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Working memory performance is reduced in children with congenital adrenal hyperplasia

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ABSTRACT

Individuals with classic congenital adrenal hyperplasia (CAH) experience impaired glucocorticoid production and are treated postnatally with glucocorticoids. Prior research with animals and other human populations indicates that glucocorticoids can influence memory, particularly working memory. We tested the hypothesis that children with CAH would show reduced working memory. Children in the United Kingdom, aged 7–11 years, with classical CAH (31 girls, 26 boys) were compared to their unaffected relatives (30 girls, 20 boys) on a test of working memory, the Digit Span test. Vocabulary was also assessed to measure verbal intelligence for control purposes. Children with CAH showed reduced working memory performance compared to controls, on both components of the Digit Span test: $p = .008$ for Digit Span Forward, and $p = .027$ for Digit Span Backward, and on a composite score, $p = .004$. These differences were of moderate size ($d = .53$ to .70). Similar differences were also seen in a subset of 23 matched pairs of children with CAH and their relatives ($d = .78$ to .92). There were no group differences on Vocabulary. Glucocorticoid abnormality, including treatment effects, could be responsible for the reduced Digit Span performance in children with CAH. Other factors related to CAH, such as salt-wasting crises, could also be involved. Additional research is needed to identify the cause of the memory reduction, which will help to determine if more rapid diagnosis or more precise glucocorticoid treatment would help prevent memory reduction. Educational interventions might also be considered for children with CAH.

Introduction

Classic congenital adrenal hyperplasia (CAH) is an autosomal recessive condition caused by an enzymatic deficiency. In over 90% of cases, the deficient enzyme is 21-hydroxylase, and this deficiency results in low levels of the glucocorticoid cortisol and in high levels of adrenal androgens, including testosterone, starting at about the seventh week of gestation (Merke and Bornstein, 2005; Speiser and White, 2003; White and Speiser, 2000). Androgen excess during the prenatal period causes genital ambiguity in newborn females with CAH. Management for both male and female patients includes treatment with glucocorticoids postnatally to normalize hormone concentrations (Speiser et al., 2010). Despite this treatment, postnatal glucocorticoid or androgen concentrations may be abnormal, for example, because of delayed diagnosis and treatment, or because of over- or under-treatment with glucocorticoids (Auchus and Arlt, 2013; Debono et al., 2009; Li et al., 2003; White and Speiser, 2000).

Girls and women with classic CAH have been found to show some behavioral masculinization, similar to that seen following experimental manipulations of androgens in other species (Collaer and Hines, 1995; Schwarz and McCarthy, 2008). For example, girls with CAH show increased male-typical childhood play behavior (Berenbaum and Hines, 1992; Hines, 2011; Hines et al., 2004; Pasterski et al., 2005, 2007, 2011), and women with CAH show increased interest in male-typical occupations and reduced heterosexual interests (Beltz et al., 2011; Hines, 2011; Hines et al., 2004; Meyer-Bahlburg et al., 2008; Servin et al., 2003).

The potential impact of glucocorticoid abnormality on behavior in individuals with CAH is relatively unexplored. However, glucocorticoids have been shown to have potent neurobehavioral influences, particularly in relation to learning and memory (Dominique et al., 2000; Kukolja et al., 2011; Lupien and McEwen, 1997; Lupien et al., 2002; Rimmele et al., 2013; Tollenaar et al., 2009). Research using rodents and non-human primates shows that the hippocampus, a neural region implicated in memory, is influenced by glucocorticoids during critical periods of

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early development (Matthews, 2001). In addition, experimentally lowering or elevating glucocorticoid levels in adult rats can cause hippocampal atrophy and memory impairments (Herbert et al., 2006; McEwen and Sapolsky, 1995).

In humans, memory deficits have been found in clinical conditions characterized by prolonged exposure to elevated glucocorticoids, such as Cushing syndrome (for a review, see Sapolsky, 2000) and in individuals receiving glucocorticoid treatment (Lupien et al., 2007; Stuart et al., 2005). In healthy adults, glucocorticoid manipulations have also been found to influence memory, particularly working memory—the short-term storage and manipulation of information (Baddeley, 1992). For example, men treated with a high dose of hydrocortisone show impaired working memory, assessed using an item-recognition working memory task (Lupien et al., 1999). Stress-induced increases in cortisol also have been associated with impaired high-load working memory performance (Oei et al., 2006).

Although glucocorticoid administration may not affect all working memory-related tasks (Vaz et al., 2011), one working memory task that has been found to be influenced in a number of studies is Digit Span, a task that requires the recall and recitation of strings of numbers both forwards and backwards. Studies of healthy young men have found impaired Digit Span performance following treatment-induced glucocorticoid elevations (Vaz et al., 2011; Wolf et al., 2001), as well as following stress-induced glucocorticoid elevations (Schoofs et al., 2009). Another study found similar impairment following stress-induced glucocorticoid elevations in both men and women who showed strong adrenergic activation following stress (Elzinga and Roelofs, 2005). Thus, research in humans, as well as in non-human animals, suggests that exposure to abnormal glucocorticoid levels, particularly glucocorticoid excess, can have a detrimental impact on working memory.

Given the evidence that glucocorticoids can influence working memory, particularly Digit Span performance, altered performance in the Digit Span test might be hypothesized in individuals with CAH. In the current study, we investigated Digit Span performance in children with CAH and in their unaffected relatives, who served as controls. We tested the hypothesis that Digit Span performance is reduced in children with CAH. Children were also given a test to assess their Vocabulary. This measure has not been related to glucocorticoid exposure, so was used as a control measure and was not anticipated to show group differences.

Methods

Subjects

A total of 107 children were studied, aged 7 to 11 years—57 with classical CAH (26 boys, 31 girls) and 50 unaffected siblings and cousins (20 boys, 30 girls) who served as controls. Table 1 shows the means (*Ms*) and standard deviations (*SDs*) of the ages for the four groups of children (boys and girls with CAH and control boys and girls). These children were part of a larger study designed to investigate gender-related behavior in 4–11 year old children with CAH. The Digit Span test was the only measure that was included with the intent of assessing behavioral effects of glucocorticoids. All other measures were included to assess the possible masculinizing effects of androgens, and results for those measures are being reported separately. Only children from the larger study who were 7 years of age or older completed the Digit Span test, because it is not age-appropriate for younger children.

Table 1
Ms (and *SDs*) for Digit Span, age and Vocabulary in boys and girls with CAH and in unaffected controls.

	CAH		Controls	
	Male ($n = 26$)	Female ($n = 31$)	Male ($n = 20$)	Female ($n = 30$)
Age	8.48 (1.25)	8.69 (1.37)	9.29 (1.56)	8.90 (1.70)
Vocab	10.50 (2.94)	9.35 (3.39)	10.65 (2.50)	10.70 (3.03)
DSF[a]	7.81 (2.00)	7.58 (1.91)	8.30 (1.81)	9.30 (2.51)
DSB[a]	5.50 (1.48)	5.58 (1.29)	6.05 (1.43)	6.47 (1.55)
DSC[a]	13.31 (2.53)	13.16 (2.42)	14.35 (2.83)	15.77 (3.31)

Vocab, Vocabulary.
[a] Children with CAH performed significantly poorer compared to unaffected controls.

Most children ($n = 95$) were Caucasian. One was African/Afro-Caribbean, 2 were Asian (Indian/Pakistani/Bangladeshi), 2 were Middle Eastern, and 6 were of mixed ethnicity along with Caucasian (African/Afro-Caribbean, Far Eastern, Middle Eastern, or Indo-Caribbean). For 1 child, information on ethnicity was not provided.

Children with CAH were recruited via National Health Service (NHS) Hospitals in the UK (18 boys, 24 girls) or CAH support groups (7 boys, 6 girls). The recruitment of 1 additional boy and 1 additional girl with CAH was achieved through contacts with other subjects (i.e., snowball sampling, a recruitment technique particularly useful for rare populations; Kalton and Anderson, 1986). All children with CAH had 21-hydroxylase enzyme deficiency; 50 had salt-wasting CAH (24 boys, 26 girls), and 7 had simple-virilizing CAH (2 boys, 5 girls). None of the children had been treated prenatally with dexamethasone, a glucocorticoid that is sometimes used to treat pregnancies where CAH is suspected. The project was approved by the NHS Health Research Authority, and children and their parents provided written assent and consent, respectively, before taking part.

Measures

Digit Span

The Digit Span test is a subtest taken from the fourth edition of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003), a standardized set of subtests with well-established reliability and validity. The Digit Span test includes a forwards phase, Digit Span Forwards (DSF), and a backwards phase, Digit Span Backwards (DSB). Each phase consists of a series of test items, and each test item involves 2 trials, made up of a series of digits of the same length. The length of the series of digits in the first item is 2 digits, and the length increases by one digit for each subsequent item. For DSF, the examiner read out a string of digits, and the child repeated the digits aloud verbatim. For DSB, the child repeated the digits aloud in reverse order. For both forward and backward phases, 1 point was awarded if all digits were repeated correctly. If the child was unable to give a correct response for a specific trial, the child received 0 points and the examiner moved on to the next trial. Once the child was unable to respond correctly to both trials in an item of a particular length, the measure was discontinued. Performance on DSF and DSB was assessed, with a maximum score of 16 points each. The two phases also were combined to form a Digit Span Composite (DSC), with a maximum score of 32 points.

Vocabulary

The Vocabulary subtest of the WISC served as a measure of verbal intelligence. Children were required to provide a definition of a word read aloud to them by the examiner. In terms of scoring, a good synonym for a word item, for example, would be awarded 2 points. A lack of content in the child's response or a vague knowledge of the word item is awarded 1 point only. An obviously incorrect response or one with no real understanding is given 0 points. The Vocabulary measure is discontinued if the child receives a score of 0 after 5 consecutive attempts.

Statistical analyses

Two-way analyses of variance (ANOVAs) were used to investigate the influence of diagnosis (CAH, control) and of sex (male, female) on working memory performance. Sex was included as a factor, as well as diagnosis, because much of the prior research showing glucocorticoid effects on memory has involved only males, and so effects might be limited to males. When age or Vocabulary correlated with a specific task