country) is the only media variable that might be viable for the present analysis. I will then propose possible explanations that reject the hypothesis.

This study represents a cross-cultural correlation of the amount of available information and stimuli in the environment with prevalence of ADHD. I proposed that if media served as a good proxy for the amount of available stimuli and information in the environment, then rates of ADHD prevalence should vary with rates of media exposure regionally in a positive direction. An increased relative level of media exposure should correlate with an increased relative prevalence of ADHD in a specific region. The analysis that did not control for GDP showed a relationship between media exposure and the prevalence of ADHD, though it was mostly negative, rejecting my prediction except with regard to television, which showed no correlation. After controlling for GDP, most media variables still showed negative association except for two TV variables (TVs per capita and television households per capita), which were positively associated. Two outliers affected the strength of the association between TVs per capita and ADHD

prevalence; however, these outliers confirm the trend and there is no justification for excluding them.

These results suggest that the initial predictions were based on a model of ADHD across cultures that may have been too simple. The results reveal important potential factors at play in the cross-cultural study of ADHD.

Explanations supporting the hypothesis

1) Though most media variables were negatively correlated with ADHD prevalence, televisions per capita and television equipped households per capita were positively correlated when controlling for GDP. There could thus be an important distinction between different forms of media – that of interactive versus that of passive, non-interactive. Christakis et al.'s (2004) study directly points to the potential of television to affect attention problems. Other evidence shows that environmental stimuli is important in the development of ADHD in individuals (Jensen et al., 1997). But there is some evidence that interactive media, specifically personal computers, can have the opposite effect, effectively relieving the symptoms of those with ADHD (Jensen et al., 1997). Some have even suggested using computers as an educational technique or as form of therapy for ADHD children (Rizzo et al., 2000). If this distinction exists, then the original hypothesis might still apply, but with a caveat: a greater degree of stimuli in the environment with which the individual does not interact should correlate with an increased prevalence of ADHD. Therefore, ADHD prevalence should positively correlate with television (which is not particularly interactive), but other media indicators (that are interactive) should correlate negatively. This hypothesis is in fact supported in

the present analysis by the strong negative correlation found with internet hosts, when multiple regression was applied.

2) A second explanation that is conditionally mutually-exclusive (see below) with the first lies in the distinction between ADHD as a disorder and as a behavior, and how this distinction holds across cultures. Important to this argument is the observation that ADHD prevalence is negatively correlated with Gross Domestic Product. Furthermore, every media indicator except TV's per capita and TV equipped households per capita are also negatively correlated with ADHD prevalence, even after controlling for GDP. This raises the question: why do countries that are poorer and have fewer media appear to have a greater prevalence of ADHD? Clearly, this goes against the simple hypothesis that increasing media saturation causes increasing ADHD. The answer probably lies in assessing the cross-cultural applicability of the DSM in the context of selection pressures on attention. One must consider how the level of stimuli effects both the prevalence of ADHD-like behavior *and* whether such behavior will be considered a disorder in a given culture, given the specific demands that environmental stimuli places on the individual.

The national studies from which ADHD prevalence data were drawn using the DSM criteria do not give a appropriate assessment of the prevalence of ADHD as a disorder, especially for less media-saturated societies. Rather, what appears to be an increased ADHD prevalence in poorer, less media-saturated societies, is actually a indication of an increased level of *ADHD-like behavior*. The DSM criteria are applied even to cultures in which there is less stimuli in the environment, and therefore, less societal demands on the attention of the individual. This raises the question of whether or

not these less-mediated cultures have allowed the ADHD-like behavior to flourish, as it might not be maladaptive to have less selective attention in an environment with less available stimuli. American diagnostic criteria are designed to assess whether ADHD-like behavior is maladaptive, but simply assume that this behavior occurs in a stimuli rich environment, where the demand for an ability to selectively attend in the presence of stimuli is great. The DSM criteria fails to make the critical culturally-contingent distinction between ADHD as a behavior and as a disorder. The DSM simply assumes that if the behaviors are displayed, the patient has ADHD; however, certain cultures may have different social requirements for selective attention, and a patient who is considered to have a disorder in America may be well adapted to another culture with less demand for selective attention. ADHD-like behavior – whether it is directly related to genetics or not – is more prevalent in less-mediated environments, but prevalence data generated with the DSM criteria gives false positives, as many individuals with the behavior may not be considered as having a disorder in a particular cultural environment.

This is an important concept in the development of an evolutionary model of ADHD, because it suggests that although the evolved *behavior* exists everywhere, it is less prevalent in those high-stimuli societies where individuals have been forced to adapt to stimuli rich environments via selective attention. I suggest that when thinking about ADHD-like behavior and genetics, we must make a distinction between those who are genetically predisposed toward "inattentive behavior", and those who display the behavior without a genetic predisposition. In high-stimuli societies (such as the US), those individuals who are the most genetically predisposed to inattentive behavior are maladaptive, and are labeled with the disorder ADHD. Other individuals who are not as

genetically predisposed toward attentional problems should display ADHD-like behavior in stimuli-poor environments because the behavior is not maladaptive; however, inattentive behavior found in those not genetically predisposed should vanish in stimuli-rich environments because there is not a genetic predisposition hindering their ability to adapt.

Thus, the prevalence of inattentive behavior should diminish as the level of stimuli increases, but those who still display the behavior are more likely genetically predisposed. It is in stimuli-rich environments, where the selection pressures for selective attention are great, that those with the strongest evolved genetic predisposition for scanning (vs. selective) attention become maladaptive. Hence, this second explanation predicts that the true disorder (as opposed to the benign behavior) is not only more likely to occur in high-stimuli environments where the behavior is maladaptive, but it is also more likely to be the result of a maladaptive phenotype of an evolved attentional genotype because those not genetically predisposed have adapted. The behavior (as opposed to the maladaptive disorder) should be more likely to occur in stimuli-poor environments, and will be falsely deemed a disorder if diagnosed with criteria from a high-stimuli culture, yielding an increased prevalence rate as compared with high-stimuli environments. Furthermore, it is in these stimuli-poor environments in which we may be able to better understand why the behavior may be adaptive.

It is important to note that, after controlling for GDP, televisions per capita and TV equipped households per capita are positively correlated with ADHD prevalence, supporting the original prediction and Christakis' finding. Television, of all forms of media, is found in the most number of countries of any media variable, and is quite

ubiquitous (see figure 4) except for China. The positive correlations weaken when outliers are removed, it is true, yet they remain positive. This supports the first explanation – that interactive and non-interactive media have divergent effects on ADHD prevalence; however, it is in contradiction with the second explanation – that a distinction must exist between ADHD as a behavior and a disorder, because television should also negatively correlate with the ADHD prevalence along with the other media data.

Thus, these two explanations are conditionally mutually exclusive, with GDP as the condition. GDP is negatively correlated with ADHD prevalence. Both explanations can only be true if controlling for GDP removes a degree of the cultural effects on the prevalence of the behavior. Then we can explain why the most universal form of media correlates positively with prevalence when those effects are diminished. The relatively strong negative correlation with GDP makes this a viable possibility.

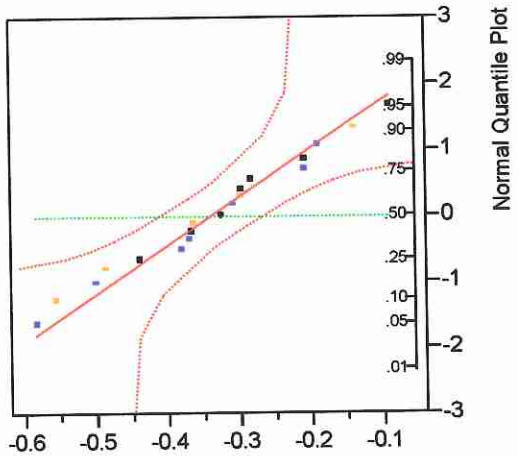

FIGURE 4: Quartile plot showing distribution of televisions per capita without the outlier (China).

3) Finally, a third simple explanation exists. Many of the media variables are not found in every country, and the correlations are rather weak, though negative. Only

television is found in every country. It could also be argued that because of its universality, television is the only media factor that can be considered for the original prediction, because it affects all societies. In this case, the original hypothesis is confirmed. This explanation is mutually exclusive with the first explanation and conditionally mutually exclusive with the second, just as the first, with GDP as the condition.

Alternative interpretations and considerations

Another issue regarding the cross-cultural applicability of the DSM concerns cultural attitudes toward ADHD-like behavior. This is in contrast to stimuli-determined cultural demands discussed in the second explanation above. The same concept of false positives as described above in the second explanation may apply, but with a different underlying reason. (For this interpretation, we need to again remember the distinction between those who are genetically predisposed toward "inattentive behavior", and those who display the behavior without a genetic predisposition.) American culture may simply value selective attention more than poorer countries *independently* of the fact that it is also a stimuli rich environment. It could be that poorer, low stimuli countries value selective attention less for cultural reasons other than that they have excess stimuli. Whereas earlier I suggested that high-stimuli societies value selective attention because of the adaptive need to ignore greater amounts of extraneous information, here I suggest that that value system may operate independently of a cultures level of stimuli and may be more of a reflection of GDP or other factors that may correlate with media data – giving the appearance that media is the cause when it may be a "side effect". A variety of possible explanations exist. Perhaps, because poorer countries (which have less media

investment) have less money for education and less corporate professional vocations – two activities that demand a high level of selective attention – this may lead their cultures to value attention less. In these countries, ADHD-like behavior might flourish regardless of genotype, leading in turn to a higher prevalence when the DSM is applied, just as in the second explanation from the previous section.

Different cultures may simply value ADHD behavior differently, and therefore the DSM would have to be discounted as an instrument to diagnose a disorder since it merely measures levels of behavior without regard to the possibility that the culture might value it. The results could be considered weak (as applied to the original hypothesis) and the high variability in prevalence data could be seen as representing the idea that ADHD is simply not cross-culturally applicable as a disorder or a behavior.

Problems with the data

There are potential problems with the validity of the data – particularly ADHD prevalence data. The present study suggests that a reappraisal of the data is necessary, and identifies important issues concerning how this type of data should be investigated in the future. In addition, the following concerns must be considered.

As mentioned previously, the data were drawn from studies that employed three sets of diagnostic criteria. It is not clear which version of the DSM gives the most accurate assessment. The DSM criteria are very consistent across versions, with the biggest difference being that the DSM-IV includes a few new subtypes of the disorder. The extent to which combining the sets may be inappropriate simply cannot be properly assessed at present. As more data are collected with the newest criteria in a wider array of countries, the patterns suggested here might become clarified.

The prevalence rate of ADHD is highly contested. Even within the US, the country for which the DSM was designed, there is a wide disparity of reported rates from national studies, indicating that the disorder itself is difficult to define, and even more difficult to observe. For example, within single studies, teacher reported rates are consistently higher than parent or doctor reports.

These problems with prevalence data are compounded by the use of multiple studies by different researchers. Each study employs it own protocol, and is performed by a different group of researchers; however, the DSM is designed to limit this problem. The present study generated weighted averages for each country taking sample size into account, which gives a best estimate for each country for which multiple studies were available. However, it is clear that some variation in incidence of ADHD is due to these sampling factors.

Optimally, one would prefer data collected in a single cross-cultural, comparative study that employs a standardized protocol to multiple nations. No such study exists. The present study calls into question the extent to which DSM criteria have cross-cultural validity, and more research on this question is needed.

The two main areas of potential inaccuracy among diagnoses are: 1) The vector of implementation (i.e. teacher v. parent v. doctor,) affects the probability of a diagnosis. For example, teacher-report rates are consistently higher than parent-report rates. 2) There are cultural differences in the subjective implementation of the diagnostic criteria. In addition to the above explanations, there are a variety of ways – other than media – that cultural differences may affect the cross- cultural applicability of the DSM, such as

differences in the value a particular culture places on education, differences in threshold of accepted behavior regarding aggressiveness, hyperactivity, etc...

Lastly, because the ADHD studies span nearly 20 years, the media data is also compiled from a broad timescale. This impacts the validity of the data because media, especially internet, has grown rapidly during the past twenty years, making the combined data set a poor technique of comparing media indicators. For many countries, media data were not available for certain indicators, reducing the power of many of our statistical analyses.

Conclusions

ADHD, regardless of genotype, is a disorder related to one's cognitive ability to process environmental stimuli, defined by a dynamic threshold – the amount of stimuli that can be processed is directly proportional to the corresponding social demands for a high level of selective attention.

An increase in the amount of available stimuli is what I propose to be the environmental factor that has begun to affect variants of the DRD4 gene in a maladaptive manner, predisposing an individual to ADHD. ADHD is a mental disorder that may have many genetic components and is also largely dependent on an individual's developmental progression. Though our model specifically addresses the cognitive features of the DRD4 gene, I suggest that available stimuli is the environmental factor that is causing ADHD in general, regardless of an individual's genotype. The forms of ADHD that are not associated with the DRD4 gene are also failing to functionally process too much available stimuli, though in different manner, which has not yet been thoroughly investigated. Thus, regardless of genotype, I suggest that certain individuals have a

threshold that limits the amount of available stimuli they can process effectively. The same environmental pressure has different effects on different genotypes but results in similar maladaptive behaviors, all of which we describe as ADHD.

There are more available stimuli in the current environment than in the environment in which these behaviors evolved, and the current social environment often demands sustained, selective and focused attention, i.e. in a classroom. The reason the current environment demands selective attention may be a direct result of the increasing amount of stimuli available, creating a selection pressure against those who have a scanning hyperactive attention. A scanning attention in the presence of so many distracters, given the social requirement of selective attention, should be maladaptive, and lead to the clinical symptoms of ADHD.

The statistical analysis reported in this paper attempts to test this hypothesis by assessing the strength of the associations between ADHD prevalence and environmental stimuli, using measures of media saturation as a proxy. The results of this analysis are not conclusive, yet they do not reject the hypothesis. These results also suggest that there are currently weaknesses in the data that may be due to theoretical flaws in the cross-cultural application of the DSM criteria.

There are three alternative explanations for the data that support my model. The positive association between ADHD prevalence and television (controlling for GDP) directly confirms my prediction, and the negative association with all other forms of media may be due to a distinction between interactive and non-interactive stimuli. There is evidence to support the validity of this distinction and it is potentially consistent with my model, as those with the 7-repeat allele of the DRD4 gene should excel in situations

that require interaction with multiple stimuli simultaneously. More research is needed to classify this distinction between forms of stimuli.

A second explanation for the results, conditionally mutually exclusive with the first, suggests the importance of another distinction that must be made when looking at the environmental interaction with ADHD-like cognition – that between ADHD-like behavior and ADHD as a disorder. If this explanation is valid, then care must be taken when looking at the presence of ADHD in other cultures because though the basic behaviors may be more prevalent, they might not be maladaptive or a problem, and will be falsely identified as such if diagnostic criteria from a stimuli-rich environment is used. Such criteria then, by definition, cannot be cross-culturally applied. This explanation emphasizes the selection forces against ADHD-like behavior in stimuli-rich environments, which in turn implies that stimuli-rich environments are those in which genetically predisposed individuals are more likely to develop a maladaptive disorder, though the behavior itself should be less prevalent. If this explanation is correct, it reinforces the idea that genetically influenced ADHD is contingent upon a high-stimuli environment in which there is a correspondingly high demand on the individual for selective focus.

A third explanation assumes no distinction between forms of media and no cultural influences on diagnosis rates. This explanation assumes that television, being the only media indicator found in every country analyzed, is the only viable indicator of media's effect. Here, television data would provide a direct support for the original prediction.

I hope to emphasize the importance of an evolutionary perspective when investigating mental disorder in general. Such a viewpoint directly addresses the importance of our changing environment for mental health, as our evolved cognitions are increasingly encountering novel environmental pressures for which we were not designed.

Platform for future research directions

Thought there are many areas available for investigation into ADHD and the environment, I will outline the directions that I plan to take regarding the development of an evolutionary model of ADHD. There are a variety of research directions that will help clarify both the genetic contribution of the DRD4 gene to ADHD and the environmental factors at play in the etiology of the disorder, regardless of genotype.

I will discuss the issues and questions surrounding future research of two issues: 1) the DRD4's evolutionary history and its contribution to a predisposition for ADHD, and 2) the current environmental factors at play with the pathogenesis of ADHD, proposing various cognitive subgroups of ADHD, one of which is that of the DRD4. I hope to place the results of this statistical analysis, in the context of this research, into the development of a dynamic evolutionary model, and outline the implications of this model for a better understanding of ADHD as a disorder.

Background: past selection of the DRD4 gene

Worldwide frequency studies of the DRD4 alleles have shown great variation between populations in the frequency of the alleles. In every population, the 4-repeat allele is the most common, and can be considered the normal variant of the gene. Though most of the other alleles are relatively rare, two variants show clear signs of positive

selection: the 7-repeat (7R) allele and the 2-repeat (2R) allele (Ding et al., 2002). Both these variants are found to be maintained at rates above the mutation rate, indicating that there must have been an adaptive benefit to these genes. Because dopaminergic functions clearly affect behavior and cognition, we can assume that these low-frequency alleles are coding for an adaptive phenotype that is behavioral because of dopamine's cognitive effects. This evidence poses the question: For what adaptive behavior or behaviors are these alleles responsible?

To answer this question we must piece together the evidence regarding the selection of these alleles with knowledge of the alleles' contribution to behavior. Worldwide frequencies of the various DRD4 alleles in ethnic populations have been documented. Most focus has been on the 7-repeat allele because it is both the second most prevalent allele (after the common 4-repeat allele), and it is known to have certain behavioral associations, such as with ADHD and novelty seeking. The 7R frequencies range from 0% to over 50% of the population (Chang et al, 1996). This is clear evidence of positive selection. Two hypotheses have been suggested to explain the variation.

Chen et al. (1999) have proposed that the 7R behavior helped those in migratory environments. This hypothesis attributes the frequency variation to worldwide population spread. This hypothesis seems to fit with a model in which the gene codes for an attentional cognition defined by a scanning, "multitasking" quality because such a cognition could easily be seen as adaptive in an environment that consistently presents high-pressure, high-stimuli situations (without the cultural demand for selective focus.) However, this hypothesis does not seem to account for frequency-dependent selection. Though the 7-repeat allele was not necessarily selected in a frequency-dependent fashion,

the consistently low frequencies imply that there should be some environmental or social factor restricting the highest frequency that can be maintained in a population

Harpending et al. (2002) suggest an alternative hypothesis that attributes the variation in 7R frequencies to the adaptive benefit of 7R behavior in Cad societies. In these societies, which Harpending refers to as "local anarchy societies," there is a high degree of male-to-male competition, loose familial ties and competition among siblings due to a level of uncertainty as to paternity. Though this hypothesis is appealing because it accounts for a frequency-dependent selection model, it more speculative than theoretically sound. First, there is no clear connection to ADHD symptomology and clinical or cognitive evidence; rather there is just intuition regarding ADHD personality traits. Second, though he supports his speculation with evidence regarding the frequency distribution among ethnic populations, his theory falls apart if the 2-repeat allele is considered to have a similar contribution to ADHD.

I suggest that both hypotheses are incomplete, and that neither explanation is specific enough to account for the attentional cognitive features that the 7R allele contributes to behavior, and that now contributes to the development of ADHD. Both hypotheses may give a clue to the greater picture, but a full explanation requires a greater understanding of the exact cognitive contributions of the gene. Furthermore, there is evidence that the 2-repeat allele may contribute to attentional cognition in a similar manner (Leung et al., 2004). Not only does this undermine previous frequency analyses among populations, such as Harpending's, but because these two alleles may occupy the same selective niche, future research may need to take 2-repeat frequencies into account. The most important consideration in the development of a model for past selection is the

broad range of behaviors that are affected by dopamine function. It is very possible that a single model of selection cannot be applied to all populations, as the cognitive contributions of the gene should manifest as modifications to a range of behaviors. Thus, despite clear evidence of positive selection, there may be a large variety of behavioral niches that define this selection history, and only a better understanding of attention and genetics will allow fruitful investigation into this area.

Data mining analysis

To address the question of what pressures selected for the 7-repeat and 2-repeat alleles of the DRD4 gene, I will perform data mining in an attempt to identify cultural patterns consistent with the available frequency data in ethnic populations. I will employ cultural anthropological databases. This method is valid because the allele frequencies appear to be the result of relatively recent selection. If possible, I would also like to correlate frequency data with media or other proxies for stimuli across regions. This is difficult because the available genetic frequency data is specific to ethnic populations, whereas the media data are for countries/regions without respect to ethnic divisions. Another proxy for stimuli may be necessary.

Media survey

Addressing the initial question of whether media can illustrate an environmental interaction with genes that results in ADHD, I have designed a survey on media usage to test whether there is any difference at all between ADHD and controls. Though this survey does not adequately address a causal relationship, it does help answer the question as to whether ADHD individuals interact with media differently. It will also help clarify whether there a distinction should be made between interactive and non-interactive

media. It is important to better research the types of stimuli that effect different types ADHD individuals.

Attention experiments with genotyping

I am also planning a series of attention experiments with genotyping to investigate the specific contributions of the 7-repeat allele to cognition. This information is essential to an understanding of the genes interaction with the environment, and thus crucial in the development of a comprehensive evolutionary model. Specifically, I will perform experiments designed to gauge the number of stimuli that an individual can attend to simultaneously. I will also introduce a temporal component with distractors to determine whether how this cognition holds or is disintegrated by intrusive stimuli. I believe that those with the allele will attend to more stimuli better than controls, but that they may be affected by any introduced distractors because their attention will quickly shift away from the initial load of multiple stimuli. This too will help better our understanding of the specific stimuli/cognition interactions effecting different types of ADHD individuals.

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APPENDIX: STATISTICS

(FOR ORIGINAL RAW DATA SET, CONSULT FILE "ADHDstat")

Descriptives Of Log-transformed Media Variables per capita and GDP per capita

Gross Domestic Product

Mean	4.0554341
Std Dev	0.5519265
Std Err Mean	0.1234145
upper 95% Mean	4.3137437
lower 95% Mean	3.7971246
N	20

Cable TV Subscribers

Mean	-1.371744
Std Dev	0.7713262
Std Err Mean	0.2061456
upper 95% Mean	-0.926393
lower 95% Mean	-1.817094
N	14

Home Satellite Antennas

Mean	-2.021599
Std Dev	0.8844153
Std Err Mean	0.2666612
upper 95% Mean	-1.42744
lower 95% Mean	-2.615757
N	11

Internet Hosts

Mean	-2.615096
Std Dev	1.0920208
Std Err Mean	0.2505268
upper 95% Mean	-2.088759
lower 95% Mean	-3.141434
N	19

Internet Users

Mean	-1.801523
Std Dev	0.9004105
Std Err Mean	0.2065683
upper 95% Mean	-1.367539
lower 95% Mean	-2.235507
N	19

ISDN Channels

Mean	-2.355533
Std Dev	1.0908735
Std Err Mean	0.3636245
upper 95% Mean	-1.517014
lower 95% Mean	-3.194053
N	9

Mobile Communications Revenue

Mean	-2.140084
Std Dev	1.0359207
Std Err Mean	0.2990445
upper 95% Mean	-1.481891
lower 95% Mean	-2.798276
N	12

ISDN Subscribers

Mean	-1.818252
Std Dev	1.904577
Std Err Mean	0.549804
upper 95% Mean	-0.608142
lower 95% Mean	-3.028363
N	12

Personal Computers

Mean	-0.727734
Std Dev	0.6913947
Std Err Mean	0.1586168
upper 95% Mean	-0.394492
lower 95% Mean	-1.060975
N	19

Telecommunications Equipment Export

Mean	1.4201799
Std Dev	0.9492915
Std Err Mean	0.2373229
upper 95% Mean	1.9260217
lower 95% Mean	0.9143382
N	16

TV Equipped Households

Mean	-0.57615
Std Dev	0.2740791
Std Err Mean	0.0628781
upper 95% Mean	-0.444048
lower 95% Mean	-0.708252
N	19

Televisions

Mean	-0.394972
Std Dev	0.3000784
Std Err Mean	0.0670996
upper 95% Mean	-0.254531
lower 95% Mean	-0.535413
N	20

L I-IV: ADHD Prevalence data and sources, including weighted means within and between studies

OUNTRY	Study Year	Author	ADHD Prevalence	PTprev	Pprev	Tprev	SBprev	PSprev	SMprev	Flprev
ustralia	1999	Gomez	7.033333333	2.4	9.9	8.8				
ustralia	2001	Graetz	7.15						7.5	
ustralia weighted			7.119468391							
azil	2000	Guardiola	18							
azil	99	Rhode	5.8							
azil weighted			9.720849934							
olumbia	1999	Pineda	16							
olumbia	2001	Pineda	17.1							
olumbia wieghted			16.42576617							
ermany	1995	Baumgaertel	17.8							
ermany	1999	Essau	8						15.8	
ermany weighted			13.05973154							
eland	1999	Magnaussen	5.2		4.7	5.7				
weden	2001	Kedesjo/Gillberg	3.7							
kraine	2000	Gadow	19.8							
nited States		many studies (see below)	11.92478497							
S	2000	Gimple/Kuhn	9.5							
	1998	Hudziak	9.9							
	2001	Nolan	15.8							
	2001	Rowland	16							
	1996	Wolraich	11.4							
	1998	Wolraich	11.45						16.1	
	2000	Gadow	9.7							

*original studies reported by Faraone et al. (2003)

DSM-III-R: ADHD Prevalence data and sources, including weighted means within and between studies

OUNTRY	Study Year	Author	ADHD Prevalence	PTprev	Pprev	Tprev	SBprev	PSprev	SMprev	Flpr
anada	1999	Breton	5.73		5	8.9	3.3			
nland	1998	Puura	3.60		6.6		0.6			
ermany	1995	Baumgaertel	10.90			10.9				
rael	1992	Zohar	3.90				3.9			
aly	1993	Gallucci	3.90			3.9				
apan	1994	Kanabayashi	7.70		7.7					
etherlands	1997	Verhulst	1.55		1.8		1.3			
ew Zealand	1993	Fergusson	2.90		3		2.8			
pain	1994	Gomez-Beneyto	14.40	14.4						
pain	"	Gomez-Beneyto	5.30	5.3						
pain	"	Gomez-Beneyto	3.00	3						
pain weighted ave	"	Gomez-Beneyto	7.08	7.08332						
weden	1996	Landgren	4.00	4						
aiwan	1993	Wang	9.90			9.9				
nited States		many studies (see below)	4.71							
S	1988	August/Garfinkel	8.60							
	1995	August	2.80							
	1992	Cohen	12.80							
	"	Cohen	8.90							
	"	Cohen	6.00							
	1992	Lewisohn	0.41							
	1993	Newcorn	18.50		11	26				
	1995	Pelham	7.10							
	1996	Simonoff	2.40							
	1995	Shaffer	3.35		4.5		2.2			
	1995	Wolraich	7.30							

*original studies reported by Faraone et al. (2003)

DSM-III: ADHD Prevalence data and sources, including weighted means within and between studies

COUNTRY	Study Year	Author	ADHD Prevalence	PTprev	Pprev	Tprev	SBprev	PSprev	SMprev	Flprev
Canada	1989	Szatmari	5.8							
China	1985	Shen	5.8							
Germany	1995	Baumgaertel	6.4							
Hong Kong	1996	Leung	6.1							
India	1991	Bhatia	11.2							
India	"	Bhatia	5.2							
Netherlands	1985	Verhulst	9.5							
UK	1991	Taylor	16.6							
United States			9.652011776							
US	1992	Bauermiester	9.1							
	1982	King	12							
	1994	Newcorn	13		8	18				
	1985	Shelim	6		12		4	2		

*original studies reported by Faraone et al. (2003)

Ongoing Research Efforts

ADHD and the Media Survey

This study is an extension of the research that began with the second article in this thesis, "Attention-Deficit/Hyperactivity Disorder (ADHD) and the Media – An Evolutionary Perspective," and is driven by the hypothesis that exposure to media may be an important aspect of the mental environment that predisposes one to the development of ADHD. Despite the mixed results of the previous article, this questionnaire task would be a more direct way to correlate media use and ADHD prevalence, a finding that is supported by other research. This questionnaire task has been approved by the Institutional Review Board of the University of Pennsylvania for the next two years, and will be implemented in an online format within that duration. The content of the survey is as follows:

Questionnaire for ADHD AND THE MEDIA STUDY

1) How many hours of TV do you watch a day

_____

2) How often do you switch channels?
Never < 1 2 3 4 5 6 7 > always

3) Do you usually watch a show from beginning to end?
Never < 1 2 3 4 5 6 7 > always

4) How much time do you usually spend watching TV in one sitting?

_____

5) How many channels do you have available?

_____

7) Please list the top three channels you watch most regularly and indicate the percentage of time that you estimate you watch to each one.
1-
2-
3-

8) Do you usually watch TV while you do schoolwork?
Never < 1 2 3 4 5 6 7 > Frequently

How much do you feel you have trouble doing multiple activities at once?

How much do you like doing multiple activities at once.

26) Do you have Attention-Deficit Hyperactivity Disorder (ADHD)?
Y/N

- Please list the top three careers that appeal to you
- What is your sex
- What is your race
- How old are you

The Attentional Cognition of ADHD Subjects and the DRD4 Gene

Overview and Funding

This is a very large project that involves multiple experimenters and facilities, and is expected to be complete within 2 years. Part of the project is funded by the prestigious undergraduate Nassau research grant, part of it is funded by the ADHD Research and Treatment Program in the Department of Psychiatry at the University of Pennsylvania, and part of it is funded by the Laboratory of Molecular Anthropology in the Department of Biology at the University of Pennsylvania. The goal is twofold: 1) To administer a battery of working memory and attention tasks to ADHD subjects from all three accepted diagnostic subgroups and one subgroup that is currently being defined. In addition to across-group analysis for all ADHD subjects, between group analysis will reveal whether specific attentional profiles correlate to distinct subgroups. 2) To then genotype all subjects who give consent to reveal whether specific attentional profiles correlate with diagnostic subgroups and/or genotypes (specifically the 2-repeat and the 7-repeat alleles of the DRD4 dopamine receptor gene).

Experimenters

Two IRB approved protocols – one for the behavioral testing of an ADHD clinical population and a separate one for the genotyping of those subjects – are guiding this study. The Principal Investigator for the administration of the behavioral tasks to ADHD subjects is Dr. Anthony Rostain, Director of the ADHD Treatment and Research Program (ADHD-TRP) at the University of Pennsylvania. The Principal Investigator of the genotyping is Dr. Theodore Schurr of the Department of Anthropology at the University of Pennsylvania. Supporting investigators are Dr. Russell Ramsay of the

ADHD Research and Treatment Program, Amishi P. Jha of the Center for Cognitive Neuroscience in the Department of Psychology at the University of Pennsylvania, and myself, Erik Malmgren-Samuel, undergraduate in Biological Anthropology, Communications and Psychology at the University of Pennsylvania.

Method

The study will consist of two phases, corresponding to the two protocol: behavioral testing and genotyping.

Phase 1:

The ADHD-TRP will recruit ADHD subjects through their clinic, and run them through a battery of diagnostic tasks, designed to rule out false positives, and to assign each subjects to one of four behavioral subgroups (the three DSM-IV-TR subgroups: Hyperactive, Inattentive, and Combined; and an experimental subgroup specific to the ADHD-TRP, called "disorganized"). Once informed consent is approved, subjects will be run through a battery of various working-memory and attention behavioral tasks, administered with a computer. Exhaustive statistical analyses will be performed to reveal any correlations between indices of working memory/attention and the diagnostic subgroups.

Phase 2:

Over the course of the behavioral testing, self-administered cheek swabs will be obtained from all subjects who give their informed consent. These samples will be preserved until all samples are collect. The samples will then be genotyped by Dr. Schurr of the Laboratory of Molecular Anthropology for the presence of either the 2-repeat and/or the 7-repeat alleles of the DRD4 dopamine receptor gene. Statistical analysis will

then be performed to reveal any significant relationships with the analysis from Phase 1, correlating genotypes with diagnostic subgroups and their performance profiles from the attention and working memory tasks.

Erik Malmgren-Samuel
graduating in May, 2006

The Role of ADHD-like Symptoms in Serial Order and Novelty in Working Memory and Attention (working paper – still in analysis stage)

Overview

This experiment, conducted over the course of the 2005-2006 academic year, was performed on normal subjects, and consisted of a simple delayed-recognition working memory task that was designed to probe the intersection between two theoretical concepts: 1) that of serial order recognition, and 2) that of attentional capture. To serve as a proxy for ADHD, subjects took the Conners' Adult ADHD Rating Scale (CAARS), which was then correlated with various indices of task performance, to see if – in the general population – the continuum of ADHD-like cognition can show distinct directionality with these specific attentional tasks. Preliminary results indicate that there are significant correlations between task measures and CAARS scores for both serial order effects and capture effects. As the paper is a working manuscript, below is presented only the raw Methods and Results with appropriate figures and tables. The manuscript will be completed and submitted for publication within the end of the year (2006).

MATERIALS AND METHODS

Subjects

45 University of Pennsylvania undergraduates were recruited as participants, using the Experimetrix online scheduling system. Students participated for partial fulfillment of credit in introductory psychology courses. Informed consent was obtained from all participants, in accordance with the protocol, which was approved by the University of Pennsylvania's Institutional Review Board. One participant's data was

excluded from analysis due to significantly slower response times from the rest of the subjects, leaving 44 participants. (n=44). 25 participants were female and 19 were male. Participants ranged in age from 17 to 22 years, with a mean age of 18.77. The only exclusion criterion was that the participants could not have a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

Experimental Task

This experiment consists of a novel working memory task design, created with E-Prime software, using a delayed-response design in which all stimuli were visual, all responses were either left or right index finger button presses, and in which stimulus duration and timing were identical. Subjects had to remember a sequence of letters. Subjects were presented with a cue image (hereafter referred to as CUE), followed by three memory items (pairs of letters) in sequence (hereafter referred to as S1a, S1b, S1c), and finally a test image of three letters (hereafter referred to as S2), in which the subjects had to indicate whether the three letters of the test image matched the cued sequence of letters from the memory items by pressing either a button for match or another for non-match. Two manipulations were introduced: 1) the absence or presence of information in the CUE image – "Sequence" or "No Sequence", and 2) the absence or presence of novel colors in selected letters from each S1 letter pair – "Neutral", "Target Novelty", or "Distractor Novelty".

The S1 items consisted of three images presented in sequence, with delays after each in which no stimulus was presented except for a central fixation cross (a cross in the center of the screen to which the subject was instructed to maintain his attention.) Each S1 image was either a pair of letters in the "Sequence" conditions, or a pair of one letter

and one ampersand in the "No Sequence" conditions. These pairs were arranged to the left and the right of another central fixation cross.

The CUE image consisted of three pairs of circles, each surrounding a cross (one to the left and one to the right of the cross.) These pairs were stacked, and corresponded (from top to bottom) to each of the three following S1 images in sequence (from the first to the third). There were two types of cue images. In the "No Sequence" trials, the cue circles were empty. In "No Sequence" trials, subjects had to remember the "Target" letters presented, ignoring the ampersands, and respond as to whether the S2 test image contained the three "Target" letters in the appropriate order. In the "Sequence" conditions, one circle in each pair of the CUE was filled in with an asterisk. Depending on which side an asterisk appeared, it indicated to the subject which letter (either the left or the right) of each S1 letter pair is the "Target" letter that he should attend to and remember. The subject must therefore ignore the other "Distractor" letter. Just as in the "No Sequence" conditions, the subject then had to respond as to whether the three letters in the S2 image were the "Target" letters in the correct order (left to right).

The novelty manipulation consisted of introducing randomized novel colors into either the "Target" letters or the "Distractor" letters or ampersands. When no color was introduced, the trial was considered a "Neutral" trial, and all S1 letters were black. To amplify the effect of color novelty, task-irrelevant black crosses appeared above and below all S1 images.

In each trial, the CUE was presented for 1500 ms, followed by a delay (D1) consisting of a fixation cross located centrally in the screen for a randomized variable duration of 500 to 1000 ms. S1a was then presented for 1000 ms, followed by another

variable-duration delay (D2) of 500-1000 ms. S1b and S1c were also 1000 ms, and the following delays (D3 and D4) were also variable between 500 and 1000 ms. S2 was presented for 1500 ms (see Figure 1A and Figure 1B). An inter-trial interval (ITI) of variable duration (2000-3000ms) was presented at the end of each trial and consisted only of the same centrally located cross as in the earlier delays.

---------- insert Figures 1A and 1B about here----------

The experiment consisted of 5 runs, each with 48 trials. The sequence and the novelty manipulations comprised a 2X3 design with 6 trial types that were equally represented and randomly presented across the 5 runs.

Subjects were seated in a closed room, with dim lights, positioned 57.3 cm from the monitor. They were instructed to keep one finger on each of the two buttons indicated for "match" and "non-match".

Accuracy and response time (RT) were recorded.

The Conners' Adult ADHD Rating Scale (CAARS)

The CAARS questionnaire was administered to all subjects following the behavioral task. The thirty-item instrument used was the self-report screening version of the CAARS. The CAAARS measures indices of ADHD-like behavioral measures. Two of the CAARS subscales (subscales A and B) measure the degree to which an individual possesses ADHD-like behaviors for both of the two major symptom clusters of ADHD (inattention and hyperactivity, respectively) used by the Diagnostic and Statistical Manual IV-TR (DSM-IV-TR). The third subscale (C) measures the combination of subscales A and B. The fourth subscale (D) measures the "ADHD Index", an index used to by clinicians to help determine whether an individual warrants a diagnosis of ADHD.

Data analysis

Mean accuracy (percent correct) was computed, though no further accuracy analyses were computed due to near perfect accuracy. Response times (RTs) measures from all subjects were entered into repeated measures analysis of variance (ANOVA) tests to determine the influence of experimental condition. Paired sample T-tests were calculated to compare means between Sequence conditions, both within each Novelty condition and when Novelty conditions were collapsed. Paired sample T-tests were calculated to compare means between Novelty conditions, both within each Sequence condition and when Sequence conditions were collapsed. Difference scores were calculated to compare conditions within both manipulations, both when conditions of either manipulation were collapsed, and within each condition.

CAARS scores were transformed into Profile Scores to normalize for age and sex. These profile scores were then correlated with RT difference scores.

RESULTS

Behavioral Results

One subject was excluded due to significantly slower response times, leaving N = 44 subjects. Response times (RTs) and accuracy were recorded; however, because accuracy was near perfect (mean = .98), all analyses were performed for RTs only. To investigate main effects of our two independent variables, a two-way ANOVA was run with 2 factors: Sequence (2 levels: Sequence and No Sequence) and Novelty (3 levels: Distractor, Neutral and Target). The results of this ANOVA revealed a significant main effect of Sequence [$F(1,43) = 12.645$, $p < .001$], no main effect of Novelty [$F(2,42) =$

.014, $p < .99$], and a significant interaction effect between Sequence and Novelty [$F(2,42) = 7.774$, $p < .001$].

Paired sample T-tests of raw RTs revealed a significant difference between Sequence (mean = 676ms) and No Sequence (mean = 691ms) [$T(1,43) = -.3556$, $p < .001$], when Novelty was collapsed (see Figure 2). This trend continued when Sequence means were compared within the Distractor Novelty and the Neutral Novelty conditions, but not for the Target Novelty condition. There was no significant difference between Distractor Novelty and Target Novelty when the Sequence condition was collapsed; however, in the No Sequence condition, there was a significant difference between Distractor Novelty (mean = 698ms) and Target Novelty (mean = 682ms), [$T(1,43) = 2.71$, $p < .01$] (see Figure 3). In the Sequence condition, there was a significant difference between Distractor Novelty (mean = 668ms) and Target Novelty (mean = 685ms), [$T(1,43) = -2.264$, $p < .05$] (see Figure 3-alternate).

----------insert Figure 2 about here----------

----------insert Figure 3 AND 4 about here----------

CAARS Correlations

When Novelty was collapsed, the Sequence difference score correlated with CAARS profile scores for subscales A, B and C. Within Distractor Novelty, the Sequence difference score correlated with subscales A and C. Within Neutral Novelty, the Sequence difference did not correlate with the CAARS. Within Target Novelty, the Sequence difference score correlated with subscales B and C.

When Sequence was collapsed, the Novelty difference score correlated with CAARS profile scores for subscale B. Within the Sequence condition, the Novelty

difference score correlated with CAARS profile scores for subscale B. Within the No Sequence condition, the Novelty difference score was not correlated with any CAARS profile scores. (see Table 1)

----------insert Table 1 about here----------

TABLE LEGENDS

Table 1. Correlation (r-values) between difference scores and CAARS subscale profile scores. CAARS A and B profile scores were correlated with the Sequence difference scores when Novelty was collapsed. CAARS C profile scores were significantly correlated with Sequence difference scores when Novelty was collapsed, as well as in the Distractor Novelty and Target Novelty conditions, but not in the Neutral Novelty condition. CAARS A profile score was correlated with Distractor Novelty, and CAARS B profile score was correlated with Target Novelty.

FIGURE LEGENDS

Figure 1. (*A*) Depicts design of a No Sequence trial, including the trial timing for all stimuli. (*B*) Depicts design of a Sequence trial, including the trial timing for all stimuli.

Figure 2. Depicts mean RTs for No Sequence and Sequence trials when Novelty was collapsed.

Figure 3. Depicts mean RTs for Distractor Novelty and Target Novelty trials in the No Sequence condition.

Figure 4. Depicts mean RTs for Distractor Novelty and Target Novelty trials in the Sequence condition.

[FIGURES AND TABLES PRESENTED IN THE FOLLOWING PAGES]

Figure 1 A

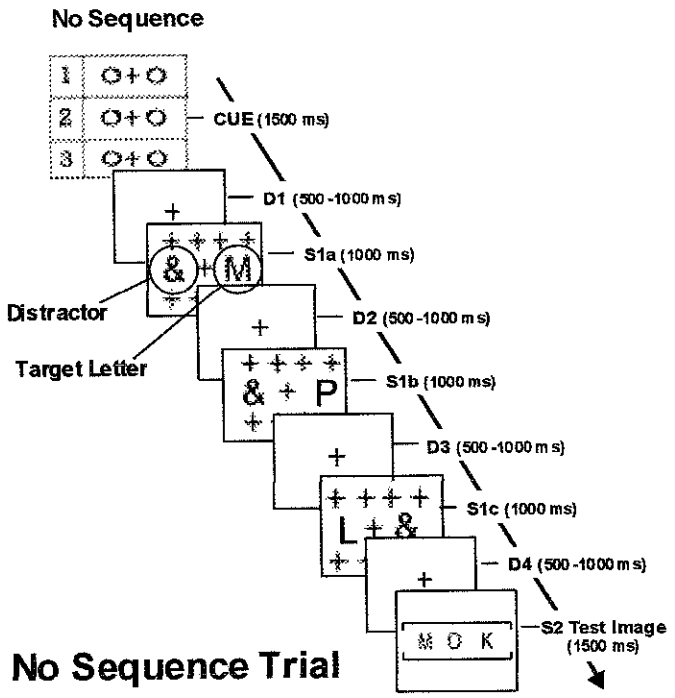

FIGURE 1a

Figure 1 B

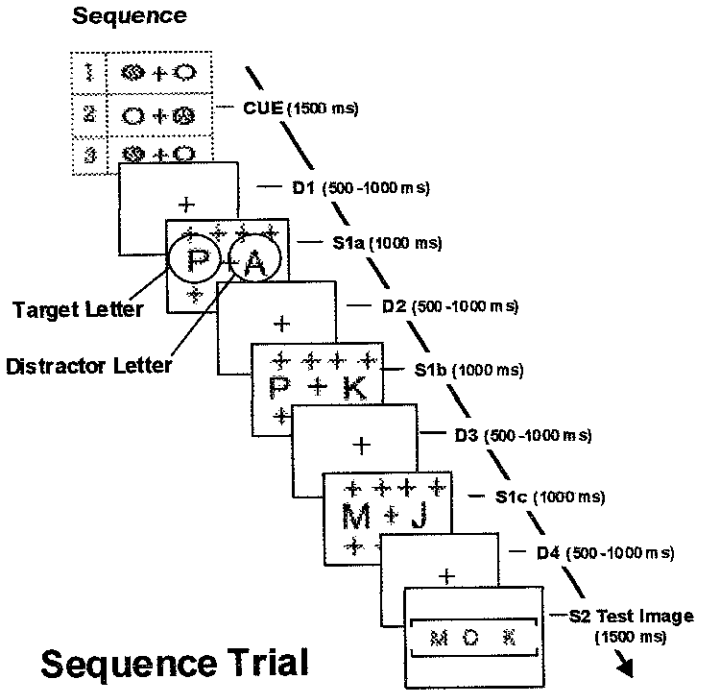

FIGURE 1b

Figure 2

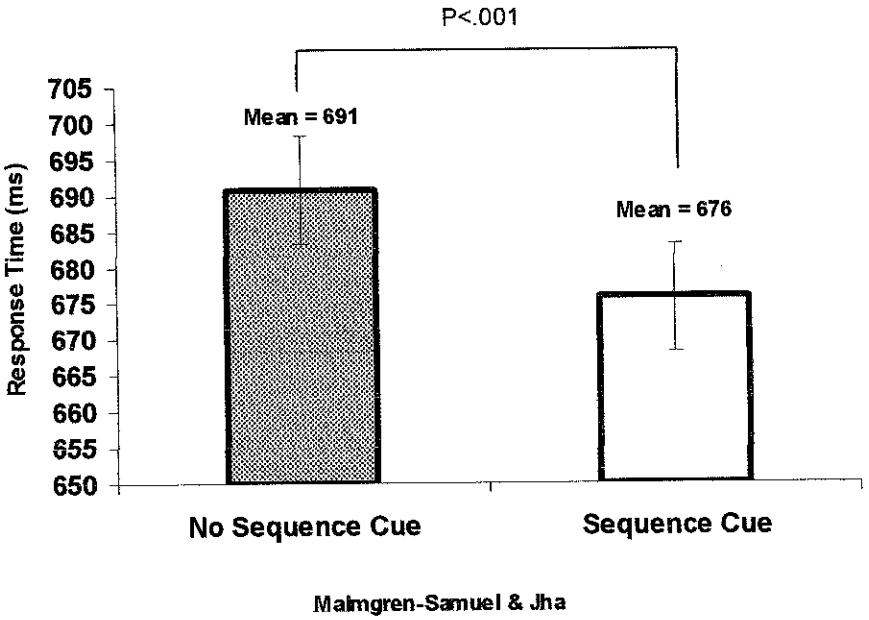

FIGURE 2

Figure 3

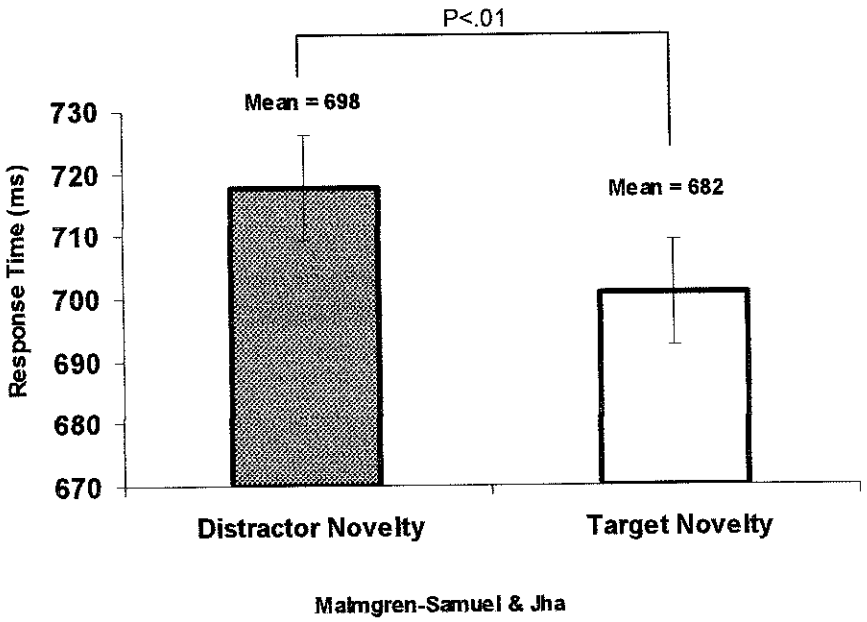

FIGURE 3

Figure 4

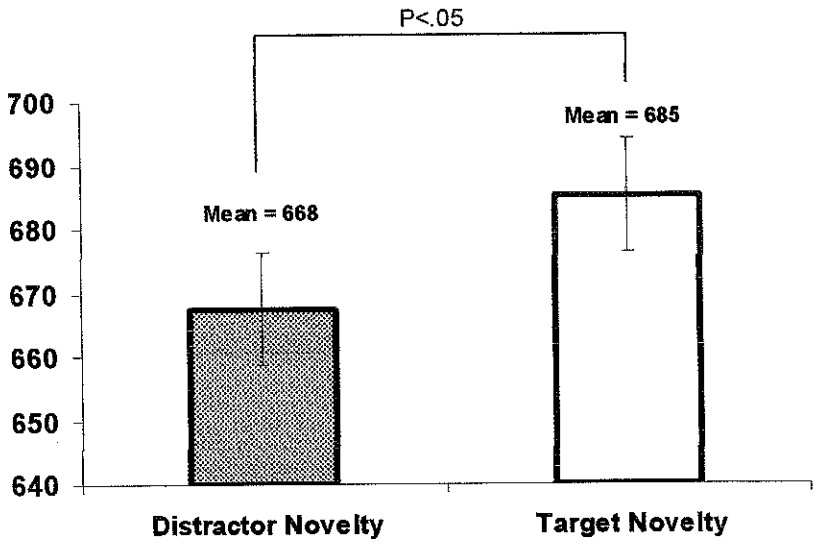

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FIGURE 4

Table 1

Difference Score	Condition	CAARS Profile Scores A	B	C	D
Sequence - No Sequence	Collapsed Novelty	**-.386***	**-.304***	**-.404****	-.018
	Distract Novelty	**-.354***	-.157	**-.326***	.049
	Neutral Novelty	-.136	-.112	-.161	-.013
	Target Novelty	-.230	**-.325***	**-.303***	-.069
Distract - Target	Collapsed Sequence	.047	**-.336***	-.106	.017
	Sequence	.089	**-.306***	-.063	-.043
	No Sequence	-.028	-.165	-.091	.074

* indicates a significance of $p < .05$
** indicates a significance of $p < .01$

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TABLE 1

General Discussion

In the present thesis I have attempted to demonstrate that an evolutionary vantage can be used to better understand the etiology mental disorders by guiding the development of research questions, regardless of what methodologies are used and regardless of under what discipline the research is operating. Methods that have been used and/or are being used currently are meta-analysis, review discussion, attention/working memory attention behavioral tasks and genotyping. Disciplines in which these investigations have been or are being conducted are Psychology, Biological and Molecular Anthropology, Neuropsychology and Psychiatry.

The sum of the research presented in this thesis provides a genuine example of interdisciplinary research, using scientists and methods from different fields. However, an overarching emphasis on generating research questions via an evolutionary vantage is maintained throughout. Interdisciplinary research is increasingly being employed in the sciences, and as the lines between the academic disciplines begin to blur, models of how to integrate and how to develop better communication between different fields of thought is of critical importance.

Perhaps the research in the present paper can contribute to the development of such a model, specifically for mental disorders with genetic components, such as ADHD. Until now, most research into the genetic bases of mental disorders has been restricted to identifying candidate genes for disorders. There has been little research into how these candidate genes express phenotypes of clinical relevance. Much of this is due to the fact that – in most cases – there is no single gene cause for mental disorders. I hope that I have demonstrated that a valuable approach for the future of investigations into the

genetic components of mental disorders is to use both an evolutionary approach theoretically, and to employ a variety of methods and disciplines to investigate those questions.

An evolutionary approach can generate research questions about specific genetic contributions to mental disorders by asking placing candidate genes in the context of predispositions that arise because once adaptive mental processes are now encountering a novel mental environment in which the phenotype has become maladaptive. From this vantage, we can not only hope to better understand the etiology of disorders, but to also develop clinical treatments based on the concept that those who are genetically predisposed to developing a complex mental disorder can avoid such an outcome if proper mechanisms are employed to cope with the mental environment during development. Similarly, those with the disorders already can develop behavioral and cognitive coping mechanisms to deal with mental disorder in everyday life.