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Background cortisol versus social anxiety as correlates of HPA-axis recovery from stress in boys with Autism Spectrum Disorder

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ABSTRACT

Children with Autism Spectrum Disorder (ASD) show dysregulation of the expected Hypothalamus-Pituitary-Adrenal (HPA) axis and elevated cortisol responses to stress and response patterns, but little has been reported regarding their recovery from stress in terms of cortisol concentrations. This response was investigated in a sample of 32 young males with ASD aged between 9 and 18 years (M = 14.3 yr, SD = 2.7 yr), using a standardised experimental protocol combined with individualised stressor and non-stressor tasks. Results indicated that about half of the sample demonstrated unexpected HPA axis response patterns, and that recovery from stress cortisol concentrations were significantly associated with a single symptom of Social Phobia and Morning cortisol. These findings suggest that one of the key diagnostic criteria for ASD may be strongly influential in the HPA axis responses of boys with ASD and that training regimesto assist them to form less fearful associations with their non-ASD peers may be central to the academic and social progress of these boys.

1. Introduction

1.1. Cortisol and stress

Few neurohormones have been more intensively or widely studied as indices of stress than cortisol, which is produced by the Hypothalamus-Pituitary-Adrenal (HPA) axis. Characterised by a diurnal fluctuation in its concentration within the circulatory system, saliva and urine, from a maximum in the morning to a nadir later in the day (Dallman and Yates, 1969), cortisol is vital to many physiological functions (Pruessner et al., 1997). It is particularly valuable for its roles in assisting the organism to cope with immediate stressors (McEwan, 2007), when it may show a short-term increase that is independent of the diurnal fluctuation (Cohen et al., 2015). This elevation in cortisol in response to stressors, in combination with Sympatho-Adrenal-Medullary adrenergic responses, enhances the organism's ability to respond immediately to attack by increasing heart rate, vasoconstriction and blood pressure to supply more oxygen to muscles, and releasing stored lipids and amino acids from fatty tissue for synthesis of glucose and protein which enhance the organism's ability to mobilise musculature for immediate and prolonged intense activity (Brillon et al., 1995). These important roles in stress adaptation have led to cortisol sometimes being referred to as the "stress hormone" (Aron et al., 2007).

Disturbance in adequate and regular HPA-axis functioning is associated with a range of illnesses including immunological disorders, susceptibility to stress, pain and fatigue (Fries et al., 2005), muscle wastage and hyperglycaemia (Aron et al., 2007), coronary heart disease (Koertge et al., 2002), acute respiratory failure (Jantz and Sahn, 1999), and depression and chronic distress (Chrousos, 2009). HPA axis functioning is often estimated by reference to the dramatic increase in cortisol concentrations of at least 2.49 nmol/L in adults from waking until 30 min later, called the Cortisol Awakening Response (CAR: Fries et al., 2009), although the definition of the CAR in children and adolescents is any rise in cortisol concentrations over the 30 min period (Rosmalen et al., 2005). Estimated to be present in about 75% of healthy individuals (Wust et al., 2000), the CAR is influenced by a range of social factors including stress and anxiety (Chida and Steptoe, 2009; Gartland et al., 2014; Smyth et al., 1997; Stone et al., 2001). Some clinical samples present with a large proportion of their members exhibiting CAR dysregulation (Day et al., 2014), perhaps reflecting the influence of genetic factors upon the presence of the CAR (Wüst et al., 2000).

1.2. Cortisol, stress and ASD

One population that has been shown to have dysregulated HPA axis patterns compared to their peers is children with Autism Spectrum Disorder (ASD) (Brosnan et al., 2009; Kidd et al., 2012; Tordjman et al.,

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2014). There is some initial evidence that this dysregulation of the HPA axis may also be associated with gastrointestinal disorders in these children (Ferguson et al., 2016). In contrast, there are studies demonstrating no significant differences in the HPA axis diurnal variation and CAR across ASD and non-ASD samples (Corbett and Schupp, 2014; Gabriels et al., 2013; Marnovic-Curin et al., 2008; Tomarken et al., 2015). As might be expected, not all participants in this kind of study react identically. For example, in a study of girls with ASD and another study of boys with ASD, Bitsika and colleagues (Bitsika et al., 2015a; Sharpley et al., 2016a,b) reported that about 15% of both samples failed to demonstrate the diurnal variation or CAR, despite the overall samples following the expected patterns of cortisol concentration change over the day.

Perhaps contributing to their HPA axis dysregulation, children with ASD also often suffer from elevated stress and anxiety (Kim et al., 2000; White et al., 2009), particularly in regard to immediate changes in their routine (Kanner, 1943; Volkmar and McPartland, 2014). Their difficulty in coping with those changes has been referred to as arising from a 'preference for sameness' (PS), which is a sub-part of the overall symptom cluster known as Restricted and Repetitive Behaviour (RRB). It has been suggested that PS is associated with anxiety regarding social interactions and may be used by children with ASD as a coping mechanism when faced with uncertain social interaction demands (Factor et al., 2016). That is, keeping things as they have been (i.e., 'the same') reduces the variability of the social environment and may function to reduce anxiety about that social environment.

Children without ASD also exhibit cortisol reactivity when faced with socially-demanding situations, particularly by those participants who experience fears about such situations (Anderson and Hope, 2009). The same kind of cortisol reactivity has been demonstrated in children with ASD when they have been subject to a stressor (Spratt et al., 2012), but again the data are not uniform across studies. For example, Edmiston et al., 2017 reported no increase in cortisol in their sample of adolescents with ASD in response to a social stress test, but a significant increase in cortisol to the same stressor in a non-ASD peer sample. In their review of cortisol responsiveness in children with ASD, Taylor and Corbett (2014) examined nine studies that used a social challenge in the form of public speaking or peer interactions. They found that cortisol concentrations did not increase in the ASD samples during public speaking but did increase when the ASD participants were asked to interact with unfamiliar or familiar peers, suggesting that social interaction might be the intervening variable in those different responses.

Thus, there may be a relationship between the CAR, cortisol responsivity to immediate stressors (particularly social stressors) and anxiety regarding social interaction challenges in children with ASD, but the nature of that association is not currently clear. There are some important clinical implications that arise from this lack of clarity, specifically the difficulties in treating PS, social anxiety, elevated or dysfunctional cortisol responsivity, and the interaction of these factors in children with ASD. Without a clear pathway between social anxiety, CAR and immediate stressor cortisol reactivity to social stressors, settings in which children with ASD are required to change tasks may continue to present them with challenges which they find insurmountable. RRBs, of which PS is a sub-category, have been significantly associated with anxiety (Sharpley et al., 2015a) and depression (Bitsika and Sharpley, 2017) in ASD children. The PS, its possible correlation with social anxiety, disruption to the CAR, and stressor reactivity cortisol, all hold implications for the mental health of young people with ASD within a typical task-change setting, and therefore are legitimate targets of research.

In addition, as mentioned above, although several studies have investigated the short-term stress response in cortisol in children with ASD, none have reported on the recovery from stress cortisol response in these children. This is important because prolonged elevation of cortisol ('hyp*er*cortisolaemia') which may lead to cortisol 'fatigue' ('hyp*o*cortisolaemia') is the HPA-axis response pattern that is associated with the range of physical and mental illnesses listed in the opening paragraph of this paper. That is, while there are some data regarding cortisol responsivity to the onset of stressors in children with ASD (Taylor and Corbett, 2014's review), relatively little is known about how well these children recover from elevated cortisol responses to stress. Techniques to assist these children to manage their stress responsivity more effectively by reducing stress-induced elevated cortisol may have important implications for their ongoing physical and mental health. Understanding how well they are able to recover from stress-induced elevations in cortisol, or what factor(s) may be correlated with that recovery, may hold important information for development and implementation of such training techniques for these children.

1.3. Aims of the study

Therefore, this study aimed to explore this issue by comparing the relative strength of association between cortisol reactivity to an immediate stressor, cortisol recovery from that stressor, and several background demographic factors (age, IQ, ASD-severity), some background HPA-axis factors (waking cortisol, morning cortisol, the CAR) and self-rated social anxiety and general anxiety in a sample of children with ASD.

Several methodological aspects were also considered in order to meet this aim. First, because of the relative preponderance of males in the ASD population (APA, 2013), a sample of boys and adolescents was recruited. Second, because there are some data suggesting that parental ratings of anxiety in boys with ASD are influenced by parental stress, anxiety or depression (Bitsika et al., 2015b) and that boys' self-ratings of anxiety correlate with physiological measures of anxiety (Bitsika et al., 2014), data regarding general and social anxiety were collected from the ASD participants themselves. Third, to reduce the likelihood of low cognitive ability hindering accurate self-report, ASD participants were selected from the population described as 'high-functioning' (IQ $>$ 70, attending mainstream school, able to self-care). Finally, the immediate stressor was chosen by the parents of the boys with ASD, based upon their observations of their sons in order to ensure that it was individually relevant and sufficiently aversive to each of the boys in the sample.

2. Methods

2.1. Participants

The ASD sample consisted of 32 boys aged 9 to 18 years (M = 14.3 yr, SD = 2.7 yr), and the parental sample consisted of 30 mothers and 2 fathers, one for each of the ASD participants. All these participants were recruited from parent support groups and other service organisations in Queensland Australia, for a study about "How it feels to have ASD". The members of the ASD sample had received their diagnoses from administration of the Autism Diagnostic Observation Schedule (ADOS-2: Lord et al., 2012) by a research-reliable ADOS-2 trained assistant during recruitment. These boys also were assessed on the second edition of the Wechsler Abbreviated Scale of Intelligence (WASI-II: PsychCorp, 1999) to ensure that they each had a Full Scale IQ above 70. Because they attended mainstream schools, and were described by their parents as able to self-care (i.e., clean, feed, dress, and generally maintain appropriate standards of hygiene and organisation), they were classified as 'high-functioning' by their parents. All participants were Anglo-Saxon in ethnicity and all had been born in Australia. The parents gave written informed consent for their sons to participate and their sons gave verbal or written assent to participate, depending upon their age. The parents reported that none of their sons had any concurrent genetic or neurological conditions or previous DSM-5 (APA, 2013) classification of comorbid psychiatric disorder.