JIDR Journal of Intellectual Disability Research
Published on behalf of MENCAP and in association with IASSIDD

Journal of Intellectual Disability Research doi: 10.1111/j.1365-2788.2012.01557.x

VOLUME 57 PART 6 pp 539–551 JUNE 2013

Hypothalamic-pituitary-adrenal (HPA) axis activity in adults with intellectual disabilities: a preliminary investigation

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Abstract

Background Cortisol is a marker of physiological arousal, exhibiting a characteristic pattern of diurnal activity. The daily cortisol profile has been examined extensively and is atypical in a number of clinical disorders. However, there are very few studies focussing on the cortisol profile in adults with intellectual disabilities (ID). This paper reports a preliminary investigation into the nature of the cortisol profile in adults with mild or moderate ID and provides reflections on the challenges of psychophysiological research in this population.
Methods On two consecutive days, 39 adults with mild or moderate ID each donated saliva samples for cortisol analysis, at multiple times between waking and evening. A comparison between these data and the published literature permitted a descriptive assessment of the cortisol awakening response (CAR) and diurnal profile. A variety of psychometric measures and an assessment of behavioural history were also collected in order to describe aspects of the participants' emotional and behavioural states.
Results Individuals with ID exhibit a diurnal cortisol secretion profile, qualitatively similar to that of the typical, healthy, adult population. However, the findings also suggested a blunted CAR, warranting further investigation. There was also some evidence that cortisol secretion was affected by anxiety and a recent history of aggression.
Conclusion While further work is required to characterise the CAR fully, there was no indication that the diurnal cortisol profile among people with ID differs from that of the typical population. This study also demonstrates that, although challenging, it is feasible, and acceptable to participants, to collect repeated physiological measures from men and women with mild and moderate ID.

Keywords adults, HPA axis, intellectual disability, salivary cortisol

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Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is a biological arousal system, which typically exhibits a characteristic pattern of diurnal activity, and is reactive to a variety of psychological and physiological 'stressors'. There is an established body of literature investigating the HPA axis in typical (healthy) and clinical populations that has highlighted the relationship between mental health and behaviour and HPA axis activity (see e.g. Burke *et al.* 2005; van Goozen *et al.* 2007; Lupien *et al.* 2009). There are, however, few studies characterising HPA axis functioning in adults or children with intellectual disabilities (ID; see Symons *et al.* 2003, 2011, for exceptions). In order to develop our understanding of the possible diagnostic and therapeutic implications of HPA axis dysfunction, more needs to be known about its activity among people with ID who do not have any additional acute disorder. The present study aims to address this need by being the first to characterise the diurnal cortisol rhythm in a community sample of adults with mild or moderate ID in their routine environments.

Hypothalamic-pituitary-adrenal axis activity may be assessed by measuring levels of its end-product, cortisol. In studies of typical individuals, the HPA axis is controlled by circadian oscillators, yielding a characteristic 24-h pattern of cortisol fluctuation, on which are superimposed a series of peaks in response to daily events (e.g. Herman & Cullinan 1997; Tsigos & Chrousos 2002; Elverson & Wilson 2005; Herman *et al.* 2005). Cortisol levels peak in the morning hours and then decline over the course of the day, reaching a nadir in the first half of the night (Edwards *et al.* 2001; although see Stone *et al.* 2001). Approximately 30–45 min after waking, there is a sharp increase in cortisol of about 50–75% of awakening levels (Pruessner *et al.* 1997; Wilhelm *et al.* 2007; Fries *et al.* 2009; Clow *et al.* 2010), observable in 75% of healthy adults (Wüst *et al.* 2000a), which is termed the cortisol awakening response (CAR; see review by Clow *et al.* 2010). Despite the inter- and intra-individual variability inherent in the HPA system (e.g. Pruessner *et al.* 1997; Stone *et al.* 2001), the CAR has relatively high intra-individual stability ($r = 0.63$ for area under curve across two consecutive days, Wüst *et al.* 2000a), although it remains sensitive to certain state factors (Kunz-Ebrecht *et al.* 2004; Hellhammer *et al.* 2007; see review by Chida & Steptoe 2009). The CAR has been studied extensively in both typical and clinical populations, and, given its relative stability, is considered to be a reliable measure of the functional integrity of the HPA system (Pruessner *et al.* 1997; Wüst *et al.* 2000b).

Atypical activation of the HPA axis is associated with a variety of adverse health states (Selye 1936; McEwen 1998; de Kloet *et al.* 2005). For example, the normal diurnal rhythm is disrupted in depression (Yehuda *et al.* 1996; Goodyer *et al.* 2001), with evidence for both an increased or reduced CAR (Bhagwager *et al.* 2005; Stetler & Miller 2005). In post-traumatic stress disorder, morning cortisol secretion is reduced (Yehuda *et al.* 1996; Wessa *et al.* 2006) and is influenced by levels of anxiety (Greaves-Lord *et al.* 2007; Kallen *et al.* 2008) or stress (see review by Chida & Steptoe 2009). Cortisol levels are reduced in chronic fatigue syndrome (Strickland *et al.* 1998; Roberts *et al.* 2004; Jerjes *et al.* 2006) and dysregulated in emotional 'burnout' (Melamed *et al.* 1999; Pruessner *et al.* 1999; Grossi *et al.* 2005). While the findings are inconsistent (Grossi *et al.* 2005; Van Bokhoven *et al.* 2005), several studies have shown that basal cortisol levels or cortisol responses to stress are reduced in behavioural disorders, such as oppositional defiant disorder and conduct disorder (Vanyukov *et al.* 1993; van Goozen *et al.* 1998; McBurnett *et al.* 2000; Pajer *et al.* 2001; Oosterlaan *et al.* 2005; Popma *et al.* 2006; Fairchild *et al.* 2008; see van Goozen *et al.* 2007, for review).

Despite this substantial literature, very little is known about HPA axis activity in people with ID, with or without a concurrent psychiatric or behavioural condition. Two factors that distinguish the experiences of those with ID from the rest of the population may, perhaps, influence cortisol secretion in this group. First, reduced psychological processing capacity in adults with ID may alter their interpretation of typical everyday situations, increasing the frequency of situations that may be perceived as stressful. Secondly, this group of men and women often live in environments (e.g. staffed residential accommodation) that differ in many regards from those of the majority of their counterparts in the typical population. The impact of these variables on basal cortisol secretion, particularly in relation to

perceived and chronic stress, is unknown, and it may be inappropriate to extrapolate data describing cortisol rhythms in typical populations to people with ID without results to support such an approach.

This preliminary study is the first to investigate the nature of the HPA axis profile in a broad sample of adults with mild or moderate ID, in order to develop an understanding of the diurnal cortisol rhythm in the absence of an acute disorder. The primary aim was to describe the nature of the CAR and the diurnal cortisol rhythm, and to compare them with reports in the literature involving both typical and clinical populations. The secondary aims were to comment on the intra-individual stability of the CAR, and the associations between HPA axis activity and psychometric assessments of mood and aggression.

Methods

Ethical approval was granted by the Cambridgeshire 3 Research Ethics Committee. Only individuals with the capacity to participate, and who provided written consent, took part.

Participants

Through contacts with local clinical services, 39 adult participants (aged 18 years or more) were recruited. All of them were regarded by their services as people with mild or moderate ID. Thirty-three participants lived in community-based settings (on their own, or in supported residential accommodation). The remaining six were men detained under the Mental Health Act 1983 (as amended 2007) in a local independent hospital. Individuals who were dependent on illegal drugs or alcohol, had acute affective or schizophrenic disorders or dementia, or whose capacity to consent to participate was uncertain or absent, were excluded.

A full list of all current prescribed medication was collected since certain drugs are known to influence HPA axis activity (Masharani *et al.* 2005; Cohrs *et al.* 2006; Hibel *et al.* 2006, 2007; Chamberlain *et al.* 2007). Any diagnosed medical condition associated with the person's ID was also recorded.

To ensure that participants would be able to understand the demands of the study, each was asked to complete the British Picture Vocabulary Scale III (BPVS; Dunn *et al.* 2009), an assessment of comprehension of single words. This test covers a wide range of ability, has a satisfactory correlation with overall intellectual functioning, and is known, from clinical experience, to be acceptable to people with ID.

Measures

Mood and behavioural assessments

Depression. The carer supplement of the Glasgow Depression Scale for people with an ID (GDS-CS; Cuthill *et al.* 2003) was completed by a carer, support worker or member of nursing staff who knew the participant well.

Anxiety. Initially, participants completed the Glasgow Anxiety Scale for people with ID (GAS; Mindham & Espie 2003). However, some participants were not able to understand the questions fully, prompting a change to the adapted version of the Zung Self-Rating Anxiety Scale for adults with ID (ZAS; Lindsay & Michie 1988; see also Ramirez & Lukenbill 2008).

Aggression. An adapted version of the Modified Overt Aggression Scale (MOAS; Sorgi *et al.* 1991; see also Oliver *et al.* 2007) was used to assess the frequency and severity of aggressive behaviour over the 6 months preceding the study.

Cortisol

As biologically active free plasma cortisol can be reliably and non-invasively measured in saliva (Arafah *et al.* 2007; Kerlik *et al.* 2010; for review, see Hellhammer *et al.* 2009), each participant was asked to donate up to eight saliva samples for cortisol analysis, each day, for two consecutive days. Four samples were collected in the first hour after waking: immediately on waking, +30 min, +45 min and +60 min after waking, to describe the CAR. Four more samples were collected through the rest of the day, approximately +3 h, +6 h, +9 h and +14 h after waking, to describe the rest of the diurnal rhythm. This protocol is consistent with the relevant literature (e.g. Wüst *et al.* 2000b; Edwards

et al. 2001; see review of salivary cortisol research techniques by Adam & Kumari 2009).

To minimise any disruption or stress to the participants, their usual carers, support workers or nursing staff were invited to assist the research team with sample collection where possible. Considerable efforts were made to explain to these supporters the importance of taking the first sample as soon as possible after participants awoke. It was also explained that if this sample were taken late, then subsequent samples should be taken at times based on the assumed waking time, not on the time of the actual first sample. For participants based in the community, members of the research team arranged, whenever possible, to be available to assist with the accurate collection of all samples, and in particular the first morning samples. For these community-based participants only, a device to monitor motor activity and heart rate was also used to attempt to measure and quantify the expected slight delay between waking time and the collection of the first 'waking' saliva sample, as described below.

To collect the saliva, initially two 'Sorbettes' were held together for each sample, but a low yield prompted a change to the 'Children's Swab' (both provided by Salimetrics Europe Ltd, Suffolk, UK). Samples were obtained according to the manufacturer's instructions, refrigerated on or shortly after collection, and frozen at −20°C within 56 h of collection, until assay. To reduce sample contamination, participants were discouraged from smoking, eating, drinking anything other than water, or brushing their teeth for the 30 min before a sample was due. No salivation aid was used.

Heart rate and motor activity

Participants recruited from the community were asked to wear an Actiheart heart monitor (CamNtech, Cambridgeshire, UK) for the duration of the study. Each monitor was pre-programmed to record motor activity and heart rate data in 15-s epochs, and was attached the evening proceeding the first day of saliva collection using standard sticky electrode patches. The information collected was used to corroborate reported waking time (Stalder *et al*. 2009, 2011). For practical reasons, the Actiheart was not used in the hospital setting.

Results

All data were analysed using SPSS for Windows v20 (IBM SPSS Statistics, New York, USA).

Participants

All participants were of White British ethnic origin, with a mean age of 42.9 years (SD 13.3, range 20–65); 62% ($n = 24$) were men. Their mean raw score on the BPVS was 108.4 (SD = 30.9, range = 47–157), indicating that, on average, their understanding of single words was at the level expected of a typically developing person aged 8 years 1 month (95% confidence band: 7 years 2 months to 8 years 8 months).

Two participants had a diagnosed genetic syndrome; in one case fragile X syndrome, and in the other, Prader–Willi syndrome. Twelve participants (31%) smoked tobacco regularly. Medications prescribed to participants that may influence HPA axis activity are shown in Table 1.

Mood and behavioural assessments

Data from the GDS-CS, GAS, ZAS and MOAS are shown in Table 2. For five participants, no anxiety data could be collected. Responses to the GDS-CS suggest that, as a group, the participants were not depressed (Cuthill *et al*. 2003). The 13 participants who scored more than 13 on the GAS may be considered to have a possible anxiety disorder (Mindham & Espie 2003); there are no equivalent

Table 1 The percentage (and number) of participants who were regularly taking prescribed medications that may influence hypothalamic-pituitary-adrenal axis activity

Medication class	Percentage (*n*)
Selective serotonin reuptake inhibitors	36% (14)
Atypical anti-psychotics	31% (12)
Anti-epileptic agents	26% (10)
Inhaled corticosteroids	18% (7)
Typical anti-psychotics	13% (5)
Benzodiazepine or benzodiazepine derivatives	10% (4)
Hormone replacement therapy or oral contraceptive	8% (3)
Selective noradrenaline reuptake inhibitors	3% (1)

Table 2 The mean, median and standard deviation (SD) of mood and behavioural measures: GDS-CS, GAS, ZAS and MOAS

Measure	*n*	Mean	Median	SD
GDS-CS	39	4.8	3	4.5
GAS	20	16.7	17	12.2
ZAS	14	6.9	6	3.1
MOAS	39	13.2	4	19.1

The total score on the MOAS was calculated according to the method described in Sorgi *et al.* (1991). Anxiety data are missing from five participants, who did not complete the GAS or the ZAS. GDS-CS, Glasgow Depression Scale for people with an intellectual disability – Carer Scale; GAS, Glasgow Anxiety Scale for people with intellectual disabilities; ZAS, Zung Self-Rating Anxiety Scale for adults with ID; MOAS, Modified Overt Aggression Scale.

clinical guidelines for assessing anxiety with the ZAS.

Cortisol

The majority (87% out of a total of 624) of the scheduled saliva samples were collected successfully. Samples were not collected when it was not possible for a member of the research team (or carer, support worker or member of nursing staff) to be with the participant to assist. Of the samples collected, 66% contained sufficient saliva for laboratory testing (in total, 57% of all possible samples were suitable for analysis). There was no identified temporal pattern to the distribution of failed samples, although some participants were more likely than others to donate samples with insufficient saliva. There was no difference between the 'Sorbettes' and the 'Children's Swab' in the proportion of viable samples collected [$X^2(1, 544) = 1.79$ with Yates' correction, $P = 0.180$].

Data from each participant-day were excluded from the analysis of cortisol levels if there were not a minimum of two viable morning and two viable afternoon/evening samples. Forty-five (of a potential 78) participant collection days (58%), from 29 participants, met these criteria. Of these, only averaged data from the 16 participants (11 men and 5 women) who contributed sufficient samples from both days of collection were used in the analysis of the CAR and diurnal cortisol production.

Data were processed in a manner consistent with the literature (e.g. Edwards *et al.* 2001; Fairchild *et al.* 2008; see also review by Adam & Kumari 2009). Prior to statistical analysis, cortisol values were normalised using a natural log transformation and winsorised at 2.5 SD to eliminate outliers (the values of three samples, <1% of the total data set, were adjusted). The mean cortisol level was calculated at each of the eight time points, for each of the 16 participants who contributed sufficient samples from both days of collection. Absolute cortisol concentrations are presented in Fig. 1 in order to be physiologically meaningful and to permit comparison with other studies. The CAR was quantified using the Area Under Curve (Pruessner *et al.* 2003) with respect to the first sample (AUC_i) with data from the first four samples only; while total cortisol secretion was quantified by the Area Under Curve with respect to zero (AUC_g) using all eight samples. Repeated-measures ANOVAs were conducted initially, with time as a within-subjects factor, missing data deleted listwise, and degrees of freedom corrected using Greenhouse–Geisser procedures. Independent or paired samples *t*-tests were performed as appropriate. Given the exploratory nature of this study, correlations (Pearson's *r*) were performed without correction to permit multiple comparisons. Participants with and without a history of aggressive behaviour were separated, on the basis of their scores on the MOAS, into two groups of equal size for analysis.

Waking time accuracy

Data from the Actiheart device were collected for 29 of the 33 community-based participants (88%). Two participants did not want to wear the device, and, for practical reasons, the equipment was not available for use in a further two cases. Data from five participant-days were lost because of equipment failure, and a further 17 participant-days were excluded because the data were invalid or of poor quality. The remaining 36 participant-days, from 25 participants, were inspected manually and used to provide an objective check on reported waking time accuracy (Stalder *et al.* 2009, 2011; see also Kupper *et al.* 2005). Waking was defined as an increase in either heart rate or activity of two or more standard deviations above the sleeping average, sustained for

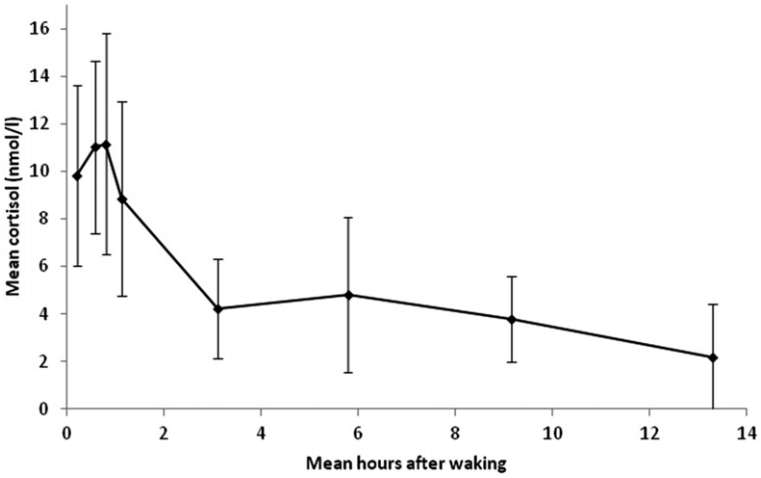

Figure 1 Mean salivary cortisol levels (nmol/L) from 16 participants, for which there are a minimum of two viable morning and two viable afternoon/evening samples on each of the two days of collection. Results are shown as a function of mean time (h) relative to reported waking, calculated independently for each of the eight saliva samples. Error bars are one standard deviation of the mean. Samples were collected at approximately the time of waking (+0 min), waking +30 min, waking +45 min, waking +60 min, waking +3 h, waking +6 h, waking +9 h, and waking +14 h.

approximately 1 min. An apparent awakening response was observed in 75% ($n = 27$) of the 36 participant-days (from 19 participants) where there were good quality night-time data. Reported and calculated waking times were significantly correlated ($r = 0.902$, $P < 0.001$, $n = 26$). The median absolute difference between reported and calculated waking time was 13.5 min (SD 24.2 min; calculated waking time precedes reported waking time).

Profile of the cortisol diurnal rhythm

Figure 1 shows the cortisol rhythm, with absolute mean salivary cortisol concentrations from the 16 participants who contributed data from both days of collection. Qualitatively, these data appeared very similar in magnitude and profile to those observed in a typical, healthy, adult population (e.g. Pruessner *et al.* 1997; Edwards *et al.* 2001). The morning samples (one to four) were averaged and shown to be significantly higher than sample eight, $t(15) = 9.612$, $P < 0.001$, demonstrating the expected decline in cortisol levels over the course of the day. Over the course of the day, women produced more cortisol than men [AUC_g, eight samples; $t(14) = 3.970$, $P = 0.001$]. Consistent with the study by Cohrs *et al.* (2006), atypical antipsychotic use was associated with a decrease in cortisol production (AUC_g eight samples; $t(14) = 2.703$, $P = 0.017$, based the seven participants in the sample taking atypical antipsychotic medication).

Cortisol awakening response

Inspection of the averaged cortisol data from 16 participants did not reveal the expected steep rise in the first hour after waking, and there was no statistically significant effect of time (first four samples only: $F_{1.9,23.2} = 2.003$, $P = 0.159$). Only six of 16 participants exhibited a significant CAR, according to the criteria in Wüst *et al.* (2000a, which define a CAR as a rise in cortisol concentration, of at least 2.5 nmol/L, within 30 min of waking). To investigate the effect of sample time accuracy on the CAR, participants were excluded if any of samples two, three or four were not collected within 5 min of the target time, and if the four afternoon and evening samples were not collected, on average, within 60 min of the target times, as calculated from reported time of waking on each of the two days. Eight participants remained after these criteria were applied. This small but optimised data set was then compared with data from the typical population (displayed in Fig. 2). To maximise case inclusion in this small data set, Friedman's non-parametric test was used to compare morning samples only. A trend towards a significant change in cortisol level was obtained, which may indicate a CAR [$X^2(3) = 7.400$, $P = 0.06$]. The findings of *post hoc* tests were not statistically significant once corrections were made for multiple comparisons. Nevertheless, the analysis suggested that, in this more accurate sample, there may have been a weak awakening response.

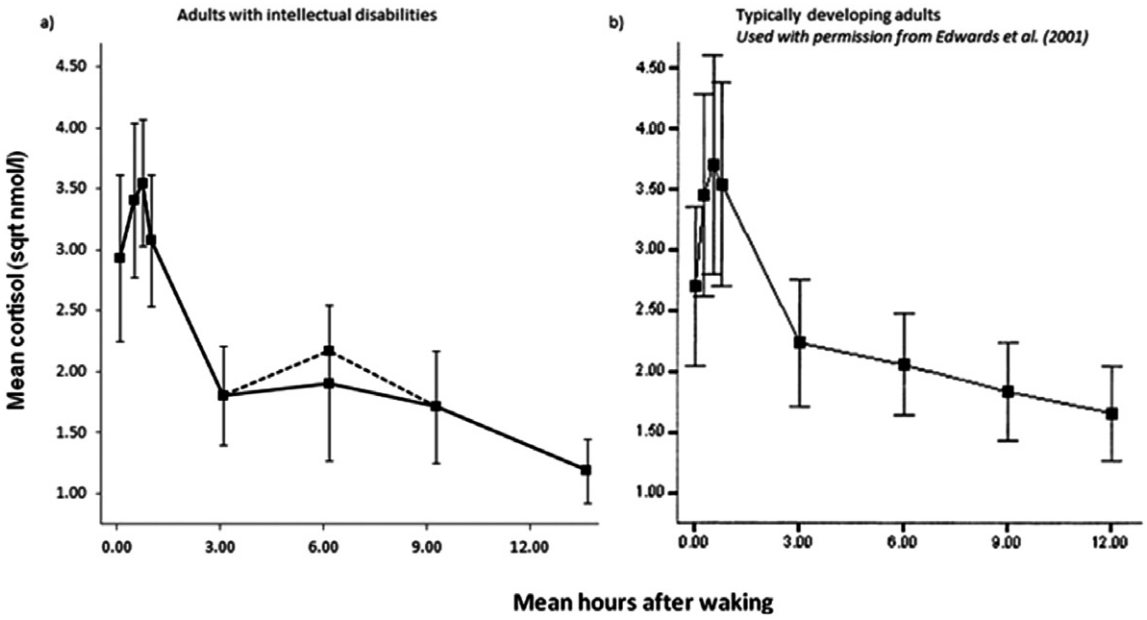

Figure 2 The square roots of mean salivary cortisol levels were calculated to allow comparison with those provided by Edwards *et al.* (2001). (a) Mean salivary cortisol levels (square root nmol/L) from eight participants, for which participant-days have a minimum of two viable morning and two viable afternoon/evening samples on each of the two days of collection, and (i) samples two (waking +30 min), three (waking +45 min) and four (waking +60 min) are all collected within 5 min of target time, as calculated from reported time of waking on each of the two days; and (ii) samples five (waking +3 h), six (waking +6 h), seven (waking +9 h) and eight (waking +14 h) are collected, on average, within 60 min of target time, as calculated from reported time of waking on each of the two days. Results are shown as a function of mean time (h) relative to reported waking, calculated independently for each of the eight saliva samples. Samples were collected at approximately waking +0 min, waking +30 min, waking +45 min, waking +60 min, waking +3 h, waking +6 h, waking +9 h and waking +14 h. The dotted line is the average of all samples; the solid line is the average of all samples excluding a single outlier at sample six (waking +6 h), which lies more than two standard deviations from the mean. (b) Mean salivary cortisol levels (square root nmol/L) in typical, healthy adults, reproduced with permission from Edwards *et al.* (2001), for comparison. Samples were collected at approximately the time of waking (+0 min), waking +15 min, waking +30 min, waking +45 min, waking +3 h, waking +6 h, waking +9 h and waking +12 h. All error bars are one standard deviation of the mean.

In this restricted data set (Fig. 2), there appeared to be a second peak at sample six (around 6 h after waking). Further examination revealed this to reflect primarily a single outlying cortisol value, almost two standard deviations above the average for sample six.

Effect of mood and behavioural measures on cortisol secretion

As mood and behaviour are known to have a subtle effect on cortisol secretion, case inclusion was maximised by combining averaged data from the 16 participants who contributed data from both days of collection with the 13 participants who contributed data from only 1 day (total $n = 29$). While there was no relationship between the GAS or GDS and any measure of daily cortisol secretion, there was a significant positive correlation between the ZAS and AUC_i (morning samples; $r = 0.637$, $P = 0.026$, $n = 12$). To explore the nature of the relationship between MOAS scores and cortisol secretion, participants were divided into two groups of equal size, with a 'low' (four or less, 15 participants), or 'high' (five or more, 14 participants), MOAS score. An independent samples *t*-test between the two groups revealed a significant relationship between a recent history of aggression, as indicated by a MOAS score ≥ 5, and the size of the minima (average time 6.59 PM) of cortisol secretion [$t(21.1) = -2.772$, $P = 0.011$, equal variances not assumed]. That is, as a group, the participants who scored more highly

on the MOAS, indicating a recent history of more frequent, or more severe, aggressive behaviour, had higher cortisol levels, at a time when cortisol secretion is typically low, than participants with a lower MOAS score.

Comparison between day one and day two

A comparison of cortisol descriptors from each day, for the 16 participants who contributed data from each day of collection, revealed significant correlations between the magnitude of the waking response, AUC_i ($r = 0.659$, $P = 0.006$, $n = 16$, although this is influenced by an outlier; $r = 0.474$, $P = 0.074$, $n = 15$ with the outlier removed), and the average diurnal cortisol concentration (average of samples five, six, seven and eight; $r = 0.551$, $P = 0.027$, $n = 16$), demonstrating some intra-individual stability for the duration of the study. Consistent with these results, for the seven participants for whom sufficient data were available, there was a significant correlation between days one and two for the maximum increase in morning cortisol levels ($r = 0.943$, $P = 0.001$, $n = 7$).

Discussion

In this preliminary, but innovative, study, our primary aim was to characterise the profiles of the CAR and diurnal cortisol rhythm across a range of adults with mild or moderate ID and no known acute disorder, and to consider these profiles in comparison with an established body of literature from healthy and clinical populations without an ID.

Importantly, the profiles obtained were similar, both in terms of absolute magnitude and in shape, to those described previously for individuals in healthy populations without ID (Pruessner *et al.* 1997; Edwards *et al.* 2001). It was also shown that, consistent with published data (Pruessner *et al.* 1997; Wüst *et al.* 2000a; Larsson *et al.* 2009; although c.f. Edwards *et al.* 2001), women produced more cortisol than men over the course of the day. Surprisingly, however, we did not find the expected 50–75% increase in the CAR in the 30 min after waking. Only six of 16 participants showed a CAR as defined by Wüst *et al.* (2000a), with the majority of participants exhibiting a flatter morning cortisol profile, or no rise after awakening.

A reduced or absent CAR has also been observed in several clinical populations (see review by Fries *et al.* 2009), such as those with mild to moderate clinical depression (Stetler & Miller 2005; c.f. Bhagwager *et al.* 2005; see review by Chida & Steptoe 2009), Asperger's syndrome (Brosnan *et al.* 2009) or some neurological conditions (Buchanan *et al.* 2004; Wolf *et al.* 2005). People with ID may have a variety of additional conditions, and it is possible that one or more of the above, although not detected, may have influenced the CAR findings obtained in our participants.

Nevertheless, aside from the morning samples, the underlying diurnal pattern of HPA axis activity was similar to that observed in the typical adult population, and was reasonably stable over the two consecutive days of the study. Although people with ID have a CAR that may differ from that of their counterparts in the general population, this would seem to be independent of an otherwise typical diurnal fall in salivary cortisol. This is important, because cortisol secretion that is either increased, reduced or dysregulated, in comparison to a normal profile, is associated with poor physical and psychological health outcomes and impaired neurocognitive performance. For example, hypercortisolism is the characteristic feature of Cushing's syndrome, and may lead to morphological brain changes and cognitive impairment, in addition to effects on mood (Sapolsky 2000; Starkman *et al.* 2001; Bourdeau *et al.* 2002; Sheline 2003). Conversely, hypocortisolism is observed in chronic fatigue and in post-traumatic stress disorder, and may enhance vulnerability to a number of other conditions such as allergy and autoimmune disease (see review by Heim *et al.* 2000).

A secondary aim was to investigate the nature of the relationship between descriptors of the mood and behaviour of the participants (state anxiety, depression and aggression) and measures of cortisol secretion. There was no evidence of any associations between depression (GDS) and measures of cortisol secretion. There was a positive relationship between the magnitude of the wakening response and anxiety measured by the ZAS, for which there is some support in the literature. For example, Greaves-Lord *et al.* (2007) showed an increased CAR in young people without ID but with persistent anxiety (although see also Therrien *et al.* 2008;

Kallen *et al.* 2008; see review by Chida & Steptoe 2009). Such a relationship was not evident in the GAS data, but this may simply reflect the participants' difficulties in understanding the questions in the scale. Our data also showed that the cortisol levels of participants with a history of aggression do not decline over the course of the day to the same levels as those of participants without such a history. An association between aggressive behaviour and elevated evening cortisol secretion, or a flatter cortisol profile, has been reported in other published studies (Popma *et al.* 2007; Fairchild *et al.* 2008), and is consistent with the findings of elevated cortisol levels among adults with ID who engage in self-injurious behaviour (Symons *et al.* 2003, 2011). We believe, therefore, that the potential relationship between cortisol levels and different types of challenging behaviour warrants further investigation.

This study has a number of limitations that deserve comment. While the use of a heterogeneous sample reflects an attempt to represent the diversity of the population of people with ID, a much larger sample would be required in order to control for various participant factors that have been shown to influence cortisol secretion, such as the presence of depression or anxiety, the effect of medication for the treatment of mental or physical health conditions, the influence of any undetected physical health problems and a history of aggressive behaviour. The strength of our conclusions is also limited by the quality of the cortisol data, and it may be that the weak CAR demonstrated in this study is a methodological artefact because of difficulties in adhering strictly to the sample collection protocol. It is noteworthy that the magnitude of the measured CAR increased slightly in the subgroup of participants with the strictest adherence to this protocol. In some of the other cases, it is possible that the waking sample was taken late, a short period after actual waking. Where this occurred, the samples may not have captured the full upstroke of the CAR (as argued in Kupper *et al.* 2005). Nevertheless, in support of our data, there was a strong correlation between reported waking time and waking time independently calculated using heart rate and motor activity data from the Actiheart device (see Stalder *et al.* 2009, 2011; $r = 0.902$, median difference 13.5 min, SD 24.2 min). This suggests reasonable compliance with the study protocol, and Dockray *et al.* (2008) observe that a delay of up to 15 min between waking and the first sample may have little effect on the CAR. Nevertheless, it is still possible that the delays may have been sufficient to influence our findings.

We encountered a number of challenges in collecting endocrine data from adults with ID. First, it was difficult to collect saliva samples accurately with respect to waking time. Participants were often unaware of their own waking times, and carers, support workers or nursing staff were unable to report precise 'eyes open' times. Given the need to record waking cortisol samples accurately with respect to waking (Kudielka *et al.* 2003; Dockray *et al.* 2008), this is a serious obstacle to HPA axis research involving people with ID. Second, while both the 'Sorbettes' and 'Children's Swab' were appropriate for use with our sample, the participants were unable to donate saliva without supervision. The samples were therefore collected with the assistance of a team of researchers, carers, support workers and nursing staff across several sites and services. Although it is promising that nearly nine-tenths of scheduled samples were collected, incorrect sample collection methodology, timing, storage or transport practices, which were primarily a consequence of locating the research in participants' normal environments, may all have contributed to the loss of cortisol data. Sample viability may be enhanced by maximising the amount of training and support provided to those who assist in collecting the saliva.

Conducting the mood assessments was also challenging. Disappointingly, since it is well-established for people with ID and psychometrically sound (Hermans *et al.* 2011), the GAS (Mindham & Espie 2003) proved unsuitable for our participants: a number were unable to comprehend the questions, as evidenced by perseveration and conflicting responses, particularly in Part One of the scale question set (subtitled 'worries'). The symptom-based ZAS (Lindsay & Michie 1988) was better suited, particularly to participants whose lower scores on the BPVS III indicated that they had more difficulties with language comprehension. There were also some difficulties around the use of the measure of aggression. While the MOAS has demonstrated utility in assessing the history of this

behaviour in people with ID (Oliver *et al*. 2007), it focuses only on the previous 6 months, and therefore may be of limited use for participants whose aggression, while serious, may be only intermittent, with long intervals between occurrences.

Despite these limitations, the demands of the study, including donation of saliva and wearing of the Actiheart device for up to 48 h were, generally, acceptable to participants, and their carers, support workers or nursing staff. One participant refused to wear the Actiheart because of previous personal experiences unrelated to the study, and another participant declined for unknown reasons. None of the participants withdrew from the study prematurely. This is encouraging. It indicates that, while there are a number of practical challenges that need to be overcome in order for the research literature regarding physiological arousal to develop, it is possible to collect repeated physiological and neuroendocrine data from adults with significant ID. Such data may, ultimately, lead to a more complete understanding of the mental health and behavioural difficulties for which people with ID are at increased risk, compared to their healthy, typically developing, counterparts.

In conclusion, this study shows, in a small sample of adults with mild to moderate ID, that the diurnal profile of cortisol secretion is similar to that of the typically developing population, although the CAR appears blunted in comparison. Moreover, we have found some evidence for intra-individual stability and for the effects of gender, anxiety and a history of aggression on cortisol secretion, for which there is support in the established literature based on the 'typical' adult population. While acknowledging a number of limitations in the study, even in our optimised data set there is evidence of a reduced awakening response superimposed upon an otherwise typical diurnal cortisol profile. Replication of our findings and further investigation of HPA axis function and, specifically, the form of the CAR, is warranted.

Acknowledgements

We would like to thank the participants and their supporters for their assistance in collecting the data; without their enthusiasm and commitment, this study would not have been possible. Liz Jones (NIHR CLAHRC for Cambridgeshire & Peterborough) helped us in recruiting participants and developing materials, while Vivien Cooper (Challenging Behaviour Foundation) and Vicky Raphael (carer) provided valuable advice in the early stages of the project; we are grateful to all three of them.

Sources of funding

The authors were supported variously by: Cambridgeshire & Peterborough NHS Foundation Trust's NIHR Flexibility & Sustainability Funding, the Health Foundation, the Isaac Newton Trust, the NIHR's Collaborations for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire & Peterborough, and the Wellcome Trust; we are grateful to all of them.

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Accepted 28 February 2012