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Incentive processing in Congenital Adrenal Hyperplasia (CAH): a reward-based antisaccade study

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Abstract

Little is known about how steroid hormones contribute to the beneficial effect of incentives on cognitive control during adolescent development. In this study, 27 adolescents with Congenital Adrenal Hyperplasia (CAH, mean age 15.6 years, 12 female), a disorder of cortisol deficiency and androgen excess, and 36 healthy participants (mean age 16.3 years, 18 female) completed a reward-based antisaccade task. In this mixed-saccade task, participants performed eye movements towards (prosaccades) or away (antisaccades) from a peripherally occuring stimulus. On incentive trials, monetary reward was provided for correct performance, while no such reward was provided on no-incentive trials. Consistent with the hypothesis, the results showed that healthy, but not CAH adolescents, significantly improved their inhibitory control (antisaccade accuracy) during incentive trials relative to no-incentive trials. These findings were not driven by severity of CAH (salt wasters vs. simple virilizers), individual hormone levels, sex, age-at-diagnosis, or medication type (dexamethasone vs. hydrocortisone). In addition, no significant differences between groups were found on orienting responses (prosaccades). Additional analyses revealed an impact of glucocorticoid (GC) dosage, such that higher GC dose predicted better antisaccade performance. However, this effect did not impact incentive processing. The data are discussed within the context of steroid hormone mediated effects on cognitive control and reward processing.

Key words: inhibitory control, androgen, development, adolescence, sex steroids, testosterone, cortisol

Introduction

Congenital Adrenal Hyperplasia (CAH), a disorder of cortisol deficiency with concurrent excess of androgen production (Merke and Bornstein, 2005), is a natural model to investigate the impact of early hormonal disturbances on cognitive and affective function. In addition to cognitive-behavioural deviances (Hines et al., 2003), perturbations in affective processing have been documented in these patients, both at the behavioural (Oner et al., 2009) and neural (Ernst et al., 2007; Mazzone et al., 2011) level. For instance, CAH adolescents show abnormal activations of the amygdala, hippocampus, and anterior cingulate cortex in response to facial emotion (Ernst et al., 2007; Mazzone et al., 2011). However, at present, no studies have examined motivational processes in CAH, or how early steroid perturbations can affect these processes in the long term (Helleday et al., 1993). Together with emotion, motivation is a critical determinant of goal-directed behaviour, and can facilitate cognitive control by strengthening self-regulation.

Indeed, studies report that motivation, by virtue of monetary incentive, can enhance cognitive control, particularly during development (Geier et al., 2010). The neurobiology of motivation implicates dopamine as a critical mediator of this function (Robbins, 2007). Despite evidence that links cortisol to dopamine function (Sanchez et al., 2000; Tsukada et al., 2011), little is known about how steroid hormones influence motivation and cognitive control (McGough et al., 2005). Such knowledge might be important in light of the higher incidence of mood and anxiety disorders in CAH youth compared to rates in the general population (Mueller et al., 2010a), which could be partly mediated by disturbances of motivational processes.

An ideal paradigm to examine motivation and inhibitory control is the incentive antisaccade task (Mueller et al., 2010b). Antisaccades require the inhibition

of a 'reflexive' eye movement to a peripherally appearing stimulus (the prosaccade) and the generation of an eye movement to the opposite direction (the antisaccade). Developmental studies document reduced antisaccade performance in healthy adolescents relative to adults (Everling and Fischer, 1998; Fischer et al., 1997), but improvement in antisaccade accuracy with monetary incentives (Geier et al., 2010). By contrast, incentives do not improve antisaccade accuracy in mood-disordered adolescents (Mueller et al., 2010a) or adolescents with a history of neglect/abuse (Mueller et al., 2012).

One clear advantage of using the antisaccade task is a well-understood neurobiology underlying eye movement behaviour. Task performance relies heavily on both the prefrontal cortex (dorsolateral PFC and the frontal and supplementary eye fields) and the basal ganglia (including the caudate nucleus and substantia nigra) (Munoz and Everling, 2004). It has been argued that the lower antisaccade accuracy in children compared to adults reflects the protracted development of the prefrontal cortex (Luna et al., 2001) and an associated difficulty in inhibiting pre-target activity in saccade neurons, which helps to suppress reflexive prosaccade responses (Munoz and Everling, 2004). However, evidence of how steroids alter the antisaccade system during development is lacking.

This study aimed to identify, in CAH patients, potential abnormalities in the motivational modulation of inhibitory control using monetary incentives during a validated oculomotor task. We sought to assess the integrity of motivational processes and their influence on cognitive control in CAH, and by inference, the potential long-term effects of early steroid disruption on these processes. Based on previous findings (Mueller et al., 2010a), we predicted that healthy participants, but not patients with CAH, would show improvement on inhibitory control during incentive relative to no

incentive trials. No significant differences would be expected during lower cognitive level processes, such as attentional orienting responses (prosaccade trials).

Methods

Participants

Twenty-seven adolescents with classic CAH (mean age 15.61 years ± 3.96 SD, 12 female) and 36 healthy participants (mean age 16.26 ± 5.67 SD, 18 female) completed the task. Of the CAH, 16 patients had the salt wasting (SW) form, while 11 had the simple virilizing (SV) form. The groups were similar on age (F(1,61)=0.26, p=.61), but differed on IQ (F(1,61)=5.48, p=.02), which was higher in the healthy group (mean = 115.72 ± 11.06 SD) than the CAH group (mean = 108.52 ± 13.34 SD). Consequently, IQ was used as a covariate of no interest in all subsequent analyses. There were no significant group differences in state anxiety (F1,61)=2.36, ns), trait anxiety (F(1,61)=0.34, ns), or level of depression (F(1,48)=0.15, ns). Healthy participants were recruited through fliers and newspaper advertisements. Patients with CAH were enrolled as part of a Natural History Study at the NIH Clinical Center in Bethesda, Maryland, USA (Clinical Trial No. NCT00250159). The study was approved by the IRB of the NIMH and National Institute of Child Health and Human Development. Parents provided written informed consent and minors written assent. All participants underwent neurologic and psychiatric evaluation, physical examination, and IQ testing. In addition, all patients underwent thorough clinical and endocrinological evaluation and all classifications were confirmed by genotype. All patients were on glucocorticoid medication at the time of testing (hydrocortisone: n = 19; dexamethasone: n = 7, prednisone: n = 1). Five of the CAH patients suffered from co-morbid psychopathology (2 ADHD, 2 anxiety disorder, 1 substance abuse). Nine

(33.3%) patients had elevated 17-hydroxyprogesterone levels; but all had normal testosterone values for age and sex.

Apparatus

Saccades were recorded using a remote mounted eye tracker with a 240 Hz sampling rate (Applied Science Laboratories; ASL Inc., Bedford, MA). Participants were required to either make an eye movement towards (prosaccades) or away (antisaccades) from a white target asterisk that was subtending 0.5 deg in visual angle (Figure 1). Each eye movement was paired with one of three incentive conditions. Prior to the target, a cue ('+', '-', '0') indicated the type of incentive and the type of saccade participants had to perform. If the color of the cue was grey an antisaccade was required. If it was white, participants had to execute a prosaccade. During the reward condition a '+' sign indicated that participants could win $1 if they executed a correct eye movement, in the punishment condition a '-' sign indicated that they would lose $1 for an incorrect eye movement, and in the no-incentive condition a '0' indicated no gain or punishment regardless of whether the eye movement was correct or incorrect. To examine potential differences in the effects of valence on performance, statistical analyses directly compared the reward and punishment on measured of latency and accuracy. As valence showed no significant effects $(t(62)=0.12, ns)$, and to increase statistical power, positive and negative incentives were pooled together for the main analysis. Participants were given immediate feedback as to whether they had won $1 (displayed in green) or lost $1 (displayed in red).

****************** FIGURE 1 ABOUT HERE PLEASE ******************

Procedure

Adolescents were seated in a chair about 66 cm away from the screen in an illuminated room and completed 3 runs of 48 randomly intermixed trials (= 144 total). Subjects started with $0.00 and could win up to $4.80 per run. In-between runs, participants' eye movements were re-calibrated if necessary. A chin-rest was used to minimize movement. Afterwards, participants were sent a check for the amount of their winnings.

Statistical analysis

Saccade *accuracy* (percent of trials that were errors) and *latency* (response time of correct responses in ms) were analysed. Correct saccades were defined by their direction and latency with a threshold criterion set at 30 deg/sec. Anticipatory (latency < 80 ms) or late (latency >700 ms) saccades were excluded from analysis. Each saccade parameter was entered separately into a three-way repeated measures analysis of variance (ANOVA), with group (Healthy vs. CAH) as the between-subjects factor and saccade type (prosaccades [PS] vs. antisaccades [AS]) and incentive (incentive vs. no-incentive) as the within-subject factors. Post-hoc analyses were used to examine the potential impact of medications, or comorbid illnesses. Correlations (*r*) were conducted to examine associations between saccadic performance and hormone levels (which were taken at 0800h and before medication). To ensure that findings were not confounded by comorbid illnesses, sex, or CAH

severity, the main analyses were repeated accounting for these differences. Finally, the impact of glucocorticoid (GC) exposure and duration of untreated hypocortisolemia and androgen excess were also assessed. For GC exposure, we calculated the hydrocortisone equivalency doses (mg/m^2/day; Hindmarsh, 2009; Rivkees and Crawford, 2000) and included this factor as an additional covariate. For the duration of untreated hypocortisolemia and androgen excess, we examined age at diagnosis in the simple-virilizing group (patients with the salt-wasting form could not be used since they are identified at birth and immediately treated).

****************** TABLE 1 ABOUT HERE PLEASE ******************

Results

Accuracy

As predicted, the three-way Saccade-type by Incentive by Group interaction was significant ($F(1,60)=5.29$, $p<.05$). To determine the directionality of the interaction, we conducted 2 two-way ANCOVAs, one for each group. In the healthy group, the Saccade-type by Incentive interaction was significant ($F(1,35)=16.89$, $p<.001$). Follow-up t-tests revealed that the incentive effect was only significant for AS ($t(35)=-3.32$, $p<.01$) but not PS ($t(35)=0.89$, $p=.38$). By contrast, in CAH, the Saccade-type by Incentive interaction was not significant ($F(1,26)=0.08$, $p=.79$).

A main effect of Saccade-type, as expected, showed that all participants elicited fewer errors on PS than AS ($F(1,60)=5.38$, $p<.05$), a finding that also emerged in the follow-

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up analyses of the 2-way interactions for both healthy ($F(1,35)=124.61$, $p<.001$) and CAH ($F(1,26)=121.04$, $p<.001$) groups.

Latency

A main effect of Saccade-type, as expected, revealed significantly faster PS than AS ($F(1,60)=4.89$, $p<.05$). The three-way interaction of Group by Saccade-type by Incentive was not significant (ns).

Additional analyses

Correlations with hormonal levels in CAH

No significant correlations of hormone levels were observed with differences between incentive and neutral trials in measures of accuracy or latency (testosterone: all $r(27)<.18$, ns; 17-hydroxyprogesterone: all $r(27)<.21$, ns).

Impact of CAH severity, sex, medication type, glucocorticoid dose, age at diagnosis, or psychiatric co-morbidity

Additional analyses comparing performance in salt-wasters (n=16) and simple virilizers (n=11) did not reveal any significant main effects of CAH type or interactions with incentive or saccade type (all $p >.05$). Analyses of sex effects in the CAH group (15 males, 12 females) did not reveal any significant differences in relation to incentive, neither for latencies ($p =.53$) or accuracy ($p=.79$). No other findings were significant. A regression analysis comparing the potential impact of medications (dexamethasone vs. hydrocortisone) did not reveal any significant effects for either saccade accuracy (all $p >.45$) or latency (all $p >.17$) on incentive or no-

incentive trials. However, when we assessed the impact of glucocorticoid dose (hydrocortisone equivalency dose), a significant interaction between saccade type and glucocorticoid dose emerged (F(1,25)=6.49, p<.02). To further examine the directionality of this interaction, correlations between glucocorticoid dose and prosaccade and antisaccade accuracy were performed. These correlations revealed that antisaccade error rate correlated significantly with equivalency rate (higher GC dose = lower error rate) (r(27)=-.40, p=.038) but had no effect on prosaccade error rate (r(27)=.14, p=.49). Furthermore, the difference between these two correlation coefficients was marginally significant using the Fisher r-to-z transform (p=.05). No other effects were significant. To assess to what extent the duration of untreated early steroid perturbation may have influenced the findings, we examined age-at-diagnosis as a potential variable of interest in the simple virilizers of the sample (N=11). These limited analyses did not reveal any effects (all p>.42). Finally, when the 5 CAH adolescents with a current psychiatric diagnosis (2 ADHD, 2 anxiety disorder, 1 substance abuse) were excluded, CAH still failed to show a significant effect of incentive (p=.38) or incentive by saccade-type interaction (p=.57). These findings suggest that psychiatric co-morbidity is not responsible for lack of sensitivity to incentive.

Discussion

      This study investigated the impact of prenatal steroid disruption on cognitive control and motivation. As predicted, inhibitory control was improved (increased antisaccade accuracy) during incentive conditions relative to no-incentive trials in healthy adolescents, but not in patients with CAH. These results suggest that early

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disturbance of the hormonal milieu in CAH may disrupt the mechanisms by which motivation can improve voluntary action.

Importantly, consistent with prior neuropsychological data in CAH adults (Malouf et al., 2006), the CAH group did not evidence general impairments of cognitive control (AS) or attentional orienting (PS), i.e., no performance differences between CAH and comparisons. These findings suggest that early hormonal dysfunction appeared not to have detectable long-term effects on basic inhibitory control or attentional orienting. Therefore, the current findings imply specific hormonal modulation of the impact of motivational processes on inhibitory function. The prefrontal cortex and striatum play an essential role in cognitive control (Robbins, 2007). Moreover, the interplay between these two regions has been implicated in the development of motivated behaviour (Ernst and Fudge, 2009). Interestingly, cortisol binds to dopamine receptors in both prefrontal cortex (Lataster et al., 2011; Mizoguchi et al., 2008b; Sanchez et al., 2000; Tops et al., 2006) and striatum (Tsukada et al., 2011; Wand et al., 2007) possibly mediating dopaminergic influences on motivational and regulatory processes. The current findings elicit novel hypotheses regarding early, organizational influences of sex steroid perturbations on the developmental trajectories of systems mediating inhibitory control and reward. For example, one question is whether early steroid deficiency alters striatal feedback mechanisms into the PFC, which are aimed to increase cognitive control during motivated behaviour.

Although a hallmark symptom of CAH is cortisol deficiency (Merke and Bornstein, 2005), an interesting alternative explanation is a potential role of excess androgen in the present findings (Aubele and Kritzer, 2011). A recent developmental fMRI study documented significant correlations between testosterone levels and

striatal activity during a monetary incentive task (Op de Macks et al., 2011). Conversely, boys suffering from androgen excess showed significant volumetric alterations in the striatum, which correlated with testosterone levels (Mueller et al., 2011). These data might suggest a mediation of motivational mechanisms by androgens.

Some limitations of the study deserve discussion. Certainly, a limitation of this study is that it cannot distinguish between the distinct effects of specific steroid hormones due to feedback loops involving both sex steroids and corticosteroids. However, natural models of steroid dysfunction, such as CAH, can aid in the formulation of research hypotheses for studies in animal models (Mizoguchi et al., 2008a; Steimer et al., 2007) or healthy volunteers (Tops et al., 2006). Another limitation concerned medication use in all patients. Although we did not find a differential effect of medication type, current glucocorticoid dose correlated with antisaccade performance in the post-hoc analyses. As this correlation suggested improved antisaccade accuracy with higher GC dose, a negative impact due to supra-threshold levels of GC seems unlikely. However, as inhibitory control and incentive processing are two distinct processes, future studies could more directly examine their sensitivity to GC modulation. To examine the extent to which the duration of untreated cortisol deficiency/androgen excess could have impacted the findings, age at diagnosis in the simple-virilizing group, for whom time of diagnosis and initiation of treatment varies, was taken into consideration. Although no effects were found, any negative findings must be interpreted with caution due to the small number of patients with the SV form. Future studies could more specifically investigate developmental effects of steroid exposure by examining other patient groups for whom cortisol perturbations develop later in life, such as Cushing disease (Starkman et al., 1992). In

summary, this is the first study, to our knowledge, that demonstrates motivational

deficits in CAH as evidenced by the rewarded antisaccade task.

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Captions

Figure 1. Stimuli were presented on a black background (for clarity of presentation, colour schemes are reversed in the figure). Each trial started with the cue, which was presented for 1250 - 1750 ms and which indicated the type of incentive and the type of saccade, both of which were randomized. Once the cue disappeared, the white target asterisk was displayed for 1850 ms on either the left hand or right hand side approximately 6.15 deg to the centrally presented cue. Then, the feedback display (subtending ~1.8 deg in visual angle) was presented for 1000 ms on the side where the correct eye movement should have occurred. This sample trial shows a rewarded antisaccade, where the cue ("+") indicated the reward and an antisaccade was correctly executed to the left.

Table 1. Latencies and accuracy rates for both groups for the different conditions.

BOLD font indicates significant three-way interaction (p<.05).

| | | Antisaccade | | Prosaccade | |
		CAH	Control	CAH	Control
Accuracy	*Incentive*	**46.76**	**40.79**	19.59	17.88
(% error, SD)		**(11.68)**	**(17.36)**	(10.66)	(9.02)
	No incentive	**47.54**	**48.38**	21.14	16.55
		(14.07)	**(15.69)**	(12.55)	(8.99)
Latency	*Incentive*	298.57	280.83	306.69	249.36
(ms, SD)		(94.60)	(75.65)	(103.60)	(100.83)
	No Incentive	335.98	295.55	308.82	275.86
		(170.46)	(110.82)	(100.11)	(138.47)