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SHORT COMMUNICATION

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

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Summary 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.
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1. 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., 2010b) 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., 2010b), 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).

2. Methods

2.1. Participants

Twenty-seven adolescents with classic CAH (mean age 15.61 years $\pm$ 3.96 SD, 12 female) and 36 healthy participants (mean age 16.26 $\pm$ 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 $\pm$ 11.06 SD) than the CAH group (mean = 108.52 $\pm$ 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 ($F(1,61) = 2.36$, 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, MD, 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.

2.2. 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° in visual angle (Fig. 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 colour 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