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Prediction of the clinical response to psychostimulant by the basal and reactive salivary cortisol in children with ADHD

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Cette thèse intitulée :

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Résumé

Le trouble du déficit de l'attention/hyperactivité (TDA/H) est un des troubles comportementaux le plus commun chez les enfants. TDAH a une étiologie complexe et des traitements efficaces. Le médicament le plus prescrit est le méthylphénidate, un psychostimulant qui bloque le transporteur de la dopamine et augmente la disponibilité de la dopamine dans la fente synaptique. Des études précliniques et cliniques suggèrent que le cortisol peut potentialiser les effets de la dopamine. Un dysfonctionnement du système hypothalamo-hypophyso-surrénalien (HHS) est associé avec plusieurs maladies psychiatriques comme la dépression, le trouble bipolaire, et l'anxiété. Nous avons fait l'hypothèse que le cortisol influence l'efficacité du traitement des symptômes du TDAH par le méthylphénidate.

L'objectif de cette étude est de mesurer les niveaux de cortisol le matin au réveil et en réponse à une prise de sang dans un échantillon d'enfants diagnostiqué avec TDAH âgé de 8 ans. Le groupe était randomisé dans un protocole en chassé croisé et en double aveugle avec trois doses de méthylphénidate et un placebo pour une période de quatre semaines. Les enseignants et les parents ont répondu aux questionnaires SWAN et à une échelle d'évaluation des effets secondaires.

Les résultats ont démontrés qu'un niveau de cortisol élevé au réveil prédit les sujets qui ne répondent pas au traitement du TDAH, si on se fie aux rapports des parents. En plus, la réactivité au stress élevé suggère un bénéfice additionnel d'une dose élevée de méthylphénidate selon les enseignants. Aussi, les parents rapportent une association entre la présence de troubles anxieux co-morbide avec le TDAH et une meilleure réponse à une dose élevée.

Cette étude suggère qu'une forte réactivité de l'axe HHS améliore la réponse clinique à des doses élevées, mais qu'une élévation chronique du niveau de cortisol pourrait être un marqueur pour les non répondeurs. Les résultats de cette étude doivent être considérés comme préliminaires et nécessitent des tests plus approfondis des interactions possibles entre les médicaments utilisés pour traiter le TDAH et l'axe HHS.

Mots-clés : TDAH, cortisol, méthylphénidate, dopamine, stress, HPA axis

Abstract

ADHD is the most common behavioural disorder in children with complex aetiology and efficacious treatments. The most prescribed medication for ADHD is methylphenidate, a psychostimulant that blocks the dopamine transporter and increases dopamine availability in the synaptic cleft. Preclinical and clinical studies show that cortisol may enhance dopamine effects. Dysregulation of the hypothalamic-pituitary-adrenal axis is also associated with many psychiatric disorders such as depression, bipolar disease, and anxiety. We hypothesized that cortisol has an influence on the efficacy of the treatment of ADHD symptoms with methylphenidate.

The objective of this study was to measure the salivary level of cortisol in a sample of 8-year-old children with ADHD upon waking and in response to a venipuncture. The children were then randomized to three doses of methylphenidate and a placebo in a double-blind cross-over design. Teachers and parents rated the behaviour of the children using the SWAN and a side effect rating scale.

The results showed that high morning cortisol is a good predictor of a non-responder under active medication, as reported by parents. Also, the high stress reactivity group, but not the low stress reactivity group, demonstrated a greater benefit going to a higher dose of methylphenidate, according to teachers. In addition, parents demonstrated an association between anxiety comorbid disorders and a better response to a high dose of methylphenidate.

This study suggests that a strong reactivity of the HPA axis improves the clinical response at high dose, but that chronically elevated cortisol might be a marker for non responders. The results of this study should be seen as preliminary and require further testing of the possible interactions between ADHD medication and HPA activity.

Keywords : ADHD, cortisol, methylphenidate, stress, HPA axis, dopamine

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Liste des abréviations

TCA- Tricyclic antidepressant

DA- Dopamine

NE- Norepinephrine

MTA- Multimodal Treatment Approach

HPA axis- Hypothalamic-Pituitary Adrenal axis

ACR- Awakening Cortisol Response

HVA- Homovanillic Acid

MHPG- 3-methoxy-4-hydroxyphenylglycol

TSST- Trier Social Stress Test

MPH- Methylphenidate

SWAN- Strengths and weaknesses of ADHD symptoms and Normal behaviours ratings Scale

HHS- Hypothalamo-hypophyso-surrénalien

TDAH- Trouble du déficit de l'attention/ hyperactivité

CPRS- Conners Parents Rating Scale

PET- Positron Emission Tomography

DAT- Dopamine transporter

LG- Licking and grooming

cAMP- cyclic adenosine monophosphate

HCN- Hyperpolarization activated cyclic nucleotide gated

PFC- Pre-frontal cortex

SES- Socioeconomic status

PLC- Phospholipase C

DAG- Diacylglycerol

PKC- Protein Kinase C

SNRT- Selective inhibitor of norepinephrine reuptake transporter

CRF- Corticotropin releasing factor

CRH- Corticotropin releasing hormone

NRI- Norepineprine reuptake inhibitor

5-HT- Serotonin

SSRI- Serotonin selective reuptake inhibitor

VNTR- Variable number tandem repeats

DRD4- Dopamine receptor D4

ICD-10- International classification of Diseases

IQ- Intelligence quotient

WISC- Wechster Intelligence Scale for children

DISC 4.0- Diagnostic Interview Schedule for children

SD- Standard deviation

Je dédie ce mémoire de maitrise à ma mère et
à mon père qui m'ont appris la persévérance
et la rigueur dans tout ce que j'entreprends.
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1. Introduction

1.1 Attention deficit hyperactivity disorder

1.1.1 Prevalence and comorbidity of ADHD

Attention deficit hyperactive disorder (ADHD) is a disorder that is commonly seen in children and it is a highly prevalent. It is estimated to affect 5-10% of children and 4% of adults (Biederman, 2005). There are many other disorders that are comorbid with ADHD such as oppositional defiant disorder, conduct disorder, mood disorders, anxiety disorders and learning disorders. Between 18 to 35% of children with ADHD have one or more associated psychiatric disorders such as anxiety disorder, oppositional defiant disorder and conduct disorder. Also up to 15 to 20% of children with ADHD have associated specific learning disorder (Karande, 2005). ADHD subjects had more lifetime psychopathology compared to non-ADHD subjects; 87% had one psychopathology and 56% had at least two psychopathology compared to 64% and 27% respectively (McGough, 2005). Anxiety disorder has been found to co-occur with ADHD in 10-40% of children. The comorbidity of ADHD with mood disorders such as major depression is 15-75%. The rate of childhood ADHD in adults with bipolar disorder is estimated in the 10-20% range; however, the reverse is not true, follow-up studies of children with ADHD have not showed that they are at increased risk of developing classic bipolar disorder in adulthood. Consequently, this disorder is highly comorbid with other psychiatric disorder which makes it more complex and harder to find the optimal treatment.

1.1.2 Diagnosis and symptoms

ADHD is the most commonly diagnosed neuropsychiatric disorder in children (Karande, 2005). The most common symptoms are inattention, impulsiveness and hyperactivity. The

diagnosis of ADHD is based on the Diagnostic and Statistical Manual (DSM-IV). The diagnosis of ADHD divides the disorder into three specific groups based on their predominant symptoms; the inattentive type, the impulsive/hyperactive type and the combined type.

The diagnosis of ADHD is based on clinical findings and the criteria for children's specific behaviours in the DSM-IV. These criteria describe the three subtypes of ADHD. To meet the diagnostic criteria for ADHD, a child needs to have at least six of the nine specific behaviours in the inattentive type or at least six of the nine behaviours in the hyperactive/impulsive type or at least nine behaviours described in both domains for the combined type. Also these behaviours need to be occurring often for the past six months to a degree that is maladaptive. Some impairment from the symptoms is present in two or more settings. In addition, these symptoms need to be present before seven years of age and there must be clear evidence of clinically significant impairment in academic or social functioning. As well, these symptoms should not be better explained by other psychiatric disorders. These core symptoms of ADHD are identified by informants (parents, teachers), by the patient or by direct observation of the behaviour of the patient. Structured interviews or a structured questionnaire are essential for the diagnosis of ADHD.

Differences exist in the diagnosis process. The primary care physician generally sees the child and attempts to assess his physical and developmental development through a series of office visits. The American Academy of Pediatrics (AAP) prepared guidelines for physicians for the evaluation of children between the ages of six to twelve years (Kirby, 2001). These guidelines are specific for children that present the symptoms of inattention, impulsiveness, hyperactivity and behavioural problems. They are used in order to assist in decision making for the physicians. However, they should always refer to the criteria in the Diagnostic and Statistical Manual for diagnosis. The guidelines emphasize the use of assessment tools in different settings such as school and home. Also, the use of teacher

assessment data is essential for the diagnosis of the children. In addition, the AAP indicates the importance of the detection of comorbid conditions for children that have been diagnosed for ADHD. As discussed earlier, ADHD is highly comorbid with other psychiatric disorders.

1.1.3 Aetiology of ADHD

ADHD is a complex and heterogeneous disorder. Both genetic and environmental factors contribute to the risk of ADHD. The aetiology of this disorder can be divided in biological and environmental causes. In terms of biological justifications, it can be further divided into genetics, brain structure and their influence on neuropsychology. In terms of environmental terms, it can be explained by parenting and diet among other possible causes.

a) Family and twin studies

The data from family studies suggest that there is a two to eightfold increase in the risk for ADHD in parents or siblings of children with ADHD. The heritability of ADHD was estimated mainly from twin studies. Heritability is a genetic measure used to establish the influence of genetic factors on the disorder (Biederman, 2005). According to twin and adoption studies from Australia, Sweden, the UK and many sites in the USA, the average heritability is estimated to 0.76. This implies that genes are very important in ADHD. The estimates of heritability from 1973 until 2004 have not changed, despite changes in the diagnostic systems. The high heritability observed for ADHD reveals a large influence of genetics on the aetiology of this disorder (Biederman, et al. 2005)

b) Genetic studies

Molecular genetic studies show that the genetic architecture of this disorder is complex. Genes with large effects are unlikely to exist. Many candidate genes studies have

used association to examine if biologically relevant gene variants affect the susceptibility of being diagnosed with ADHD. For the sake of clarity, we will only present two examples of association with candidate genes (DRD4 and DAT1).

Among the candidate genes, the dopamine genes have been a large focus by researchers. These genes are important for the susceptibility of this disorder because dopamine plays an important role in attention and motivation. The dopamine receptor D4 gene contains a highly polymorphic 48 base pair variable number of tandem repeats sequence. (48 bp VNTR) This polymorphism varies between two and seven copies but the four and the seven repeats allele are the most common number of repeats found in the population. The seven repeats allele is proven to show a blunted intracellular response to dopamine and to exhibit a lower affinity to antagonists in vitro (Asghari et al., 1995; Van Tol et al., 1992)

There are four sets of pooled or meta-analyses that convincingly show that the 7 repeats allele is associated with ADHD (Faraone, Doyle, Mick, & Biederman, 2001; Faraone et al., 2005; Li, Sham, Owen, & He, 2006; Maher, Marazita, Ferrell, & Vanyukov, 2002). The odds ratio reported in these studies ranged from 1.13 (1.03 to 1.24) to 1.9 (1.5 to 2.2). This is the range of odds ratio found for venous thrombosis when taking oral contraceptives or risk of for cardiovascular disease in passive smokers, after adjustment for confounding variables.

The dopamine transporter (DAT) gene has been studied because it is the principal target of the first-line medications for ADHD (stimulant). The stimulant, and especially methylphenidate, inhibit the activity of dopamine transporter and diminish the symptoms of this disorder. If the first meta-analysis reported an association (Maher et al., 2002; Faraone et al., 2005), subsequent ones show no association (Li et al., 2006; Purper-Ouakil et al.,

2005). This may be due to the heterogeneity of the polymorphism as well as to gene-environment interactions (Brookes et al., 2006).

c) Risk factors

Neurobiology of ADHD is not known but imbalances in the dopaminergic and noradrenergic systems are likely to be involved in the symptoms of this disorder. Several environmental biological factors contribute to ADHD such as food additives, cigarette and alcohol exposure, low birth weight and maternal smoking during pregnancy (Biederman, 2005).

d) Imaging studies

Neuroimaging suggest that dysfunctions in the fronto-subcortical pathways are related to the core ADHD symptoms (Biederman, 2005). Structural brain imaging found evidence for a smaller volume in the frontal cortex, cerebellum and subcortical structures. Functional imaging studies support a dysfunction in the fronto-subcortical pathways. These pathways are rich in catecholamines which are involved in the mechanism of action of ADHD medication. For example, when completing a Go/No-go task, children with ADHD do not activate frontostriatal regions as efficiently as children without this disorder. Instead, these children activate a more diffuse network of regions in the brain including more posterior and dorsolateral prefrontal regions compared to the control subjects (Booth et al., 2005; Schulz et al., 2004; Smith, Taylor, Brammer, Toone, & Rubia, 2006). This deficit in striatal activation is supported by the observation that dopamine D2 receptor level in the striatum predicts the reinforcing effects of the psychostimulant. Levels of the receptors were highly correlated (r=0.82) with the rating of drug-liking (Volkow et al., 1999; Volkow et al., 2002b).

f) Neuropsychology of ADHD

In contrast to the dominant view explained above, some researchers suggest that ADHD is not characterized by cognitive dysregulation but as a motivational style. ADHD is viewed as a functional response by the child aiming at avoiding delay. When the child has control over his environment, he can choose to minimize the time by acting impulsively. When the child is not in control of his environment, he will choose to distract himself from the passing of time. For example, in a classroom, the child will distract himself by daydreaming or by fidgeting. Based on these findings, some researchers proposed the dual pathway model of ADHD. This model suggests two possible routes between biology and ADHD behaviour. One pathway is via cognitive dysregulation and the other one via motivational style. This model is viewed clinically to target different sub-types with different treatments (Sonuga-Barke, 2002; Sonuga-Barke, 2003). Also this model could allow the development of novel interventions such as using delay fading, a technique to reorganize the child's delay experience in order to increase tolerance to delay and reduce ADHD symptoms (Sonuga-Barke, 2004).

g) Environmental causes

Parenting and diet were the 2 possible ways proposed to explain how the environment affects a child. ADHD is then viewed as the result of a gene-environment interaction. If a child has the genetic predisposition of ADHD, he will express the disorder but only if he is put in the pathogenic environment such as chaotic parenting. The best evidence for the effect of parenting on ADHD symptoms comes from intervention studies where parents were taught alternative parenting skills. The results of these studies show that the influence of parenting is important for the child. The relationship between ADHD and parenting may result from the negative effects of the child on the parent's behaviour and the negative effects of the parents influencing the child's behaviour (Bor, 2002).

Diet is another environmental influence on children with this disorder. Bad diets such as food additives, refined sugars and fatty acid deficiencies have been associated with

ADHD symptoms. In a large randomized controlled trial, researchers studied the influence of food coloring and benzoate preservatives on preschool hyperactivity. The results showed an adverse effect of food coloring and benzoate preservatives on the behaviour of these children. However, these results were based on parental reports but not on simple clinical assessment. The improvement of diet has an impact on the health of the children and overall behaviour (Bateman et al., 2004; McCann et al., 2007; Schab & Trinh, 2004).

1.1.4 Treatment

There are three treatments that are efficacious for ADHD. The first treatment is using medications; the second treatment available is behavioural therapy and the third treatment for this disorder consists of the combination of the two above treatments. The management of ADHD by medication is proven to achieve amelioration of the core symptoms of this disorder. The two most common medications given for children are stimulants and atomoxetine. The use of medication is proven to be a superior for the control of symptoms compared to behavioural therapy (Karande, 2005). The medication given for the treatment of ADHD is mostly the stimulants. The most commonly prescribed stimulant is methylphenidate. Some subjects are non-responsive or respond badly to stimulants and they are given the non-stimulants drugs such as atomoxetine. Further, other drugs can be used for ADHD treatment such as antidepressants and alpha-adrenergic antagonists.

a) Stimulant medication: methylphenidate

Amphetamine and methylphenidate are the most commonly prescribed medication for the treatment of children with ADHD. Both these drugs are rapidly acting stimulants and their effects are seen within 30 to 45 minutes of their oral administration. Their behavioural effects peak within 2 to 4 hours after ingestion. Their effect will dissipate within 3 to 7 hours. These drugs have a short half-life so they must be taken 2 to 3 times per day. This dosing schedule causes inconvenience for children and parents. These medications are

available in slow-release doses to reduce the number of times the medication has to be taken. The improvement in behaviour for children taking one of these two drugs occurs in sustained attention, impulse control and reduction of task-irrelevant activity. There are other drug-related improvement such as in self-esteem, aggression, handwriting, academic productivity, persistence in effort, working memory, peer relations, emotional control and participation in sports. Individually tailored doses of methylphenidate improved attentional functioning of children with ADHD. These differences were mostly of small or medium size, but the children with ADHD who were on methylphenidate treatment were still considerably impaired (Dafny & Yang, 2006). The effects of the medications are idiosyncratic, with some children having maximal improvement at lower doses and other children show maximal improvement at higher doses. Mild insomnia and appetite reduction are the most common side effects of stimulants (Barkley, 2004).

Methylphenidate hydrochloride is a central nervous system stimulant that is closely related to the structure of dextroamphetamine, an isomer of amphetamine. The drug was first synthesized in 1944 and was used as an analeptic for numerous barbiturate-induced comas. Later, it was used to improve memory in depressed and elderly patients. Since then, it has been used to improve the alertness in children with emotional, behavioural and learning difficulties. MPH is metabolized via de-esterification to ritalinic acid and released in the urine within 48 hours. Brain concentrations of this drug exceed those of plasma as MPH passes through the blood brain barrier easily. The therapeutic effect of MPH has been attributed to its ability to bind to the DAT in the presynaptic terminal and block the reuptake of DA. This blockade causes an increase in DA in the synaptic cleft which is the effect that is linked to the reinforcing properties of MPH (Dafny et al., 2006). MPH does not stimulate catecholaminergic receptors but facilitates the action of DA. It slows down dopamine reuptake from the extracellular space. Its behavioural effects are seen within 30 min of oral administration of the drug and its effects last for three to five hours. The daily dose should be individualized by titration and monitored for children. The doses

recommended are between 5 to 20 mg two to three times daily. Side effects include anorexia, stomach-ache, headache, irritable mood, tics and sleep difficulties. However, these side effects are mild and disappear after continuous use of this medication. Side effects increase with the increase of the dose. In some children, methylphenidate has slowed their physical growth during the first to third year of their administration. In addition, long acting methylphenidate is available for a better compliance of the medication. The long acting dose is taken once daily and its action is on a period up to 10 hours (Karande, 2005).

Methylphenidate is the drug of choice for treating ADHD and it is effective in 60-70% of individuals. There exist individual differences in the actions of methylphenidate which are not completely elucidated. This explains the different doses required to achieve the clinical response in ADHD subjects. Positron emission tomography (PET) was used to image the blockade of dopamine in real time after the administration of the drug. Cocaine is a dopamine transporter (DAT) ligand and raclopride is a dopamine D2 receptor ligand and competes with dopamine to bind the receptor. Cocaine radioligand is used to assess the level of DAT blockade with methylphenidate. Raclopride radioligand is used to measure methylphenidate induced changes in extracellular dopamine. Hence the two radioligands were used to determine the effects of methylphenidate on the DAT and on extracellular dopamine (Volkow et al., 2002b).

There exist differences in dopamine cell activity that cause the inter-subject variability of methylphenidate. Methylphenidate is a DAT blocker and its ability to block this transporter is a function of the level of DAT blockade but also of dopamine cell activity. Dopamine (DA) release is dependent on DA cell activity. If a subject has a high dopamine cell activity, dopamine will be released faster in the synapse. Homovanilic acid (HVA) which is the principal metabolite of dopamine serves as a marker for dopamine activity in the cerebrospinal fluid. Hence, DA cell activity may cause the variability of

methylphenidate observed between subjects with ADHD. It is estimated that 15-30% of subjects do not respond to methylphenidate. This non responsiveness could reflect very low dopamine activity because the rate of DA released is determined by DA cell activity. Using PET scans, subjects were tested before and after the dose of methylphenidate to estimate the DAT occupancy with cocaine or raclopride as radioligands. Methylphenidate significantly blocked DAT and increased extracellular dopamine in the brain. However, the correlation between DAT blockade and dopamine increase was not significant. This leads to the conclusion that individual differences in DAT blockade are not the only source of this variability seen in the effect of the drug. Hence the variability in the effects of the drug is seen for an equivalent level of DAT blockade, methylphenidate would induce smaller dopamine changes in subjects with low dopamine cell activity (Volkow et al., 2002a).

b) Stimulant medication: amphetamine

Amphetamine is another psychostimulant. It acts on the central nervous system as a direct sympatomimetic. Its mode of action is via the release and reuptake inhibition of NE and DA. The activity of amphetamine on the vesicular monoamine transporter is crucial in the release process of the monoamines except serotonin. Amphetamine is responsible for releasing DA in the nucleus accumbens. The reinforcing effects of stimulants are mediated by the increase in DA in this region of the brain (Hearn et al., 2004). The beneficial effect for the treatment of ADHD include improved impulse control, improved concentration, decreased sensory overstimulation and decreased irritability. The side effects are the same as for methylphenidate but the effects on appetite and sleep tend to be stronger for amphetamine. Also amphetamines last longer in the body than methylphenidate. Its half life is between 10 to 13 hours.

c) Non-stimulant medication: Atomoxetine

Atomoxetine blocks the reuptake of noradrenaline selectively. This is a new drug and represents an important advance in the pharmacological management of ADHD. This medication shows an efficacy similar to methylphenidate. It consists of a daily dose. Its main side effects are nausea, vomiting, decreased appetite and weight loss (Karande, 2005).

Atomoxetine is highly specific for the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or other neurotransmitter transporters or receptors. Methylphenidate, placebo or atomoxetine were used in a double-blind study in a total of 291 children. Atomoxetine efficacy was different from placebo and it was an effective drug for the treatment of ADHD. Also atomoxetine was shown to be safe and well tolerated in patients treated for a period of nine weeks (Spencer et al., 2002). Three different doses of atomoxetine were examined in children and adolescent with ADHD. The results obtained with the lowest dose 0.5 mg/kg/day showed an intermediate efficacy between the placebo and the two higher doses. The two higher doses 1.2 and 1.8 mg/kg/day are associated with superior outcomes compared to placebo but were not different between each other (Michelson, 2001). Atomoxetine was also tested in the adult population that has ADHD. The researchers found that it appears to be an efficacious treatment for adult ADHD (Michelson, 2003).

d) Bupropion

Bupropion is another antidepressant that also was found effective in treating ADHD. Bupropion affects the noradrenergic and dopaminergic system. Bupropion produces improvements in ADHD symptoms but is not as efficacious as stimulant medications. It reduces the symptoms of ADHD. The side effects include oedema, rashes, irritability, loss of appetite and insomnia (Barkley, 2004).

e) Other medications

Other drugs can also be used to treat ADHD. Examples of such drugs antidepressant and alpha-adrenergic antagonist have been used for the treatment of ADHD as a substitute to stimulants. Tricyclics antidepressants (TCA) have been found effective to treat ADHD patients. These drugs act by increasing the levels of norepinephrine in the brain, as atomoxetine, and result in a positive response from 70-90% of children with ADHD. Examples of TCA are imipramine, nortriptyline, desipramine and amitriptyline. Less is known about the pharmacokinetics and behavioural effects of these drugs on children with ADHD than with stimulants. These medications are given twice a day and their action is longer than stimulants. The most common side effects are drowsiness, dry mouth, constipation, and flushing. The TCA's are recommended to be used as a treatment for ADHD in the case that stimulants and atomoxetine are not effective. Also, clinicians need to evaluate the cardiac functioning of children before starting the treatment with TCA and then monitoring it during the course of the treatment. TCA have risks of impairing cardiac functioning (Barkley, 2004).

Alpha-adrenergic drugs such as clonidine and guanfacine have shown positive effects on the symptoms of ADHD (Kirby, 2001). These drugs act as an alpha-2 adrenergic receptor agonist. However, the scientific literature on the efficacy of these drugs is limited (Karande, 2005). From the limited research available, clonidine is less effective than stimulants in improving inattention and school productivity but equally effective in reducing hyperactivity and moodiness. The common side effects are drowsiness, dizziness, weakness and occasional sleep disturbance (Barkley, 2004).

f) Behavioural therapy

During behaviour therapy, parents are taught by psychologist how to achieve consistent and positive interactions with their children. They are taught how to reinforce positive behaviours, how to extinguish negative behaviours and how to effectively punish a child for wrong behaviour. Psychoeducational intervention at school such as seating the child beside

the teacher to minimize distractions by other students or assigning a specific teacher daily to review with the child his homework is an effective way to improve the academic achievement of these children (Karande, 2005).

The combined therapy is the optimal treatment for ADHD children. Although it does not does not achieve better symptoms control than the medication alone, it helps reduce the total daily dose of medication and helps achieve positive functioning outcomes for peer interactions and parents-child interactions (Karande, 2005). The Multi-modal treatment study of ADHD (MTA) compared the efficacy of the use of medication alone, psychosocial intervention and the combination of both methods. The results of the MTA study showed that medical management alone was more effective for the core symptoms of ADHD than psychosocial treatment alone. Also, psychosocial intervention did not significantly improve the result when it is combined with medical treatment (Jensen, 1999).

There are a number of concerns for the use of psychostimulants for children especially young children. One concern of the use of this medication regards the ethical objections to utilize medication to change child's behaviour. Other concerns for the long-term use of the psychostimulants are the lack of evidence of long-term effectiveness of psychostimulants. Also research showed that pre-school children are at high risk of developing short-term side effects (Greenhill et al., 2006; Swanson et al., 2006). There is also a lack of evidence of the long-term consequence on the physical and neurological development of pre-school children. In addition, sub-group analysis of the MTA study indicated a large effect of psychosocial intervention in certain groups and settings. For example, 75% of the patients assigned for the behavioural group were successfully maintained without medication for 14 months. Also, the combined group had the same outcome as the medical treatment group but this was achieved with a 20% reduction of the dose of medication used in long-term treatment. The behavioural intervention mediates improvements in the parent-reported

comorbid anxiety, in the negative parenting and ineffective discipline and in decreasing parental conflicts (Vitiello et al., 2007; Swanson et al., 2002; Barkley, 2000).

g) Alternative therapy

For treating ADHD, alternative therapies such as diets have been used. It is sought as a natural method to control the symptoms of ADHD. Diets are the most common alternative treatment to stimulant therapy. The Feingold diet is based on the elimination of food additives, preservatives (Kirby, 2001). This diet is based on the theory that some children are sensitive to dietary salicylates and artificial added colors, flavours and preservatives. Some recent meta-analyses and controlled double-blind placebo studies seem to support the value of the Feingold diet (Bateman et al., 2004; McCann et al., 2007; Schab et al., 2004).

Another dietary intervention is eliminating all sugars from the diet. This diet is based on the belief that sugars causes hyperactivity. These claims have not been supported. Some theories of a relation between sugar, mood and behaviour were proposed in the early 1990's. It was suggested that these states of anxiety and frustration were reported at the same time as intake of sweeteners was increased. The belief that avoiding sugar would help a child with ADHD comes from this theory. The studies so far showed weak and conflicting clinical evidence so this hypothesis needs yet to be validated (Marcason, 2005).

Vitamins and supplements is another hypothesis for the symptoms of ADHD. Zinc is another dietary supplement that is involved in the regulation of dopamine. Hence there are zinc supplements sold for the treatment of ADHD. However, zinc supplementation should be monitored because of zinc's possible toxicity in higher doses than normal (Kirby, 2001).

Supplementation with high doses of vitamins and minerals is another option that has been proposed. The hypothesis for this theory is from the observation that some people have genetic abnormalities that result in increased requirements for vitamins and minerals. However, there is a lack of scientific evidence for this treatment. In addition, the American Psychiatric Association and the American Academy of Pediatrics have concluded that the

use of megavitamins and minerals to treat behavioural and learning problems is not justified by clinical evidence (Marcason, 2005).

Another intervention is the use of fatty acids (EFA) supplementation for ADHD. Numerous studies have reported that children with ADHD have low levels of EFA and supplementation would be beneficial for them. However, the studies with EFA supplementation have not established for all behavioural characteristics of ADHD. More research needs to be done for the use of EFA supplementation as a treatment option (Marcason, 2005).

Herbal treatments are another option for ADHD. Calming herbs such as chamomile, lemon balm, valerian are some herbs that are used to treat the symptoms of sleepiness and restlessness often found in children with ADHD. However, the lack of clinical trials to prove the side effects of these herbs requires physicians to be cautious in recommending this alternative for ADHD patients. Another natural herb such as ginkgo biloba has shown to have a beneficial effect on concentration and cognition. Evening primrose oil is another herb that contains important essential fatty acids that could be used for ADHD. However, it is important to understand that there are no clinical trials that prove the efficacy of these alternative treatments for ADHD (Kirby, 2001). Hence, clinicians should advise parents that want to use natural herbs as an alternative treatment should be cautious in administrating these herbs to their child.

Overall there are many different treatment options for ADHD. It is not a simple task to find a good treatment that works for every person with ADHD. The treatment needs to be updated with current research findings and also it needs to be adapted to accommodate each child or person's individual needs. The multimodal treatment option remains a very successful choice including medication, parent/school counselling and behavioural therapy. More research needs to be done on dietary interventions in order to fully assess the impact

of this alternative treatment. Improved study design and clinical trials need to be expanded for more precise and accurate results on the treatment options.

1.1.5 Anxiety disorders

Anxiety disorders are comorbid with ADHD in approximately 50% of ADHD children (Bowen et al., 2008). Children with ADHD tend to worry about competence, future events and they show a great need of reassurance. Anxiety disorders as a comorbid condition may affect the functioning and treatment outcome of children with ADHD. The presence of comorbid anxiety increases the risk for interpersonal deficits, difficulties interacting with peers and self-esteem problems. The presence of both these disorders is associated with more attentional problems, school fears and lower levels of social competence compared to the ADHD only group. Data from studies suggest that anxiety is often a precursor to mood and substance disorders and among children with ADHD, the pathway to depression is often via anxiety. Therefore, treatment of ADHD children with comorbid anxiety is more complex and an array of symptoms need to be considered in the intervention.

1.2 Stress

The high proportion of children having anxiety disorders with ADHD suggested a possible disruption of the hypothalamic pituitary adrenal (HPA) axis. As ADHD is thought to be primarily a dopamine system disorder, improved by dopaminergic drugs, the relationship between cortisol and dopamine is of interest. The stress system is a complex network composed of cells that release hormones that act as mediators for survival. This large network of cells is regulated by negative and positive feedback.

1.2.1 HPA axis

The HPA axis is a complex set of direct influences and feedback interactions between the hypothalamus, the pituitary gland and the adrenal gland. These interactions are important to maintain homeostasis. They are a major part of the neuroendocrine system that controls reactions to stress and regulates various body processes such as digestion, the immune system, mood and sexuality, and energy usage.

Cortisol is a hormone secreted by the adrenal glands in response to a stressful situation. It helps the body to adapt to the new environment. Cortisol is secreted by the activation of the hypothalamic-pituitary-adrenal axis. The hypothalamus is related to the pituitary by the portal blood system. Therefore the releasing factors liberated by the hypothalamus reach quickly the pituitary where a mediator is again released. Then that hormone reaches the adrenal glands and causes the secretion of cortisol. In addition, when cortisol concentrations are high, it negatively feedback to the hypothalamus and the pituitary to stop releasing the hormones that causes its secretion from the adrenal glands. Hence this system is composed of many hormones that act together in response to stress.

Cortisol has widespread actions to help restore homeostasis following stress. It acts as a physiological antagonist to insulin by promoting gluconeogenesis, breakdown of lipids and proteins, mobilization of extra hepatic amino acids and ketone bodies. This results to increased blood glucose concentrations. It also increases blood pressure, lowers the activity of the immune system and bone formation. Cortisol has also effects on brain cells. Long-term exposure to cortisol leads to damage to cells in the hippocampus. This damage impairs learning. However, short-term exposure to cortisol helps to create memories. This mechanism for memory storage is called flash bulb memories. This type of memory is stored with great detail during a highly personally significant event or a shocking event.

The formation of glucocorticoids hormones is the final step of the hypothalamic pituitary adrenal axis that allows the human to respond to environmental stressors.

Glucocorticoid hormones formation is characterized by a circadian rhythm. The levels of these hormones are at their peak in the morning and are their lowest level during the night. Also the secretion of these hormones is increased during stressful situations, as an adaptive response of the body to stress. It helps the body to adjust during these stressful situations by increasing heart rate, lipolysis and glyconeogenesis. The two latter effects increase blood glucose and help the body to cope with stressful situations by increasing the amount of energy available (Marinelli & Piazza, 2002).

1.2.2 Awakening cortisol response

The awakening cortisol response consists of a rapid and a marked rise of cortisol and ACTH after awakening and continues for about 60 minutes, detectable in about 75% of healthy subjects (Buckley & Schatzberg, 2005). The ACR is independent of the mode of awakening, naturally or with an alarm. ACR is distinct from the cortisol rhythm and it is defined as the increase in cortisol concentration by 50 to 75% in a period of 30 to 45 minutes following awakening. The transition from sleep to awake is essential for the presence of the ACR. It appears to be a true response to awakening superimposing on the circadian cycle, and not the continuation of the increasing level of cortisol in the second half of the night (Wilhelm, 2007). ACR has been measured in many patients and control subjects. ACR was increased in relation with perceived stress (Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Schlotz, Hellhammer, Schulz, & Stone, 2004), with neuroticism (Portella, Harmer, Flint, Cowen, & Goodwin, 2005), depressive symptoms (Pruessner et al., 2003), even in recovered depressed patients (Bhagwagar, Hafizi, & Cowen, 2003). However, ACR was decreased after poor sleep due to primary insomnia, chronic fatigue syndrome (Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004), post-traumatic stress disorder (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004), early loss experience (Meinlschmidt & Heim, 2005). Thus, ACR is an important measure that indicates whether HPA axis functioning is normal or abnormal.

1.2.3 Cortisol reactivity

Perceived stress activates the central nervous system, causing the release of corticotrophin releasing hormone from the hypothalamus which causes the release of adrenal corticotrophic hormone from the anterior pituitary and results in cortisol secretion from the adrenal glands (Burke, 2005). Elevations of cortisol will act on the hypothalamus and anterior pituitary to inhibit the HPA system via negative feedback in the hippocampus. The dynamics of the HPA system consists of three phases described by the unstimulated basal activity which is the non-stressed HPA activity, the stress reactivity phase in which cortisol increase from baseline following the onset of a stressor and a stress recovery phase in which cortisol levels return to baseline following the offset of the stressor. Each of these phases are described by different physiological processes with mineralocorticoid receptors regulating cortisol levels during periods of low HPA activity and glucocorticoid receptors regulating cortisol responses to stress and cortisol levels during periods of high HPA activity. Thus, cortisol reactivity will be examined in ADHD children for its possible role with methylphenidate treatment.

1.2.4 Cortisol and DA interaction

1.2.4.1 Cortisol and cocaine interactions: preclinical studies

There are many examples in preclinical studies of interactions between the dopamine systems and the HPA axis. They have been reviewed briefly in the introduction of the presented paper. The role of the HPA axis in cocaine reinforcement will be reviewed more in detail, using the intravenous self-administration model. Cocaine share with psychostimulant the same mechanism of action (blockade of the dopamine transporter in the presynaptic neuron). Therefore, the interaction between cocaine and dopamine in the self-administration procedure might inform us about the possible relations between psychostimulant and cortisol while using them as medication for ADHD.

The first phase of cocaine self-administration is the acquisition phase. During this phase, the rat learns to make the response that delivers cocaine, which in turn reinforces the response. Different forms of social stress increase cocaine or stimulant self administration: social isolation (Schenk, Lacelle, Gorman, & Amit, 1987), rats seeing other rats receiving footshocks (Ramsey & Van Ree, 1993), males rats housed with female rats (Lemaire, Deminiere, & Mormede, 1994), exposure to threat or attack (Haney, Maccari, Le, Simon, & Piazza, 1995; Tidey & Miczek, 1997; Miczek & Mutschler, 1996).

Physical stress can also influence the acquisition phase of cocaine self-administration. The effects on the acquisition phase of cocaine self-administration of exposure to footshocks either when the rat presses a lever that delivers food or regardless of whether or not it has pressed the food delivering lever have been studied. In the former condition, there was a conflict between obtaining food and avoiding pain, while in the latter condition, there was no conflict as obtaining food and avoiding pain were unrelated. In the contingent condition, the animal had some control over the stressor while in the non contingent condition, the animal had none. In control rats that did not receive any electric footshock and pressed the food delivering level, the dose-response curve followed a typical inverted U shape during the acquisition phase. Rats exposed to the non contingent condition (uncontrollable stress) demonstrated higher drug self-administration by session for the same dose of cocaine, as compared with those in the contingent condition. However, this shift upward and to the left of the dose-response curve was only observed in the ascending limb of the dose-response curve. For higher dose of cocaine infusion, the condition no longer influenced cocaine self-administration (Goeders & Guerin, 1994). Rats exposed to the contingent condition did not show a different dose-response curve as compared to control animals.

Stress-induced increases in plasma corticosterone were positively associated with the ability of non-contingent electric footshocks to shift the ascending limb of the

acquisition dose-response curve upwards and to the left. Accordingly, rats treated with repeated exogenous injections of corticosterone during the two preceding weeks prior the start of the self-administration procedure in order to mimic the HPA activation during the uncontrollable footshock condition, also showed a leftward shift of the ascending limb of the dose-response curve (Goeders & Guerin, 1996b). Surgical removal of the adrenal gland completely flattened the dose-response curve, as compared with sham-operated controls, although there were no differences between these two groups for the food delivery level responding (Goeders & Guerin, 1996a). Similarly, rats treated with repeated injection of high dose of dexamethazone during the two weeks preceding the self-administration procedure did not acquire cocaine administration, at any dose tested (Goeders et al., 1996a). As high dose of dexamethasone practically suppressed corticosterone secretion by the adrenal gland, it realised a pharmacological adrenalectomy and replicated the results of the surgical removal of the adrenal glands. Glucocorticoid thus seems necessary for the acquisition of cocaine self-administration and it does not occur unless corticosterone level is increased above a threshold level.

The activity of the HPA axis is also critical during the maintenance phase, once the animal has learned the behaviour that is reinforced by cocaine infusion. Ongoing cocaine self-administration can be decreased by drugs that reduce the corticosterone secretion, but this effect is only observed for low dose of cocaine infusion. Metapyrone blocks the 11 beta-hydroxylation and ketoconazole both the 11 beta- and 18-hydroxylation, reducing the corticosterone synthesis. Pre-treatment with ketoconazole reduced self-administration of low dose of cocaine without affecting the food-reinforced behaviour and led to extinction of cocaine self-administration (Goeders, Peltier, & Guerin, 1998). Cocaine self-administration was also decreased by a drug that blocked the central CRH receptors, but this effect was not dose-dependent (Goeders & Guerin, 2000). This further reinforces the role of the HPA axis in cocaine self-administration, as cocaine might influence the HPA axis at the level of hypothalamic CRH.

Once the cocaine self-administration is stable, extinction is obtained by no longer reinforcing the responding by the delivery of the drug. Once the extinction is obtained, various manipulations can re-instate the self-administration behaviour. Exposure to non-contingent electric footshocks is a form of stress that can reinstate cocaine self-administration. However, pre-treatment with ketoconazole prior to exposure to the stressor prevented this re-instatement (Mantsch & Goeders, 1999).

To conclude, the HPA axis is involved in the acquisition, the maintenance and the re-instatement of cocaine self-administration. The fact that cocaine can induce anxiogenic-like responses in rats could have led to the opposite prediction that corticosterone would antagonize the reinforcing effect of cocaine. However, pressing the cocaine delivery lever is under the control of the animal and the reinforcement by cocaine infusion makes the effects of pressing the lever controllable and predictable. The controlled and predictable effects of the activation of the HPA axis may result in an internal state of motivated behaviour whereby the animal actually seeks out specific sensations in an internal state that might be compared with that of individual who engage themselves in thrill-seeking activities. If we extrapolate the results of these experiments to humans treated with stimulant, it is tempting to propose that the individuals who have a strong HPA response to a stressor could demonstrate a stronger sensitivity to stimulant medication and respond to lower dose of stimulant, or continue to respond at higher dose, reproducing the upward and left shift of the dose-response curve observed during the acquisition phase. Also, individuals with higher level of basal HPA activity would have a decreased sensitivity to stimulant medication, reproducing the effect of pre-treatment by high dose of dexamethasone.

1.2.4.2 Cortisol and cocaine interactions: clinical studies

In healthy volunteers receiving intravenous injection of methamphetamine in a double-blind randomized cross-over design, pre-treatment by repeated injection of hydrocortisone over 7 consecutive days did not affect the expected decrease in prolactin level in the plasma. As prolactin is under tonic inhibitory control of dopamine neurons from the zona incerta in the hypothalamus, prolactin level was expected to decrease since methamphetamine increases dopamine release. Pre-treatment neither affected the increased subjective mood rating nor the performance on a task of sustained attention, which have been showed to be sensitive markers of changes in dopamine levels (Hearn et al., 2004). This lack of effect may be due to the type of glucocorticoid regimen, the lack of sensitivity of the individuals tested, as those individuals with a greater vulnerability to addiction would have altered regulation of HPA system. In another study, the subjective effects of intravenous injection methamphetamine were evaluated in humans with previous experience of methamphetamine injection in two opposite conditions. In the first condition, cortisol levels were directly increased by administering orally hydrocortisone while in the second condition, the cortisol response was blocked with the cortisol synthesis inhibitor oral metyrapone. Neither raising cortisol level nor blunting cortisol response altered the pleasurable effects of methamphetamine (Harris, Reus, Wolkowitz, Mendelson, & Jones, 2003). However, homovanillic acid (HVA) levels were greater after hydrocortisone or metyrapone pre-treatment, as compared to placebo. Moreover, 3-methoxy-4-hydroxyphenylglycol (MHPG) levels were greater after metyrapone pre-treatment. Hydrocortisone pre-treatment diminished HVA and MHPG increases after methamphetamine (perhaps explaining the lack of expected increase in pleasurable effects), but metyrapone did not. Thus, raising cortisol concentration did affect the cathecholamine response to methamphetamine, but blocking cortisol synthesis did not produce opposite effects (Harris et al., 2006).

Positron emission tomography (PET) can be used to measure extracellular dopamine release in the brain, with [11C]raclopride as D2 receptor radioligand.

[11C]raclopride competes with endogenous dopamine for the D2 receptors, and a stronger fixation of the radioligand indicates smaller release of extracellular dopamine (Volkow et al., 2002b). By measuring also the HPA activity, it is thus possible to assess directly in humans the possible interactions between cortisol and dopamine levels. In healthy human volunteers, a greater dopamine release in several regions of the striatum was also associated with stronger positive effects of amphetamine. Dopamine release in ventral striatum by amphetamine was positively correlated with cortisol increase in response to the same dose of amphetamine (Oswald et al., 2005). The subjects with a stronger cortisol response also reported more positive subjective effects with amphetamine, i.e. 'high, rush, drug liking, good effects and desire for drug'. Although the cortisol levels in response to amphetamine were greater in magnitude than the cortisol responses to placebo, a significant correlation was found between the cortisol levels in response to the amphetamine and the placebo sessions. The individuals with greater cortisol reactivity in response to amphetamine were also higher cortisol producers in response to placebo. The high responders would thus have a larger HPA activation in response to the placebo, and amphetamine would further increase this already enhanced response. These individuals may have a sensitized HPA axis and/or a sensitized dopaminergic mesolimibic pathway. In another study, the amphetamine-induced dopamine release in ventral striatum was also found positively correlated with the cortisol response to an acute standardized psychosocial stressor measured independently (Trier Social Stress Test), again in human healthy volunteers (Wand et al., 2007). This suggests that high dopamine releasers in response to amphetamine may have a sensitized HPA axis across various types of stressors. In fact, an acute social stressor (a mental arithmetic task was set to be too difficult in the stress session, accompanied by negative comments) can also directly induce dopamine release. Overall, this dopamine release was also correlated with the cortisol response to the acute psychosocial stressor. All subjects also rated their perceived levels of parental care and protection and were divided into low and high groups. The increase in dopamine release during the mental arithmetic task as compared to a rest session was only significant in the low care group. Similarly, the cortisol

response increase in the stress condition, as compared to rest, was larger in the low than in the high care group (Pruessner, Champagne, Meaney, & Dagher, 2004).

1.3 Research questions:

Based on the interaction between cortisol and dopamine released observed both in preclinical and in clinical studies, this research aimed at testing four hypotheses.

1. The dose-response curve will depict an overall linear relation between ADHD symptoms and methylphenidate doses, although the increase in symptom improvement may be larger going from placebo to low dose, as compared to medium to high dose.
2. Children with higher level of salivary cortisol in response to a venipuncture will exhibit a steeper slope in the dose-response curve, as they would be more sensitive to the effects of methylphenidate. The same change in dose-response will be observed in children with comorbid anxiety problems.
3. Children with a higher level of salivary cortisol upon waking will exhibit a flattened dose-response curve, as they would be more resistant to the effects of methylphenidate.
4. Side-effects of medication are expected to reflect the same trend as symptoms, with more side effects in children with a high salivary cortisol in response to the venipuncture and fewer side effects in children with a high level of salivary cortisol upon waking.

In order to test these hypotheses, we used a double blind placebo control prospective study in children diagnosed with ADHD, with three different doses of MPH to assess the response to MPH over a week. Salivary sample was obtained just after waking and before and after a standard stress (venipuncture) in order to assess HPA axis.

2. Article

Clinical response to methylphenidate and free salivary cortisol in children with Attention Deficit Hyperactivity Disorder

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Running head: Methylphenidate response and cortisol in ADHD

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Abstract

Pre-clinical studies support the hypothesis of the hypothalamic-pituitary-adrenal (HPA) axis as predictor of the stimulant response for ADHD-like behaviors. A double blind placebo control prospective study was used with three different doses of MPH to assess the response to MPH over a week. Salivary sample was obtained just after waking and before and after a standard stress (venipuncture) in order to assess HPA axis. The therapeutic effect of increasing doses and the side effect severity were function of the level of cortisol upon waking according to parents' ratings, resulting in decreasing efficacy at higher doses and increased side effects at lower doses. However, the effect of dose assessed by the teacher was unaffected by the level of cortisol upon waking. With regard to the cortisol stress reactivity, the teachers, but not the parents, reported an additional benefit of a high versus a medium dose only in children with a high reactivity level. However, a similar benefit was described by the parents, but not by the teachers, when the presence of an anxiety comorbid condition was used instead of a high cortisol stress response. Cortisol stress reactivity was not related to any side effect rating.

Introduction

Predicting which children with ADHD will respond favorably to stimulant medication has been proved challenging. In their review Gray & Kagan (2000), concluded that «despite considerable effort by capable and creative investigators, predicting response to methylphenidate (MPH) has been perhaps most remarkable for its lack of success». However, some conclusions can be drawn. Generally, the response to stimulant medication is increased at younger age and when symptoms (Efron, Jarman, & Barker, 1997a; Gray & Kagan, 2000) or cognitive deficits, especially inhibitory control or attention (Barkley, 1976), are more severe before treatment, although the relations are weak. Age and severity are not independent as ADHD symptoms and associated deficits tend to decrease with age. However, the better response at younger age may not hold for children below the age of 6. In preschool-age children, the effect size of stimulant medication is smaller than for school-age children, the optimal dosage lower (Greenhill et al., 2006) and adverse effect of stimulant more frequent (Wigal et al., 2006). With regard to severity, it should be stressed that response to stimulant is also lower in children with comorbid conditions (Ghuman et al., 2007; DuPaul, Barkley, & McMurray, 1994; MTA Cooperative Group, 1999; Owens et al., 2003). In order to predict a better response, severity might have to be restricted to ADHD symptoms. Among the Multimodal Treatment Study of Children with ADHD participants, those diagnosed with the ICD-10 criteria for Hyperkinetic Disorder (i.e., no anxious or depressive comorbidities; symptom threshold met for hyperactivity, impulsiveness and inattention; pervasiveness across school and home setting, and impairment endorsed) responded better to medication than those with ADHD failing to meet these ICD-10 more stringent criteria (Owens et al., 2003; Santosh et al., 2005). The predictive power of symptom severity may not always be unequivocal. ADHD symptom severity was showed to predict a poorer not a better response, but only in those children with a parent afflicted with a relatively high level of depressive symptoms (Owens et al., 2003). Similarly, if ADHD-specific cognitive deficits predicted a better response to

stimulant, broader deficits captured by an IQ below 50 were associated with a less favorable response to MPH (Aman, Buican, & Arnold, 2003). Beyond clinical characteristics, some physiological measures have been tested as predictor of the response to stimulant. Homovanillic acid (HVA) is the major dopamine metabolite. Its cerebrospinal fluid concentration has been showed to be correlated with the rating of hyperactivity and with the response to stimulant: higher HVA predicted a modest portion (up to 25% on some measures) of better drug response (Castellanos et al., 1996). The present study aimed at testing the role of the functioning of the hypothalamic-pituitary-adrenal axis (HPA axis) as a predictor of the stimulant response.

There are many pre-clinical studies that support the hypothesis of the HPA axis as predictor of the stimulant response for ADHD-like behaviors. Rats can be divided into high and low responders according to spontaneous difference in levels of locomotor activity in a novel environment (Piazza, Deminiere, Le Moal M., & Simon, 1989). High responders differ from low responders in their behavioral response to psychostimulants. High responders show more locomotor activation in response to psychostimulants (Piazza et al., 1990), develop stronger contextual conditioning to drug effects (Jodogne, Marinelli, Le, & Piazza, 1994), develop behavioral sensitization more readily than do low responders (Pierre & Vezina, 1997) and are more likely to acquire and maintain psychostimulant self-administration (Piazza et al., 1989; Pierre et al., 1997). These high responders also showed a higher corticosterone response after exposure to novelty (Piazza et al., 1991). Moreover, glucocorticoids affect the response to stimulants. Glucocorticoids have a facilitatory effect on acute stimulant-induced locomotor activity (Marinelli et al., 1997; Cador, Dulluc, & Mormede, 1993), which can not be accounted by a drug-induced increase of glucocorticoids (Marinelli et al., 1997). Stimulant-induced sensitization is increased in psychomotor effects of psychostimulants after repeated injections. Suppression or reduction of circulating glucocorticoids reduce the expression of sensitization, although it cannot prevent its development (Marinelli et al., 1997). It also decreases the reinforcing effects of psychostimulants as measured by self-administration. These effects are reversed dose-

dependently by exogenous administration of glucocorticoids (Deroche, Marinelli, Le Moal M., & Piazza, 1997). The psychomotor effects of psychostimulant drugs may increase under stressful conditions (stress-induced sensitization). The stress-induced sensitization depends on the glucocorticoid level increase induced by the stressor (Deroche et al., 1992; Deroche, Piazza, Casolini, Le Moal M., & Simon, 1993; Deroche, Piazza, Le, & Simon, 1994; Prasad, Ulibarri, & Sorg, 1998). Stress also increases psychostimulant self-administration, and this increase also depends on stress-induced glucocorticoid secretion (Piazza & Le Moal, 1998). To conclude, in rats, higher behavioral response to novelty is associated with higher glucocorticoid response; the behavioral response to novelty predicts the behavioral response to stimulants and glucocorticoid level influences the response to stimulants. It is thus tempting to hypothesize that the response to stimulant medication in patients with hyperactivity would depend on their cortisol level.

However, findings from human studies have not been very consistent with the preclinical literature. In healthy human volunteers, sub-chronic hydrocortisone administration had no effect on methamphetamine-induced subjective mood changes and objective performance on a task of sustained attention (Hearn et al., 2004). Acute hydrocortisone pretreatment did not affect any of the physiological, behavioral, or subjective effects of d-amphetamine (Wachtel, Charnot, & de Wit, 2001). Blocking cortisol response with the cortisol synthesis inhibitor, metyrapone, did not produce significant mean changes in most subjective effects of intravenous methamphetamine in humans (Harris, Reus, Wolkowitz, Mendelson, & Jones, 2003). One explanation for this discrepancy is that repeated exposure to stress levels of glucocorticoids may be necessary for the association between glucocorticoid and dopamine to develop. During early repeated stress situations, the repeated increases in glucocorticoid hormones and dopamine would render the subject durably more responsive to stimulant.

Therefore, it was predicted that among the children with ADHD, those with an enhanced salivary cortisol level in response to a stressor would have a better response to stimulant medication. As children with comorbid anxious problems exhibited greater

cortisol reactivity to the same stressor used in this study (Hastings, Fortier, Utendale, Simard, & Robaey, 2008), they were expected to show an enhanced response to stimulants. Higher basal level of cortisol are generally associated with smaller reactivity to a stressor, and high level of cortisol over sustained period of time are often associated with comorbid mixed mood/anxiety symptoms (Nestler et al., 2002). As in humans, glucocorticoids are low during inactivity period at night and increase to reach a peak after waking up, it was predicted that high morning levels of cortisol upon waking would be associated with worse response to stimulant on the core ADHD symptoms.

In order to test these hypotheses, we used a double blind placebo control prospective study in children diagnosed with ADHD, with three different doses of MPH to assess the response to MPH over a week. Salivary sample was obtained just after waking and before and after a standard stress (venipuncture) in order to assess HPA axis. We thus followed with Taylor's design criteria for the prediction of stimulant response: blindness and placebo control, reliability, compliance, flexible dosage, and prospective design (Taylor et al., 1987), as well as the additional criteria proposed by Gray and Kagan: accurate diagnosis, predictor is not a proxy for age or IQ (Gray et al., 2000).

Material and methods

Subjects

Children between 6 and 12 years of age referred by their physician with a suspected diagnosis of ADHD were recruited for a MPH titration procedure through the Interdisciplinary Research Program on Hyperactivity at Sainte-Justine Hospital, a university-based pediatric hospital in Montreal, Canada. One parent was administered the French version of the Diagnostic Interview Schedule for Children (DISC4.0) by a trained interviewer. The DISC4.0 is a structured computerized interview that is used for the diagnosis of psychiatric disorders in children such as ADHD, ODD, CD, tic disorders and Tourette's syndrome (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). This interview allowed the classification of the children among three ADHD subtypes: inattentive, hyperactive/impulsive or combined. A French-language version of the DISC4.0 was obtained through iterative translation and back-translation by bilingual health professionals in collaboration with the DISC4.0 authors. The Wechsler Intelligence Scale for Children (WISC-III) was administered to all children (Wechsler, 1991): M IQ = 100.19, SD = 16.39. A structured questionnaire addressed to a parent was used to collect information on age (M age = 8.35, SD = 1.37), sex (44 males. 8 females), parent's education (27.1% of the fathers and 40.4% of the mothers had a college degree), previous MPH use (57.7% used psychostimulant before the trial, with mean daily dosage of 19.8 mg, SD: 7,6 mg, range 10-40 mg), as well as the family income (40.4% less that CAN $55,000 per year) and structure (11.5% reconstituted families). Children with an IQ lower than 70, born prematurely (<35 weeks of gestation), with severe learning and language retardation, any neurological disease, Obsessive Compulsive Disorders, and Tourette's disorders as a diagnosis were not eligible to participate in the study.

Medication trial

The medication trial was developed based on the titration process of the MTA study. The procedure consisted of a double-blind, placebo-controlled crossover trial with randomized dose schedule. The 4 week trial was done after the 3 days pre-test with MPH at increasing doses. During the trial, children either took placebo or one of the three doses of immediate-release MPH. Low, medium and high doses were 15, 25 and 35 mg per day. For children who weighted 25 kg or more the high dose was 50 mg/day. Each daily dose was distributed in 3 intakes, at 8 am, noon and 4 pm. Each dose or the placebo was taken for one week of the 4-week trial. A code number was allocated by the research pharmacist to the recruited patients. Each number corresponded to a random treatment schedule except that the higher dosage (35 or 50 mg) could not be assigned for the first week. Parents, children, teachers, research assistants and investigators were all blinded to the MPH dose given throughout the study. A written consent was obtained from the children, their parents and teachers before the beginning of the study. This study was approved by the Research Ethic Board of Sainte-Justine Hospital Research Center.

Cortisol sampling and procedures

Prior to a scheduled family visit to the ADHD clinic, parents were instructed in how to use the salivettes with their child. A sample upon waking was collected from each child on the morning of the scheduled clinic visit, within 15 minutes of waking and prior to eating, drinking or brushing teeth. Out of the 52 children who participated in the titration process, 43 parents brought waking samples, and 35 had enough saliva to perform assays of cortisol. Among these 35 children, 17 were diagnosed with combined type ADHD, 3 with the Hyperactive-Impulsive subtype and 15 with the Inattentive subtype. An anxiety problem was diagnosed using the DISC4.0 in 9, 1 and 4 of the ADHD subjects, within each

respective subtype category. Each family attended a 3-hour testing session at the clinic. 17 (39.5%) families were seen in the morning (9 AM to 11 AM start-time), and 26 (59.5%) were seen in the afternoon (1 PM to 3 PM start time). Parents completed the DISC4.0 and other questionnaires not relevant for the present study in one room of the clinic, while the child was assessed in another room. The WISC-III was administered to the child, along with other procedures and measures not pertinent to the current analyses. Two hours after arriving at the clinic, a second saliva sample was collected from the child (Pre-stress). The child was then told that a nurse needed to collect a blood sample[1]. A topical analgesic was applied to the child's arm, which the child was told would make the needle not hurt. The child and interviewer then went to the phlebotomy clinic, where a nurse drew the blood. The child and interviewer returned to the ADHD clinic, and 20 minutes after the venipuncture, a third saliva sample (Post-stress) was obtained. Among the 52 children who participated in the titration process, 10 refused the blood draw. Thus 42 pre- and the post-stress saliva samples were collected. Of the 42 pre- and the post-stress saliva samples collected, 41 were usable. Among these 41 children for which pre- and post-samples were usable, 20 were diagnosed with combined type ADHD, 4 with the Hyperactive-Impulsive subtype and 17 with the Inattentive subtype. An anxiety problem was diagnosed using the DISC4.0 in 11, 1 and 4 of them, within each respective subtype category. The 10 boys who refused to provide pre- or post-stress samples did not differ from the other children in prevalence of anxiety problems.

Saliva samples were stored in a -80C medical freezer, then shipped to the Pennsylvania State University Behavioral Endocrinology Laboratory (Salimetrics ™) to be thawed, centrifuged, and have 50 µl of clear samples pippetted into test-wells for enzyme-immunoassay of cortisol. All samples were tested in duplicate; samples that varied by more than 5% across duplicates were re-tested; correlation across duplicates r = .99. Mean values of duplicates were used in analyses, in units of microgram per deciliter (µg/dL). Raw

[1] The broader protocol for this study included a blood draw for the purpose of genotyping, which also provided an opportunity to examine the physiology of stress reactivity.

cortisol data were leptokurtic and positively skewed, therefore log-transformations were used to establish normality. The transformations corrected the skew and eliminated outliers; therefore, log-transformed data were used in all analyses. Untransformed data are reported in text for ease of interpretability. In order to assess cortisol response to the blood draw stressor, while controlling for individual differences in the pre-stress level, linear correlations were computed between log-transformations of pre- and post-stress sample dosages and the residuals were retained for further analyses. The increases in salivary cortisol levels in response to venipuncture were larger when the blood draw was done later in the day (Pearson's correlation: 0.409; p=0.008). However, in a larger sample (N=151) the salivary cortisol levels in response to venipuncture were similar in the morning and in the afternoon (Hastings et al., 2008). Also, the increases in salivary cortisol levels in response to venipuncture increased with age (Pearson's correlation: 0.402; p=0.009).

Outcome measures

The French version of the Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors ratings Scale (SWAN-F) (Robaey, Amre, Schachar, & Simard, 2007) was completed daily by teachers (5 days/week) and parents (7 days/week) throughout the trial. The SWAN (Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors ratings Scale - SWAN) is a scale where the informant is asked to assess the strength opposite to the ADHD symptoms (Swanson et al., 2005). Without changing the content, each item of the SNAP-IV rating scale (Swanson et al., 2001) was re-worded in order to capture the strength corresponding to the weakness. For example: "Often does not seem to listen when spoken to directly" becomes "Listen when spoken to directly" and is rated from "far below average" (-3) to "far above average" (+3) relative to children of the same age. This approach yielded a normal distribution of ADHD scores (Hay, Bennett, Levy, Sergeant, & Swanson, 2007). The SWAN-F scores were averaged across the 18 DSM-IV

ADHD symptoms each day and then averaged for the placebo week and each MPH dose week for parents and teachers separately.

Medication side effects were evaluated daily by parents and teachers using the Side Effect Rating Scale (SERS; (Barkley, McMurray, Edelbrock, & Robbins, 1990). The SERS is composed of a variety of side effects experienced by stimulant medications and it is used to measure the prevalence and severity of the side effects in several treatment studies. The teacher's form included 14 items while the parents form included 3 additional items that rated appetite, insomnia and nightmares. Each item was scored using a 10 point scale reflecting side effect intensities ranging from 0 to 9 (0=absent, 1-3=mild, 4-6=moderate, 7-9=severe). Scores were averaged to give the total side effect score.

To ensure compliance by the parents and teachers in the filling out of the questionnaires, they were contacted weekly. Also parents and teachers had to maintain a daily diary for the recording of the medication intake.

Statistical analyses

Repeated-measures of analyses of variance were conducted. The outcomes analyzed were the parent or teacher-rated SWAN-F and SERS global scores under placebo and the three doses of MPH. The main effect of dose (within subject factor with four levels) and the effect of the cortisol upon waking or cortisol reactivity (used as covariate) were tested. When testing cortisol reactivity, age and time of the blood draw were also used as covariate. When the covariate was significant, the effect of a between-group factor was tested using the median as cut-off point, and the different between increasing doses were test in each subgroup. The analyses were performed using the statistical software SPSS16.0.

Results

1. Effect of raters.

Globally, teachers rated the ADHD behavior as more severe than the parent did (Rater: $F(1,50) = 5.041$; $P=0.029$). However, there was no difference between the rating of the effect of increasing MPH doses at school and at home. Correlations between SWAN rating of parents and teacher were generally low and non significant, ranging from 0.15 to 0.19 (0.25 to 0.29 after controlling for cortisol level). With regard to side effects, the teachers differ from the parents in their reports of the dosage (Rater x Dose: $F(3,150) = 4.831$; $P=0.003$), but paradoxically they reported more side effects under placebo than under active medication (Dose: $F(1,51) = 23.426$; $P<0.001$). Pearson correlations between side effects rated by parents and teachers were very low (<0.15) and insignificant, the stronger coefficient being obtained for the somatic symptoms under placebo (Pearson correlation: 0,246, ns; 0.297, ns, after controlling for cortisol level).

The correlation between cortisol level upon waking and cortisol stress reactivity was low and non significant (Pearson correlation: 0.-119; ns). However, when correlation were computed for the participants below the median waking cortisol and equal or above separately, the correlation were in opposite directions, although still non significant: Pearson correlations: 0.294 and -0.361, respectively. However, the difference in correlation was significant ($dr = 0.655$; $z = 1.75827$; $p=0.0394$), which suggest that going from the low to the high cortisol upon waking group, the cortisol reactivity tend to increase, then to decrease with increasing morning cortisol level.

2. Effect of cortisol level upon waking (Figure 1 p: 57-58)

MPH therapeutic effects

According to the parents, increasing the MPH doses significantly improved ADHD global scores (Dose; $F(2.5, 125.9) = 22.344$; $P<0.001$, $\varepsilon = 0.823$). This dose effect was no longer significant when the level of cortisol upon waking used as covariate. The improvement in ADHD score with increasing doses tended to depend on the level of cortisol upon waking (Dose x Waking; $F(3, 99) = 2.351$; $P= 0.077$). Specifically, under high dose of MPH, the global ADHD ratings by the parents were negatively correlated with the cortisol upon waking (Pearson correlation -0.357; P=0.035), as was the difference between the high dose and the placebo (Pearson correlation -0.347; P=0.041). In order to further analyze these effects, we divided the children into two groups, below the median level of cortisol upon waking, and equal or above. The correlation with the SWAN scores under high dose of MPH was strong in those with a cortisol upon waking above the group median (Pearson correlation -0.597; P=0.019), but almost null for those beyond (Pearson correlation -0.010; ns). Similarly, the correlation between the difference in total scores on high dose and placebo and the cortisol level was high in the high cortisol group (Pearson correlation -0.467; P=0.080) and almost null in the low cortisol group (Pearson correlation -0.069; ns).

A clinical consequence of the decrease of the pharmacological effect with increasing cortisol levels upon waking is that a high cortisol level is a good predictor of being a non-responder under active medication, whatever the dose. We defined a responder by two conditions. First, the parents had to rate the ADHD symptoms as improved under active medication, whatever the dose, as compared to placebo. Second, one of these ratings had to be above - 0.6, which is considered the lower limit for the normal range (Robaey et al, 2007). A receiver operating characteristic (ROC) analysis showed a cortisol level upon

waking above .37µg/dL allowed identifying the non-responders with a sensitivity of 0.75 and specificity of 0.87 (Area under the curve = 0.855; P=0.023).

Similar to parents', teacher's ratings showed a very significant effect of increasing doses on the ADHD global scores: Dose; $F(2.5, 128.3) = 46.154$; $P<0.001$, $\varepsilon = 0.839$. However, contrary to the parents, the dose effect assessed by teachers did not interact with the level of cortisol upon waking when used as a covariate.

MPH side effects

In parent ratings, the side effect total score was low (0.48 ± 0.59) and did not increase with dose. However, when the level of cortisol upon waking was used as a covariate, side-effects globally increased with MPH doses (Dose; $F(2.1, 68.1) = 3.775$; $P=0.027$, $\varepsilon = 0.688$) and the effect of the dosage depended on the level of cortisol upon waking (Dose x Waking; $F(2.1, 68.1) = 4.834$; $P=0.010$, $\varepsilon = 0.688$). The covariate effect on the global side-effect level was also significant (Waking; $F(1,33) = 7.538$; p=010). Specifically, the level of salivary cortisol upon waking was positively correlated with the parents' ratings of side effect under placebo (Pearson correlation: 0.511; P=002) and under a low dose of MPH (Pearson correlation: 0.504; P=002).

By using the separation into two groups, below the median level of cortisol upon waking, and equal or above, side effects were higher in the high waking cortisol group than in the low cortisol group (mean 0.73 ± 0.68 vs. 0.34 ± 0.44). Within the low cortisol group, escalating MPH doses increased the side effect severity (Dose; $F(1.5, 28.5) = 4.536$; $P=0.028$, $\varepsilon = 0.500$), while in the high cortisol group, side effect rating was not influenced by escalating MPH doses (Dose; $F(2.0, 27.3) = 0.230$; $P=0.790$, $\varepsilon = 0.650$). As for the therapeutic effects, the cortisol level upon waking predicted the side effect rating in the placebo condition in the high cortisol group (Pearson correlation 0.515; P=0.049), but not in the low cortisol group (Pearson correlation 0.054; ns).

In teachers ratings, the total score for side effect varied with dose (Dose; F(2.6, 131.8)= 9.575; P<0.001, ε = 0.862). It showed a quadratic trend (F(1,51)= 8.652; p=005), decreasing from the placebo (0.97 ± 0.94) to low dose (0.67 ± 0.78) and to medium dose (0.54 ± 0.59), with an small increase at high dose (0.62 ± 0.66). However, when the level of cortisol upon waking was used as covariate, the effect of dose decreased and was no longer significant and neither was its interaction with the covariate. Correlations between side effects rating and cortisol upon awakening were almost null.

2. Effect on cortisol stress reactivity (figure 2 p: 59-60)

MPH therapeutic effects

In school, the effect of increasing doses on the total ADHD scores improvement was significant (Dose; F(2.5, 128.3) = 46.154; P<0.001, ε = 0.839). When the cortisol stress reactivity was used as covariate, the effect of increasing doses depended on the cortisol stress reactivity (Dose x Stress; (F (3, 117) = 3.760; p=0.013). When the time of the blood draw was also used as covariate, the interaction remained significant (Dose x Stress; (F (3, 111) = 2.861; p=0.040). When age was also used as covariate, the effect of increasing dose was related to cortisol stress reactivity (Dose x Stress; (F (3, 111) = 3.563; p=0.017), to age (Dose x Age; (F (3, 111) = 4.954; p=0.003), as well to the combined effect of both age and cortisol response (Dose x Stress x Age; (F (3, 111) = 2.943; p=0.036).

In order to describe this effect of the cortisol response to a stressor, we divided the sample into two groups: below and equal or above the median cortisol stress reactivity in order to make a trend analysis. In addition to the linear trend across doses in both groups, only children with low cortisol stress reactivity showed a significant quadratic trend (Dose; F(1, 19) = 8.318; P<0.010), with an inverted J-shaped dose-response curve.

Further, we compared the improvement in ADHD global ratings in children with low and high stress cortisol reactivity for each increase in MPH dose. For the low dose, as compared the placebo, improvement in global ADHD ratings was significant both in the high ($t = -2.36$; $df = 20$; $p= 0.028$) and in the low reactivity groups ($t = -4.53$; $df = 19$; $p< 0.001$). Going from low to medium dose, global ADHD ratings again significantly improved in both the high ($t = -2.47$; $df = 20$; $p= 0.023$) and the low reactivity groups ($t = -3.54$; $df = 19$; $p= 0.002$). However, further increasing MPH from medium to high dose did improve ADHD behavior in the high reactivity group ($t = -2.193$; $df = 20$; $p= 0.040$), but not in the low reactivity group ($t = 0.302$; $df = 19$; ns). The same results held for more extreme subjects with regard to cortisol stress reactivity, when comparing those below the percentile 30 and above the percentile 70: going from medium to high MPH dose yielded an additional improvement on ADHD global rating in the very high reactivity group ($t = -2.275$; $df = 13$; $p= 0.040$), but not in the very low reactivity group ($t = 0.054$; $df = 11$; ns).

At home, the effect of increasing dose on parent's ADHD global ratings was very significant (Dose; $F(2.5, 125.9)= 22.344$; $P<0.001$, $\varepsilon = 0.823$). However, this effect of doses was still significant when the cortisol stress reactivity was used as covariate and did not interact with the covariate.

Anxiety disorders

We found that boys' comorbid anxiety diagnoses and problems were consistently associated with exaggerated cortisol reactivity. We found that out of 52 subjects, 19 also had a diagnosis of anxious disorder. Their cortisol stress reactivity was increased by 38.85%, which was not statistically significant. When the presence of any anxiety comorbid disorder was used as between-subjects factor, the parents reported that the improvement with dose of the ADHD global ratings differed according the anxiety status (Dose X Anx: $F (2.6, 130.5) = 6.975$; $P<0.001$; $\varepsilon= 0.870$). We compared the improvement in ADHD global ratings with increasing dose in children with or without anxiety comorbid condition. Improvement in global ADHD ratings was significant for the low dose, as compared the

placebo, both in the anxious (t = -2.28; df = 18; p= 0.035) and in the non anxious groups (t = -2.75; df = 32; p= 0.035). Going from low to medium dose, global ADHD ratings again significantly improved in both anxious (t = -2.83; df = 18; p= 0.011) and non anxious groups (t = -2.07; df = 32; p= 0.047). However, further increasing MPH from medium to high dose tended to improve ADHD behavior in the anxiety comorbid group (t = -1.934; df = 18; p= 0.069), but not the group without anxiety disorder (t = - 0.067; df = 32; p= 0.947).

However, for teacher's global ADHD ratings, this interaction between dose effect and anxiety status did not reach the statistical significance level (Dose X Anx: F (2.5, 124.9) = 1.821; P=0.156; ε= 0.833).

MPH side effects

There was no effect of stress cortisol reactivity and the rating of side effects observed by neither the parents nor the teachers.

Discussion

The benefit of the medication on ADHD symptoms progressively decreased with increasing morning cortisol levels, up to the point that the children with the highest morning cortisol levels could be defined as non responders to stimulant. This result can be linked to previous demonstrated predictors of the response to psychostimulant. Parental depression is one of the main factors that has been showed to decrease the rate of favorable outcome on ADHD symptoms, following well monitored treatment with MPH (Owens et al., 2003). Depressive symptoms in the parent were supposed to interfere with the primary caregiver's involvement in the treatment and consequently with the child ability to benefit from the treatment. However, the child inability to benefit from treatment could not only be the consequence of the lack of parental involvement in the treatment, but also be related to another characteristic specific to the child with a depressed parent. Maternal depression at 2 month post-partum was found to be associated with higher and more variable morning cortisol in 13-year-old adolescent offspring. Mothers with post-natal depression were also more likely to experience further depression in the following years (Halligan, Herbert, Goodyer, & Murray, 2004). Moreover, elevated morning cortisol at 13 years mediated the association between postnatal depression in the mother and depressive symptoms at 16 years, over and above 13-year depressive symptom levels and other possible confounding factors (Halligan, Herbert, Goodyer, & Murray, 2007). The sensitive period for the influence of maternal depression on elevated cortisol in offspring may extend over the first or even the second year after birth, and can be detected in 7-8 year- and even 4.5 year-old children (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Essex, Klein, Cho, & Kalin, 2002). Increased waking salivary cortisol level has been proposed to be a stable endophenotype in individuals at risk of depression (Mannie, Harmer, & Cowen, 2007). Thus the dysfunction of the HPA axis in poor MPH responders with a depressive parent could have been acquired earlier in life in response to already present depressive symptoms of their mother. Those children with ADHD who have a high cortisol level and depressive

parent are themselves at risk of depression. Stimulant medication have been showed to potentially increase mood problems: 7- to 9-year-old children with ADHD showed initial increases in their Children's Depression Inventory (CDI) scores after 5 weeks of MPH treatment, followed by a significant decrease in CDI scores after 6 months of treatment with MPH (Hechtman et al., 2004). In preschool children ages 3–5.5 years, parent rated depression and dysthymia as worsened by methylphenidate during a 4-week double-blind placebo controlled trial similar to the one we used (Abikoff et al., 2007). A significant increase in emotional outburst and crying with MPH compared to placebo was also found in the titration phase of the same study (Hechtman et al., 2004; Wigal et al., 2006). ADHD children at risk for depression, identified by high level of morning salivary cortisol, would exhibit more readily mood-related features under MPH treatment. These depressive symptoms can constitute a halo which could hinder the rating of the improvement of ADHD symptoms themselves. We did not include mood assessment in this study. The hypothesis of aggravation of mood symptoms secondary to treatment initiation attenuating treatment outcome in some children with high morning cortisol level has to be further investigated.

Alternatively to this hypothesis of treatment-related mood symptoms hindering the improvement of ADHD symptoms, a high level of cortisol upon waking acquired early in life could identify a subset of patients whose ADHD syndrome comprises features that are usually considered as side effects but are in fact part of a form of ADHD that would be more resistant to stimulant treatment. These symptoms associated with a high morning level of salivary cortisol would be primarily observed by the parents because they would be more readily observable when the child is waking up. Some children with ADHD have difficulty getting out of bed; some are slowed down or agitated during morning, starring into space when expected to do the morning routine. In adult, poor rest and recovery from work was associated with high levels of morning cortisol. The strongest relationships with high cortisol levels emerged for questions about feeling "thoroughly rested", "energetic", "very tired", "had sufficient sleep" with the early morning cortisol level (Gustafsson,

Lindfors, Aronsson, & Lundberg, 2008). In preschool-age children, disruptive behaviors were found to be associated with more negative affect, higher afternoon cortisol levels, and a smaller decrement in cortisol from morning to afternoon (Ward, Gay, Alkon, Anders, & Lee, 2008). Parents could thus report poorer response to treatment and more symptoms under placebo in the high-cortisol subgroup of children with poorer rest and recovery, and marked psychomotor retardation or activation after waking. This specificity to the morning home setting could explain why the teachers were blind to the effect of the morning cortisol.

The influence of cortisol on the dose-response curve for side effects also contributed to define poor responder. When the cortisol level upon waking was used as a covariate, the cortisol level was significantly associated with increasing side effects as rated by the parents, and increasing MPH doses worsened side effects. In addition, the cortisol level influenced the side effects ratings, but only for the placebo or the low dose of MPH: The higher the cortisol level, the worse the side effects. The most parsimonious explanation for both the presence of side effects under placebo or low dose of MPH and the increase in side effect with higher MPH doses is that what is usually described as side effects are in fact a mixture of symptoms that are part of the ADHD syndrome and real MPH-related side effects. The latter symptoms are aggravated by increasing MPH doses. The former symptoms are expressed by the children with high level of morning cortisol and did not seem to improve with treatment. However, their relation with the cortisol level is observed for the placebo and low dose of MPH only, when the real side-effects are low.

The observation of paradoxical stimulant side effects on placebo has already been reported. A study on side effect that used a double blind cross-over design to compare the side effect profile of MPH and dexamphetamine also concluded that in more than 50% of the children, parents reported during the initial baseline symptoms (irritability, anxiousness, proneness to crying, sadness/unhappiness, trouble sleeping, daydreaming) that improved significantly on stimulant (Efron, Jarman, & Barker, 1997b). These authors suggested that these symptoms may represent features of the behavioral phenotype of ADHD.

Alternatively, they suggested that the high rating of side effects could be due to a halo effect of a globally negative view of the child, especially during the baseline before treatment. However, this latter explanation is not supported by the high frequency of side effects under placebo (especially staring, sadness, irritable, euphoria, anxiousness, proneness to crying and insomnia) also reported by parents in the validation study on the Stimulant Drug Side Effect Rating Scale that used a placebo-controlled design (Barkley et al., 1990). In teachers' ratings, staring, sadness and anxiety also declined with increasing doses of medication (Barkley et al., 1990). In the present study, the severity of the side effects reported by the parents under placebo or low dose of methylphenidate was predicted by the level of salivary cortisol upon waking. Hypersecretion of cortisol is one of the most often reported findings in depression (Nestler et al., 2002). Side effects associated with high level of cortisol may be depression-related features (such as psychomotor retardation or activation symptoms, sleep problems, lack of interactiveness, psychosomatic symptoms, etc.) associated with ADHD that are more prominent under placebo or low dose of stimulant. The level of cortisol upon waking predicted the level of side effects, especially for the placebo or the low dose condition, but only in the subgroup of children at or above the 50^{th} percentile for morning salivary cortisol. In this subgroup, side effects are not worsened with increasing MPH doses, but increased in severity with the cortisol level, which suggests that they are part of a broader ADHD syndrome that they may help to recognize. Thus both SWAN and SERS rating by the parents tend to support the hypothesis of a broader ADHD syndrome more resistant to stimulant medication, in relation with the morning cortisol level.

On the other hand the teachers did report that the children with ADHD who showed the highest reactivity salivary cortisol to the venipuncture stressor also showed a different dose-response curve. More specifically, they reported an additional improvement in ADHD behavior when going from a medium to a high dose of MPH in the children with the larger cortisol response to the stress of the blood draw, while those with a lower response did not show any additional gain. It should be noted that this additional improvement could only be

detected by a strength-based questionnaire like the SWAN. The average rating to a high MPH dose in high reactivity cortisol participants was slightly positive (0.14) and thus included some ratings above zero. A symptom-based instrument would likely be less sensitive by not rating strength but only the absence of symptoms as zero (Robaey et al., 2007). This influence of cortisol reactivity might increase with age, and the time of the day, but this suggestion has to be confirmed in independent studies and may be due to a sample effect.

In a previous paper, we showed that boys with comorbid anxious disorders and problems exhibited greater cortisol reactivity to the same venipuncture procedure (Hastings et al., 2008). Remarkably, parents reported the same effect of an additional benefit of a high MPH dose, but in relation with comorbid anxious disorders and problems. Parents would thus be more sensitive to the anxious symptoms while teacher would be more sensitive to coping with stress. Using the State- Trait Anxiety Inventory for Children (STAIC), higher anxiety in children with ADHD predicted better outcome after 10 weeks of MPH or combined MPH- multimodal behavior therapy in teacher ratings (Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Pre-treatment comorbid anxious symptoms did not predict a clinically significant attenuation of response to MPH in children with both ADHD and chronic multiple tic disorder, at least with regard to the core features of ADHD. On the contrary, when the contribution of oppositional behavior was controlled, there was some evidence suggesting anxiety symptoms at intake were associated with a more favorable response of hyperactive and inattentive behaviors to medication (Gadow, Nolan, Sverd, Sprafkin, & Schwartz, 2002). In the Multimodal Treatment Study of Children with ADHD (MTA), no adverse effect of anxiety on medication response for core ADHD or other outcomes was demonstrated. To the contrary, a robust response to optimal medication management was found in anxious subjects with teacher-reported inattention (March et al., 2000). A further examination of predictors of treatment response in the MTA study, using a categorical measure of ‘‘excellent response’’ rather that a continuous outcome measure, comorbid anxiety was not a predictor (Owens et al., 2003). A few other studies concluded

to a weaker response in children with ADHD and comorbid anxiety, but not conclusively. Prediction of the response to a relatively low dose of MPH (10 mg bid) in a 4-week trial was only possible for recovery at home and at school: lower rating of anxiety at home (as measured by the anxiety subscale of the Conners Parent Rating Scale, CPRS) was a predictor, but behind a higher Full Scale IQ, more inattentiveness at school, younger age, and lower severity of the disorder (Van der Oord et al., 2008; Buitelaar, van der Gaag, Swaab-Barneveld, & Kuiper, 1995). Children with ADHD and Overanxious Disorder were found to have a decreased response to MPH for inattention/overactivity, as compared to the non anxious group. However, but this interaction was mostly due to an improvement of the comorbid group while on placebo and another decline on drug. For the non anxious group, the baseline and the placebo were not different from each other but were significantly worse than the low and high drug condition, which were in turn not different from each other (Pliszka, 1989). Other studies (Taylor et al., 1987; DuPaul et al., 1994) have included anxiety symptoms into a broader spectrum of internalizing or emotional problems and can not specifically assess the effect of anxiety, independently of mood symptoms.

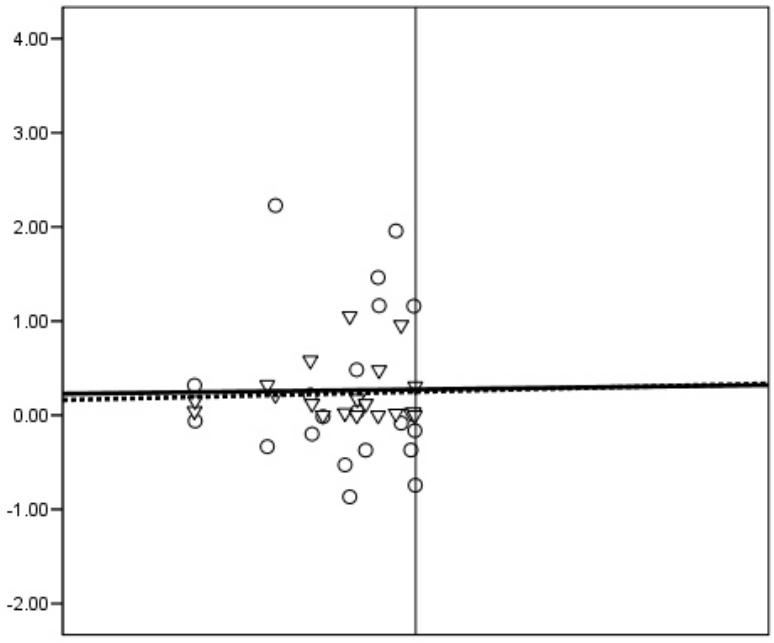
Methylphenidate effects are in part due to increase in extracellular dopamine secondary to blockade of dopamine transporter that recaptures the dopamine into the pre-synaptic neuron. Positron emission tomography (PET) allows to measure extracellular dopamine using [^{11}C]raclopride as D2 receptor radioligand that competes with endogenous dopamine. PET studies showed that MPH increased dopamine release in the brain. However, individual differences in dopamine increases are not due to differences in DAT blockade, as measured in PET using [^{11}C]cocaine as DAT radioligand, but more likely to individual differences in DA activity (Volkow et al., 2002). Other studies looked at individual differences that could account for individual differences in dopamine activity or release by MPH. In healthy human volunteers, dopamine release in ventral striatum by amphetamine is increased in the subjects who showed a stronger cortisol increase in response to amphetamine; these high cortisol response subjects also reported liking more the drug effect (Oswald et al., 2005). Although the cortisol increase in response to

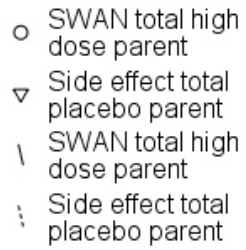
amphetamine was larger than the raise in cortisol in responses placebo, significant correlations were found in cortisol levels between amphetamine and placebo sessions. The amount dopamine released by amphetamine is thus related to the amplitude of the cortisol response in response to a drug challenge, but also to the experimental situation itself. Amphetamine-induced dopamine release in ventral striatum was also found positively correlated with the cortisol response to an acute standardized psychosocial stressor measured independently (Trier Social Stress Test), again in human healthy volunteers (Wand et al., 2007). Subjects with a stronger dopamine response to amphetamine may thus have a stronger cortisol response to both pharmacological and social stressors. Conversely, an acute social stressor (a mental arithmetic task set to be too difficult and accompanied by negative comments) can directly induce dopamine release in the ventral striatum. This dopamine release was positively correlated with the cortisol response to the same acute psychosocial stressor. All subjects also rated their perceived levels of parental care and protection and were divided into low and high groups. The increase in dopamine release during the mental arithmetic task as compared to a rest session was only significant in the low care group. Similarly, the cortisol response increase in the stress condition, as compared to rest, was larger in the low than in the high care group (Pruessner, Champagne, Meaney, & Dagher, 2004). Thus both enhanced cortisol and dopamine release in response to stress seems more strongly associated in the subject with a lower level of perceived parental protection and care. In the present study, the children with a higher cortisol response to the blood draw also showed a larger decrease in ADHD behaviors using a high dose of stimulant. It is most likely that cortisol elevations to venipuncture are primarily attributable to emotional arousal than physical stress or pain (Hubert, Moller, & Nieschlag, 1989; Bellitti, Valeriano, Gasperi, Sodini, & Barletta, 1994; Meeran, Hattersley, Mould, & Bloom, 1993). It is thus possible that children with ADHD and a stronger cortisol response to stress would have a higher increase in dopamine release in response to high dose of methylphenidate, which would in turn account for the larger improvement in behaviour. Teacher reported more accurately the enhanced clinical response in children with a stronger

cortisol response to the venipucture. Both the hospital and school situations require responding to a demand outside the family circle. Parent would report more accurately the better response associated with manifest anxiety symptoms as their children would report them more easily at home, such as separation anxiety or specific phobia.

Limitations: The prediction of cortisol was limited to a one week-period during the titration trial; it needs to be replicated and validated in an independent sample followed longitudinally. The cortisol morning level was expected to reflect the circadian rhythm, as the early morning peak in cortisol is reliably established at three months of age (Price, Close, & Fielding, 1983). However, as the saliva samples were collected up to 15 minutes after waking, it could also capture part of the awakening cortisol response (ACR). ACR is a discrete and distinctive part of the cortisol circadian cycle. In healthy adults salivary free cortisol concentrations increase by between 50 and 160% in the first 45 min immediately post-awakening and is thus rising during the first 15 minutes upon waking (Clow, Thorn, Evans, & Hucklebridge, 2004). However, a delay between waking and sampling below 15 minutes was not found to have a significant influence on cortisol level (Dockray, Bhattacharyya, Molloy, & Steptoe, 2008). How the cortisol response to a blood draw can be generalized to psychosocial stressor, as well as the role of the stimulant-induced rise in cortisol have also to be established in further studies. The relatively small number of subjects did not allow exploring whether all ADHD subtypes are equally sensitive to cortisol levels. Further studies are also needed to establish whether the side-effects correlated with the morning cortisol and those related to increasing dose of stimulant are distinguishable or not, as this would help identifying potential non responders. Specific measures of mood, anxiety, and sleep problems would also be important in future studies to tackle this issue. However, despite its limitations, this first study using a double blind placebo controlled trial in a well defined ADHD group, and a standard stressor, provided evidence that the HPA axis circadian rhythm and reactivity is likely to be a strong predictor of the response to stimulant medication. Given the relative lack of success of previous studies, it is worth pursuing in further investigations.

Low cortisol upon waking





High cortisol upon waking

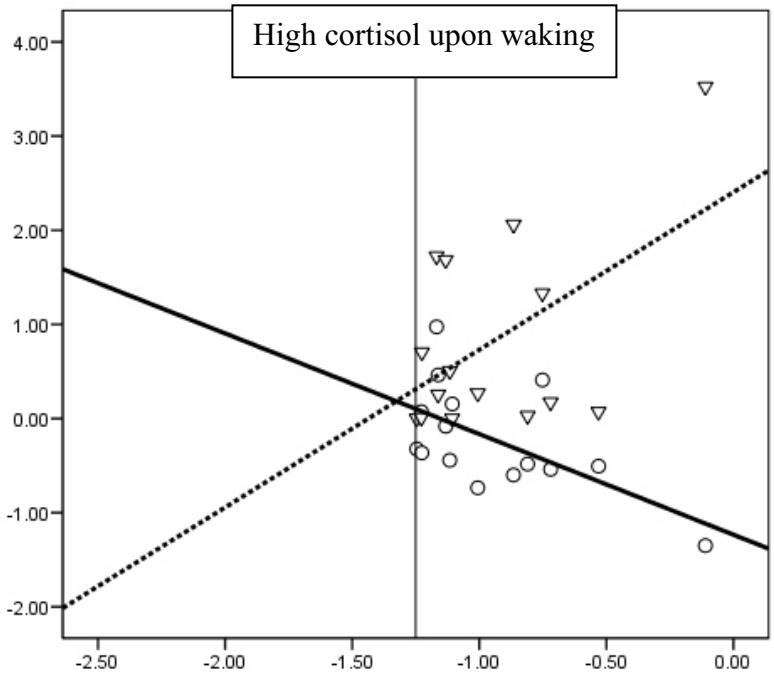


Figure 1 legend: Correlations between Log of cortisol upon waking (x-coordinate) and ADHD global rating at high dose (circles/y-coordinate) and total side effects with placebo (triangles/y-coordinate) in the low (upper panel) and high (lower panel) cortisol upon waking groups. In the high awakening group, Pearson's correlation was -0.60 (P=0.019) with the ADHD score and +0.53 (P=0.044) with the total side effect score.

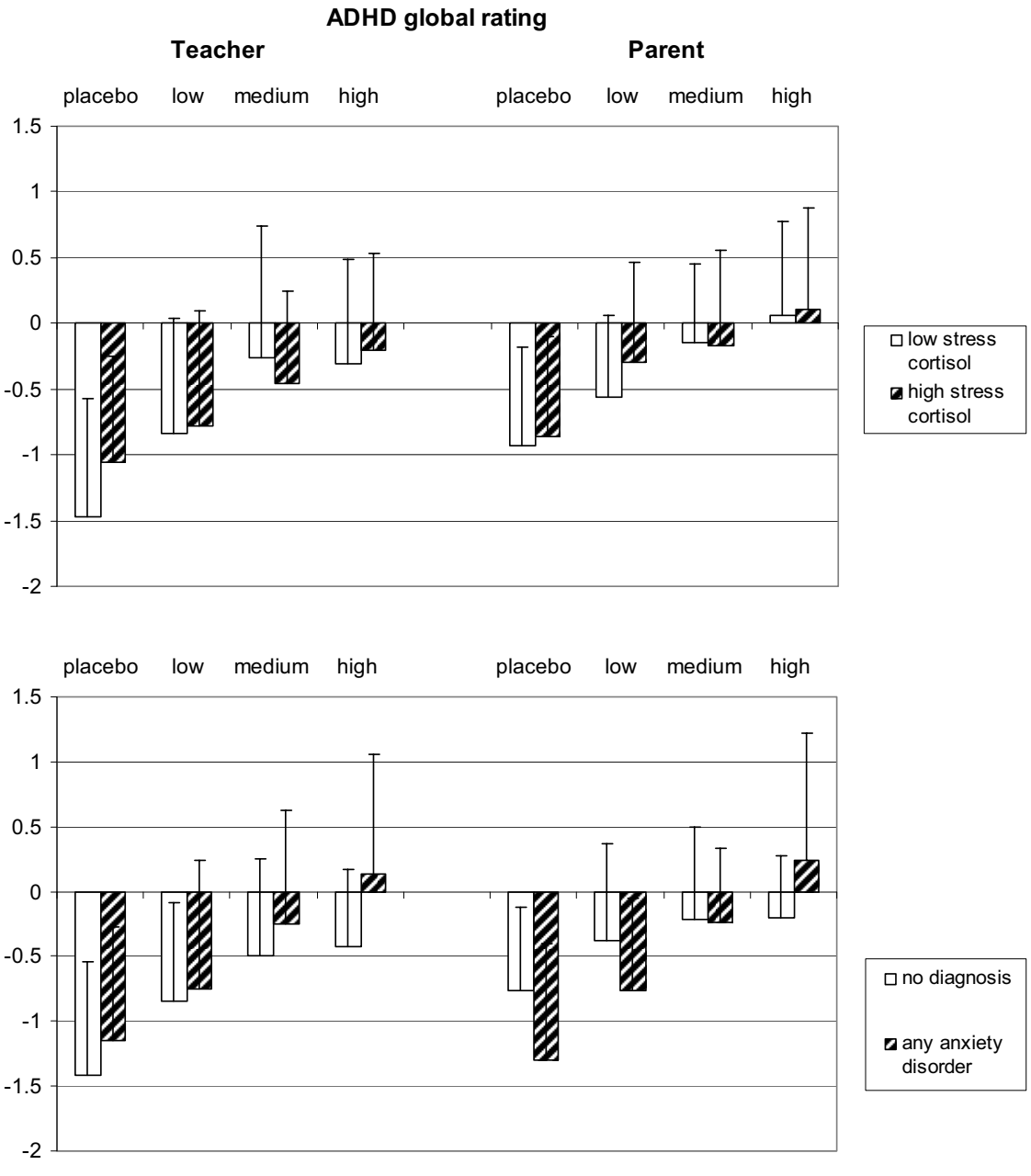

ADHD global rating
Teacher
Parent
placebo
low
medium
high
placebo
low
medium
high
1.5
1
0.5
0
-0.5
-1
-1.5
-2
low stress cortisol
high stress cortisol
placebo
low
medium
high
placebo
low
medium
high
1.5
1
0.5
0
-0.5
-1
-1.5
-2
no diagnosis
any anxiety disorder

Figure 2 legend: SWAN ADHD scores by parents and teacher under the placebo, the low, medium and high dose of MPH in each low vs. high stress cortisol or no diagnosis vs. any anxiety diagnosis groups.

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3. Discussion

3.1 Overall presentation

The present study demonstrated differences in effects of dose of methylphenidate in children with ADHD according to their morning cortisol or cortisol reactivity levels. The results obtained suggest that the effect of methylphenidate treatment should be considered in relation with cortisol levels. Children with ADHD and high morning cortisol are poor responders to methylphenidate while those with high cortisol reactivity continue to improve with higher doses of methylphenidate. Thus cortisol can partially predict the response to treatment of methylphenidate. In addition, children with comorbid anxiety disorders displayed similar results as the children with high cortisol reactivity. This is in line with previous results showing that children with ADHD and anxiety disorders have stronger cortisol response to stressor than children with ADHD alone. Conversely, low level of morning cortisol was not a marker of anxiety level. These findings have important clinical implications for the most prescribed medication in child psychiatry for the treatment of children with ADHD; stimulants such as methylphenidate or amphetamine salts. However, they raise different issues in order to fully understand the implications for treatment. First, it is primordial to examine if these results could be generalized to all age groups, as diurnal cortisol rhythm and cortisol reactivity is affected by age. Furthermore, other factors could affect cortisol levels such as gender, socioeconomic status, race, etc. Such factors have been found to influence cortisol levels and hence may have an effect on the efficacy of the stimulant medication.

Also, the influence of cortisol level and reactivity on the response to other medications used in children with ADHD should be examined. Cortisol-norepinephrine or cortisol-serotonin interactions will be discussed in relation with the cortisol-dopamine interactions. In addition, there are differences in individual dopamine activity that may have an effect on the treatment of ADHD. Lastly, we will review the limitations and the general clinical implications of the present study.

3.2 Cortisol diurnal rhythm and morning level

3.2.1. Influence of the circadian rhythm of cortisol with age

It is typically at three months that the early morning peak is clearly established at an individual level, although it is detectable as early as at six weeks in group average. The circadian rhythm is characterized by a decrease of cortisol throughout the day. A significant decrease in salivary cortisol levels has been consistently observed between the sample obtained approximately 30 minutes after wake up and the sample obtained within 30 minutes of bedtime, from 3 to 36 months (Gunnar & Donzella, 2002). However, the expected smaller decrease from mid-morning to mid-afternoon is not reliably observed before 48 months. This diurnal change at 48 months may be related to the development of a mature sleep/wake pattern over this period. Cortisol level also decreased during the nap and its decrease from morning to afternoon predicted the duration of the nap in preschoolers. The basal activity of the HPA axis continues to mature until the late preschool years, in relation with changes in daytime napping.

The development of the circadian rhythm of cortisol is also changing later in life. There is consistent evidence of an age-related phase advance (i.e., to an earlier phase) in the timing of the biological cycle. This was shown with circadian rhythm markers such as the sleep-wake cycle, melatonin cycle, body temperature and cortisol cycles. A phase difference of about one hour is typically found between young and old subjects such that older adults have an earlier phase than younger adults (Monk, 2005). Hence older adults tend to wake up and sleep earlier. Nocturnal exercise is capable of delaying the circadian melatonin rhythm in older adults who have advanced sleep-wake cycle and of restoring synchrony of the sleep-wake cycle with the external environment (Baehr et al., 2003). Napping in the evening is common in older adults and it is related to early morning awakening. Evening napping could thus be a manifestation of advanced circadian rhythm. This is partly

supported by the finding that older adults with evening naps showed a more advanced acrophase melatonin excretion than those without evening naps.

In the elderly, humans also show an attenuation of diurnal rhythm of cortisol and ACTH secretion, resulting in higher evening cortisol (Deuschle et al., 1997; Van Cauter E., Leproult, & Kupfer, 1996) since other studies confirmed that ACTH and cortisol level are higher in the evening than in younger subjects (Giordano et al., 2005). The basal HPA activity was also enhanced during sleep in the elderly, as indicated by significantly elevated nadirs of plasma cortisol and ACTH concentrations during early nocturnal sleep (Dodt, Theine, Uthgenannt, Born, & Fehm, 1994).

The clinical response to stimulant could thus be more predictable when the circadian rhythm is reliably established. However, in practice, stimulants are not prescribed in children less than 4 years. Older adults could have a better response to methylphenidate due to the lower morning cortisol levels.

3.2.2 SES (socioeconomic status) and race

Cortisol waking responses were positively associated with high job demands, but this effect was attenuated by higher SES. Gender may also interact with SES and job demand, as over the remainder of the day were elevated in lower SES female participants who experienced high job demands (Kunz-Ebrecht, Kirschbaum, & Steptoe, 2004). In children, the basal salivary cortisol level in the morning was significantly higher in low family income, and this effect emerges at age 6 (Lupien, King, Meaney, & McEwen, 2000). Children from low family income may thus be at higher risk to not respond to psychostimulant medication, due to chronically elevated levels of cortisol.

Afro-American people also showed a higher evening salivary cortisol, and thus a flatter rhythm at the end of the day. This association was independent of SES and could not be explained by behavioral, social, or emotional mediators (Cohen et al., 2006). Conversely,

whites with higher education had a steeper awakening response as compared to other groups, after adjustment for relevant covariates (Bennett, Merritt, & Wolin, 2004).

Interactions have also been described between SES and gender: For example, cortisol concentration was greater in lower than higher grade men but was more elevated in higher than lower grade women, which may reflect the higher stress experienced by women in high-status occupation (Steptoe et al., 2003).

3.2.3 Sampling day and gender effect

Salivary cortisol levels on waking did not differ between work and weekend days. However, the cortisol awakening response (defined as the difference between waking and 30 min later) was greater on work than weekend days (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004; Thorn, Hucklebridge, Evans, & Clow, 2006) Although salivary cortisol levels on waking did not differ by gender, women showed a larger cortisol awakening response (defined as the difference between waking and 30 min later) on work days but not on weekend days (Bennett et al., 2004; Kunz-Ebrecht et al., 2004). The anticipation of the day could thus play a role in morning cortisol level and these findings could have lead to hypothesize that girls would be more likely to be non responders to stimulant treatment on stressful days since their morning cortisol would be increased compared to men. This is also true in lower primates, as a study in female monkeys showed that age had a significant effect on the diurnal pattern of cortisol so that older monkeys had lower morning cortisol levels and higher evening cortisol levels (Gust et al., 2000).

3.3 Cortisol reactivity

Cortisol reactivity is defined as the amount of cortisol secreted when faced with a stress. Like cortisol rhythm, cortisol reactivity is affected by many factors such as age, gender, race, and dopamine activity.

3.3.1 Cortisol reactivity: effect of age

In the newborn, the cortisol response to stressor is high from the first week of life up to 10-11 weeks. However, the cortisol response quickly habituates. A separation of 30 minutes from the parents in the presence of an unknown non engaging babysitter only produces small increase of cortisol at 9 months of age (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992), but by 13 months the cortisol increase was not significant (Gunnar & Nelson, 1994). Using immunization inoculation as standard stressors, cortisol responses were large in 2-to-6 month-infants, but by 12 months and up to 18 months, significant increases were no longer observed for most infants (Gunnar, Brodersen, Krueger, & Rigatuso, 1996). The dampening of the cortisol response is not tightly linked to the expression of emotional distress and does not decrease for the average toddler, 12- to 18-months of age. This dampening of the cortisol response seems to persist throughout toddlerhood and in preschool age. Mean cortisol values for 3-to 5-year old children during the early weeks in the nursery school were not elevated over levels obtained at home (Gunnar, Tout, de, Pierce, & Stansbury, 1997). This lack of overall cortisol reactivity should not hide individual differences that can be detected across different contexts. For example, the cortisol response in children with an insecure attachment and temperamentally fearful was larger at 15 months, than the average response of all 6-month-old infants (Gunnar et al., 1996). At 18 months, elevation of cortisol in the Ainsworth Strange Situation was only found for toddlers with insecure attachment (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Thus quality of care can prevent the cortisol rise in potentially stressful situations, even in children at risk, although the nature of the most important aspects of care for regulating children's cortisol response to challenge remains to be studied.

In rat, normally occurring differences in maternal care quality (as measured by the frequency of pup licking and grooming or LG) during the first week of life are associated with individual differences in the adult offspring. As compared to high LG mother,

offspring of low LG mother show increased HPA response to stress (Liu et al., 1997). The maternal effects on HPA response to stress partly depend on epigenetic programming of gene expression. The non-coding exon 1 region of the hippocampal glucocorticoid receptor (GR) includes a promoter region, exon I_7, containing a binding site for nerve growth factor-inducible protein A (NGFl-A, a transcription factor). In adult offspring of low LG mother, hypermethylation of exon I_7 GR contributes to the decrease in expression of GR, and hence in higher cortisol response to stress (Weaver et al., 2004). Increased level of cortisol reactivity is a potential adaptive advantage in an adverse environment. For example, adult offspring of low LG mother showed enhanced memory relative to offspring of high LG mother, but only when tested in a hippocampal-dependent, contextual fear-conditioning paradigm (Champagne et al., 2008). This epigenetic process imprints environmental experience on the fixed genome, resulting in stable alteration of the phenotype. Children inherit not only genes but also an environment. However, the signalling pathway that informs the genome on the level of environmental demand is mediated by the caring behaviour of the parent. The microenvironment of the parent-child relationship can also considerably alter the nature of the larger environment. The cost of this adaptation is the increase of the risk of stress-related disorders, brain-based or cardio-vascular and metabolic, especially in environment that require opposite adaptive strategies later in life.

By using the Trier Social Stress Test, the response pattern of free cortisol measure in saliva did not differ between children and younger adults and older adults (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004). However, in elderly humans, prolonged basal cortisol level correlate strongly with reduced hippocampal volume and deficits in hippocampus-dependent memory tasks (Lupien et al., 1998). Individual differences in hippocampal damage could thus emerge with age as a decrease in glucocorticoid receptor expression could be responsible for abnormal cortisol response (Nichols, Zieba, & Bye, 2001).

3.3.2 Gender and cortisol reactivity

ACTH and total plasma cortisol response using the Trier Social Stress Test appeared enhanced in younger men and decreased with age in men only. Younger females have a greater adrenal sensitivity to ACTH stimulation, but this effect could be accounted for by differences in corticosteroid binding globulin (CBG) and/or sex steroids, like estrogens. Women in the luteal phase have comparable saliva cortisol stress responses compared to men whereas women in the follicular phase or taking oral contraceptives show significantly lower free cortisol responses (Kudielka et al., 2004). This may account for fluctuations in responsiveness to methylphenidate treatment in adult ADHD.

3.3.3 SES (socioeconomic status) and race

Using the Trier Social Stress Test Caucasian participants showed a greater HPA axis response than Afro-American participants. These differences remain significant after adjustment for potential social and psychological confounders (Chong, Uhart, McCaul, Johnson, & Wand, 2008). However, such racial related difference are absent for cortisol response following physical stimuli, as exercise, at least in females (Giannopoulou, Carhart, Sauro, & Kanaley, 2003; Yanovski et al., 2000).

3.3.4 Individual difference in DA activity

In normal humans, usual therapeutic dose of methylphenidate (0.5 mg/kg) increased extracellular dopamine in the striatum (including the nucleus accumbens) by blocking the DAT transporter (Volkow et al., 2002). However, the level of DAT blockade by methylphenidate could not predict the DA increase; individual differences in DA neuron tonic firing rate are likely to be the main source of individual differences in DA methylphenidate-induced increase, and therapeutic effects (Volkow et al., 2002). There was also a significant association between methylphenidate induced DA increases in the

striatum and the interest and motivation for the task (Volkow et al., 2004) or the subject's expectation of a positive experience (Volkow et al., 2006). Individual difference in DA activity could thus modulate the antagonistic effect of high morning cortisol on the response to stimulants.

3.4. Interaction between dopamine and norepinephrine

Many neuroimaging and neuropsychological studies support the hypothesis of prefrontal cortex (PFC) abnormalities in ADHD. The PFC is an important brain structure for executive functions such as inhibition of the processing of irrelevant stimuli, sustaining attention over long delays, coordinating attention, all functions that were showed to be deficient in children with ADHD and responsible for their symptoms. DA modulated PFC functions through D1 (D1, D5) and D2 (D2, D3, D4) families of dopamine receptors. D1 dopamine receptor agonists infused in the PFC of rats produces an inverted U dose-response curve on their ability to sustain and divide attention (Granon et al., 2000) or keep spatial information in working memory (Zahrt, Taylor, Mathew, & Arnsten, 1997). Using spatial working memory task, modest levels of D1 agonist suppressed delay-related firing for nonpreferred spatial directions (i.e., increased "spatial tuning" and decreased "noise") at a cellular level. On the contrary, higher levels of D1 stimulation reduced delay-related firing for all directions, eroding spatial tuning (Williams & Goldman-Rakic, 1995; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). D1 receptors are also critical for spatial working memory performance in humans (Muller, von Cramon, & Pollmann, 1998).

As for dopamine, modest levels of NE are critical to proper PFC functions and high levels released during stress are impairing PFC functions. Postsynaptic alpha-2A adreno-receptors (and not presynaptic receptors reducing NE release as previously thought) mediate the enhancing effects of alpha2-agonist on PFC functions. Alpha-2A agonist guanfacine improves both lateral and ventro-medial prefrontal cortex functions, and thus potentiates

both sensory-motor and emotional responses. In contrast to D1 agonist that decreased noise, NE alpha2A agonist increased delayed-related firing for the preferred spatial direction (i.e., increased signal). Pyramidal cells of the PFC form reverberating microcircuits through mutual connection for axons to the dendritic spines of neurons sharing the same spatial preferences. Stimulation of alpha-2A adreno-receptors inhibits the production of cAMP through G-couple receptors, which closes Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels and increase the efficacy of synaptic input, strengthening the functional connectivity of PFC microcircuits (Wang et al., 2007). At the opposite high level of stimulation of G-couple D1 receptors would activate cAMP production, open HCN channels and shunt synaptic input, rendering the PFC functionally disconnected (Vijayraghavan et al., 2007).

In contrast to the enhancing effects of modest levels of NE, higher levels of NE (e.g., during stress) impair PFC function and this impairment is mediated by alpha1-adrenoreceptors. Alpha1-adrenoreceptors are coupled to G proteins that activates phospholipase C (PLC) releasing diacylglycerol (DAG) which subsequently binds to and activates protein kinase C (PKC). Thus NE indirectly activates PKC. High levels of PKC activity in prefrontal cortex, as seen for example during stress exposure, markedly impair behavioral performance in a working memory test and decreased delayed related activity for the preferred spatial direction (Birnbaum et al., 2004). Lithium and valproate are common treatments for patients with bipolar disorder. Although disparate in many of their actions, both agents attenuate PKC activity; both lithium and valproate protected prefrontal cortical cognitive function from alpha1 adrenergic receptor-induced impairment (Birnbaum et al., 2004). Most atypical antipsychotic also are potent alpha1 receptor blockers. At dose that reduce locomotor activity in male Sprague-Dawley rats, methylphenidate produces a substantial increase of NE and DA efflux within the PFC, (Berridge et al., 2006) and the hippocampus (Kuczenski & Segal, 2002), but not in other regions of the brain, especially not in the nucleus accumbens. This may be explained by the efficient uptake of DA by the

NE transporter in the PFC, similar to the efficiency of NE uptake (Bymaster et al., 2002). α2 antagonist and the D1 antagonist were able in male rats to reverse the cognitive enhancing effects of methylphenidate in the spatial delayed alternation task (Arnsten & Dudley, 2005). Methylphenidate may thus improve performance by increasing the availability of NE and DA in the PFC, which in turn stimulate α2 and D1 receptors.

3.5. Interaction between NE and cortisol

Animal studies (McGaugh, 2004) have shown that the amygdala (especially the basolateral complex of the amygdala) mediates the memory-modulating effects of adrenal stress hormones. The availability of NE in the amygdala appears to be a prerequisite for this effect. To examine this interaction NE-cortisol interaction in humans, a group of healthy subjects were shown emotional stimulating images. Results showed that endogenous cortisol level interacted with Ne activation within the amygdala. Subjects with high cortisol levels showed significantly more amygdala activation during emotional pictures than in the low cortisol group. Hence a significant interaction of the endogenous cortisol with the activation of the amygdala was proven. Emotional stimuli lead to activation of the amygdala, an effect that is Ne dependent (van Stegeren et al., 2007). Thus, endogenous cortisol amplifies the noradrenergic effect in humans. This interaction can also be studied in patients treated for ADHD with noradrenergic drugs.

Clonidine (Catapres®) is an alpha2-agonist that has been used off label as a potential treatment for ADHD. It has relatively high affinity for the three subtypes of alpha2 adrenoreceptors (A, B, C). All three subtypes are found on the post-ganglionic sympathetic neurons. The hypotensive effect is likely to be due to stimulation of post-synaptic alpha2-adrenoreceptors of inhibitory neurons within the caudal ventro-lateral medulla in the brainstem. The sedative effects arise from various effects, including presynaptic alpha2A and alpha 2C autoreceptors on locus coeruleus neurons as well as postsynaptic receptors throughout the cortex and in the thalamus (alpha2B). Clonidine is used to treat not only

ADHD symptoms, but also tic and explosive behaviours. As the more common side effects are sedation, hypotension and dizziness, many physicians are also prescribing clonidine at bedtime for its sedative effects. In combination with methylphenidate, clonidine was well tolerated in children with ADHD only (Tourette's Syndrome Study Group, 2002) or with ADHD and tics (Palumbo et al., 2008; Daviss et al., 2008). Clonidine was supposed to decrease the severity of the tics through activation of adrenergic receptors and negative feedback on the HPA axis. The same reasoning could be applied to guanfacine (Tenex®), another alpha2-agonist that could be used in the treatment of ADHD (Posey & McDougle, 2007). Guanfacine is much less sedating than clonidine, and its pre-synaptic inhibition of NE release in locus coeruleus neurons is also much weaker. However, the use of alpha2-agonist was limited by the need to re-dose throughout the day. On June 24, 2007, the U.S. Food and Drug Administration (FDA) gave an approval letter for Intuniv (guanfacine) extended release tablets. The combination of guanfacine IR and a stimulant has not yet been evaluated.

The involvement of brain catecholamine in the regulation of the pineal gland hormone secretion, especially through the action of alpha-adrenergic agonist has long been recognized. The clonidine test has been proposed in 1979 to test for the growth hormone reserve in children evaluated for short stature (Gil-Ad, Topper, & Laron, 1979). In children, 30 minutes after oral administration of clonidine, ACTH and cortisol decreased in the plasma reaching lowest values at 90 min. This suggests the existence of alpha2-adrenergic receptors in the pineal gland, as in lower vertebrates, and an inhibitory alpha2-adrenergic influence on the HPA axis (Munoz-Hoyos et al., 2000). The same effect is observed using guanfacine (Dura et al., 1996).

Atomoxetine is a selective inhibitor of norepinephrine reuptake transporter (SNRI) and constitutes a non-stimulant alternative in the treatment of ADHD. Norepinephrine reuptake inhibitor atomoxetine blocks the transporters, which causes accumulation of endogenous

NE, which in turn leads the alpha2-adrenoreceptor to shut down firing activity. The administration of atomoxetine in healthy male volunteers also led to significant increases in salivary cortisol. The time course of the response corresponded to approximately the pharmacokinetics of the drug, peaking 1 to 2 hours after oral dosing. Thus, norepinephrine is thought to augment HPA axis function by increasing CRF secretion in the paraventricular nucleus of the hypothalamus (Chamberlain, Muller, Cleary, Robbins, & Sahakian, 2007). The findings are consistent with previous studies (Nutt, Middleton, & Franklin, 1987) that used other less selective NE reuptake inhibitors such as tricyclic antidepressants (desipramine, imipramine, clomipramine, maprotiline). Reboxetine is a novel antidepressant drug that selectively inhibits norepinephrine reuptake, with a very similar pharmacological profile to atomoxetine. It also has been showed to be effective and safe in the long-term treatment of ADHD (Toren et al., 2007). A transient increase in ACTH and cortisol release after acute administration of reboxetine was observed in healthy volunteers (Schule et al., 2004) or in volunteer scoring high for depression but not clinically depressed (Hennig, Lange, Haag, Rohrmann, & Netter, 2000). This increase is likely caused by enhancing NE concentration and stimulating CRH via hypothalamic alpha1-adrenoreceptors. However, the long-term effects of norepinephrine reuptake inhibitor (NRIs) appeared opposed to the acute effects. In patients treated for major depressive episode with reboxetine, the combined dexamethasone suppression/corticotrophin releasing hormone challenge showed that HPA axis decreased in activity. This decreased was largest after 5 weeks of treatment, especially in the patients who showed a clinical response to the treatment (Schule et al., 2006). The results also showed a significant decrease in the baseline level of cortisol, before the CRH injection.

3.6. Interaction between cortisol and serotonin

Stress is an important precipitant factor in depression, and many changes that occur in depression are similar to those observed in response to stress .Many symptoms of ADHD are overlapping with symptoms found in depression, such as the inability to concentrate, or

impulsiveness. In addition many mood symptoms are usually found in children with ADHD such as emotional lability. Mood and anxiety disorder are also frequently comorbid with ADHD, as well as mood symptoms of Oppositional Defiant Disorder (touchy and easily annoyed, angry and resentful, loses temper). Serotoninergic neurons in the dorsal raphe nuclei do not increase firing rate in response to stress, but the synthesis and outflow of 5-HT increases in the raphe and its projections area (for a review see (Lanfumey, Mongeau, Cohen-Salmon, & Hamon, 2008). This effect seems to be mediated by the stimulatory influence of adrenal steroid hormones on tryptophan hydroxylase, and hence on 5-HT turn-over (Singh, Corley, Phan, & Boadle-Biber, 1990).

On the other hand, 5-HT receptors are central to the antidepressant effects of serotonin selective reuptake inhibitors (SSRIs). SSRIs by blocking 5-HT reuptake produce an increase in brain levels of extracellular 5-HT within minutes following their administration. However, this increase in cancelled by the negative feedback mediated by the activation of 5-HT1A autoreceptors at the 5-HT cell body/dendrite level in the dorsal raphe nuclei. However, after prolonged SSRI treatment, 5-HT1A autoreceptors desensitize, which inactivates the 5-HT inhibitory feedback control. Extracellular 5-HT concentration raises markedly as in projection areas of 5-HT fibres, In turn this change has an effect on cortisol levels. Increase in plasma cortisol after two hours was observed in healthy volunteers after a single dosage of 20 mg of the SSRI citalopram, as compared to the placebo condition (Chamberlain et al., 2007; Hennig & Netter, 2002) or after receiving 20 mg of the SSRI paroxetine (Kojima et al., 2003). Another study tested the effect of oral citalopram but on salivary cortisol levels in healthy volunteers. The results demonstrated an increase in salivary cortisol and hence an increase in HPA activity (Nadeem, Attenburrow, & Cowen, 2004). However, a gradual downregulation of HPA axis hyperactivity was demonstrated by serial Dexamethasone/CRH tests in depressed patients treated with the SSRI paroxetine (Nickel et al., 2003).

3.7 Other predictors of the response to methylphenidate

In addition to the interaction between the HPA axis and the different medication used to treat children with ADHD, genetic factors may play a role in difference in the clinical response. For example, twice higher doses were required for symptom improvement for children possessing a DRD4 7R allele, a common polymorphism found in 44.4% of the sample (Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004). An excess transmission of DRD4-7 allele was also more likely in methylphenidate responders than in non responders, as defined in an open titration procedure (Tahir et al., 2000). A positive but not significant trend was found between the presence of one or two DRD4 7 repeat allele and a higher response rate of methylphenidate, as reported by parents during treatment (van der Meulen et al., 2005). However, in Korean children where the 7 repeat allele is rare, it is the 2-repeat allele at DRD4 that may be associated with poor outcome of methylphenidate treatment, while the children homozygous for the 4-repeat allele showed a better response (Cheon, Kim, & Cho, 2007). However, no association between the 48-bp VNTR polymorphism at the D4 dopamine receptor (DRD4) and response to methylphenidate have also been reported (Zeni et al., 2007; Winsberg & Comings, 1999).

Other clinical characteristics may also influence the response to stimulant medication is increased at younger age and when symptoms (Efron, Jarman, & Barker, 1997; Gray & Kagan, 2000) or cognitive deficits, especially inhibitory control or attention (Barkley, 1976), are more severe before treatment, although the relations are weak. Age and severity are not independent as ADHD symptoms and associated deficits tend to decrease with age. However, the better response at younger age may not hold for children below the age of 6. In preschool-age children, the effect size of stimulant medication is smaller than for school-age children, the optimal dosage lower (Greenhill et al., 2006) and adverse effect of stimulant more frequent (Wigal et al., 2006). With regard to severity, it should be stressed that response to stimulant is also lower in children with comorbid conditions (DuPaul, Barkley, & McMurray, 1994; Ghuman et al., 2007; MTA Cooperative Group, 1999; Owens

et al., 2003). In order to predict a better response, severity might have to be restricted to ADHD symptoms. Among the Multimodal Treatment Study of Children with ADHD participants, those diagnosed with the ICD-10 criteria for Hyperkinetic Disorder (i.e., no anxious or depressive comorbidities; symptom threshold met for hyperactivity, impulsiveness and inattention; pervasiveness across school and home setting, and impairment endorsed) responded better to medication than those with ADHD failing to meet these ICD-10 more stringent criteria (Santosh et al., 2005). The predictive power of symptom severity may not always be unequivocal. ADHD symptom severity was showed to predict a poorer not a better response, but only in those children with a parent afflicted with a relatively high level of depressive symptoms (Owens et al., 2003). Similarly, if ADHD-specific cognitive deficits predicted a better response to stimulant, broader deficits captured by an IQ below 50 were associated with a less favourable response to MPH (Aman, Buican, & Arnold, 2003). Beyond clinical characteristics, some physiological measures have been tested as predictor of the response to stimulant. Homovanillic acid (HVA) is the major dopamine metabolite. Its cerebrospinal fluid concentration has been showed to be correlated with the rating of hyperactivity and with the response to stimulant: higher HVA predicted a modest portion (up to 25% on some measures) of better drug response (Castellanos et al., 1996).

3.8 Clinical implications

This review of the interaction between the cortisol secretion and the various ADHD drug suggest that the NE and DA interacting systems are involved in treating the ADHD symptoms. The efficacy of the different types of drugs may differ according to the balance between these systems have in the expression of the ADHD symptoms. To summarize, the dopamine is crucial for creating habit memories in striatal loops though a reward brain circuit which is the basis for motivated behaviours. Norepinephrine plays a crucial role in a less enduring form of memory creation: working memory which depends primarily on the prefrontal cortex and maintains information in a temporary buffer that is constantly updated

according to cognitive demand. Executive functions depend critically on working memory which is the basis for an interactive aroused behaviour. NE cells of the locus coeruleus fire according to levels of arousal, with low levels of both tonic and phasic firing under drowsy conditions, moderate tonic firing and clear phasic firing in response to relevant stimuli when animals are alert, and high tonic firing and poor phasic firing when animals are stressed (Aston-Jones & Cohen, 2005). Similarly DA cells in the ventral tegmental area may fire according to the level of motivation, with low levels of both tonic and high phasic firing under non motivating state, with interest for irrelevant stimuli, moderate tonic firing and clear phasic firing in response to relevant stimuli when the subject is motivated, and high tonic firing and poor phasic firing when animals are too strongly motivated and stressed.

The medications used to treat ADHD symptoms modulate the firing balance of the DA and NE cells. Methylphenidate may thus improve performance by increasing the availability of NE and DA in the PFC, which in turn stimulate alpha2 and D1 receptors. But methylphenidate also increases extracellular dopamine in the striatum (including the nucleus accumbens) by blocking the DAT transporter. By increasing the tonic rate of DA cell, methylphenidate improves the motivational state, decreasing irrelevant responding and enhancing the interest of the relevant behaviors. When the motivational factors are relevant for the expression of ADHD symptoms, subjects are likely to respond well to stimulant medication. However, if a chronically high level of stress is the most relevant factor in the expression of ADHD symptoms (impairing executive functions), methylphenidate may have a reduced therapeutic effect. In fact it may even have a negative effect if the tonic activation of alpha2 and D1 receptors is already increased. A high level of cortisol would be a marker of a chronically elevated stress level. This would explain why children with high morning cortisol were more likely to be classified as non responders. NE medication may be a better choice, as they would reduce NE cell tonic firing in the locus coeruleus and restore a normal and more adapted level of alertness. Long term treatment may also

desensitize the HPA axis and restore a normal diurnal rhythm of cortisol. This normalization of the stress level could in turn restore the effect of methylphenidate on the motivational state, as NRI (especially atomoxetine) do not change DA level in the striatum (Bymaster et al., 2002).

It is thus possible that alpha2 adrenergic drug could potentiate the effect of methylphenidate in those with a high level of morning cortisol. A long term treatment using atomoxetine could also be an alternative in order to decrease the HPA axis activity and restore the responsiveness to stimulant if necessary. Other NRIs such as tricyclic antidepressants (desipramine, imipramine, clomipramine, maprotiline) are likely to have the same effect. Although selective serotonin reuptake inhibitors are not effective in decreasing ADHD symptoms, augmenting stimulant treatment with SSRI could also potentiate the effect of stimulant medication, through desensitizing the HPA axis.

Beyond the capacity to predict the response to stimulant, these results point to the heterogeneity of ADHD and the need to better define the symptoms, by including more systematic assessment of what is considered nowadays as side effect of the medication but are likely to be further defined as part of the ADHD symptoms. It is also important to better define the co-mordid conditions, especially stress-related disorder, as some but not all of them may hinder the efficacy of the treatment. High doses of stimulant may be beneficial for children with ADHD and with a high level of cortisol reactivity or with ADHD and some forms comorbid anxiety disorders, characterized with low levels of both tonic and phasic firing. Maternal depression increases the vulnerability of depression in children, and increases the risk of HPA dysregulation. Maternal depression is likely to contribute to poor response to treatment both through psycho-social and biological mechanisms. A depressed mother is less likely to be able to meet all the organizational challenges of the treatment but may also induce a biological resistance to treatment, though increased HPA axis activity. Therefore, depression should be assessed in the mothers of children with ADHD as an

important determinant of the outcome. Depression should be assessed in children with ADHD to differentiate some symptoms that are caused by underlying depression undiagnosed and not caused by methylphenidate, such as psychomotor retardation.

Further, biological measures could also become part of the assessment of children with ADHD in order to assess the level of activity of NE and DA brain pathways. Although much work is needed before any firm conclusion could be drawn, morning salivary cortisol or ACR could become part of the assessment of children with ADHD and help diagnosing subtype and orient treatment. This would allow more individualized and potent treatment.

3.9 Limitations of the present study:

The protocol stated that the morning saliva sample should be taken 15 minutes after awakening. However, some variability could have occurred in the exact timing of the saliva collection by the parents and we cannot exclude that the sample also reflect the awakening cortisol response. It is necessary to replicate the study with at least three samples in order to differentiate the morning level of cortisol and the cortisol response to awakening. It would be also important to have cortisol sample during the titration trials and in the maintenance phase, once the child is on the optimal dosage, in order to understand the acute and long term effects of stimulant both in responders and non responders. Previous result have suggested that cortisol level are not affected by long term treatment with stimulants, but this has to be examined as a function of the initial cortisol morning level and response to stress. Age is also a factor that has to be controlled. In this study, the blood draw was used as a psychological stressor. It would be interesting to use another psychological stressor such as the Trier Social Stress Test to compare the results obtained with a physical stressor.

4. Conclusion

In conclusion, we studied the association of salivary cortisol upon waking and stress cortisol with the outcome of treatment of ADHD using methylphenidate. Venipuncture was the stress used to increase cortisol level.

The results suggest that children with high morning cortisol are treatment resistant to methylphenidate. Morning cortisol might be a reliable marker for a depression endophenotype, which would predict a lack of response to stimulant. A greater benefit of a high dose of methylphenidate was observed for the high stress reactivity group but not the low stress reactivity group. Also, the presence of anxiety disorders comorbid with ADHD was related to a greater benefit from going to a high dose of methylphenidate.

The results of this study stress the relation between ADHD, mood and anxiety disorder. The activity of the HPA axis might be used to separate the children with ADHD in subgroups with different response to medication affecting either dopamine or norepinephrine.

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DATE:_____/_____/_____
(jour/mois/année)

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SWAN – VERSION COURTE - ENSEIGNANT

Cocher les cases correspondants à la journée et la semaine de l'évaluation**:**

☐ Lundi ☐ Mardi ☐ Mercredi ☐ Jeudi ☐ vendredi.

☐ Pré-test ☐ Semaine 1 ☐ Semaine 2 ☐ Semaine 3 ☐ Semaine 4.

		Beaucoup en dessous de la moyenne	En dessous de la moyenne	Un peu en dessous de la moyenne	Dans la moyenne	Un peu au -dessus de la moyenne	Au-dessus de la moyenne	Beaucoup au-dessus de la moyenne	Ne s'applique pas
1	Est capable de se mettre d'accord avec les adultes.	-3	-2	-1	0	1	2	3	9
2	Est capable de s'amuser calmement (dans les jeux ou les activités de loisirs).	-3	-2	-1	0	1	2	3	9
3	Est capable de s'organiser dans ses travaux ou ses activités.	-3	-2	-1	0	1	2	3	9
4	Est capable de s'arrêter et de rester tranquille.	-3	-2	-1	0	1	2	3	9
5	Est capable de garder son sang froid, de rester calme.	-3	-2	-1	0	1	2	3	9
6	Selon le contexte, est capable de rester assis sans se lever (en classe ou ailleurs).	-3	-2	-1	0	1	2	3	9
7	Est capable de se joindre sans s'imposer à une conversation ou à un jeu.	-3	-2	-1	0	1	2	3	9
8	Reconnaît la responsabilité de ses erreurs et de ses mauvaises conduites.	-3	-2	-1	0	1	2	3	9
9	Écoute quand on lui parle personnellement.	-3	-2	-1	0	1	2	3	9
10	Est capable de faire attention aux détails et d'éviter de faire des fautes d'étourderie.	-3	-2	-1	0	1	2	3	9

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11	Est capable de suivre les consignes et de terminer ses devoirs/tâches.	-3	-2	-1	0	1	2	3	9
12	Est capable d'oublier sa rancune et de ne pas vouloir se venger.	-3	-2	-1	0	1	2	3	9
13	Est capable de veiller sur les choses nécessaires à son travail (livres, crayons, etc.) ou à ses activités (jouets, etc.).	-3	-2	-1	0	1	2	3	9
14	Ne se laisse pas froisser, vexer ou ennuyer par les autres.	-3	-2	-1	0	1	2	3	9
15	Ne se sent pas victime d'injustice et contrôle sa colère.	-3	-2	-1	0	1	2	3	9

		Beaucoup en dessous de la moyenne	En dessous de la moyenne	Un peu en dessous de la moyenne	Dans la moyenne	Un peu au -dessus de la moyenne	Au-dessus de la moyenne	Beaucoup au-dessus de la moyenne	Ne s'applique pas
16	Est capable de soutenir son attention au travail ou dans les jeux.	-3	-2	-1	0	1	2	3	9
17	Est capable d'entreprendre des tâches qui nécessitent un effort mental soutenu (à l'école ou à la maison).	-3	-2	-1	0	1	2	3	9
18	Dans la vie quotidienne, est capable de retenir ce qu'on lui dit ou ce qu'il doit faire.	-3	-2	-1	0	1	2	3	9
19	Selon le contexte, est capable de se retenir de courir ou de grimper, (n'a pas "des fourmis dans les jambes").	-3	-2	-1	0	1	2	3	9
20	Évite de faire délibérément des choses qui pourraient fâcher les autres.	-3	-2	-1	0	1	2	3	9
21	Est capable de se concentrer, de ne pas se laisser distraire par des stimuli externes.	-3	-2	-1	0	1	2	3	9

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22	Attends qu'une question soit entièrement posée avant d'y répondre.	-3	-2	-1	0	1	2	3	9
23	Accepte de suivre les règles et de répondre aux demandes des adultes.	-3	-2	-1	0	1	2	3	9
24	Est capable de rester assis sans s'agiter, en contrôlant les mouvements de ses mains et ses pieds.	-3	-2	-1	0	1	2	3	9
25	Quand il parle, est capable de régler son débit suivant le contexte.	-3	-2	-1	0	1	2	3	9
26	Est capable d'attendre son tour	-3	-2	-1	0	1	2	3	9

IMPORTANT : Y aurait-il un évènement de la journée qui aurait pu influencer le comportement de l'enfant aujourd'hui? ☐ NON ☐ OUI, lequel : _____

_____

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DATE:_____/_____/_____
(jour/mois/année)

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SWAN – VERSION COURTE - PARENT

Veuillez indiquer qui complète le questionnaire :

☐ mère ☐ père ☐ tuteur légal ☐ autre (spécifier :_____)

Cocher les cases correspondants à la journée et la semaine de l'évaluation:

☐ Lundi ☐ Mardi ☐ Mercredi ☐ Jeudi ☐ Vendredi ☐ Samedi ☐ Dimanche.

☐ Pré-test ☐ Semaine 1 ☐ Semaine 2 ☐ Semaine 3 ☐ Semaine 4.

		Beaucoup en dessous de la moyenne	En dessous de la moyenne	Un peu en dessous de la moyenne	Dans la moyenne	Un peu au -dessus de la moyenne	Au-dessus de la moyenne	Beaucoup au-dessus de la moyenne	Ne s'applique pas
1	Est capable de se mettre d'accord avec les adultes.	-3	-2	-1	0	1	2	3	9
2	Est capable de s'amuser calmement (dans les jeux ou les activités de loisirs).	-3	-2	-1	0	1	2	3	9
3	Est capable de s'organiser dans ses travaux ou ses activités.	-3	-2	-1	0	1	2	3	9
4	Est capable de s'arrêter et de rester tranquille.	-3	-2	-1	0	1	2	3	9
5	Est capable de garder son sang froid, de rester calme.	-3	-2	-1	0	1	2	3	9
6	Selon le contexte, est capable de rester assis sans se lever (en classe ou ailleurs).	-3	-2	-1	0	1	2	3	9
7	Est capable de se joindre sans s'imposer à une conversation ou à un jeu.	-3	-2	-1	0	1	2	3	9
8	Reconnaît la responsabilité de ses erreurs et de ses mauvaises conduites.	-3	-2	-1	0	1	2	3	9
9	Écoute quand on lui parle personnellement.	-3	-2	-1	0	1	2	3	9

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10	Est capable de faire attention aux détails et d'éviter de faire des fautes d'étourderie.	-3	-2	-1	0	1	2	3	9
11	Est capable de suivre les consignes et de terminer ses devoirs/tâches.	-3	-2	-1	0	1	2	3	9
12	Est capable d'oublier sa rancune et de ne pas vouloir se venger.	-3	-2	-1	0	1	2	3	9
13	Est capable de veiller sur les choses nécessaires à son travail (livres, crayons, etc.) ou à ses activités (jouets, etc.).	-3	-2	-1	0	1	2	3	9
14	Ne se laisse pas froisser, vexer ou ennuyer par les autres.	-3	-2	-1	0	1	2	3	9
		Beaucoup en dessous de la moyenne	En dessous de la moyenne	Un peu en dessous de la moyenne	Dans la moyenne	Un peu au -dessus de la moyenne	Au-dessus de la moyenne	Beaucoup au-dessus de la moyenne	Ne s'applique pas
15	Ne se sent pas victime d'injustice et contrôle sa colère.	-3	-2	-1	0	1	2	3	9
16	Est capable de soutenir son attention au travail ou dans les jeux.	-3	-2	-1	0	1	2	3	9
17	Est capable d'entreprendre des tâches qui nécessitent un effort mental soutenu (à l'école ou à la maison).	-3	-2	-1	0	1	2	3	9
18	Dans la vie quotidienne, est capable de retenir ce qu'on lui dit ou ce qu'il doit faire.	-3	-2	-1	0	1	2	3	9
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20	Évite de faire délibérément des choses qui pourraient fâcher les autres.	-3	-2	-1	0	1	2	3	9

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21	Est capable de se concentrer, de ne pas se laisser distraire par des stimuli externes.	-3	-2	-1	0	1	2	3	9
22	Attends qu'une question soit entièrement posée avant d'y répondre.	-3	-2	-1	0	1	2	3	9
23	Accepte de suivre les règles et de répondre aux demandes des adultes.	-3	-2	-1	0	1	2	3	9
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26	Est capable d'attendre son tour	-3	-2	-1	0	1	2	3	9

IMPORTANT : Y aurait-il un évènement de la journée qui aurait pu influencer le comportement de l'enfant aujourd'hui? ☐ NON ☐ OUI, lequel : _____

_____

_____

French Version of the Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors (SWAN-F) Questionnaire

Philippe Robaey MD, PhD[1,2]; Devendra Amre MBBS, PhD[1,4]; Russell Schachar MD[5]; Louise Simard PhD[1,4]

Abstract

Objective: To evaluate internal and external consistency of a French adaptation of the SWAN (a 7-point rating strength-based scale, from far below to far above average) and its accuracy as a diagnostic test among children with Attention Deficit/Hyperactivity Disorder (ADHD). **Method:** Parents of 88 children referred for ADHD were interviewed using the SWAN-F, a structured interview (DISC-4.0) and the Conners' Rating Scale. Internal consistency and divergent and convergent validity of the SWAN-F were examined using the DISC-4.0 and Conners' Rating Scales as reference standards for four dimensions: Inattention, Hyperactivity/Impulsivity, ADHD, Oppositional Defiant Disorder. **Results:** The internal consistency of SWAN-F was within acceptable ranges for all dimensions (Cronbach's alpha greater than 0.80). Scores of the SWAN-F subscales were strongly associated with the DISC-4.0 diagnostic assignments and Conners' Rating Scales, following logical patterns of correspondence between diagnoses. Its accuracy as a diagnostic test was comparable to Conners' Rating Scale, with a lower rate of false positives. **Conclusions:** The information gathered with the SWAN-F is compatible with that obtained using the DISC-4.0 and Conners' Rating Scale. Strength-based rating scales have the potential to evaluate the normal distribution of behaviors and to provide reliable cut-off defining abnormal behavior.

Key words: Pharmacogenetic, Attention Deficit/Hyperactivity Disorder, Methylphenidate Treatment

Résumé

Introduction: Évaluer la cohérence du questionnaire SWAN-F lorsqu'il est administré à des enfants atteints de trouble du déficit d'attention avec hyperactivité (TDAH). **Méthodologie:** Les parents of 88 enfants qui ont reçu un diagnostic de TDAH ont rempli le SWAN-F, le DISC-4.0 et l'échelle d'évaluation Conners. Les sous-échelles du SWAN-F étaient basées sur une cotation en sept points qui classait les symptômes du DSM-IV de « nettement inférieurs à la moyenne » à « nettement supérieurs à la moyenne » chez des enfants d'âge identique. La cohérence, la validité discriminante et la validité convergente du SWAN-F ont été analysées au moyen du DISC4.0 et des échelles d'évaluation Conners qui ont servi de référence pour quatre dimensions: inattention, hyperactivité/impulsivité, TDAH, trouble oppositionnel. **Résultats:** Pour toutes les composantes du SWAN-F, la consiistence interne se situaient dans la zone acceptable (le coefficient alpha de Cronbach était supérieur à 0,80). Les scores des sous-échelles du SWAN-F étaient fortement associés avec les diagnostics du DISC4.0 et aux scores de l'échelle d'évaluation Conners, correspondant logiquement aux diagnostics. **Conclusions:** Les données recueillies au moyen du SWAN-F sont compatibles avec celles obtenues au moyen du DISC-4.0 et de l'échelle d'évaluation Conners. Les échelles basées sur l'évaluation des forces pourraient être utilisées pour l'évaluation quantitative des symptômes dans les études longitudinales et génétiques et pour mesurer la réponse au traitement.

Mots clés: pharmacogénétique; trouble du déficit d'attention avec hyperactivité; traitement au méthylphénidate

Introduction

Most clinical rating scales quantify behaviors on a Likert scale anchored by standard descriptors, e.g., going from "never" to "very often", through "sometimes" and "often". When a weakness frequency (or intensity) is rated beyond "normal" limits, it becomes a symptom. Symptoms can thus be observed in subjects considered as healthy, as long as their number is beyond threshold and as long as they do not cause a significant impairment. For example, each ADHD behavioral descriptor has to be inappropriate for the child developmental level to be considered as a symptom. The diagnosis requires a symptom count above threshold and the associated impairment must be clinically significant, not specific to a situation (American Psychiatric Association, 1994). Normal variability is thus crucial at each level of the diagnosis process. However, in a pathological perspective, normality is only defined by an absence or a low level of symptoms. This perspective creates problems as the distributions of symptoms are highly skewed and truncated in the normal population and as statistical cutoffs are generally based on the assumption of a normal distribution. For example, in an epidemiological sample, nearly 80% of children had scores of 1 or 0 (Just a Little or Not at All) for the ADHD items of the SNAP-IV. As a consequence, small changes in

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Submitted: February 21, 2007; Accepted: May 3, 2007

cutoffs can have quite dramatic effect in the number of children above threshold (Swanson et al, 2005). Conversely, patients who show a low but near-threshold level of symptoms are defined as in remission. As it is not possible to determine where these children are placed within the normal distribution before and after treatment, therapeutic effects could also be overestimated.

These problems led some researchers to propose full-range rating scales. For example, Waschbusch and Sparkes (2003) designed an ADHD rating scale based on the assumption that symptoms can be rated below or above "normal" level. For example: "Does not seem to listen when spoken to directly" is rated with five anchor points from "much less" to "much more" than other (normal) children of the same age and sex. This attempt to break down the "Just a Little" and "Not at All" rating into categories from "much less" to "less" to "same" yielded a more normal distribution, although still negatively skewed, the "much less" rating being significantly overrepresented, especially in teacher ratings. Also, the proportion of children rated as "more" or "much more" symptomatic was strongly decreased (Waschbusch & Sparkes, 2003). Such a symptom-based full-range scale has the inherent difficulty of evaluating the relative rate of occurrence of behavioral descriptors that are by definition infrequent. A "much less" rating is also quite broad as it encompasses different levels of the corresponding strength. On the other side, evaluating the opposite strengths is likely to be easier and more reliable, as parents and teachers observed them much more frequently and generally define a weakness as a lack of strength.

The SWAN (Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors ratings Scale - SWAN) is a scale where the informant is asked to assess the strength opposite to the ADHD symptoms (Swanson et al, 2005). Without changing the content, each item of the SNAP-IV rating scale (Swanson et al, 2001) was re-worded in order to capture the strength corresponding to the weakness. For example: "Often does not seem to listen when spoken to directly" becomes "Listen when spoken to directly" and is rated from "far below average" (-3) to "far above average" (+3) relative to children of the same age. This approach yielded a normal distribution of ADHD scores (Hay et al, 2007) with a small positive skewness, the above average rating being somewhat overrepresented. The proportion of children rated as symptomatic (below and far below average) was also decreased.

The objectives of this study was to test internal and external consistency of a French adaptation of the SWAN and its accuracy as a diagnostic test, by using a symptom-based interview (DISC-4.0) and different problem-based scales (Conner's Parent and Teacher Rating Scale) in a sample of children referred for ADHD in a university-based specialized clinic in Montreal, Canada.

Methods

Participants

Children of 6-9 years of age (n=124) referred by their physicians with a suspected diagnosis of ADHD were recruited through the Interdisciplinary Research Program on Hyperactivity at Sainte-Justine Hospital (Montreal, Canada). Children with an IQ of less than 80 (Wechsler, 1991), born prematurely (<35 weeks of gestation), with severe learning or language disabilities and with neurological diseases (e.g. epilepsy) were excluded. Following Ethics Board approval, informed consent was obtained from all participating families.

Measures

DISC-4.0: During the scheduled hospital visit, the parent was administered a structured computerized interview, the Diagnostic Interview Schedule for Children 4.0 (DISC-4.0), by a trained interviewer. The DISC-4.0 has been translated into French by two independent research teams in Montreal. These French versions have been compared systematically and standardized to build the DISC-4.0 version used in this study. The French DISC-4.0 has not been specifically validated, but the test-retest reliabilities of the English version of the DISC-4.0 (Shaffer et al, 2000) and of the previous French version (DISC2.3) (Breton et al, 1998) are considered satisfactory. Diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD) were obtained from the

DISC-4.0 computerized algorithms. The presence (or not) of each ADHD symptom and the number of positive symptoms rated with the DISC-4.0 were evaluated.

SWAN-F: The original SWAN is based on the DSM-IV criteria and is available through http://www.adhd.net/. In the SWAN, symptoms from the DSM-IV criteria list were reworded using a strength-based formulation; for example, "often has difficulty sustaining attention in tasks or play activities" was modified to "is able to sustain attention in tasks or play activities". We adapted the SWAN, as the original version retained some symptom-based explanations and translated it in French (using a back-translation): see appendix. The SWAN-F includes the items for the DSM symptoms for Inattention (9 items), Hyperactivity/ Impulsivity (9 items), Oppositional Defiant Disorder (8 items) but not the 3 additional "sluggish tempo" items and a 30th item "Avoid quarrelling" of the downloadable SWAN. Three Conduct Disorder items and 5 prosocial items were also included, but not analyzed.

The SWAN-F items are scored according to a seven-point scale ranging from "far below average" (-3) to "far above average" (+3) relative to children of the same age, a score of 0 is "in the average". For each child, scores for SWAN-F Inattention (S-IN scores) and Hyperactivity/Impulsivity (S-HY/IM scores) subscales were calculated as the average of the ratings obtained for the 9 inattention and the 9 hyperactivity/impulsivity items, respectively. The overall SWAN-F ADHD score (S-ADHD scores) was the average of the 18 ratings. Scores for the SWAN-F Oppositional Defiant Disorder (S-ODD scores) was estimated as the average of the ratings obtained for the 8 ODD items. Two to three weeks prior to the scheduled evaluation at Sainte-Justine Hospital, the parent (84% mothers) received and completed the SWAN-F.

Revised Conners' Parents and Teachers Rating Scales (CPRS-R and CTRS-R; Conners et al, 1998a,b): The French version of the Conners' Parent and Teacher Revised Rating Scales (long version) were administered to the parent and the teacher of the child respectively. As age or sex-corrected scores are not available for the SWAN or the SWAN-F, and as the age range was small, the raw ratings of the SWAN-F scales were compared with the raw scores of the Conners' subscales, rather than the usual standardized T-scores. Conners' subscales were calculated as weighted addition (total of the ratings x number of items in the scale/number of completed items) of the respective items rated from zero to three.

General Information Questionnaire: Information on epidemiological, socio-demographic and medical variables was collected using a structured questionnaire addressed to the parent. Specifically, information on the age of the child, sex, mother's and father's education, Canadian origin and family income and structure was collected.

Wechsler Intelligence Scale for Children third edition (WISC-III) (Wechsler, 1991): This scale was used by the psychologist to assess the IQ of the child to determine if the child met inclusion/exclusion criteria for this study.

Data Analyses

Preliminary analyses involved studying the association between SWAN-F scores and socio-demographic variables such as age (in months), sex, mother's and father's education (less than college/college or university level), Canadian origin (one or two parents born outside Canada/both parent born in Canada), family income (<35 000$CAN/≥35 000$CAN) or family structure (both biological parents vs. other: mono-parental/reconstituted). Internal consistency of the SWAN-F subscales was assessed by estimating the Cronbach's alpha and correlations coefficients of each item with the corresponding scale (item-total correlation). To investigate external consistency, student t-tests were performed to compare mean SWAN-F scores between children with and without ADHD, ODD and CD, diagnosed using the DISC-4.0. SWAN-F scores within specific ADHD subtypes (DISC-4.0) were compared using one-way ANOVA. Pearson correlation coefficients were calculated to assess the association between Conners' and SWAN-F scores. Finally, using DISC-4.0 ADHD diagnostic assignment as reference, Receiver Operating Characteristic curves (or ROC curves) (Beck and Shultz, 1986) were generated to investigate the capacity of the Conners' Parent Rating Scale and SWAN-F ADHD scores to discriminate ADHD cases versus non-cases. SPSS 15.0 was used for the analyses.

Table 1: Internal consistency of SWAN-F subscales (N=88)

Subscales	Number of items	Cronbach's Alpha coefficients	Range of item-total correlation coefficients
S-IN	9	0.89	0.31-0.77
S-HY/IM	9	0.88	0.33-0.80
S-ADHD	18	0.91	0.28-0.71
S-ODD	8	0.88	0.56-0.77

Table 2: Comparison of mean SWAN-F scores between children with and without ADHD, ODD and CD

DISC-4.0 diagnosis	SWAN-F subscales Mean Scores (Standard Deviation)			
	S-IN	S-HY/IM	S-ADHD	S-ODD
Non-ADHD (n=14)	-0.61 (0.72)	0.01 (0.90)	-0.30 (0.67)	-0.35 (0.97)
ADHD (n=74)	-1.59 (0.84)***	-1.16 (0.90)***	-1.38 (0.74)***	-0.85 (1.04)
Non ODD (n=43)	-1.27 (0.74)	-0.56 (0.90)	-0.91 (0.72)	-0.12 (0.89)
ODD (n=45)	-1.59 (1.00)	-1.37 (0.93)***	-1.48 (0.83)**	-1.38 (0.75)***
Non-CD (n=63)	-1.34 (0.89)	-0.77 (1.00)	-1.06 (0.80)	-0.55 (1.00)
CD (n=25)	-1.66 (0.88)	-1.48 (0.82)**	-1.57 (0.78)**	-1.31 (0.93)**

* p<0.05, ** p<0.01, ***p<0.001

Note: DISC-4.0 diagnosis: ADHD; Attention Deficit Hyperactivity Disorder, ODD; Oppositional Defiant Disorder, CD; Conduct Disorder. SWAN-F scales: S-IN; Inattention, S-HY/IM; Hyperactivity/Impulsivity, S-ADHD; Attention Deficit Hyperactivity Disorder, S-ODD, Oppositional Defiant Disorder.

Results

Among the 124 referred families, 94 (76%) accepted to participate and 6 children were excluded because they presented with an IQ of less than 80. Thus, the study sample consisted of 88 subjects; 68 (78%) boys and 20 (22%) girls. The age distribution of the children was as follow: 19%, 32%, 34% and 15% were 6, 7, 8 and 9 years of age, respectively. Both parents were of Canadian origin for 76% of the children. College education was completed by 61% of the fathers and 56% of the mothers.

Among the 88 children investigated, 74 (84%) were diagnosed with ADHD according to DISC-4.0. Of these, 26 (35%) were categorized as Inattentive, 15 (20%) as Hyperactive/ Impulsive and 33 (45%) as Combined type. A total of 57 (77%) cases presented at least one other psychiatric disorder; 46 (62%) presented with CD or ODD, 24 (32%) with at least one Mood or Anxiety Disorder, 10 (14%) with Tic or Tourette's Disorder and 4 (5%) with Elimination or Eating Disorders. Forty nine subjects (56%) were currently being treated with psychostimulants, this frequency was similar among subjects classified as ADHD and non-ADHD according to DISC-4.0.

The SWAN-F scores were normally distributed within subscales among the study population. Multiple linear regression revealed no association between any of the socio-demographic variables and the different SWAN-F scores. However, the modes of the S-ADHD scores distribution, were very similar (Mean=-1.22; S.D. = .77 in boys and Mean=-1.15; S.D.= .85 in girls), as the medians (-1.36 for boys and-1.0 for girls), the modes of the S-ADHD scores distribution were -2.06 in boys and only -0.78 in girls.

Internal consistency

Internal consistency of SWAN-F was within an acceptable range for all subscales (Table 1), yielding coefficients above 0.80 (Nunnally & Bernstein, 1994). A Cronbach's alpha coefficient of 0.91 was observed for the S-ADHD subscale (18 ADHD items). While all other item-correlations with the S-IN subscale were above 0.53, the item "listen when spoken directly" (DSM-IV 1c ADHD item; American Psychiatric Association, 1994) had an item-total correlation of 0.31. The "able to talk with a normal flow" item (DSM-IV 2f ADHD item; American

Psychiatric Association, 1994) had a coefficient of 0.33 when item-correlation with S-HY/IM subscale was investigated. Coefficients were greater than 0.51 for the remaining items. The item-total correlations for the S-ODD subscale were all above 0.64.

External consistency

Table 2 presents the mean SWAN-F scores for children with and without ADHD, ODD and CD, respectively. Significant differences in mean SWAN-F scores between ADHD and non-ADHD cases were observed for S-IN ($t=4.08$, $p<0.001$), S-HY/IM ($t=4.44$, $p<0.001$) and S-ADHD ($t=5.06$, $p<0.001$) subscales, with children with ADHD presenting lower scores (more impaired) then non-ADHD children. When ODD and non-ODD children were compared, significant differences between mean SWAN-F scores were observed for all scales except the S-IN subscale, with children with ODD presenting lower scores (more impaired) than non-ODD children. Finally, significant differences in mean scores of the S-HY/IM, S-ADHD and S-ODD were observed between children with and without CD. Children with ODD and CD presented lower SWAN-F scores then non-impaired children.

ANOVA results evaluating the consistency between SWAN-F scores and ADHD subtypes are presented in Table 3. Predictably, mean scores of the S-IN subscale were significantly lower for children with Inattentive or Combined subtypes compared to non-ADHD children and children presenting with the Hyperactive/Impulsive subtype. Consistently, mean scores of the S-HY/IM subscale were significantly lower for children with Hyperactive/Impulsive or Combined subtypes compared to non-ADHD and Inattentive children. These specific patterns were no longer observed for the mean global S-ADHD scores. S-ADHD scores were significantly lower for children with the combined subtype compared to children with each specific subtype and for children with ADHD, whatever the subtype, compared to non-ADHD children.

The mean SWAN-F ratings for each specific DSM-IV item were compared between children with or without the respective symptoms as assessed with the DISC-4.0. The mean SWAN-F ratings were significantly lower ($p<0.05$) among children with the symptoms for 7 of the 9 Inattentive ("listen when spoken to directly" $p=.15$, and "organize work and activities"; $p=.08$ in a bilateral test) and all the Hyperamore, significant negative correlations were observed between the number of Inattentive symptoms and the S-IN score ($r= -0.57$, $p<0.001$) and the number of Hyperactivity/Impulsivity symptoms and the S-HY/IM score ($r= -0.69$, $p<0.001$): the more negative the scores, the more numerous the symptoms.

When studying the relationship between ratings of the SWAN-F and Conners' Parent

Table 3: Comparison of SWAN-F scores between ADHD subtypes.

	S-IN scores		S-HY/IM scores		S-ADHD scores	
DISC-4.0 diagnosis	Mean (SD)	Group differences	Mean (SD)	Group differences	Mean (SD)	Group differences
Non-ADHD (n=14)	-0.61 (0.71)	Non-ADHD vs, IN***, Non ADHD vs, COM**	0.01 (0.90)	Non ADHD vs, HY/IM**, Non ADHD vs, COM***	-0.30 (0.67)	Non ADHD vs, IN**, Non-ADHD vs, HY/IM*, Non ADHD vs,COM***
ADHD subtypes (N=74)						
Inattentive (IN) (n=26)	-1.76 (0.64)	IN vs, HY/IM**	-0.54 (0.81)	IN vs. COM***	-1.15 (0.65)	IN vs, COM*
Hyperactive/Impulsive (HY/IM) (n=15)	-0.92 (1.18)	HY/IM vs. COM**	-1.17 (0.93)		-1.05 (0.92)	HY/IM vs, COM*
Combined (COM) (n=33)	-1.77 (0.65)		-1.63 (0.66)		-1.70 (0.59)	

* $p<0.05$, ** $p<0.01$, ***$p<0.001$.

Note: SWAN-F scales: S-IN; Inattention, S-HY/IM; Hyperactivity/Impulsivity, S-ADHD; Attention Deficit Hyperactivity Disorder.

Table 4: Item-by-item Pearson correlation coefficients between SWAN-F scores and Conners' Parent Inattention or Hyperactivity/Impulsivity subscale scores.

	Correlation between specific item SWAN-F scores and Conners' Parent Inattention scores		Correlation between specific item SWAN-F scores and Conners'Parent Hyperactivity/Impulsivity scores
a) attending to detail	-0.44***	a) sitting still	-0.65***
b) sustaining attention	-0.51***	b) staying seated	-0.68**
c) listening	-0.14	c) modulating motor activity	-0.56***
d) following through	-0.52***	d) playing quietly	-0.58***
e) organizing	-0.60***	e) settling down	-0.71***
f) engaging in sustained effort	-0.61***	f) modulating verbal activity	-0.47***
g) keeping track of things	-0.59***	g) reflecting on questions	-0.54***
h) ignoring extraneous stimuli	-0.54***	h) awaiting turn	-0.59***
i) remembering	-0.47***	i) entering into others activities	-0.66***
Inattention subscale	-0.79***	Hyperactivity/impulsivity subscale	-0.85***

*p<0.05, ** p<0.01, ***p<0.001
NB: all correlations are negative as impairment is rated as more negative in SWAN-F scores and more positive in Conners' subscales

Rating Scale, we observed significant correlations for Conners' Parent subscale scores and all specific SWAN-F scores except the "listen when spoken directly" item (Table 4). Among the 45 teachers (51%) who completed the Conners-Teacher scale, significant correlations were observed between Conners' Teacher and Conners' Parent scores for the Inattention ($r=0.36$ $p<0.05$) and Hyperactivity/Impulsivity ($r=0.56$ $p<0.001$) subscales. Furthermore, significant correlations were also observed between SWAN-F and Conners' Teacher scores for the Inattention ($r= -0.30$ $p<0.05$) and Hyperactivity/Impulsivity ($r= -0.32$ $p<0.05$) subscales.

ROC curves were generated to evaluate the discriminant capacity of the Conners' Global Index and S-ADHD subscale, using the DISC-4.0 diagnosis assignment (gold standard) for any type of ADHD as reference. The estimated areas under the curves (AUC) were similar and significantly different from 0.5 (no possible discrimination) for the Conners' Global Index' (AUC= 0.79; CI 95%: 0.66-0.92) and SWAN-F scores (AUC= 0.89; CI 95%: 0.81-0.97). For the S-ADHD scores the optimal sensitivity (0.86) and specificity (0.88) corresponded to a cut-off of –0.60. For the Conners' Global Index, the optimal cut-off corresponded to a sensitivity of 0.75 and a specificity of 0.80. Increasing the sensitivity to 0.85 by lowering the cut-off resulted in a sudden drop in specificity (0.50), an observation that suggests that the SWAN could yield a lower false positive rate than the Conners' Rating Scale near cut-off. Results were similar when using the DSM-IV global symptom scale of the Conners' Rating Scale: optimal sensitivity and specificity were 0.80, but any further increase in sensitivity generated a sudden decrease in specificity.

Discussion

Overall, the criteria used to assess the reliability and accuracy of the SWAN-F in this study sample showed that the SWAN-F was consistent with the DISC-4.0 and the CPRS-R. SWAN-F showed high internal consistency for all subscales. Meaningful patterns of correspondence were observed between S-IN, S-HY/IM and S-ADHD scores and ADHD, ODD and CD diagnoses, as well as with ADHD subtypes. Although high correlations were observed for almost all DSM-IV ADHD symptoms (item-by-item comparisons), the item "listen when spoken to directly" showed low internal as well as external consistency. The DSM-IV wording of the corresponding criterion is "often does not seem to listen when spoken directly". The lower consistency may result from a misunderstanding of the question by the parents who scored the symptom as one of "opposition" rather than "inattention". "Does not listen" ("N'écoute pas") is often used to mean "does not obey" in French. It may be appropriate to modify the SWAN-F symptom

question to "Fais attention quand on lui parle directement-Pay attention when spoken to directly". One Hyperactivity/Impulsivity item worded "Quand il parle, est capable de régler son débit suivant le contexte" in the SWAN-F - for "modulate verbal activity (control excess talking)" in the SWAN (corresponding to "often talks excessively" as DSM-IV criterion) also showed low internal consistency. This may be related to the relative complexity of the item. A simpler wording of this item (e.g., "Se retient de trop parler, sur n'importe quoi- Keep themselves from talking too much, whatever the topic") could possibly increase the observed internal and external consistencies.

The SWAN was developed in response to concerns that the SNAP-IV as well as the other available symptom-based truncated checklist may overestimate the number of youths with ADHD, because of the skewed distribution. The summary scores of the SWAN-F were normally distributed even in a clinical sample and thus departed from the J curve generated by one-tailed ADHD rating scales. The use of normally distributed ADHD ratings could also be of interest for other clinical and research issues in which the estimation of the normal variability is central.

For example, it may improve our understanding of the gender impact on ADHD expression. According to the polygenic multiple threshold model, girls are less likely than boys to be diagnosed with ADHD because girls require greater liability to manifest ADHD than boys. Mothers also perceived the DSM-IV ADHD, ODD, and CD criteria as more descriptive of boys (Ohan & Johnston, 2006). However, in order to determine sex-specific cut-off, the full sex-specific distribution should be known. In an epidemiological sample of 872 boys and 812 girls, more girls than boys seemed to have moderate symptomatic level using the SWAN (Manly et al, 2005). By using a symptomatic rating scale going from much less to much more that other children, Waschbusch & King (2006) found in an epidemiological sample of 781 boys and 710 girls that a small percentage of girls with a higher than average ADHD and ODD symptom count did not meet DSM–IV diagnostic threshold. In the present clinical sample, we found no significant difference according to gender for the mean SWAN-F scores. However, the large difference in mode, more negative for boys than for girls, suggests an over-representation of near-threshold ratings in girls, even in a referred sample. Further research is thus needed to explore the full distribution of scores according to gender, and to develop age and gender norms for the SWAN.

The use of SWAN-F is also pertinent in genetic studies. In a twin design, the structural equation modeling is very sensitive to departure from normal distribution and truncated measures are by definition skewed. In addition, scoring individuals struggling with difficulties as well as those performing well above average increases the validity of the correlations within twin pairs. The direct comparison of truncated (Australian Twin Behaviour Rating Scale - ATBRS) with full-range scores (SWAN) suggests (Hay et al, 2007) that the proportion of children rated as having problems is inflated by using a problem-based truncated scale, as compared to a full-range strength-based scale. As the "not at all" descriptor is also used to describe a much wider range of behaviors than the other descriptors (normal but also different degrees of strength), parents seem to re-distribute their scores and to use more frequently the "negative" standard descriptors (from sometimes to very often). Not only is the highly skewed distribution problematic in genetic studies, but increasingly, association studies are using discordant or concordant pairs to detect linkages. Full-range questionnaires are obviously more appropriate to identify extremely discordant pairs than truncated ones and may be preferred (Cornish et al, 2005). The same reasoning holds for studies that look for an association between any biological or neuropsychological measures and behaviors by selecting subjects at both ends of the distribution of behavioral descriptors. For example, the SWAN was used to select children at the extremes of a "normal" ADHD continuum in a study on the relationship between rightward visuo-spatial bias and poor attention within the normal child population using the Line Bisection test (Manly et al, 2005).

Limitations

Some limitations of the study should be considered prior to interpretation. The accuracy of the SWAN-F was evaluated among ADHD

SWAN-F

		Beaucoup en dessous de la moyenne	En dessous de la moyenne	Un peu en dessous de la moyenne	Dans la moyenne	Un peu au dessus dessus moyenne	Au dessus de la moyenne	Beaucoup au dessus de la moyenne	code
1	Est capable de se mettre d'accord avec les adultes.	-3	-2	-1	0	1	2	3	2
2	Est capable de s'amuser calmement (dans les jeux ou les activités de loisirs).	-3	-2	-1	0	1	2	3	1
3	Console un enfant qui pleure ou qui est bouleversé.	-3	-2	-1	0	1	2	3	3
4	Est capable de s'organiser dans ses travaux ou ses activités.	-3	-2	-1	0	1	2	3	0
5	Est capable de s'arrêter et de rester tranquille.	-3	-2	-1	0	1	2	3	1
6	Est capable de garder son sang froid, de rester calme.	-3	-2	-1	0	1	2	3	2
7	Selon le contexte, est capable de rester assis sans se lever (en classe ou ailleurs).	-3	-2	-1	0	1	2	3	1
8	Évite de bousculer, de menacer ou d'intimider les autres.	-3	-2	-1	0	1	2	3	4
9	Est capable de se joindre sans s'imposer à une conversation ou à un jeu.	-3	-2	-1	0	1	2	3	1
10	Reconnaît la responsabilité de ses erreurs et de ses mauvaises conduites.	-3	-2	-1	0	1	2	3	2
11	Évite d'être impliqué dans des bagarres.	-3	-2	-1	0	1	2	3	4
12	Écoute quand on lui parle personnellement.	-3	-2	-1	0	1	2	3	0
13	Aide un enfant qui se sent malade, qui s'est blessé.	-3	-2	-1	0	1	2	3	3
14	Est capable de faire attention aux détails et d'éviter de faire des fautes d'étourderie.	-3	-2	-1	0	1	2	3	0
15	Est capable de suivre les consignes et de terminer ses devoirs/tâches.	-3	-2	-1	0	1	2	3	0
16	Est capable d'oublier sa rancune et de ne pas vouloir se venger.	-3	-2	-1	0	1	2	3	2
17	Est capable de veiller sur les choses nécessaires à son travail (livres, crayons, etc.) ou à ses activités (jouets, etc.).	-3	-2	-1	0	1	2	3	0
18	Ne se laisse pas froisser, vexer ou ennuyer par les autres.	-3	-2	-1	0	1	2	3	2
19	Ne se sent pas victime d'injustice et contrôle sa colère.	-3	-2	-1	0	1	2	3	2
20	Est capable de soutenir son attention au travail ou dans les jeux.	-3	-2	-1	0	1	2	3	0
21	Est capable d'entreprendre des tâches qui nécessitent un effort mental soutenu (à l'école ou à la maison).	-3	-2	-1	0	1	2	3	0
22	Dans la vie quotidienne, est capable de retenir ce qu'on lui dit ou ce qu'il doit faire.	-3	-2	-1	0	1	2	3	0
23	Invite un enfant qui se tient à l'écart à se joindre à son groupe de jeu.	-3	-2	-1	0	1	2	3	3
24	Selon le contexte, est capable de se retenir de courir ou de grimper, (n'a pas "des fourmis dans les jambes").	-3 1	-2	-1	0	1	2	3	3
25	Évite de faire délibérément des choses qui pourraient fâcher les autres.	-3	-2	-1	0	1	2	3	2
26	Est capable de se concentrer, de ne pas se laisser distraire par des stimuli externes.	-3	-2	-1	0	1	2	3	0
27	Évite de commencer les bagarres.	-3	-2	-1	0	1	2	3	4
28	Attends qu'une question soit entièrement posée avant d'y répondre.	-3	-2	-1	0	1	2	3	1
29	Accepte de suivre les règles et de répondre aux demandes des adultes.	-3	-2	-1	0	1	2	3	2
30	Devant une querelle ou une dispute, essaie de l'arrêter	-3	-2	-1	0	1	2	3	3
31	Est capable de rester assis sans s'agiter, en contrôlant les mouvements de ses mains et ses pieds.	-3	-2	-1	0	1	2	3	1
32	Quand il parle, est capable de régler son débit suivant le contexte.	-3	-2	-1	0	1	2	3	1
33	Est capable d'attendre son tour	-3	-2	-1	0	1	2	3	1
34	Se propose pour aider à nettoyer un dégât fait par quelqu'un d'autre.	-3	-2	-1	0	1	2	3	3

Scoring: S-IN: average item code 0; S-HY; average items code 1; S-ODD: average code 2; S-PRO: average code 3; S-CD: average code 4.

patients referred to clinicians as part of an ongoing research program. Thus the population was in many ways a "selected population" and extrapolation of findings to the "general" or similar "ADHD" populations may be inappropriate. Further studies among larger unselected populations will be necessary to further evaluate the utility of the SWAN-F. Although, information gathered with the SWAN-F significantly correlated with that obtained by the Conners' Teachers Rating Scale, the low response rate among the teachers may have influenced the results. In the present study, classification as ADHD or non-ADHD was based on the findings obtained using DISC-4.0. Diagnosis using DISC-4.0 has inherent limitations. Information is collected from only 1 informant and judging the exactness of the information is not possible.

Clinical implications

To our knowledge, this is the first validation study of the SWAN assessing internal and external consistency in a referred sample. Although, the investigation of their psychometric properties needs to be further pursued, the SWAN and SWAN-F could nonetheless in their present form have good potential for use in clinical and research setting because they retain the advantages of other rating scales: simple to comprehend, rapidly completed, providing quantitative scores. In addition, as they are based on strengths, they allow parents to recognize them when they exist and thus may decrease guilt and stigmatization associated with reporting the child's difficulties. Moreover, these scales may allow limiting some bias in clinical decision-making. A study by Lewczyk et al (2003) showed that the poor concordance among clinicians when diagnosing ADHD and disruptive disorder partly resulted from the concern to avoid false positives, even at the cost of increasing the risk for false negatives. The Conner's Parent Rating Scale was reported to have a sensitivity of 0.92 and a specificity of 0.94 (Conners et al, 1998a), in separating children with a confirmed diagnosis of ADHD and an epidemiological sample (mean age = 10.16 years; SD = 3.40). However, the present data suggest that the accuracy could be lower in a clinically referred sample (around 0.80), comparable to the SWAN. Moreover, if further studies confirm the lower false positive rate associated with the SWAN-F, it could constitute a more reliable tool for clinicians than symptom-based scales.

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