Northumbria Research Link

Objectively Assessed Prospective Memory Failures and Diurnal Cortisol Secretion in

Caregivers of Children with ASD

Caregivers of children with autism spectrum disorder (ASD) self-report more prospective memory (PM) failures compared with controls. Subjective and objective measures of PM however tend to be poorly correlated. This study therefore explored the cognitive impact of caring for a child with ASD using the Cambridge Prospective Memory Test (CAMPROMPT), a more objective, performance based, assessment of PM failures. Whether atypical cortisol secretion patterns might mediate caregivers' compromised cognition was also explored. A sample of n=23 caregivers of children with ASD and n=11 parent controls completed time and event cued PM tasks with CAMPROMPT. Diurnal cortisol indices, the cortisol awakening response, diurnal cortisol slope and mean diurnal output were estimated from saliva samples on multiple days. Results indicated objectively assessed event, but not time, cued PM failures were greater in caregivers compared with controls. Variations in cortisol secretion patterns however did not mediate the group effect. In conclusion, caring for a child with ASD was associated with greater deficits in event cued PM. Future studies might examine the influence of caregivers' event cued PM failures on quality of provided care.

Introduction

The psychosocial consequences of caring for a child with autism spectrum disorder (ASD) are well documented. It has been widely reported that caregivers of children with ASD, largely owing to elevated burden, score higher than normative (i.e., non-caregiving) controls on measures of psychological distress such as anxiety and depression (Al-Farsi et al., 2016; Bekhet & Garnier-Villarreal, in press). As for social functioning, caregivers report lower social support and fewer social relationships compared with their non-caregiving counterparts (Gallagher and Whiteley, 2012). While the psychosocial consequences of the caregiving experience are well established, far fewer studies, and fewer still involving caregivers of children with ASD, have considered the cognitive impact of caregiving.

To date, caregivers of children with ASD have been found to be more impaired on tasks of declarative and episodic memory, and perform more poorly on tests of executive function, compared with controls (Chan et al., 2017; Romero-Martínez et al., 2015; Song et al., 2016). Other cognitive processes such as prospective memory (PM), which describes the process of remembering to execute delayed intentions, have also been found to be impaired in caregivers of children with ASD (Lovell et al., 2014; McBean et al., 2016). PM would seem particularly important for ASD caregivers, who, like paid healthcare professionals, must remember to administer medications and arrange important (i.e., medical, education) appointments (Meadan et al., 2015). Other studies have highlighted the predictive value of caregivers' cognitive failures for various quality of care outcomes (Burgess & Gutstein, 2007). Particularly noteworthy are findings from de Vugt et al (2006), in which cognitively compromised caregivers reported feeling less confident about providing quality care.

To date, studies examining the impact of caring for a child with ASD on PM have relied exclusively on self-report assessments (Lovell et al., 2014; McBean et al., 2016). The poor concordance between participants' subjective perceptions of PM failures and those

detected using objective measures however has been widely reported (Thompson et al., 2015). The disassociation between subjective and objective measures has been observed for other health related variables such as sleep quality (Okifugi & Hare, 2011). With this in mind, the current study sought to explore the impact of caring for a child with ASD on cognition using the Cambridge Prospective Memory Test (CAMPROMPT), a more objective, performance based, assessment.

The study also sought to identify physiological processes mediating caregivers' compromised cognition. Cortisol, the final effector hormone of the Hypothalamic Pituitary Adrenal (HPA) axis, displays a robust basal diurnal pattern. Indeed, the cortisol awakening response (CAR), which provides one index of HPA function, is characterised by a marked increase in cortisol between waking and 30-45 minutes post waking. The diurnal cortisol slope, which captures the rate of change across the day, and mean diurnal output, which captures overall daily secretion, are also well-established HPA markers (Lovell & Wetherell, 2011). Atypical cortisol secretion patterns characterised by flatter diurnal slopes (Seltzer et al. 2009), blunted CAR magnitude (Ruiz-Robledillo et al., 2014) and mean diurnal hypo-secretion (Seltzer et al., 2010) have been observed in the context of caring for a child with DD, including ASD. Cortisol, in addition to its cardiovascular, metabolic and immunomodulatory properties, also regulates cognitive functioning (Sapolksy, 2000). Flatter cortisol slopes and increased CAR magnitude, along with diurnal cortisol hypersecretion, have been implicated as physiological markers of cognitive impairment, particularly in domains such as memory (Correra et al., 2014; Hidalgo et al., 2015). Longitudinal research also found diurnal cortisol hypersecretion to be prospectively associated with poorer performance on memory tasks (Li et al., 2006). Moreover, chronic (i.e., caregiving) stress induced elevation of cortisol has been linked with atrophy of the hippocampus and other brain regions (i.e., prefrontal cortex) that underpin cognitive processes including memory

(Stomby et al., 2016; Travis et al., 2016). Atypical patterns of cortisol secretion therefore might provide one physiological pathway by which caring for a child with ASD is associated with compromised cognition. This study sought to test this.

It was hypothesised objectively assessed PM failures would be greater in ASD caregivers compared with controls, with variations in diurnal cortisol secretion partially mediating this group effect.

Methods

Participants

A total n=49 participants were recruited via invitation letters distributed by local schools and charities, and via adverts posted on social media pages of caregiving/parenting support groups. Participants were recruited according to strict criteria. For caregivers, these were: (a) parenting at least one child, aged 3-21 years, with clinically verified (as confirmed by the parent) ASD who lives at home full time, (b) not pregnant, breast feeding, or taking steroidal medication, (c) not managing a serious medical condition, and (d) not providing care for another person (e.g., spouse, parent, or friend) with chronic illness. The control group (parents of neuro-typical children) were recruited according to the same criteria with the exception of caring for a child with ASD.

Of n=49 participants recruited, n=7 withdrew citing time pressures. Data for n=3 who did not return any saliva samples was removed, as was data for n=1 who reported failing to adhere with the saliva collection protocol on all sampling days. A further n=13 reported partial compliance with the saliva collection protocol; they adhered on one or two days only. As poor adherence with the saliva collection protocol, particularly in the morning, can lead to erroneous cortisol measurement (Stalder et al., 2015), only data from protocol adherent sampling days was taken forward for analysis. z scores were generated for all outcome

variables to screen for outliers. As per Tabachnick and Fidell (2013), $n=4$ participants with z scores >3.24 on one of more outcome variables were also excluded. The final sample included $n=23$ caregivers and $n=11$ controls. The institutional ethics committee approved the study and all participants provided informed consent. Participants were recompensed £10.00.

Measures

Potential confounds

   Data were collected with respect to a range of socio-demographic (age, gender, annual income, relationship status) and lifestyle (exercise, smoking, alcohol, sleep) variables, and child characteristics (age of child, years caregiving) that might influence PM.

Objectively assessed prospective memory

   The Cambridge Prospective Memory Test (CAMPROMPT) was used to objectively capture PM failures (Wilson et al., 2005). CAMPROMPT requires participants to complete six PM tasks, three cued by *time* (e.g., return keys to the researcher at 2.30pm) and three cued by *event* (e.g., retrieve pen from the table when cued by the sound of a bell), while attending to distractor tasks (e.g., puzzles). Participants are awarded six points if tasks are completed unaided (i.e., without a prompt from the researcher). Where a single prompt is required, four points are awarded, and two points are awarded where participants require two prompts to complete tasks. Participants unable to complete the task after a second prompt receive no points. With each time and event cued task yielding a possible 6 points, and with three time and event based tasks to complete, total subscale scores can range from 0-18, with higher scores reflecting better memory. In the current study however, rather than points awarded, points lost were recorded; higher scores therefore reflect poorer PM (i.e., more failures). Reliability of CAMPROMPT has been well-documented (Dawkins et al., 2013).

Diurnal cortisol secretion

Salivary cortisol collected at waking, 30 and 45 minutes post waking, 1200h and before bed on three consecutive, and typical, weekdays was used to estimate the cortisol awakening response (CAR), diurnal cortisol slope and mean diurnal output. Kolmogorov-Smirnov tests revealed cortisol values to be positively skewed at all sampling times (all ps < 0.01). Data therefore was $\log^{10}$ transformed to correct the skew. Two way (day*time) mixed ANOVA yielded a significant main effect of time ($F_{(3.0, 262.8)} = 180.1$, $p < .001$, $\eta p2 = .70$), reflecting the typical descending pattern of cortisol. No between day differences ($F_{(2, 89)} = .52$, $p = .60$, $\eta p2 = .01$) or day*time interaction effect ($F_{(5.9, 262.8)} = 1.8$, $p = .11$, $\eta p2 = .04$) was observed. Cortisol values for each sampling point therefore were averaged across collection days to increase the reliability resultant data.

CAR magnitude was calculated as the difference between cortisol values at waking and the peak value during the post-waking period (Stalder et al., 2015). A linear regression that predicted rate of cortisol decline from time since waking was used to estimate the diurnal cortisol slope (Hidalgo et al., 2016). Cortisol values at each sampling point were summed to yield an index of mean diurnal output (Lovell et al., 2012).

Procedure

Consenting participants were invited to the university to complete questionnaires assessing socio-demographic and lifestyle information, and provide details about the care recipient. Participants were provided salivettes and asked, on three consecutive weekdays, to collect saliva at waking, 30 and 45 minutes post waking, 1200h and before bed. Compliance with the saliva collection protocol tends to be better when participants are provided clear instructions (Saxbe, 2008). All participants therefore were asked to abstain from behaviours (e.g., eating, drinking, exercise) known to influence salivary cortisol for at least 45 minutes

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prior to sample collection (Kudielka et al., 2012). Participants were also asked to record waking and sampling times using paper diaries. Not only preferred by participants (Kraemer et al., 2006), but paper diaries show good concordance with more objective, electronic, measures of timing compliance such as actigraphy (Okun et al., 2010). Participants were asked to store saliva samples in a domestic freezer until returned to the research team. Assays were performed in house; samples were centrifuged for 10 minutes, 400 x g at 20∘C and tested using an enzyme-linked immunosorbant assay (ELISA), Salimetrics Ltd, Suffolk, England. Mean inter and intra assay coefficients were 7.1% and 10.7% respectively.

Statistical Analysis

Independent t tests and chi square (χ^2) was used to compare groups on socio-demographic and lifestyle variables, and child characteristics. Group differences on time and event cued PM failures, and cortisol indices, were explored via one-way ANCOVA. Bivariate correlation was used to explore whether time and event cued PM failures were related to cortisol indices. The SPSS PROCESS macro (model 4) with bootstrapping (5000 iterations), as per Hayes (2014), was used to explore indirect (i.e., mediation) effects.

Results

Potential Confounds

Groups were comparable with respect to gender, weight, annual income, relationship status, smoking, alcohol, sleep duration, and number of children (all ps > .19). Age ($t_{(30)}$ = 2. 27, p = .03) and exercise ($t_{(32)}$ = -2. 11, p = .04) differentiated the groups; caregivers were older (45.1 ± 6.9 vs. 38.9 ± 7.8) and exercised less often (2.3 ± 1.8 vs. 3.8 ± 2.1). Age of the child with ASD (M, 10.8, SD, 5.0), and years caregiving (M, 5.5, SD, 4.3) were unrelated to time or event cued PM failures (all ps > .23). Table 1 displays sample characteristics by group.

INSERT TABLE 1 HERE

Mediation Analysis

The effect of the independent variable (group) on the dependent variable (PM failures) was significant; caregivers performed more poorly on event ($F_{(1, 32)} = 11.7$, $p < .01$, $\eta p2 = .27$), but not time ($F_{(1, 32)} = .31$, $p = .58$, $\eta p2 = .01$), cued PM tasks. This finding satisfies the first criterion for mediation as per Baron and Kenny (1986). Data revealed no effect of the independent variable (group) on proposed mediators, CAR magnitude ($F_{(1, 32)} = .03$, $p = .87$, $\eta p2 = .00$), diurnal cortisol slope ($F_{(1, 32)} = 1.47$, $p = .23$, $\eta p2 = .04$) or mean diurnal output ($F_{(1, 32)} = .01$, $p = .93$, $\eta p2 = .00$). As this second criterion for mediation was not satisfied, formal tests of mediation via PROCESS were not required. Time (all ps > .08) and event (all ps > .20) cued PM failures were unrelated to any of the cortisol indices. Results were unchanged following statistical adjustment for age and exercise, and inclusion of outliers. Table 2 displays means and standard deviations for time and event cued PM failures, and cortisol indices, by group.

INSERT TABLE 2 HERE

Discussion

This study explored the impact of caring for a child with ASD on objectively assessed PM. Whether atypical cortisol secretion patterns might mediate caregivers' compromised cognition was also explored. As predicted, and commensurate with studies incorporating subjective measures, objectively assessed PM failures were greater in ASD caregivers (Lovell et al., 2014, McBean et al., 2016). Studies involving non-caregiving samples have observed poor concordance between subjective and objective checks on PM, with self-report data often

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underestimating the degree of impairment (Thompson et al., 2015). In the context of caring for a child with ASD however, findings from subjective and objective assessments appear to converge; caregivers are more impaired on PM tasks relative to their non-caregiving counterparts. Here, caring for a child with ASD was associated with greater deficits in event, but not time, cued PM. This might not be altogether surprising. Indeed, time cued PM is important for caregivers of children with ASD, who are routinely tasked with remembering to administer medications at various time intervals throughout the day. The healthy caregiving hypothesis posits, because caregivers regularly use cognitive processes such as memory in their day-to-day care for the child, they are less likely to experience cognitive decline. Indeed, Leipold et al (2008) found familial caregivers to be less impaired on cognitive, especially memory, tasks compared with controls, and Bertrand et al (2012) later substantiated this finding. Qualitative studies, including a recent meta synthesis, highlight the importance of time, particularly scheduling and planning, for caregivers in terms of managing behavioural difficulties of the child with ASD (Kuhaneck et al., 2010; O'Nions et al., 2018). This might explain, at least in part, why caregivers were more likely to be impaired on event, but not time, cued PM tasks. Future research might follow this up; whether coping behaviours based around planning/scheduling moderate the association between caring for a child with ASD and time cued PM failures might be particularly pertinent.

That caring for a child with ASD appears to be associated with more failures in cued PM might have implications for quality of provided care. Indeed, impaired PM, particularly for event-cued tasks, has been shown to predict greater difficulties completing the kinds of everyday functional tasks that characterise the caregiving role, e.g., managing medications and problem solving (Kim et al., 2002; Pirogovsky et al., 2012). Moreover, research has found caring for a loved one with chronic illness to be associated with greater difficulties completing these kinds of instrumental tasks of daily living (Vitaliano et al., 2007). Whether

caring for a child with ASD predicts greater difficulties completing everyday functional tasks, and whether greater failures in event cued PM underlie this effect, might be explored in future research. Encouragingly, event cued PM appears to be amenable to improvement via intervention. For example, objectively assessed PM failures were reduced in stroke survivors who, twice hourly for four consecutive weeks, used virtual reality technology (VRT) to practice visual imagery techniques based around remembering tasks and their event related cues. Most encouragingly, the adaptive effect of VRT supported visual imagery training for event cued PM was maintained four weeks post intervention (Mathews et al., 2016). Future studies might assess whether VRT induced visual imagery training might be effective for improving event cued PM in caregivers of children with ASD.

The current study also sought to identify physiological processes possibly mediating caregivers' poorer PM. Caregivers and controls however were comparable on all cortisol indices; both groups displayed a CAR followed by the typical descending pattern across the day. That groups could not be differentiated on basal cortisol secretion is not altogether surprising. Indeed, while some studies have linked caring for a child with DD such as ASD with dysregulated HPA activity (Ruiz-Robledillo et al., 2014; Seltzer et al., 2010), other studies observed no effect (Lovell et al., 2012; Ruiz-Robledillo & Moya-Albiol, 2013). These discrepancies might be explained by the HPA rebound effect, which posits that whilst stressor onset is associated with HPA axis hyper-secretion, over time, cortisol levels diminish as a likely function of increased HPA axis feedback sensitivity (Miller et al., 2007). In support, researchers have observed an inverse relationship between time since stressor onset and diurnal cortisol output (Miller et al., 2007). Caregiving related differences in cortisol secretion therefore are perhaps more likely to be observed at stressor onset. In terms of other plausible mediators, testosterone, which displays a robust basal diurnal pattern in non-stressed populations, has been shown to be dysregulated in caregivers of children with ASD

Moreover, in this same study, basal levels of testosterone positively predicted difficulties completing memory tasks (Romero-Martinez et al., 2016). Dysregulated basal testosterone therefore might provide one alternative pathway by which caring for a child with ASD predicts poorer cognitive functioning. In addition, sleep problems, which tend to be greater in ASD caregivers, have been found to predict difficulties completing memory, and other cognitive, tasks (McBean et al., 2016; Pawl et al., 2013). Future studies might explore the mediating role of other physiological outcomes such as testosterone, as well as sleep problems, on the relationship between caring for a child with ASD and cognitive impairment.

Limitations of the current study include its cross sectional design and small sample. The sample size, while comparable with other similar studies (Correa et al., 2015), was small; post-hoc power analysis indicated a sample of $n=102$ was required to provide adequate power (80%; $a = 0.05$) to detect a moderate effect size ($f2 = 0.15$). The sample size here was $n=34$. Results therefore should interpreted with caution. Longitudinal studies with larger samples that explore how caregivers' compromised cognition might change over time, and how this relates to quality of care, are required. Moreover, here we observed a statistical trend for caregivers' time cued PM failures to be inversely related to mean diurnal cortisol output. This might have reached statistical significance with a larger sample. Child characteristics, particularly problematic behaviours and level of functioning, have been found to account for significant variability in caregivers' cognitive failures (de Vugt et al., 2006). That we did not collect more information about characteristics of the care recipient, and did not clinically authenticate ASD diagnosis, represent notable limitations of the current study. In addition, parents of children with ASD have been shown to be at greater risk for developing characteristics of the broad autism phenotype (BAP) compared with controls, and this effect is particularly amplified in parents with more than one ASD child (Losh et al., 2008; Lyall et al., 2009). This might suggests parents with greater genetic susceptibility to ASD are more

likely to develop BAP characteristics, which have been shown to predict cognitive functioning in domains such as memory (Gokcen et al., 2009). Future research might explore whether any detrimental effect of caring for a child with ASD on PM exists independently of BAP characteristics in the parents. This study however also boasts a number of methodological strengths including rigorous assessment of basal cortisol functioning, as well as more objective, performance based measures of cognition.

In conclusion, caregivers of children with ASD were more impaired than controls on event, but not time, cued PM tasks. In other studies, event cued PM impairment has been associated with difficulties completing instrumental tasks of everyday functioning, and tasks fundamental to the caretaking role, such as managing medications. Future research therefore might assess whether the negative impact of caring for a child with ASD on everyday functioning might be underpinned by greater failures in event cued PM.

Ethical Considerations

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Table 1.

Sample Characteristics by Group

	ASD Caregivers	Controls	p =
	n=23	*n*=11	
Gender			.69
Male	3	2	
Female	20	9	
Relationship Status			.34
Partnered	19	8	
Not partnered	3	3	
Smoking			.18
Yes	1	2	
No	22	9	
Number of Children			.86
One	2	1	
Two or three	20	9	
Four or more	1	1	
Mean Age	45.1 ±6.9	38.9±7.8	**.03**
Mean Weight (lbs)	153.5±25.8	148.9±39.2	.68
Mean Annual Income	54590.9±33812.7	44450.0±32884.0	.80
Mean Alcohol (drinks per week)	4.2±5.7	5.4±5.9	.77
Mean Exercise (times per week)	2.3±1.8	3.8±2.1	**.04**
Mean Hours Sleep	6.5±1.1	7.1±0.6	.19

Table 2.

Means (Standard Deviations) for Objectively Assessed Prospective Memory Failures and

Cortisol Indices by Group

	ASD Caregivers	Controls	$p =$
	n=23	n=11	
Objectively Assessed PM Failures			
Time cued	2.7±2.7	2.2±2.9	.58
Event cued	3.6±2.4	.91±1.4	**< .01**
Cortisol Indices			
Waking	.94±1.4	.91±2.0	.68
30 minutes post waking	1.0±.17	1.0±.23	.34
45 minutes post waking	1.0±.18	.98±.26	.80
1200h	.47±.19	.61±.21	.14
Before bed	.10±.26	.14±.21	.49
Cortisol Awakening Response (CAR)	.12±.20	.11±.16	.87
Diurnal Cortisol Slope	-.95±.06	-.92±.06	.23
Mean Diurnal Output	.75±.13	.74±.16	.93

Notes: Log^{10} transformed cortisol values are presented here, hence low means and standard deviations. Pre transformed values were as follows: *waking* (Caregivers, $_M$ = 9.5, $_{SD}$, 3.8 vs. Controls, $_M$ = 9.4, $_{SD}$, 3.7), *30 minutes post waking* (Caregivers, $_M$ = 13.0, $_{SD}$, 4.6 vs. Controls, $_M$ = 12.8, $_{SD}$, 6.5), *45 minutes post waking* (Caregivers, $_M$ = 12.5, $_{SD}$, 4.7 vs. Controls, $_M$ = 10.7, $_{SD}$, 4.6), *1200h* (Caregivers, $_M$ = 3.7, $_{SD}$, 1.7 vs. Controls, $_M$ = 4.6, $_{SD}$, 2.1), *before bed* (Caregivers, $_M$ = 1.7, $_{SD}$, 1.2 vs. Controls, $_M$ = 1.8, $_{SD}$, 1.0).