DOWNLOAD PDF ADHD GENETIC RESEARCH: ACTIVITY DESERVING OF ATTENTION, OR STUDIES DISORDERED BY DEFICITS?

Chapter 1 : The Genetics of ADHD

The adult form of attention deficit/hyperactivity disorder (aADHD) has a prevalence of up to 5% and is the most severe long-term outcome of this common neurodevelopmental disorder. Family studies in clinical samples suggest an increased familial liability for aADHD compared with childhood ADHD.

Published online Nov To view a copy of this license, visit http: Results of candidate gene as well as genome-wide molecular genetic studies in aADHD samples implicate some of the same genes involved in ADHD in children, although in some cases different alleles and different genes may be responsible for adult versus childhood ADHD. In addition, studies of rare genetic variants have identified probable causative mutations for aADHD. Use of endophenotypes based on neuropsychology and neuroimaging, as well as next-generation genome analysis and improved statistical and bioinformatic analysis methods hold the promise of identifying additional genetic variants involved in disease etiology. Large, international collaborations have paved the way for well-powered studies. Progress in identifying aADHD risk genes may provide us with tools for the prediction of disease progression in the clinic and better treatment, and ultimately may help to prevent persistence of ADHD into adulthood. Symptoms of inattention, impulsiveness, restlessness and emotional dysregulation in adults were considered not to reflect ADHD, but to be unspecific problems secondary to other disorders. This idea was challenged when systematic follow-up studies of children documented the persistence of ADHD into adulthood. The notion that the total number of people affected by aADHD is even larger than those suffering from ADHD during childhood and adolescence also shows that the societal consequences of this chronic debilitating condition may have been vastly underestimated in the past. The lack of age-appropriate clinical measures has hampered progress in this field, including genetic research. Future versions of the Diagnostic and Statistical Manual of Mental Disorders 1 may provide diagnostic measures that are better suited for all relevant age groups. Longitudinal twin studies show that the continuity of symptoms from childhood through to adolescence is predominantly due to common genetic influences. Genetic research on ADHD started with the finding that hyperactivity tends to aggregate in families. Adoption studies found that ADHD is transmitted only to biological relatives, which strongly implicates genetic factors as the main causal influences on familial risk for the disorder. However, both adoption and family studies identify discrepancies related to different sources of ratings, with self-evaluation of ADHD symptoms by adults providing less evidence of familial effects than informants or cognitive performance data. The situation is similar in adolescence, as adolescent twin studies using self-ratings show lower heritability estimates than studies of parent or teacher ratings, 26 , 27 suggesting that self-ratings may be a poorer measure of the underlying genetic liability to ADHD than informant reports or clinical interviews. Although the estimated heritability in self-rated ADHD symptoms in adult populations is lower than that derived from parent or teacher ratings of cADHD, the pattern of findings is identical. This suggests that for both child and adult ADHD the disorder is best perceived as the impairing extreme of a quantitative trait Larsson et al. Despite these common features, the relatively low heritability estimates for ADHD symptoms in adults derived from population twin studies need some explanation, because they appear to be at odds with heritability estimates of ADHD symptoms in children, as well as the family studies that show a high familial risk for persistent forms of ADHD. We have already mentioned the consistent finding that self-ratings of ADHD symptoms give lower estimates of heritability compared with informant ratings in twin studies. One source of measurement error that is, variance of the true diagnostic status that is not predicted by the measurement instrument is the reliability of the self-rated measures of ADHD symptoms. In one of the heritability studies by Boomsma and co-workers, 25 this was estimated to be around 0. For example, Kessler et al. Similar findings were reported by Daigre Blanco et al. Single raters may inflate identical twin pair similarities, potentially leading to an overestimation of heritability in the reported studies on cADHD, whereas the lower reliability of ratings between two raters may lead to lower estimates. Another

relevant difference between child and adult samples is the expected range of ADHD symptom scores. It is well known that ADHD symptoms decline through adolescence into adulthood. Although some of this symptom decline is likely due to true remission of ADHD, some have argued that the diagnostic criteria for ADHD, which were originally developed for children, are developmentally insensitive and thus become less sensitive to ADHD with age see above and refs. Added to this is the possibility that in cross-sectional studies of adult population twin studies that do not apply clinical criteria for ADHD , ADHD symptoms may emerge in some individuals owing to adult-onset conditions, such as anxiety, depression and drug use. The family studies that showed high familial risk for ADHD used caseâ€"control methods to ascertain adult patients who were self-referred for severe ADHD-like problems. There are notable differences between the clinically referred and population-based samples. The former have a more skewed male-to-female ratio, higher rates of psychiatric comorbidity and lower rates of primarily inattentive ADHD. Moreover, the family and twin studies used differing assessment methodologies. The family studies diagnosed subjects with structured interviews that evaluated childhood onset of impairing symptoms and the presence of impairment in multiple settings as required by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. In contrast, with the exception of Schultz et al. Analogous to this, cluster A personality disorders show low heritability estimates in analyses based on limited phenotypic information that become much higher when adding more information from interviews. This might reflect the importance of developmental processes that are sensitive to person-specific environmental factors affecting the longitudinal outcome of ADHD in adults. Since heritability estimates do not relate directly to the frequency or effect size of specific genetic risk factors, 36 it is not yet clear as to what the lower heritability estimates actually mean for molecular genetic studies of aADHD. For example, some disorders with low heritabilities, such as prostate and breast cancer, have identified genes with moderate to large effects, 37 yet this is not the case for many highly heritable phenotypes including ADHD. The evidence for strong familial risks in the relatives of adolescent and adult ADHD probands suggests that the clinical diagnosis of aADHD may represent a more familial measure, although there are no studies to date that directly address this question. The difference could arise because the clinical diagnosis takes a developmental perspective in which the adult phenotype reflects persistence of the childhood disorder, whereas the cross-sectional data used in twin studies may include adult-onset causes of ADHD-like symptoms that reflect phenocopies involving different etiological processes. We conclude that aADHD is influenced by familial factors that are genetic in origin. The available studies indicate that self-ratings of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-defined ADHD symptoms may not be the best measure of the underlying genetic risk for aADHD and that other factors such as childhood onset, pervasiveness and impairment should be taken into account. Most of these studies are based on clinically assessed patients.

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Chapter 2 : ADHD Genetic Research -- www.nxgvision.com

A great deal of research has been carried out on the genetic factors that may play a role in attention deficit hyperactivity disorder ().Over 1, studies have been published on the subject to date.

All rights reserved This article has been cited by other articles in PMC. Abstract Molecular genetic studies have identified several genes that may mediate susceptibility to attention deficit hyperactivity disorder ADHD. This high-risk genetic trait leads to multiple drug-seeking behaviors, because the drugs activate release of dopamine, which can diminish abnormal cravings. Moreover, this genetic trait is due in part to a form of a gene DRD2 A1 allele that prevents the expression of the normal laying down of dopamine receptors in brain reward sites. This gene, and others involved in neurophysiological processing of specific neurotransmitters, have been associated with deficient functions and predispose individuals to have a high risk for addictive, impulsive, and compulsive behavioral propensities. We further hypothesize that early diagnosis through genetic polymorphic identification in combination with DNA-based customized nutraceutical administration to young children may attenuate behavioral symptoms associated with ADHD. Moreover, it is concluded that dopamine and serotonin releasers might be useful therapeutic adjuncts for the treatment of other RDS behavioral subtypes, including addictions. The condition is usually diagnosed in childhood, when difficulties arise during play and school, and it is marked by lack of concentration, short attention span, and physical restlessness APA ; APA However, brain-imaging studies have shown that children with this disorder have an underlying neurological dysfunction, which likely accounts for their behavior Zametkin et al ; Lou et al ADHD is a widespread affliction that we are just beginning to understand. That is, they have heightened awareness of incoming stimuli, particularly sight, sound, and touch. They are so bombarded by the normal stimuli in their environment that they cannot filter out the background noise, and they have trouble focusing or concentrating on a problem or a task. Because of their inability to focus, those with ADHD have trouble completing what they start. They have difficulties with making plans and even more difficulty in carrying out plans in an orderly fashion. People with ADHD tend to be disorganized. Children have messy rooms; adults have cluttered desks; daily activities tend to be chaotic. Attics and basements are likely to be filled with partly completed sewing projects, woodworking projects, repairs, and notebooks; desk drawers are likely to be cluttered with unfinished letters, outlines, and project plans. Many people with the disorder are highly intelligent, but they tend to be underachievers because they cannot concentrate or sustain interest. As a result, family, friends, teachers, and coworkers become impatient and expect them to fail. People with ADHD also have trouble adapting to change. Their life is so full of tumult that even a minor additional change in their routine can be upsetting or can even create a crisis, eg, a parent goes away on a trip, a new teacher takes over a class, the family moves to a new city, or a pet dies. ADHD afflicted people live under stress so severe they cannot tolerate frustration, and when they are frustrated, they are likely to become angry. The anger tends to come suddenly and explosively, accompanied by slamming doors, harsh words, tantrums, and leaving important meetings in a frenzy. Children get into fights; adults lose jobs and alienate friends. Afterwards, they may be sorry, but the damage is done. With their high level of frustration, people with ADHD are impatient. They hate to wait in line, and delays of any kind can make them frantic. Whatever is going on â€” a trip, a movie, a class, a discussion â€” they want it to go quickly and be finished. Their impatience makes people with ADHD impulsive. As children, they leap into action without thinking of consequences. As adults, they drive too fast, use power tools carelessly, and plunge into activities without thinking of the danger. The result is they often hurt themselves or others. People with ADHD have trouble with their orientation to time and space. They may have trouble differentiating their right hand from their left; they may have difficulty following a set of instructions, reading a map, or telling time. As babies or children they constantly are on the move, squirming, twisting, and getting into everything. As adults, they are restless, easily bored, rebellious when asked to follow a routine, and always on the move. Table 1 lists these criteria. There have been a number

of similar criteria set out in earlier versions of the DSM. While the names have changed somewhat, all have embraced the letters ADD in one form or another, representing the core of the disorder â€" attention deficit disorder. Either 1 or 2 six or more of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: Inattention often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities often has difficulty sustaining attention in tasks or play activities often does not seem to listen when spoken to directly often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace not due to oppositional behavior or failure to understand instructions often has difficulty organizing tasks and activities often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as schoolwork or homework often loses things necessary for tasks or activities eg, toys, school assignments, pencils, books, or tools is often easily distracted by extraneous stimuli is often forgetful in daily activities six or more of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: Some hyperactivity-impulsive or inattentive symptoms that caused impairment were present before age 7 years C. Some impairment from the symptoms is present in two or more settings eg, at school [or work] and at home D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by other mental disorder eg, Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder. Code based on type: In the present paper, we discuss ADHD as an important putative complex subtype of a general condition or umbrella disorder known as reward deficiency syndrome RDS Blum et al a. RDS refers to the breakdown of a cascade of neurotransmitters in the brain in which one reaction triggers another â€" the reward cascade Blum and Kozlowski b â€" and resultant aberrant conduct Blum et al a. At the level of individual neurons, the reward cascade is catalyzed by a number of specific neurotransmitters, each of which binds to certain types of receptors and serves a specific function. The binding of the neurotransmitter to neuronal receptors triggers a reaction that is part of the cascade. RDS has genetic and environmental influences, and it predisposes individuals to high risk for multiple addictive, impulsive, and compulsive behaviors. Depending on genes that control different parts of the reward neurotransmitter pathways, a person may display anything from mild anxiety, irritability, hyperactivity, or risk taking, to compulsive shopping, gambling, sexual behaviors, drug addiction, alcoholism, smoking, and even eating disorders. It is not limited to children. Approximately one-half to twoâ€"thirds of children with ADHD will continue to have significant problems with ADHD symptoms and behaviors as adults, where it impacts their lives on the job, within the family, and in social relationships. Appropriate and reasonable accommodations are sometimes made at school for children with ADHD, and in the workplace for adults with ADHD, which help the individual to work more efficiently and productively. While teachers are not equipped to make a definitive diagnosis, they are a meaningful source of initiation of the process to attain a sound diagnosis Biederman et al However, less than half of those individuals who have been targeted by teachers receive appropriate diagnosis and corrective intervention. Of those who are diagnosed, few are receiving appropriate multi-modal treatment apart from pharmacological manipulation. Boys are four times more likely to have this illness than girls. Approximately one-half of parents who had ADHD have a child with the disorder. There may be non-genetic factors as well, including prenatal exposure to nicotine by mothers who smoked, anoxia in the neonatal period of infancy, and childhood exposure to high quantities of lead. Dopamine is a powerful brain neurotransmitter that controls feelings of well being Blum and Kozlowski b ; Blum and Payne ; Blum et al a. Dopamine interacts with other powerful brain chemicals and neurotransmitters eg, serotonin and the opioids , which themselves are associated with control of moods. In individuals possessing an abnormality in the DRD2 dopamine receptor gene, the brain lacks sufficient numbers of dopamine receptor sites to use the normal amount of dopamine in reward centers and thus reduces the amount of dopamine produced in this area. In individuals not possessing the variant in the

dopamine receptor gene, but who have engaged in risky behaviors such as cocaine abuse, extremely low caloric diet, high levels of stress over an extended period of time , the brain functions as though it had the DRD2 genetic variant or other specific gene variants Faraone The overall effect is inadequate dopaminergic activity in brain reward centers. This defect drives individuals to engage in activities that will increase brain dopamine function. At least one genetic aberration has been identified that leads to an alteration in the reward pathways of the brain Bowirrat and Oscar-Berman It is a variant form of the gene for the dopamine D2 receptor, called the A1 allele. This genetic variant also is associated with a spectrum of impulsive, compulsive, and addictive behaviors. The concept of the RDS unites those disorders and may explain how simple genetic anomalies give rise to complex aberrant behaviors. While this polymorphic gene may play a significant role in ADHD predisposition, it must be tied to a certain subset of additional genes for the clinical expression of ADHD. This is called polygenic inheritance. Recent associations of certain alleles of both the dopamine D4 and dopamine D2 genes and novelty seeking behavior have confirmed previous work suggesting polygenic inheritance Comings et al ; Lee et al Biology of reward The reward system in the brain was discovered by accident in the s by James Olds Olds Olds had been studying brain mechanisms of attention using laboratory rats, when he mistakenly placed electrodes in a region of the limbic system. When the electrodes were attached so that the animals could self-stimulate this region by pressing a lever, rats would press the lever almost nonstop, as much as 5, times an hour. The animals would stimulate themselves to the exclusion of everything else except sleep. They also would endure tremendous pain and deprivation for an opportunity to press the lever. Olds had clearly found an area in the limbic system that provided a powerful reward for these animals. Later research on human subjects revealed that the electrical stimulation of the medial hypothalamus in the limbic system produced a feeling of quasi-orgasmic sexual arousal. If certain other areas of the brain were stimulated, an individual experienced a type of light-headedness that banished negative thoughts Olds ; Blum et al These discoveries demonstrated that pleasure is a distinct neurological function that is linked to a complex reward and reinforcement system. During the past several decades, research has been able to better define some of the brain regions and neurotransmitters involved in reward Blum et al a , A neuronal circuit deep in the brain involving the limbic system, the nucleus accumbens, and the globus pallidus, appears to be critical in the expression of reward Wise and Bozarth Although each substance of abuse or each addictive behavior may act on different parts of this circuit, the end result is the same: Dopamine appears to be the primary neurotransmitter released in brain reward sites Koob and Bloom Cascade theory of reward Considerable attention has been devoted to the investigation of the neurochemical and neuroanatomical systems that underlie a variety of substance-seeking behaviors. In healthy people, neurotransmitters work together in a pattern of stimulation or inhibition, the effects spreading downward, like a cascade, from stimulus input to complex patterns of response leading to feelings of well-being cascade theory of reward; Stein and Belluzzi ; Blum and Kozlowski b ; Cloninger et al As can be seen in Figure 1 , the following interactions take place in brain reward areas Blum and Payne ; Stein and Belluzzi The enkephalins inhibit the firing of gamma-aminobutyric acid neurotransmitter GABA , which originates in the substantia nigra A9 region. When dopamine is released in the nucleus accumbens, it activates dopamine D2 receptors. This release also is regulated by enkephalins acting through GABA. The supply of enkephalins is controlled by the amount of the neuropeptidases, which destroy them. From the amygdala, dopamine exerts an effect on neurons within the hippocampus.

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Chapter 3 : Jay Joseph, Psy.D. Licensed Psychologist - "The Missing Gene"

Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder observed during childhood, detected in 3% to 5% of school-age children. The disorder is characterised by marked.

They are looking for adult, aged years, who have been diagnosed with ADHD, to participate in this study. If you would like to participate or would like further information, please contact: Other 2 or 3 additional training sessions will be needed. Moreover, subjects who agree to participate will be randomly assigned to a biofeedback training called Self-Alert Training SAT group and a standard attentional training group. They will identify goals for the application of this strategy to key situations in everyday life. Participants will then practice self-alerting over a 2 week period at home using a home Electrodermal Activity EDA device that includes a remote monitoring system. The participant will be contacted twice a week during this period and their progress reviewed. There will be a final top-up training session. Both groups will be reassessed after 5 weeks session 2 and 17 weeks session 3 using the cognitive, psychological, EEG and fMRI measures. The study aims to evaluate the effectiveness of attentional training for adult with ADHD aged form 18 y. Jessica Braham from San Patrick Hospital. It is thought that many genes contribute to these disorders, each having a small effect. The study we are conducting aims to identify the genes involved, which will increase our understanding of these disorders. This is important, and may eventually lead to better treatment or even prevention of these common disorders. You will be visited at home or invited to attend an appointment with a member of the research team at a time that is convenient for you. Be asked a series of questions about your child with ADHD. Be asked if your child with ADHD and both biological parents can each give a blood sample. This study is strictly confidential and no one else will have access to your personal details. No individual results will be generated by this study, but by being involved you are helping researchers understand the causes of ADHD. Inclusion Exclusion Criteria To be suitable to take part in the study, we recommend: The child has been diagnosed with ADHD by a health professional The child is not adopted and will be able to give a small blood sample There are two biological parents available to give a blood sample each The child does not have the following conditions: Each of these may influence the liability of the clinical diagnosis of ADHD to a small degree. However, it is most unlikely that genes map directly to the clinical phenotype of ADHD. It is more likely that individual genes influence individual neuropsychological systems, which in certain combinations, result in the clinical diagnosis. Clear abnormalities in specific neuropsychological measures of attention and executive function are known to exist in ADHD and one of our researchers has been influential in developing new measures of attention that build on recent theoretical advances in understanding the differing attention systems of the brain. The aim of this study is to measure patterns of attentional and executive dysfunction in a large sample of children diagnosed as suffering from ADHD. This will establish neuropsychological phenotypes to be used as quantitative traits in a genetic association study of gene polymorphisms. For more information contact:

Chapter 4 : Attention-deficit-hyperactivity disorder and reward deficiency syndrome

CHAPTER TWO | ADHD Genetic Research: Activity Deserving of Attention, or Studies Disordered by Deficits? Chapter 2 examines the argument that attention-deficit hyperactivity disorder (ADHD).

We review this literature, with a particular emphasis on molecular genetic studies. Family, twin, and adoption studies provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD. This fact is most clearly seen in the 20 extant twin studies, which estimate the heritability of ADHD to be. Molecular genetic studies suggest that the genetic architecture of ADHD is complex. The few genome-wide scans conducted thus far are not conclusive. In contrast, the many candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. For the eight genes for which the same variant has been studied in three or more case-control or family-based studies, seven show statistically significant evidence of association with ADHD on the basis of the pooled odds ratio across studies: Biased paternal transmission of SNAP risk alleles in attention-deficit hyperactivity disorder. Mol Psychiatry Mar;8 3: Although the biological basis of this disorder is unknown, twin and family studies provide strong evidence that ADHD has a genetic basis involving multiple genes. Most notable is the coloboma mouse mutant, which displays spontaneous hyperactivity and is hemizygous for a deletion spanning this gene. We have screened the SNAP gene using denaturing high-performance liquid chromatography and sequencing, and genotyped six polymorphic single-nucleotide polymorphisms and two microsatellites in a clinically ascertained sample of probands. Several markers were found to show association with ADHD, both individually and in combination with other markers to form multimarker haplotypes. Analyses of transmission by parental sex suggested that the association of SNAP with ADHD is largely due to transmission of alleles from paternal chromosomes to affected probands, suggesting that this locus may be subject to genomic imprinting. Overall our data provide some evidence for a role of this gene in ADHD, although the precise causal functional variant is yet to be ascertained. Mol Psychiatry ;7 8: Synaptosomal-associated protein 25 SNAP is a presynaptic plasma membrane protein which is expressed highly and specifically in the nerve cells. The gene encodes a protein essential for synaptic vesicle fusion and neurotransmitter release. Animal model studies showed that the coloboma mouse mutant has a hyperactive phenotype similar to that of ADHD. The hyperactive phenotype of this model has been shown to be the result of a deletion of the SNAP gene. DNA variations within or closely mapped to the SNAP gene may alter the level of expression and hence may have an effect on the function of synaptic vesicle fusion and neurotransmitter release. In contrast to our findings, Barr et al 1 reported an increased transmission of allele 2 of the DdeI polymorphism though this was not statistically significant. This strain is hemizygous for the SNAP25 gene and displays hyperactivity that responds to dextroamphetamine, but not to methylphenidate. To further investigate this gene, we screened the exons for DNA variation and genotyped ten additional polymorphisms in an expanded sample of families from Toronto and a second sample of families collected in Irvine, CA. Significant results were observed in the Toronto sample for four markers, although not in the Irvine sample. The paper discusses the possible influence of the selection criteria on these differential results. Differences in ethnicity, differential medication response, and other clinical characteristics of the samples cannot be ruled out at this time. Genetic associations have been reported with polymorphic variants within or near to dopamine pathway genes. Recently snap has also shown association with ADHD in several datasets. We therefore investigated other genes that produce proteins that interact with SNAP in the mechanism of vesicular release of neurotransmitters at the synapse. One SNP in the synaptophysin gene showed suggestive evidence of association following case-control and TDT analysis and warrants further investigation. Follow-up of genetic linkage findings on chromosome 16p Recently reported linkage findings suggested evidence of a susceptibility locus on chromosome 16p13 maximum LOD score of 4. As this is also a good functional candidate gene for ADHD, we undertook family-based association analysis in a sample of families. Our data suggest that genetic variation in GRIN2A may confer increased risk

for ADHD and that this, at least in part, might be responsible for the linkage result on 16p reported by Smalley et al. A follow-up study of the first genome scan for ADHD identified significant evidence for linkage to the 16p13 region. We tested for linkage between the alleles and haplotypes of four polymorphisms at the GRIN2A locus and ADHD in our sample of nuclear families with affected children. In contrast to previous findings, we did not identify any evidence for a relationship of these markers and ADHD. Owing to the role of GRIN2A in aspects of cognition, we investigated the relationship of this gene to the cognitive phenotypes of inhibitory control, verbal short-term memory and verbal working memory. While the results were not significant in our sample, the previous association finding suggests that further study of this gene is warranted. The glutamatergic system, the major excitatory neurotransmitter system in the central nervous system CNS has been proposed as contributing a possible role in the etiology of attention deficit hyperactivity disorder ADHD. This is based upon observations from animal, neuroimaging, neuroanatomical and neuropsychological studies. Genes related to glutamate function are therefore good functional candidates for this disorder. We have undertaken detailed association analysis of SLC1A3 using a multi-stage approach for candidate gene analysis. Genes involved in neuronal development and growth are, thus, important etiological candidates and brain-derived neurotrophic factor BDNF , has been hypothesized to play a role in the pathogenesis of ADHD. BDNF is a member of the neurotrophin family and is involved in the survival and differentiation of dopaminergic neurons in the developing brain of relevance because drugs that block the dopamine transporter can be effective therapeutically. The transmission difference between parents raises the possibility that an epigenetic process may be involved. Several lines of evidence indicate an involvement of brain derived neurotrophic factor BDNF in body weight regulation and activity: Additionally, we genotyped two common polymorphisms rs Three rare variants c. A role of the I2 allele in the etiology of obesity cannot be excluded. We found no association between p. V66M or the additionally genotyped variant c. This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at http: Tryptophan hydroxylase TPH is a rate-limiting enzyme in the biosynthesis of serotonin from tryptophan. In addition, several haplotypes all including the associated marker were associated with ADHD. Molecular Psychiatry advance online publication, 7 June ; doi: NheI and MboI were used to detect different alleles of the two polymorphisms separately. The serotonin 5-HT1B receptor gene and attention deficit hyperactivity disorder. Mol Psychiatry ;8 1: Serotonin regulates dopaminergic neurotransmission in some areas of the brain via several 5-HT receptors including 5-HT1B. Animal studies have suggested the involvement of the 5-HT1B receptors in locomotor behaviour. Although preliminary, results from this study provide additional evidence that serotonin genes may be important risk factors for the development of ADHD. Serotonergic system and attention deficit hyperactivity disorder ADHD: Mol Psychiatry ;7 7: Imbalance in dopamine neurotransmission has been suggested as a factor predisposing to ADHD. However, evidence has suggested an interaction between dopamine and serotonin systems in the pathophysiology of the disorder. Studies using selective agonists of the different 5-HT receptors microinjected into selected brain structures have shown a positive modulating effect on the functional activities of the mesotelencephalic dopaminergic system. These preliminary data suggest an important role for the serotonin system in the development of ADHD. Further studies, preferentially including different ethnic groups are required to substantiate these findings. Serotonin is an endogenous neurotransmitter that regulates aggressive and impulsive behavior and may be involved in the development of attention deficit hyperactivity disorder ADHD. Many of these same behaviors are seen in patients with ADHD. Mol Psychiatry Sep;5 5: The complex interaction between the serotonergic and dopaminergic neurotransmitter systems suggests that a balance between the two systems may be necessary for mediating hyperactive behaviour. Defects in serotonin system genes, therefore, may disrupt normal brain serotonin function causing an imbalance between these neurotransmitter systems leading to the development of attention deficit hyperactivity disorder ADHD. This may open a new door in ADHD molecular genetics research, expanding the existing view of a catecholaminergic hypothesis to include a serotonergic hypothesis and should help elucidate the complex interplay among the neurotransmitter systems in the etiology of ADHD.

Blood samples were taken from 6 approximately Polymorphism of the serotonin-2A receptor gene HTR2A associated with childhood attention deficit hyperactivity disorder ADHD in adult women with seasonal affective disorder. J Affect Disord Sep;71 Several lines of research point to a possible overlap between seasonal affective disorder SAD and attention deficit hyperactivity disorder ADHD , particularly in females. The current sample size is small, and childhood ADHD diagnoses were based on retrospective recall. As the importance of genetic factors is well established, genes encoding for proteins of the serotonergic pathway are important candidates to unravel the underlying genetic contribution. We previously demonstrated that the polymorphisms of the serotonin transporter gene promoter and regions of variable number of tandem repeats were involved in the pathogenesis of ADHD. There was no significant difference between the frequencies of the T, C, G and A alleles of both groups. Am J Hum Genet May;70 5: Molecular genetic studies of ADHD have previously focused on examining the roles of specific candidate genes, primarily those involved in dopaminergic pathways. We have performed the first systematic genomewide linkage scan for loci influencing ADHD in affected sib pairs, using a approximately cM grid of microsatellite markers. Qualitative trait maximum LOD score analyses pointed to a number of chromosomal sites that may contain genetic risk factors of moderate effect. Two of the regions highlighted in the present study, 2q24 and 16p13, coincided with the top linkage peaks reported by a recent genome-scan study of autistic sib pairs. Am J Hum Genet May;72 5: As part of an ongoing study of the genetic etiology of ADHD, we have performed a genomewide linkage scan in nuclear families comprising individuals and affected sibling pairs ASPs. Previously, we reported genomewide linkage analysis of a "first wave" of these families composed of ASPs. A follow-up investigation of one region on 16p yielded significant linkage in an extended sample. The current study extends the original sample of ASPs to ASPs and provides linkage analyses of the entire sample, using polymorphic microsatellite markers that define an approximately cM map across the genome. These data, taken together with the fine mapping on 16p13, suggest two regions as highly likely to harbor risk genes for ADHD: Interestingly, both regions, as well as 5p13, have been highlighted in genomewide scans for autism. Am J Hum Genet. The candidate chromosomal regions were selected from all three published genomewide scans for ADHD, and fine mapping was done to comprehensively validate these positional candidate regions in our sample. In conjunction with the previously reported significant linkage on the basis of fine mapping 16p13 in the same sample as this report, the analyses presented here indicate that four chromosomal regionsp13, 6q12, 16p13, and 17pare likely to harbor susceptibility genes for ADHD.

Chapter 5 : Attention Deficit Hyperactivity Disorder | ADHD | ADD | MedlinePlus

"Family and twin studies have shown that there is a substantial genetic contribution to both reading disabilities (RD) and attention deficit hyperactivity disorder (ADHD), and recent twin studies have suggested that the overlap between these phenotypes is largely due to common genetic influences.

As a Attention deficit hyperactivity disorder ADHD has been result, ADHD has been the focus of considerable genetic the focus of considerable genetic research over the last few research. The results of recent genetic studies are reviewed years. Since the initial family and twin studies of the early with a focus on the emerging picture and future trends. ADHD s [1, 2], there have been about 2, publications on appears to be a complex disorder in which multiple genetic ADHD and genetics with over appearing in â€" and environmental risks contribute to a quantitative trait. These publications include numerous family and the same time, there is growing evidence that in a proportion twin studies, 24 genome-wide association studies, and 32 of cases, individually rare variants such as copy number meta-analyses of genetic findings exploring the genetic variants may play an important causal role. The more genetic architecture of ADHD. These studies support the role of risks, both common and rare, the more extreme the trait. Increased sample size that are used, the population one is studying, and the specific is an urgent necessity if we are to discover potentially causal diagnostic criteria and thresholds that are applied in particular variants. Non-behavioral markers of genetic risk known as criteria for pervasiveness of symptoms and impairment [3]. Genetic studies in ADHD hold the agreed threshold [4], and is measured indirectly using parents potential for refined nosology, more precise diagnosis, and or teachers as informants rather than directly with a laboratory differential diagnosis, improved early identification leading to test there are no known biomarkers or tests for ADHD. Many cases remit although most con- tinue. Many individuals with an ADHD diagnosis exhibit other disorders comorbidity raising the possibility that Keywords Attention deficit hyperactivity disorder. ADHD could be a non-specific consequence or epiphenome- Genetics. Numerous biological, psychological and social fac- tors such as prenatal exposure to alcohol, traumatic brain injury [6, 7], prematurity, low birth weight [8], treatment for Family Studies of ADHD leukemia and psychosocial adversity increase the risk for ADHD. The distribution of a trait tical to that found in other disorders including most medical within families has been used to reveal the influence of genetic conditions, many use it to challenge the existence of ADHD. Also, families are more homogeneous in genetic back- implications of current genetic discoveries for clinical practice. But if a person is related, e. The greater the ies: Proximally, genetic variants influence synthesis, tions and demonstrating genetic influence on ADHD. If comorbidity delineates a genetically distinct sub- dysfunction which, in turn, engender variations in the observ- type of ADHD, one should see that particular subtype clus- able phenotypic manifestations of the disorder. Typically, tering breeding true, cosegregating among relatives within phenotype refers to observable phenomena associated with families. By contrast, if a comorbid condition is a variable disease even though any variation that is not genetic, strictly manifestation of common genetic risks pleiotropy , one speaking, is a phenotype. In complex disorders, environmen- would not expect that a comorbid condition would breed true tal factors play an important role by influencing gene expres- within families. Family risk studies indicate that ADHD with sion, by shaping the pathway from gene to phenotype or comorbid conduct disorder CD [15], pediatric-onset bipolar directly impacting on disease expression. This model is con- [16] disorder or ASD [17] tend to cosegregate in families and, sistent with the fact that restlessness, inattentiveness and im- therefore, could represent potentially distinct genetic sub- pulsiveness vary widely in the general population and gener- types. By contrast, similar designs have not revealed ally follow a normal, bell-shaped distribution. By contrast, a rare variant model postulates that there Twin Studies of ADHD are many individual genetic variants any one of which could cause ADHD or contribute a great deal to the pheno- Although family studies provide clear evidence for genetic type in a particular individual. A single causal variant could influence on a trait, they do not allow for an estimate of the be limited to only one

family or to very few families in the heritability of that trait because family members also share an population. Other rare variants might cause the same disor- unspecified amount of environmental influences. Heritability der in other individuals. Some cases might be genetic but is the proportion of phenotypic variation due to additive not inherited because the abnormal gene or genes arises de genetic factors. For the most part, heritability has been esti- novo. For the most part it appears that both common and mated from twin studies, which allow for estimation of genetic Curr Dev Disord Rep 1: If one assumes for the moment that MZ and DZ twins lower h2 estimates than in children. Estimates of genetic share common environments to a comparable extent, the de- influences on ADHD are also affected by the nature of the gree to which genetic factors influence a trait or disease will be rating scales that are used to measure ADHD with more evident in the extent to which MZ twins are more alike than detailed questionnaires, teacher ratings and objective mea- DZ twins. Twin models partition covariance between MZ and sures of ADHD traits such as actigraphs movement detectors DZ twins into additive genetic influences on a trait A , com- yielding lower heritability estimates for overall clinician or mon environmental influences C, those that make twins more parent ratings [19]. MZ and DZ may not those that make twins less alike. Heritability h2 is a number have equally common environments due to sharing of placen- that reflects the proportion of variation in a trait among indi- tal environments, for example, and twin analyses cannot easily viduals in a population that is due to their genotypes. Despite these limitations, high heritabil- whether ADHD it is measured as a disorder affected versus ity of ADHD underscores the value of genetic research and unaffected , a trait more or less restless, inattentive and bodes well for gene mapping. High heritability indicates that impulsive , as the extreme of a trait distribution, and by there is a strong correlation between the phenotype and geno- either parent or teacher ratings [19]. However, high heritability does not although twin studies tend to underestimate the contribu- establish that a trait has a simple genetic architecture. Herita- tion of environmental and over-estimate the extent of ge- bility could, instead, be a result of many loci contributing to netic risk factors. Moreover, twin studies cannot easily high as estimates for other mental illness such as ASD and identify genetic interactions with environmental influences. Recently, twin studies have been exploited to address im- Although family and twin studies demonstrate the role of portant issues in the nature of ADHD beyond the question of genetic influences in ADHD, they do not provide any means heritability. Analyses of longitudinal twin data show that there of identifying the specific genetic risks. A candidate gene are genetic influences that are stable thereby affecting ADHD study, which involves what one might think of as an educated traits throughout childhood and into adolescence, genetic guess about the mechanism of a disease, is one strategy to influences that emerge with time and those that influence early investigate specific risks. The method involves assessing the development but attenuate with development [22]. Moreover, association of a particular allele or set of alleles of a gene and the longitudinal relationship between the ADHD dimensions the disease itself to determine if the alleles are found more appears to be unidirectional, with hyperactivity-impulsivity in often in affected than unaffected individuals or is transmitted middle childhood predicting the presence of inattentiveness in along with the disease. But which genes should be studied? In early adolescence, but not vice versa [23]. However, ADHD is known to respond to stim- ies reveal correlated familial genetic liabilities contributing to ulant medication which in turn is recognized to affect release the comorbidity of ADHD and other neurodevelopmental and reuptake of neurotransmitters in particular dopamine. Candidate gene studies have regularly conduct problems, alcohol and substance use [30â€”32]. Candidate gene studies run a might lead to apparently common phenotypic consequences substantial risk of generating false positives because of the genetic heterogeneity [37, 38]. The problem of small sample large number of gene associations that are tested individually size is a serious one and has been tackled by formation of the without correction for the total number of possible associa- Psychiatric Genomics Consortium PGC; http: The PGC aims but not negative results. It is not surprising then that it has been to undertake mega-analyses using individual-level genotype uncommon for genetic associations arising candidate gene and phenotype data rather than meta-analyses which are based studies to be replicated in genome-wide association studies on summary data such as odds

ratios. Building and maintain- [34]. Consequently, single association studies must be consid- ing the necessary databases and shaping the required collab- ered tentative and thoroughly replicated [35]. Being a com- oration have been great achievements. In , the PGC pub- role of any single risk difficult in the absence of very large lished the results of the largest genome-wide analysis of populations. Finally, candidate gene studies focus on particu- psychiatric disorders to date by examining GWAS data in five lar genetic markers, which may not be the causal gene but are disorders ADHD, ASD, major depression, bipolar disorder linked or inherited along with the causative gene as it is passed and schizophrenia in 33, cases and 27, controls of from generation to generation. SNPs at four loci surpassed the have been replicated in genome-wide studies. These results implicate a specific Genome-wide Approaches biological pathwayâ€"voltage-gated calcium-channel signalingâ€"as a contributor to the pathogenesis of several Both linkage and association designs use regularly spaced, psychiatric disorders, and support the potential of this path- highly variable i. In exome sequencing, these markers are enologically distinct disorder pleiotropy. Having said that, ge- number variants to be discussed below. Moreover, the netic associations in other diseases have identified risks as so- PGC analyses cannot yet control for diagnostic misclassifica- called gene deserts, which are regions with no known protein- tion, heterogeneity or comorbidity. In association studies, genomes of in the PGC analysis was the smallest of all disorders 1, individuals with ADHD are compared with genomes of unaf- child, mother and father trios and cases compared with, fected individuals controls in order to identify differences. Any SNP marker that is found in disordered individuals Genome-wide analyses set high levels for statistical signif- significantly more often than in unaffected individuals is said icance because they involve a large number of statistical tests to be associated with the disease. In linkage studies, genomes millions depending on the density of the array used. How- of various members of the same family with the same disorder ever, rigorous levels for significance in genome-wide studies are compared for sharing. Regions that are shared among could obscure the role of genes that individually contribute similarly affected family members are said to be linked to only modestly to ADHD. Pathway analysis is an approach for the disease. In both linkage and association studies, identified grouping individual, low intensity, genetic findings into Curr Dev Disord Rep 1: Large CNVs may be more likely to affect gene cognitive deficits. These results, however, are limited by the function than are smaller ones. Using this approach to priori- inadequacy of our knowledge about gene function. Genetic markers spread throughout the Several of these CNVs were found in multiple cases providing genome such as those assessed by microarrays can be used to good candidates for future work. Many of the CNVs that have estimate relatedness between pairs of individuals, because the been found in ADHD are known to appear in other more that individuals are related, the greater the sharing of neurodevelopmental disorders such as intellectual deficiency marker alleles. The extent of estimated relatedness can be and ASD. For that reason, we studied a sample of ASD correlated with the magnitude of phenotypic similarity en- participants for the ADHD-related CNVs and were able to find abling heritability to be estimated. Applying this method, Wray and CNVs. This estimate is lower than twin estimates because it nisms in neurodevelopmental disorders in particular ADHD omits the contribution of some causal variants that are not and ASD [41]. In a subsequent and larger study, Williams et al. The Wray et al. Copy number variation CNVs is one possible source of genetic variation in human diseases. Copy number variants Environmental Risks and Genetics are segments of DNA of various sizes in which there is a deletion, insertion or duplication, abnormal position Many individual environmental risks have been associated translocations or orientation inversions of a DNA segment with ADHD including low birth weight, maternal smoking, involving many SNPs. CNVs are not visible under a micro- extreme environmental deprivation, maternal stress and alco- scope like chromosomal abnormalities but they are much hol use. What is less clear is whether these environmental larger than single nucleotide variants SNV. For example, it is possible that the in- human genome than do SNPs. CNVs can be inherited or be creased risk for ADHD among offspring of mothers who drink de novo mutations, can disrupt gene function much like a is a result of in utero exposure to alcohol or a result of SNP, and can increase or decrease the dose of a gene product. Recent parents of individuals with ADHD have deficient response research on these topics involves

the use of genetically in- inhibition, slow and processing speed and several other traits formed designs such as comparison of the risk to offspring [50]. Another approach [44] examines outcomes lation sample of about 15, children and youth and ob- in relationship to specific candidate genes e. Twin studies afford another critical test of the same smoke exposure. Collectively, these studies have not found hypothesis. There is a clear need for further research of this kind. Others have observed that response time variability is under genetic control in ADHD [53]. Endophenotypes On the horizon are studies in which brain structure and function as assessed using neuroimaging techniques of in- One of the more interesting current debates in ADHD genetics creasing sophistication are linked to increasingly more de- has been about the potential role of endophenotypes in genetic tailed mapping of individual genomes for identification of research. Neuroimaging genetics deserves a review in its underlying genetic risk and phenotypic manifestations of dis- own right and will not be discussed here. Cholesterol level has been used as an endophenotype in the study of cardiovascular disease [45] and as a marker of long life [46] because it is known to be influenced both by genetic Conclusions and environmental factors [47] and is known to be moderated by a number of gene products.

DOWNLOAD PDF ADHD GENETIC RESEARCH: ACTIVITY DESERVING OF ATTENTION, OR STUDIES DISORDERED BY DEFICITS?

Chapter 6 : ADHD - School of Medicine - Trinity College Dublin

Clinical trials are research studies that look at new ways to prevent, detect, or treat diseases and conditions, including ADHD. During clinical trials, investigated treatments might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments.

Abstract Electroencephalography EEG is an ideal neuroscientific approach, providing a direct measurement of neural activity that demonstrates reliability, developmental stability and high heritability. This systematic review of a subset of domains evaluates the utility of electrophysiological measures as potential intermediate phenotypes for ADHD in the domains of quantitative EEG indices of arousal and intra-individual variability, and functional investigations of inhibitory and error processing using the event-related potential ERP technique. Each domain demonstrates consistent and meaningful associations with ADHD, a degree of genetic overlap with ADHD and potential links to specific genetic variants. Such research will aid in the precise characterisation of the clinical deficits seen in ADHD and guide the development of novel intervention and prevention strategies for those at risk. ADHD, arousal, default-mode, electrophysiology, endophenotype, executive function, genetics, heritability Attention deficit hyperactivity disorder ADHD is a developmental condition characterised by impairing levels of inattentive, impulsive and hyperactive symptoms Ref. ADHD tends to run in families, with a risk of ADHD to first-degree relatives of an affected proband around four to ten times the general population rate Ref. Such quantitative genetic studies suggest that ADHD represents the extreme of one or more continuously distributed traits, rather than a distinct categorical disorder Ref. Overall, quantitative genetic studies support the use of both categorical and quantitative trait locus QTL approaches in the investigation of genetic risk factors for ADHD Ref. Candidate gene studies implicate genetic variants involved in the regulation of dopamine and related neurotransmitter systems, predicted by the effects of stimulant medications that increase the amount of synaptic dopamine Ref. The most consistent evidence of genetic associations with ADHD are for variants within or near the dopamine D4 and D5 receptor genes Ref. There are numerous, yet inconsistent, reports of association with the dopamine transporter gene, which nevertheless seem to implicate this gene with associated polymorphisms found in two distinct regions Ref. Other neurotransmitter systems are also likely to be involved. For example, serotonin is linked to poor impulse regulation Ref. Such studies have, however, only had limited success in identifying risk alleles for ADHD, major limitations being the low risk conferred by individual genetic variants and insufficient sample size Ref. Recent genomewide association scans found no genetic variants that passed genomewide levels of significance, although there was evidence for association in a group analysis of 51 nominated candidate genes Ref. This finding and other hints from GWAS indicate that genes involved in cell division, cell adhesion, neuronal migration and neuronal plasticity may also be implicated in ADHD Ref. Despite some advances, it is necessary to consider the reasons for the overall lack of progress. The most likely reasons are the presence of multiple genes of very small effect, heterogeneity of aetiological influences, and interactions between genes and environment Ref. In addition, we do not yet understand the contribution made to ADHD from rare copy number variants CNVs , which confer moderate to large effects in some cases Ref. One approach to these problems is to gather very large sample sizes needed for sufficient power to detect genes of very small effect. Yet there are complementary strategies that posit that molecular genetic research should not be restricted to the clinical phenotype alone, but should also investigate genetic factors that account for neurobiological processes that underlie the heterogeneity of ADHD. The intermediate phenotype endophenotype concept Intermediate phenotype research aims to identify neurobiological processes that mediate between genes and behaviour and might therefore be more proximal to gene function Ref. Key criteria for endophenotypes are listed in Box 1. Intermediate phenotypes may be less heterogeneous and genetically less complex than behavioural phenotypes, and potentially associated with greater effect sizes from individual genes. Furthermore, investigation of measures related directly to brain function are required if we wish to elucidate

the neurobiological processes that underlie risk for ADHD. BOX 1 Criteria for intermediate-phenotypes Ref. Any deviations from perfect reliability will increase measurement error and therefore nonshared environmental influences Ref. In a similar way, cognitive performance and other neurobiological measures that share genetic influences with ADHD may reflect the multiple outcomes of the genes involved, rather than necessarily representing processes that mediate between genes and ADHD behaviours. Tests of mediation versus pleiotropy can be used to specifically infer the causal role of a neurobiological process once specific genetic risk factors are identified that are associated with both ADHD and associated neurobiological measure. One other approach would be to test for co-variation of ADHD and neurobiological measures during the treatment response Ref. Here we focus on electrophysiological approaches using electroencephalography EEG , which records the ongoing electrical activity generated by underlying brain structures, recorded from electrodes placed on the scalp. Electrophysiological parameters are ideal for intermediate-phenotype research in ADHD because of the supreme temporal resolution that enables investigation of the stages of information processing that are impaired and abnormal state processes such as arousal or default mode network impairments, and the high reliability and heritability of many electrophysiological measures Ref. Furthermore, there are consistent findings across studies suggesting abnormal electrophysiological processes in ADHD Ref. Finally, the non-invasive and cost-effective nature of EEG helps to generate the relatively large sample sizes required for molecular genetic studies. This systematic review evaluates the use of a subset of candidate electrophysiological measures as potential intermediate-phenotypes for ADHD, assessing the following:

Chapter 7 : The genetics of attention deficit/hyperactivity disorder in adults, a review

Molecular genetic studies have identified several genes that may mediate susceptibility to attention deficit hyperactivity disorder (ADHD). A consensus of the literature suggests that when there is a dysfunction in the "brain reward cascade," especially in the dopamine system, causing a low or hypo-dopaminergic trait, the brain may require dopamine for individuals to avoid unpleasant feelings.

Magnetic resonance spectroscopy was performed within the research institute. It has been suggested that a deficit in behavioral inhibition lies at the core of ADHD. Given these findings, we hypothesized that children with ADHD would show reduced GABA concentration in a measurement volume that included primary somatosensory and motor cortices. Before examination, assent was obtained from each participant, and written informed consent was obtained from all parents or legal guardians. Included in the study were 13 children with ADHD 11 boys and 2 girls , with a mean age of Also included were 19 age-matched typically developing TD control subjects 12 boys and 7 girls , with a mean age of Diagnosis of ADHD was based on the following instruments: Children with full-scale IQ scores below 80 were excluded from participation. Children who met criteria for conduct disorder, mood disorders, generalized anxiety disorder, separation anxiety disorder, social phobia, or obsessive-compulsive disorder were excluded from the study. Children with comorbid oppositional defiant disorder ODD were included in the study given evidence from family studies 12 , 13 suggesting that ADHD associated with ODD does not represent a distinct subtype. No participant had a history of other neurological disorders, including Gilles de la Tourette syndrome. Of 13 children with ADHD, 7 were being treated with stimulant medication at the time of the study. For those children, medication was withheld the day before and the day of testing. Children with ADHD taking longer-acting medications were excluded from the study. Children were included in the TD comparison group only if they did not meet ADHD diagnostic criteria on any of the administered rating scales and questionnaires. No children in the TD group were taking psychoactive medications. All children in this study were assessed as right-handed using the Edinburgh Inventory. In addition, participants were administered the Physical Development Scale Tanner , 14 a brief questionnaire describing physical and sexual development. For 7 of 9 female participants, scores established that menarche had not been reached at the time of enrollment, making it unlikely that cyclical hormonal status had an effect on GABA measures in the group of girls. Mrs and imaging All experimental data were acquired on a 3-T imaging system Achieva; Philips. Fourteen-millisecond editing pulses were applied at 1. Three hundred twenty transients of data points 2-kHz spectral width were acquired as twenty step phase cycles, with the editing pulse frequency switched on alternate-phase cycles. Other experimental parameters included repetition time and echo time of and 68 milliseconds, respectively; refocusing pulse bandwidth of 1. As a quantitative metric of fit quality, the root mean square residual for this fit was quantified as a percentage of the fitted peak amplitude. The unsuppressed water signal from the same volume was fit using a gaussian-lorentzian model, and the model was integrated. GABA concentration in institutional units was calculated using the following equation: Owing to the few female participants in one quadrant 2 girls in the ADHD group , no interaction term was included. A t test was performed to assess for a main effect of diagnosis on GABA concentration. As a secondary analysis, an equivalent linear regression was performed to investigate changes in the coedited total glutamate plus glutamine Glx signal. Successful application of this method in a pediatric population even one with ADHD is not assured a priori because J-difference editing is inherently sensitive to participant movement. No significant effect of age on GABA concentration was observed in univariate or regression analysis P.