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Differential stress response to psychological and physical stressors in children using spatial versus response-dependent navigation strategies

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ABSTRACT

Previous work from our lab has shown that basal cortisol levels are different between healthy young adults who spontaneously use caudate nucleus-dependent response strategies compared to young adults who use hippocampus-dependent spatial navigation strategies. Young adults who use caudate nucleus dependent strategies display lower basal cortisol levels compared to those who use hippocampus-dependent strategies. In the current study, we assessed navigation strategies in children using a virtual navigation task and measured cortisol at baseline as well as cortisol reactivity to both a psychological and to a physical stressor. Replicating what is observed in adults, we found that children who used caudate nucleus-dependent navigation strategies displayed lower cortisol levels at baseline compared to those who used hippocampus-dependent strategies. The psychological stressor, knowledge that a blood draw would be performed by a nurse, caused a significant increase in cortisol uniquely in response learners. The physical stressor, the actual blood draw, produced a significant increase in cortisol amongst spatial learners that was then comparable to levels observed in response learners. Lower baseline cortisol and higher cortisol psychological stress response observed amongst children who used response strategies may therefore reflect early biological changes during development which may have an impact later in life when considering risk for neuropsychiatric disorders.

1. Introduction

Cortisol is a hormone that naturally fluctuates with the circadian cycle that is also released in response to acute stress. This stress response is largely mediated by the hypothalamus-pituitary-adrenal (HPA) axis [1,2] which comprises the hypothalamus and pituitary gland located in the brain, and the adrenal gland located above the kidney. The HPA axis is regulated by a negative feedback loop, where released cortisol binds to receptors in the hippocampus and pituitary gland to inhibit further release [3,4]. Further, the downregulation of cortisol receptors in the hippocampus through chronic glucocorticoid exposure has been show to interrupt this process, resulting in the disinhibition of cortisol release well beyond stressful events. [70] Many studies have reported that both physical and psychological stressors can lead to distinct activation of the HPA axis resulting in increased cortisol release. Physical stressors known to increase cortisol include extended periods of exercise [5] or the administration of an acute pain [6], while psychological stressors include public speaking [7] or knowledge that one has to perform a parachute jump [8].

Basal cortisol levels also show individual variation, some of which depend on genetic factors and life history [9]; Ouellet-Morin et al., 2009; Kloet, Joëls, & Holsboer, 2005), which in turn can have an impact on brain structure and function, including the hippocampus (Cahill, Gorski, & Le, 2003; Christianson, 1992; Lupien et al., 1998, 2002; Moriarty et al.,

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2014). It has been reported that moderate levels of cortisol or stress are optimal for learning and memory supported by the hippocampus while higher levels will impair memory performance, following an inverted-U pattern [10,11]. In rats, a moderate level of cortisol or a mild stressor elevates hippocampal long-term potentiation [12] and improves spatial memory performance [10,11]. In contrast, chronic levels of stress or higher cortisol levels will lower hippocampal LTP and spatial memory performance [13,14]. It is thought that this differential impact of cortisol is mediated by mineralocorticoid receptors (MRs) which have a higher affinity for cortisol and support the encoding of new stimuli and glucocorticoid receptors (GRs) which have a lower affinity for cortisol, are involved in normalizing the stress response and the encoding of stress-related information for future events [15,16]. In other words, cortisol will bind to MRs at lower concentrations, supporting memory, while at higher concentrations once the MRs are saturated, it will bind to GRs and mediate the response to acutely stressful events.

Altered sensitivity of MRs and GRs through experience or genetic variation within the hippocampus could explain individual differences in cortisol stress responses and its impact on learning and memory. Other identified individual differences depend on the navigation strategy people adopt, which are associated with differences in grey matter and function within the hippocampus [17–19]. When humans navigate, they spontaneously adopt different strategies, which rely on distinct parts of the brain [18,20]. People can use a *spatial strategy* (i.e., spatial learners) that involves building relationships between landmarks in the environment, resulting in the formation of an internal cognitive map of the environment. Based on evidence from the rodent literature and adult humans, this type of learning is supported by the hippocampus [18, 20–27]. In contrast, the *response strategy* (i.e., response learners) involves learning a series of stimulus-response associations without encoding spatial relations among multiple landmarks. Based on evidence from the rodent literature and adult humans, this strategy is supported by the caudate nucleus of the striatum, and is a form of procedural memory, which allows acquisition of motor skills and is involved in the formation of habits [21,26,28,29]. In rodents [24], demonstrated that training using a spatial or response navigational strategy leads to increased grey matter volume in the hippocampus and striatum (which include the caudate nucleus in humans), respectively**.** People who use spatial strategies have more grey matter and functional activity in the hippocampus, while in contrast, response learners have more grey matter and activity in the caudate nucleus [18–20,22,30]. Navigation strategy can also be an important factor when considering experience-dependent plasticity within the hippocampus. The impact of training young adults on action video games (e.g., Call of Duty) was beneficial or detrimental depending on a person's navigation strategy [19]. Following a 90-h training period, a decrease in hippocampal grey matter was observed uniquely in response learners. In contrast, spatial learners demonstrated an increase in hippocampal grey matter. It is hypothesized that the differential impact of action video game training on spatial and response learners could be due, in part, to differences in stress response and resultant cortisol release, however this remains to be determined.

Stress not only affects cortisol release, but the navigation strategies that people use. Humans exposed to acute stress shift towards using a caudate nucleus-dependent response strategy [31]. This is thought to be due to the fact that under acute stress, more speeded reactions are required for on organism to evade a potential environmental danger. Using a caudate nucleus-dependent response strategy is more rigid, but also more efficient and less cognitively demanding, thus allowing the organism to react and evade more quickly [31]**.** Further, people who reported experiencing chronic stress were more likely to adopt a caudate nucleus-dependent response strategy [32,33]. Cortisol's effect on learning and memory also appears to interact with navigation strategies. Adults using response strategies display lower basal cortisol levels and have poorer performance on the delayed recall of standard neuropsychological tests of memory (in both the verbal and visuo-spatial domains), compared to spatial learners [17]. In children [34], demonstrated that children who used a hippocampus-dependent navigation strategy to solve a maze (i.e., memorizing using external landmarks) displayed better memory performance associated with higher basal cortisol levels. In contrast, children using caudate nucleus dependent navigation strategies (i.e., memorizing using a rigid series of turns) displayed poorer memory performance associated with higher basal cortisol levels. In other words, cortisol appears to be associated with increased memory performance uniquely in individuals who rely on hippocampus-dependent navigation strategies. Together, these results suggest that spatial and response learners display opposing effects of cortisol on learning and memory and both acute and chronic stress can shift navigational strategies away from those that depend on the hippocampus towards those that depend on the caudate nucleus.

Alteration of cortisol secretion is also a common feature in many psychiatric disorders. Individuals with Post-Traumatic Stress Disorder (PTSD) have lower levels of basal cortisol (D [35–41]. but show higher levels when exposed to trauma [42–44], however, see conflicting data from Refs. [38,45,46]. It is therefore not well understood whether such alterations in cortisol secretion that vary between individuals are present before traumatic exposure, thus, it is not clear whether cortisol dysregulation earlier in life present as a risk factor for developing certain neuropsychiatric illnesses. Therefore, better understanding of individual differences in cortisol regulation early in development remains an important topic of study.

In the current study, we measured the cortisol stress response in reaction to both a psychological and physical stressor in children who were 8 years old. A previous study from our group reported another phenomenon observed in this dataset related to learning and memory that was independent of stress responses [34]. Specifically, following observations in adults [17], we found that higher basal cortisol levels at age 8 was associated with better spatial memory performance amoungst spatial learners. In contrast, response learners displayed poorer memory performance associated with higher basal cortisol levels. The research question presented in Ref. [34] did not involve stress responses and data related to changes in cortisol in response to stress were analyzed at a later time and therefore reported separately.

Cortisol samples were collected during the morning of when a nurse performed a blood draw at the child's home. The psychological stressor was characterized as the knowledge that the nurse would be arriving to collect a blood sample from the child. The physical stressor was characterized by the actual blood draw being performed. During a separate session on another day, participants completed the 4 on 8 Virtual Maze adapted for children (a4/8 VM) to assess navigation strategy and learning and memory performance. We predicted that children response learners, as observed in adults, would display lower basal cortisol levels. Because of this known difference and since cortisol has a different impact on memory in spatial and response learners, we also expected that stress would have a different impact on cortisol reactivity of spatial and response learners. Further, due to the fact that response strategies are associated with less grey matter in the hippocampus, we also predicted that response learners would display less cortisol regulation and a greater cortisol stress response in reaction to the presented stressor.

2. Methods

2.1. Participants & testing sessions

Participants were from the Quebec Newborn Twin Study (QNTS), a prospective longitudinal study of twins born between 1995 and 1998 in the greater Montreal area, Quebec, Canada [47]. Participants discussed in the current study were tested at the age of 8. A total of 299 children were included in the study and a subset of 196 completed the 4 on 8 Virtual Maze adapted for children (a4/8 VM). Out of this total, we obtained cortisol samples and a complete a4/8 VM navigation strategy from 160 children (79 boys, 80 girls; mean age: 8.4 $\pm$ 0.1 years; range = 8.2–8.8 years). Because this group of children was followed

longitudinally since infancy, baseline cortisol levels that were collected at 5 months were available. These data were included for comparison purposes**.** Written consent from the parents of participants was obtained in accordance with the standards set by the Sainte-Justine University Research Center ethics committee. The Research Ethics Board at the Sainte-Justine University Research Center approved the study, including all recruitment and testing procedures.

Participants had their salivary cortisol sample collected and their a4/8 VM testing sessions on different days. On average, the number of days separating the two sessions was 3.34 days (median = 7 days; SD = 141.50) with a range of 312 days before or 258 days after the a4/8 VM testing session. Baseline cortisol patterns as measured by salivary sample have been demonstrated to be stable within this time delay [48].

2.2. Measure of psychological and physical cortisol stress response

To measure changes in children's cortisol as a result of a psychological and physical stressor, salivary cortisol samples were collected four times on the morning a nurse was scheduled to obtain a blood sample from them at the child's home. The psychological stressor was characterized as the knowledge that the nurse would be arriving to collect a blood sample from the child. The physical stressor was characterized by the actual blood draw being performed. A first cortisol sample was obtained at awakening (sample 1; Time = 7h46, SD = 0h48). A second baseline cortisol sample was collected ~15 min before the arrival of the nurse (sample 2; Time = 10h09, SD = 1h18). The research coordinator had called the parents the day before to confirm the date and time of the nurse's visit, and to review the saliva sampling protocol with the parents. At their arrival, the nurse completed questionnaires about the general health of the children, checked the time when the previous saliva collection was performed by the parents, and obtained the informed consent. A third cortisol sample was collected right before the blood draw was performed, about 20–30 min after the nurse's arrival (sample 3; Time = 10h26, SD = 1h20). This third sample was therefore able to measure the response to the psychological stress pertaining to the arrival of the nurse at home as both parents and the children knew that the nurse would perform a blood draw on the child. A final fourth cortisol sample was then collected 20–30 min after the actual blood collection occurred (sample 4; Time = 10h45, SD = 1h08). This fourth sample was therefore able to measure the response to the physical stressor pertaining to the actual blood draw. The delay of at least 20 min between cortisol samples is adequate for the detection of changes in cortisol in response to stress [49–51]. The cortisol response to the psychological stressor was computed as the delta between samples 3 and 2, while the cortisol response to the physical stressor was computed as the delta between samples 4 and 3. No other cortisol samples were collected on the day of the blood draw. No other experimental tasks were completed by the participants on the day of the cortisol sampling and blood draw**.** Cortisol samples were analyzed in the laboratory of Claire-Dominique Walker at the Douglas Institute. Planned independent *t*-tests were used to compare both groups. All samples were submitted to a Shapiro-Wilk test which revealed no significant deviations from normality.

2.3. 4 on 8 Virtual Maze adapted for children (a4/8 VM)

The 4 on 8 Virtual Maze adapted for children (a4/8 VM) is used to assess navigation strategy and learning and memory performance (see Fig. 1; [52]. Learning and memory performance data within the a4/8 VM from the current sample has been reported elsewhere [34]. The a4/8 VM is a behavioral task created using a commercially available computer game (Unreal: Epic Games, Raleigh, NC). It is used to assess the spontaneous navigation strategy employed by an individual. It consists of a central platform surrounded by several proximal and distal landmarks (e.g., mountains, a pyramid, piles of boxes, etc.) from which eight paths branch out which is surrounded by several proximal and distal landmarks (ex. mountains, a pyramid, piles of boxes etc.). At the end of each arm are stairs leading down to a pit. In four of the eight arms, a target object is placed at the bottom of the pit. The participant starts each trial at the center of the platform facing the same direction. Arms that contain target objects are indiscernible from the empty ones because the objects are not visible from the center of the platform.

A habituation phase first occurs where the participant is asked to familiarize themselves with the controls as well as the virtual environment. They are asked to move around using the arrows at the top, left and right of the keyboard in front of them. When the habituation phase is completed, and the participant feels comfortable navigating in the virtual environment, they begin the experimental task. For this age group this typically lasts about 5 min.

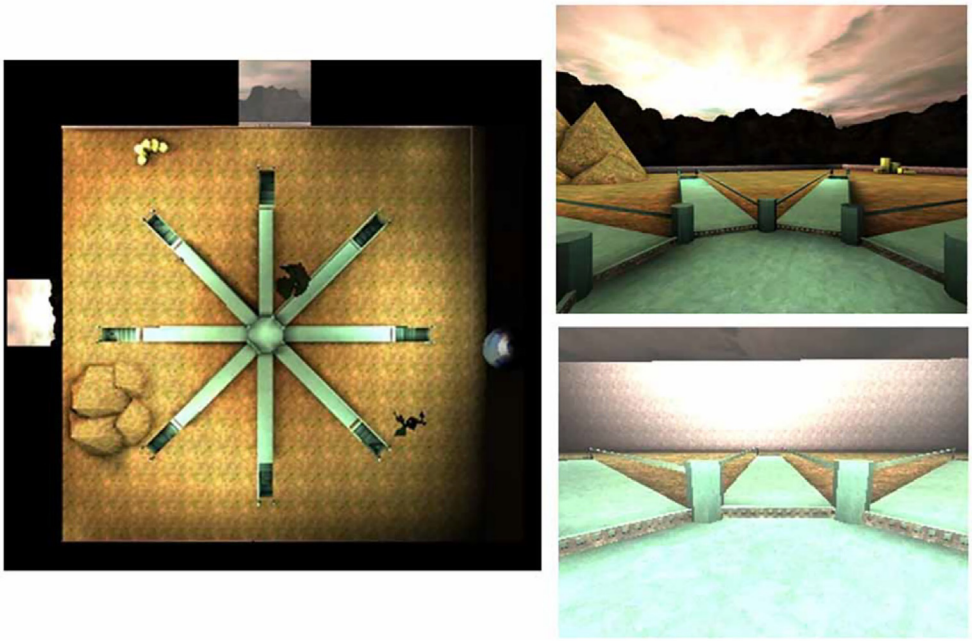

Fig. 1. Top down (left) and first person (right) views of the a4/8VM environment.

The experimental task consists of a minimum of five trials, including one probe trial. Target objects are always located in the same four paths out of the available eight paths. Participants are asked to collect all four objects on each trial. A trial ends when all four target objects have been collected. To reach criteria, participants are required to have completed three out of four previous trials without error. Once criterion is reached, a probe trial is administered. In the probe trial, the participant must retrieve the four target objects as usual, however, unlike regular trials the landscape is entirely hidden and landmarks are removed from the virtual environment. Therefore, only participants that rely on landmarks will make errors in the probe trial. Therefore, the probe trial makes it possible to dissociate between participants who use landmarks (the spatial strategy) from those who use a sequence to memorize which pathways from a single starting position contain the objects (response strategy). Probe errors are measured during the probe trial when all landmarks are removed.

To determine spontaneous navigational strategies used to complete the a4/8 VM, the task ends with a standardized semi-structured interview where the participant is asked how they memorized which paths to visit and which ones to avoid. If no sequence is mentioned and more than two landmarks are used to memorize the paths, the participant is categorized as using a spatial strategy. In contrast, if the participant mentions counting or numbering paths from a starting point (i.e. using a rigid pattern of open and closed pathways) they are categorized as a response learner. Since children's verbal reports are often less detailed, any verbal report that was ambiguous or did not describe a clear strategy, was excluded from the analysis to avoid misclassification. Each verbal report was evaluated by at least two independent raters ($\alpha = 0.92$). When there was a disagreement between raters, a third rater's evaluation was used to determine the spontaneous navigation strategy used. Specifically, the verbal report was used first to determine the navigation strategy (as described above) and errors on the probe trial were used to confirm this strategy.

3. Results

Amongst participants who completed the a4/8 VM, 83.2% (N = 163) used a spatial strategy and 16.8% (N = 33) used a response strategy. Spatial learners made more probe errors in the probe trial (mean = 0.90 ± 0.64) compared to response learners (mean = 0.70 ± 0.59; t (194) = 1.80, $p < 0.05$, one-tailed). Cortisol samples during the blood collection procedure were obtained for a subset of these participants resulting in 138 spatial learners and 22 response learners.

We then examined the cortisol data, first conducting an ANOVA followed by planned a priori comparisons specifically examining relative changes in cortisol in response to both the psychological and physical stressors. Cortisol levels were submitted to a 2 (Group: response learner; spatial learner) x 4 (Time: Sample 1; Sample 2; Sample 3; Sample 4) mixed factorial ANOVA. This revealed a main effect of Time (F (1, 125) = 6.46; $p < 0.05$; Fig. 2). The interaction effect was non-significant as was the overall between-subjects effect. Simple effect analysis examining pairwise comparisons revealed that for sample 2 (baseline cortisol sample) response learners displayed significantly lower cortisol levels compared to spatial learners (mean difference = 0.03; $p < 0.01$, bonferroni corrected).

Planned a priori comparisons were conducted using t-test. We first compared basal cortisol levels at awakening (sample 1) between spatial learners ($M = 0.14 \pm 0.09$) and response learners ($M = 0.12 \pm 0.07$), which was non-significant ($t < 1$). We next examined the baseline cortisol levels before the impact of stress could be detected (sample 2), data for one spatial learner was not collected. Mirroring the significant effect revealed in the ANOVA, we found that response learners displayed lower cortisol levels ($M = 0.04 \pm 0.03$) compared to spatial learners ($M = 0.07 \pm 0.04$; t (157) = 2.71, p < 0.01; Fig. 3b). We also compared this to baseline cortisol samples collected from the same participants at 5 months of age. A similar pattern was observed where response learners displayed lower cortisol levels ($M = 0.33 \pm 0.24$) compared to spatial learners ($M = 0.44 \pm 0.41$), however this was not significant ($p > 0.2$; Fig. 3a). The impact of the psychological stressor was next examined (sample 3 – sample 2). We obtained both samples 2 and 3 from 121 spatial learners and 20 response leaners. This revealed a differential impact of psychological stress on cortisol levels between response and spatial learners where response learners displayed an increase in cortisol ($M = 0.016 \pm 0.04$) in contrast to spatial learners who displayed a decrease ($M = -0.011 \pm 0.05$; t (138) = 2.35, $p < 0.01$; Fig. 4a). The impact of the physical stressor was next examined (sample 4 – sample 3). No significant difference between response learners ($M = 0.016 \pm 0.08$) and spatial learners ($M = 0.033 \pm 0.09$) was observed ($t < 1$), however spatial learners' increase change in cortisol in response to the physical stressor was significant (t (135) = 4.43, $p < 0.001$; Fig. 4b). Therefore, response learners displayed an increased cortisol stress response to the psychological stressor relative to spatial learners, while spatial learners subsequently displayed a cortisol stress response to the physical stressor.

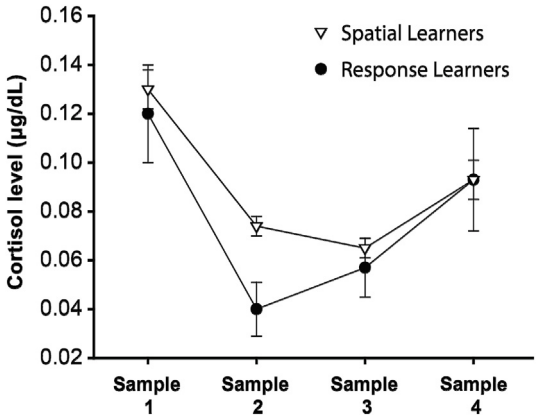

Fig. 2. Average cortisol levels for samples 1, 2, 3, & 4. Error bars represent standard errors.

4. Discussion

The present study examined the relationship between navigational strategies, baseline cortisol levels and the cortisol stress response in reaction to both a psychological and physical stressor in children who were 8 years old. The effect of cortisol is highly variable and can have either a facilitating or deleterious effect on brain and behaviour (Cahill et al., 2003; Christianson, 1992; Karl et al., 2006; Lupien et al., 1998, 2002; McEwen & Sapolsky, 1995; McKittrick et al., 2000; Swaab et al., 2005; Vythilingam et al., 2004; Wolf et al., 2002). We have found evidence demonstrating that individual differences in navigation strategy are associated with differences in baseline cortisol and the cortisol stress response in children. Specifically, as observed in adults [17], children who are response learners display lower cortisol levels at baseline compared to spatial learners (Fig. 2b). The same sample of children whose cortisol was also sampled at 5 months old displayed the same pattern, although this was not significant (Fig. 2a). This suggests that the difference in baseline cortisol levels between spatial and response learners could begin very early in life, although this remains to be determined through further experimentation. One possible factor mediating the observed lower baseline cortisol levels amongst response learners could be exposure to early adversity. For example, many studies of children exposed to early adverse care display lower basal and daytime cortisol levels (see Ref. [53] for review). Another possible cause of lower baseline cortisol observed amongst response learners early in life could be due to exposure to prenatal stress (e.g. divorce or death of a close family member). Indeed, it was found that young adults with prenatal stress exposure used rigid response learning strategies more often than spatial learning strategies compared with participants whose mothers did

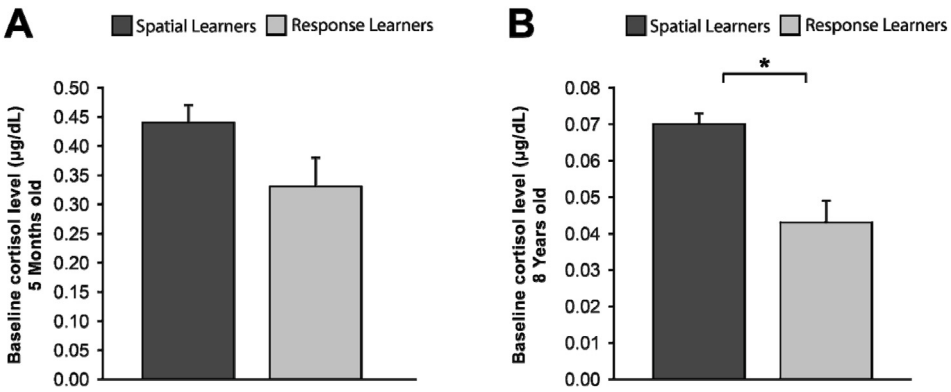

Fig. 3. Baseline cortisol levels comparing spatial and response learners at (A) 5 months old and (B) 8 years old.

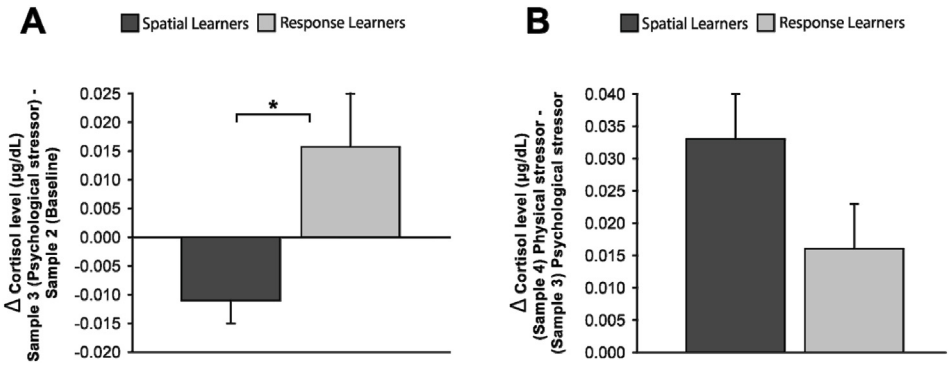

Fig. 4. (A) Change in cortisol level in response to a psychological stressor compared to baseline sample. (B) Change in cortisol level in response to the subsequent physical stressor compared to the previous cortisol sample taken to measure the impact of the psychological stressor.

not experience major negative life events during pregnancy [32]. Further, it has been observed that mothers who are exposed to major life stressors during pregnancy expose the fetus to increased cortisol during gestation that may influence the development of brain areas that are critical for memory and healthy cognition, including the hippocampus [54]. Both exposure to early life adversity and prenatal stress are thought to cause lower baseline cortisol levels as an adaptation to chronic stress.

Spatial and response learners displayed a differential stress response to a psychological and physical stressor, suggesting that the two groups processed the two types of stressor events differently. Response learners displayed an increase in cortisol in response to the psychological stressor in contrast to spatial learners who displayed a decrease in cortisol. This would suggest that spatial learners are able to use some information to regulate their stress response when it is psychological, but produce a typical stress response for a physical stressor. Lower cortisol at baseline displayed by response learners could also explain why these same individuals showed a relatively higher increase in cortisol in response to a psychological stressor compared to spatial learners. Because response learners show a blunted level of cortisol at baseline before a stressor is introduced, a higher degree of cortisol reactivity compared to spatial learners may be possible. In contrast, spatial learners displayed an increase in cortisol in response to the physical stressor only. Early adversity and prenatal stress could again also present as a factor explaining the difference in the psychological stress response observed between response and spatial learners. Although it has not yet been determined if children response learners previously experienced higher levels of adversity, it remains an important hypothesis to test based on previous results showing that early adversity is associated with increased cortisol reactivity in response to stress. For example, greater familial adversity [9] and higher negative parent child interactions [55] were associated with a greater cortisol response in reaction to a psychological stressor. Another study showed that young children exposed to psychosocial deprivation and displayed depressive symptoms showed a greater cortisol psychological stress response compared to controls [56]. Prenatal stress has been shown to be associated with response learning strategies in young adulthood [32]. This coupled with the fact that prenatal stress is also associated with an increased cortisol psychological stress response in children [57,58] highlights this as another possible factor that could explain our current results. Future research directly linking exposure to early adversity/prenatal stress, cortisol dysregulation and response learning is therefore needed.

Further evidence for experience-dependent changes in cortisol regulation come from studies showing that dysregulation of cortisol is involved in certain neuropsychiatric illnesses such as PTSD. Experience could possibly change the regulation of cortisol reactivity and have possible consequences in regulating behaviour and brain structures. Supporting this hypothesis, it has previously been shown that offspring of parents with PTSD or parents exposed to trauma are also at risk of such stress response dysregulations, as they also show lower basal cortisol levels compared to offspring of parents without PTSD or trauma exposure [59–61]. Alcoholics similarly display reduced basal cortisol levels [62]. Further, exposure to stress can cause a differential acute cortisol response, depending on the presence or absence of a neuropsychiatric disorder. For example, when exposed to the Trier Social Stress Test (TSST) which is a psychological stressor involving public speaking, individuals with social anxiety disorder, while having the same baseline cortisol levels as healthy controls [50,51], show a higher cortisol stress response [50]. Along with cortisol dysregulation, there are also differences in specific brain areas associated with these psychiatric illnesses. For example, bilateral hippocampal atrophy is found in PTSD for both combat-related and physical or sexual abuse (J. D. [63]; J. D [64–66]. Therefore, individual differences in cortisol reactivity can be affected by

a number of factors and could possibly explain how differences in cortisol levels can impact brain and behaviour. Our current results suggest that the relationship between using non-hippocampus dependent memory systems and alteration in cortisol in response to stress could begin early in life, and have consequences on future brain development and behaviour.

Dysregulation of cortisol is also be involved in addiction. For example, alcohol intake causes an increase in cortisol, and is one mechanism that causes alcohol's stimulating and rewarding effects [67]. However, alcoholics display reduced basal cortisol levels due to habituation of the HPA-axis response, possibly due to the chronic consumption of alcohol [62]. Another possibility is that people prone to addiction display decreased levels of cortisol before their addiction develops. It is possible that these individuals seek substances that raise previously lower cortisol amongst several other hormones and neurotransmitters including norepinephrine and dopamine, and in turn stimulate the central nervous system to achieve a short term rise to more optimal levels [68]. In line with this reasoning, it has been shown that young adult response learners, who display lower levels of baseline cortisol [17], consume higher amounts of addictive substances including alcohol, tobacco and cannabis [52]. Cortisol below optimal levels (i.e., concentrations that do not bind to an adequate number of MRs) could also explain, in part, poorer performance on cognitive tasks sensitive to learning and memory because optimal cortisol levels in the central nervous system (i.e., high enough to bind to MRs but low enough to not bind to GRs) are associated with lower levels of inflammation and associated cytokines, which in turn at higher levels have deleterious effects brain structures sensitive to injury such as the hippocampus [68]. This relation between higher cortisol levels at baseline and spatial learning could be one possible reason why spatial learners display higher volume in the hippocampus and neocortex [18,20,30], which are both sensitive to injury. This relationship between cortisol and volume of the hippocampus could emerge early on in development. For example, moderate levels of cortisol are critical for the normal development of the hippocampus [69]. It is therefore possible that early stress during that causes an adaptation to cortisol, resulting in lower basal levels, could result in the underdevelopment of the hippocampus, resulting in poorer hippocampus-dependent memory performance during the lifespan. Indeed, response learners, who showed lower baseline cortisol, display poorer performance on a test of episodic memory that is supported by the hippocampus [17]. Similarly, children who are response learners had poorer spatial memory performance associated with higher cortisol levels [34]. Further, it could be possible that alterations in cortisol regulation resulting in lower baseline levels, that can occur very early in life and are associated with response learning, could increase reward seeking behaviours that temporarily raise cortisol levels in an effort to temporarily return cortisol to homeostasis, and could ultimately lead to addiction later in life. This hypothesis, however, remains untested and further longitudinal research is therefore needed.

Although the research team did not instruct the parents to tell the children in advance of the nurses visit, we could not rule out this possibility. Prior knowledge of a nurses visit could potentially alter cortisol production and should be mentioned a potential limitation of this study. We, however, have no reason to believe that this source of variability would be present more in on group or the other. We also observed a similar difference in baseline cortisol between spatial and response learners that we have previously seen in adults [17]. Another potential limitation of the current study is that evidence linking navigation strategies to the hippocampus and caudate nucleus come from rodent and adult human studies. Future research needs to confirm if these same structures support the distinct navigation strategies observed in children.

This study investigated the relation between individual differences in cortisol stress response and navigational strategies in children. Response learners displayed lower cortisol levels at baseline, however, showed a significantly higher cortisol stress response to a psychological stressor compared to spatial learners. Because lower baseline cortisol levels and higher cortisol reactivity in response to stress are associated with early adversity, certain neuropsychiatric illnesses and addictive behaviours, future work should examine the possibility of assessing navigational strategies in conjunction with measuring cortisol to predict risk for such outcomes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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