Acute hydrocortisone administration pre-learning impairs memory in Chronic Adrenal Insufficiency

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ABSTRACT

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Cortisol and psychosocial stress are known to affect learning and memory. Individuals with chronic adrenal insufficiency (CAI), who must substitute basal cortisol levels pharmacologically and do not exhibit a cortisol response to stress, provide a unique opportunity to explore the relationship between stress, cortisol, and memory performance. Twenty-eight patients with CAI learned one wordlist prior to exposure to the Trier Social Stress Test (TSST)

and one wordlist following TSST exposure. Delayed recall of wordlist 1 occurred immediately after the TSST and delayed recall of wordlist 2 occurred 100 minutes post-TSST. Thirteen patients received an injection of hydrocortisone (HC) after the TSST to mimic a stress response and the other 15 received an injection of saline (NaCl). Among CAI patients treated with NaCl, exposure to the TSST did not impact learning (*p*s > .46). When recall occurred post-TSST and after the injections, the NaCl and HC treatment groups did not differ in delayed recall performance of the wordlist 1 (*p*s > .30). Patients treated with HC recalled fewer words from wordlist 2, which was learned following stress exposure and injection administration, than those treated with NaCl at both immediate and delayed recall ($F = 4.60$, $p = .042$). Both groups recalled more negative than neutral words. These findings may indicate that psychosocial stress and cortisol impact memory differently among patients with CAI as compared to healthy individuals. This also suggests that acute administration of HC is detrimental to memory in CAI patients. Future work should explore the potentially negative effect of cortisol replacement therapy on cognitive function.

Keywords: cortisol, memory, chronic adrenal insufficiency

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Chronic Adrenal Insufficiency and Memory Performance

Acute stress has an array of psychological and biological correlates in humans. Exposure to a psychosocial stressor increases subjective stress, anxiety, and negative mood and activates the two major physiological stress axes, the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; Dickerson & Kemeny, 2004). Stress responses in these biological systems are marked by increases in the catecholamines adrenaline and noradrenaline as well as cortisol (Allen et al., 2014). In turn, these downstream mediators of biological stress responses not only interact with each other, but also affect a multitude of other effector systems. Most importantly in the current context, they have implications for cognitive functioning.

In particular, the stress hormone cortisol has a unique and complex relationship with memory, with findings suggesting cortisol to have both enhancing as well as impairing effects on memory (Ackermann, Hartmann, Papassotiropoulos, De Quervain, & Rasch, 2013; Allen et al., 2014; Almela et al., 2014; Wolf, 2009). More specifically, cortisol has been shown to augment memory consolidation while impairing long-term memory retrieval in healthy individuals and in rodent models (Roozendaal, 2002; Wolf, 2009). Differential effects are thereby partially determined by the time at which learning and retrieval are performed relative to the introduction of cortisol. For example, acute cortisol administration in humans has been shown to result in

significant memory impairment if delivered prior to retrieval, whereas delivery prior to learning does not affect performance (Het, Ramlow, & Wolf, 2005).

Memory effects appear to be further dependent on the context in which elevated cortisol levels occur. For instance, in contrast to cortisol administration, learning that occurred after exposure to an acute stressor reduced performance on both immediate free recall and recognition tasks 24-hours later (Schwabe & Wolf, 2010; Zoladz et al., 2013), while stress exposure prior to retrieval impaired performance at delayed recall only (Zoladz et al., 2014). The latter was observed specifically in male participants exhibiting a blunted cortisol stress response. In summary, while stress and/or cortisol exposure appear to have negative effects on delayed retrieval, learning does not seem to be negatively affected by cortisol itself, but by the more complex circumstances occurring in the context of stress exposure.

In addition to timing and context, features of the memory task itself can moderate cortisol effects. One prominent aspect is the valence of learned information. Generally, positively and negatively-valenced information is recalled with more frequency than neutral information (Zimmerman & Kelley, 2010) and emotional words are recalled with fewer errors than neutral words (Majerus & D'Argembeau, 2011). However, while learning under stress appears to specifically enhance memory for neutral words independently of cortisol, memory performance with regard to negative words is better in participants who show a cortisol stress response compared to non-responders and controls (Schwabe, Bohringer, Chatterjee, & Schachinger, 2008).

These findings give rise to further questions about the role that cortisol plays in the context of stress, particularly of the consequences of lacking a cortisol stress response. For example, the positive memory consolidation effects of cortisol might act as a buffer in the context of stress exposure and thus the negative effects of other stress mediators and processes might become worse without cortisol. The study of individuals with chronic adrenal insufficiency (CAI) offers a unique avenue through which to address this question. Patients with CAI do not produce any cortisol mostly due to destroyed adrenal cortex cells and thus receive glucocorticoid replacement therapy (Arlt & Allolio, 2003; Betterle, Dal Pra, Mantero, & Zanchetta, 2002; Oelkers, 1996; Ten, New, & Maclaren, 2001). This therapy substitutes basal cortisol levels but does not adjust for increased cortisol levels typically observed in healthy individuals in response to stress exposure. Thus, when exposed to stress, CAI patients are characterized by the absence of cortisol increases (Geiger, Pitts, Feldkamp, Kirschbaum, & Wolf, 2015).

Interestingly, several studies describe memory problems associated with CAI. For example, Henry & Thomas (2014) found that CAI patients recalled fewer words than healthy participants at immediate and delayed recall, with significantly larger decreases in performance between immediate and delayed recall in patients. The same effect was described for visual and auditory memory tasks (Tiemensma, Andelab, Biermaszb, Romijnc, & Pereirab, 2016). The latter effect was independent of substitution therapy dosage or regimen (Tiemensma et al., 2016), while the former became more pronounced with longer illness duration. This suggests that rather than being a symptom of the disease or treatment itself, side-effects such as the inability to mount a cortisol stress response may accumulate over time to affect memory performance.

To date, no study has assessed memory effects of stress exposure in CAI patients. Besides the implications for patients' well-being, studying CAI patients under such conditions provides the unique opportunity to disentangle the role of cortisol from the broader effects of stress. The current study aimed to characterize how memory performance for valenced and non-valence information in CAI patients is affected by stress and whether performance can be influenced pharmacologically by administering exogenous cortisol. Specifically, we aimed to assess (1) how psychosocial stress exposure affects learning in CAI patients, (2) how stress exposure post-learning affects delayed recall in CAI patients and how this effect is influenced by an acute hydrocortisone injection to mimic a cortisol stress response, and (3) how stress exposure affects subsequent learning and delayed recall in CAI patients dependent on presence or absence of cortisol.

Method

Participants

Thirty-six patients with chronic adrenal insufficiency took part in this study. Two patients were excluded from analysis because they did not supply information on the type of cortisol replacement therapy they received. Two cases were excluded due to missing cognitive data, one for having an unusable saliva sample, and one for exceeding the cutoff score of C23 on the German short version of the *Center for Epidemiological Studies Depression Scale* (Hautzinger & Bailer, 1993). Additionally, two cases were excluded for dishonest completion (i.e., writing down and rehearsing the words between testing) of the recall task. The final sample thus consisted of $N = 28$ patients.

Twenty patients were diagnosed with autoimmune Addison's disease occurring from the presence of autoantibodies (Betterle et al., 2002; Peterson, Uibo, & Krohn, 2000) or comorbidities fulfilling the criteria for Autoimmune Polygladular Syndrome (APS) (Neufeld, Maclaren, & Blizzard, 1981). Three patients acquired Addison's disease from former Cushing's disease and one patient from former infection. The remaining four patients could not supply detailed information for differential diagnosis (primary adrenal insufficiency). Consistent with the prevalence of the disease, more women ($n = 21$) than men ($n = 7$) were tested. Due to the low prevalence of CAI, the use of medication, oral contraceptives, or cigarettes was not included as exclusion criteria. Patients were required to omit their midday glucocorticoid replacement

medication (hydrocortisone: $n = 23$, mean daily dose: 26.41mg; cortisone acetate: $n = 5$, mean daily dose: 40.00mg) on the day of testing to ensure low baseline cortisol levels. The descriptive statistics of the patient subgroups are summarized in Table 1.

Procedure

Patients were recruited from across Germany (travel distance: 287 ± 157 km, $t = 1.69$, $p = .20$). Testing began at 1:00PM and after obtaining informed written consent, the first wordlist was presented, learned, and recalled immediately. Twenty minutes later, the baseline saliva and blood samples (-1 min.) were taken and the *Trier Social Stress Test* (TSST) was performed. This was immediately followed by an injection of either hydrocortisone (HC) or saline (NaCl) and a second saliva sample. A third saliva sample (+10 min.) was taken 10 minutes after the conclusion of the TSST, when the cortisol stress response peaks in healthy participants. Additional saliva samples were taken 20, 30, 45, 60, 90, and 120 minutes post-stress to capture the full cortisol response and recovery. A surprise delayed recall of the first wordlist – 75 minutes after first recall – was performed, followed by the presentation and immediate recall of a second wordlist. Delayed recall of the second list occurred 75 minutes later. The ethics committee of the University of Düsseldorf approved the study protocol.

Manipulations

Pharmacological manipulation. As patients with CAI do not display a cortisol stress response, half of the patients were injected with 0.03mg/kg hydrocortisone to simulate a normal stress response. This dose successfully increased cortisol levels by approximately 15 nmol/L in a pilot study assessing the effects of various doses of hydrocortisone in healthy adults with a wide range of body types. The placebo group was injected with 4mL of saline. The patients were

randomly assigned to HC treatment or the placebo (NaCl) group, with 13 and 15 participants, respectively.

Trier Social Stress Test (TSST). The TSST is a standardized psychosocial laboratory stressor consisting of a three-minute preparation period followed by a five-minute speech task and a five-minute mental arithmetic task performed in front of a two-person panel. Additionally, this situation is videotaped. In healthy participants, this procedure elicits increased activity of the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis (Kirschbaum, Pirke & Hellhammer, 1993).

Measures

Free cortisol. Free cortisol was measured to assess the cortisol stress response. Saliva samples were collected using Salivette collection devices (Sarstedt, Nüembrecht, Germany). All samples were frozen at -30 °C and upon study completion, cortisol concentrations were measured using an immunoassay with chemiluminescence detection (IBL-Hamburg, Germany). Samples were assessed in duplicates and averaged for analysis. Inter- and intra-assay CVs were below 8%.

Memory. Verbal memory was assessed using two wordlists. Each list contained 10 neutral and 10 emotional (negative) German nouns. Neutral and emotional words were matched for complexity. The wordlists were presented in written form for one minute followed by immediate verbal recall and all recall was video recorded. This was repeated immediately, resulting in two learning trials – recall 1 and recall 2 – wherein the first trial served as a familiarization condition. The surprise delayed recall condition – recall 3 – required participants to recall the nouns 75 minutes after the second learning trial (recall 2).

The first wordlist was learned prior to stress exposure and delayed recall for this list took place 15 minutes after the cessation of the stressor and 10 minutes post-treatment (HC or NaCl). This allowed the investigation of the effect of psychosocial stress with versus without cortisol present during delayed recall. The second list was learned shortly after the delayed recall of the first list. This allowed testing of the effects of cortisol on learning and encoding under stress. In total, participants completed six separate recall tasks: recall 1 and 2 (where learning took place before the TSST), recall 3 (where the first list was recalled post-TSST and post-treatment), recall 4 and 5 (learning the second wordlist post-TSST and post-treatment), and recall 6 (recalling the second list after the effects of the TSST and the treatment had diminished).

Analysis Plan

Change in cortisol level across the time of testing was assessed with a repeated-measures ANOVA in which each cortisol assessment was included as a within-subjects factor (nine levels) and treatment (HC and NaCl) was included as a between-subjects factor. The effect of stress on learning (aim 1) was investigated in patients treated with saline only by computing a repeated-measures ANOVA with wordlist (1 and 2), trial (1 and 2), and valence (negative and neutral) as within-subjects factors. The effects of cortisol replacement on stress effects on delayed recall performance (aim 2) of the first wordlist was investigated with a repeated-measures ANOVA with valence (negative and neutral) as a within-subjects factor and treatment (HC and NaCl) as a between-subjects factor. Recall performance of the second wordlist, which was learned after the TSST and during peak hormone levels in the HC group and recalled after these effects has diminished (aim 3), was assessed by a repeated-measures ANOVA with time of recall (two immediate, one delayed) and valence (negative and neural) as within-subjects factors and treatment (HC and NaCl) as a between-subjects factor.

Results

Preliminary analyses revealed that the placebo and HC groups did not significantly differ in age, gender composition, origin of CAI, type of cortisol substitution medication, or daily dose of cortisol substitution medication (mg) (all *p*s > .13). These results are summarized in Table 1. Repeated saliva sampling indicated that as expected, the placebo group's cortisol profile remained flat, while the HC injection significantly increased cortisol levels (group $F = 20.88$, $\eta^2 = .46$, time $F = 12.65$, $\eta^2 = .34$, time-group interaction $F = 13.80$, $\eta^2 = .36$, all *p*s < .001), as illustrated in Figure 1.

To assess the effects of stress exposure on learning (aim 1), pre- and post-stress performance was compared in patients treated with saline. Repeated-measures ANOVA revealed an effect of valence, with overall better performance for negative compared to neutral words ($F = 20.13$, $p = .001$, $\eta^2 = .59$) as well as a practice effect, with significantly more words remembers after the second learning trial than first learning trial ($F = 27.97$, $p < .001$, $\eta^2 = .67$). However, no effect of stress on learning was observed (all *ps* > .46). These results are depicted in Figure 2.

Next, we tested whether the effects of stress exposure on delayed recall of the first word list (learned pre-stress) differed depending on the presence of cortisol (aim 2). Results of this analysis, illustrated in Figure 3, indicated no effect of treatment or valence and no interaction effect of treatment and valence (treatment: $F = .38$, valence $F = .00$, treatment*valence: $F = 1.16$,

all *p*s > .30). The placebo and HC groups did not significantly differ in their delayed recall of the first wordlist, regardless of word type.

Testing aim 3, a repeated-measures ANOVA including the three recall time points of the second wordlist – learned under stress and recalled under no stress – yielded statistically significant effects of time of recall ($F = 37.54$, $p < .00$, $\eta^2 = .80$), valence ($F = 6.41$, $p = .018$, $\eta^2 = .20$), and the interaction of time and valence ($F = 8.40$, $p = .001$, $\eta^2 = .24$). Results of this analysis are summarized in Table 2. Independent of treatment, more negative than neutral words were learned and negative words were learned more quickly than neutral words, as indicated by the larger number of words recalled at the first trial and the smaller gain at the second learning trail. This interaction is depicted in Figure 4. Furthermore, a significant main effect of treatment ($F = 4.60$, $p = .042$, $\eta^2 = .15$) indicated that independent of word valence, patients treated with HC recalled fewer words both in the two learning trials as well as at delayed recall.

Discussion

Among CAI patients treated with NaCl, there was no difference in pre- versus post-stress learning performance (aim 1). A comparison of delayed recall of the first wordlist (learned pre-stress) between the NaCl and HC treatment groups indicated that neither treatment with HC nor valence had an effect on delayed recall performance (aim 2). Finally, patients treated with HC post-stress exposure recalled fewer words than those treated with NaCl during learning trials as well as delayed recall (aim 3).

Patients with CAI frequently report problems with fatigue, weight loss, depression and memory impairment (Arlt & Allolio, 2003; Betterle, Dal Pra, Mantero, & Zanchetta, 2002; Henry & Thomas, 2014; Oelkers, 1996; Ten, New, & Maclaren, 2001). Memory functioning is of particular importance due to its vital role in daily functioning. CAI patients' memory complaints may be partially explained by their chronic inability to produce cortisol, especially in light of the role that corticosteroids play in memory consolidation in animal models (Oitzl & De Kloet, 1992).

The current study sought to determine how stress affects learning in CAI patients (aim1). Among patients treated with NaCl, we found that exposure to psychosocial stress alone – at either learning or recall – is not sufficient to impair or enhance recall performance, which is in contrast to other findings (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006; Schwabe & Wolf, 2010; Zoladz et al., 2013). While the effect of stress on recall was absent, patients exhibited an

enhanced memory for negative words over neutral words, which is consistent with the literature (Majerus & D'Argembeau, 2011; Zimmerman & Kelley, 2010), as well as a practice effect. Studies that report the memory-enhancing effect of pre-learning stress for cortisol responders only (Schwabe et al., 2008) as well as the impairing effect of pre-retrieval stress only in men with blunted cortisol responses (Zoladz et al., 2014) suggest that the memory effects of stress may be contingent on the presence or strength of a cortisol stress response. Thus, the absence of a stress effect on NaCl patients' immediate recall may be due to their inability to mount a cortisol stress response and their treatment with NaCl as opposed to HC. However, the patients' enhanced memory for negative words is akin to what is expected in healthy populations, so patients seem to be susceptible to normative influences on memory, but with a specific immunity to stress effects on memory.

The second aim of this study was to explore how stress exposure post-learning affects delayed recall in CAI patients and how this effect is influenced by an acute hydrocortisone injection to mimic a cortisol stress response. The NaCl and HC groups did not significantly differ in their delayed recall of the first wordlist, regardless of word type. As opposed to the impairment that is observed when healthy controls are administered cortisol prior to retrieval (Het et al., 2005), memory performance of CAI patients treated with HC was not affected. This suggests that neither psychosocial stress alone nor psychosocial stress accompanied by elevated cortisol levels during retrieval influence recall in CAI patients. This lack of impairment is especially interesting given evidence suggesting CAI patients' memory deficits relative to healthy controls (Henry & Thomas, 2014; Tiemensma et al., 2016). It may be that while CAI

patients suffer from a general cognitive deficit, their delayed recall is less susceptible to the stress effects of memory, as also suggested by the results of aim 1. It could be that because current treatment options for CAI result in large spikes in cortisol following HC administration, resulting in fluctuating states between hyper and hypocortisolism (Peacey et al., 1997), acute administration of HC does not interfere as much in CAI patients' memory function than in healthy controls.

The final objective of this study was to examine how stress exposure affects subsequent learning and delayed recall in CAI patients dependent on the presence or absence of cortisol (aim 3). After psychosocial stress exposure, elevated cortisol levels during learning were detrimental to learning itself as well as later memory recall performance (aim 3). This recall impairment is contrary to the findings of a meta-analysis that reports no effect on memory when healthy individuals are administered cortisol during learning (Het et al., 2005). Rather, the findings of this study are similar to studies wherein exposure to an acute stressor hinders learning and recall in healthy participants (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Schwabe & Wolf, 2010; Zoladz et al., 2013) and studies wherein acute cortisol administration inhibits recall in animal models (De Quervain, Roozendaal, McGaugh, 1998). Additionally, time of recall, valence, and the interaction of time and valence impacted memory performance. Again, more negative than neutral words were recalled by both patients treated with HC and with NaCl. It seems that the combination of acute psychosocial stress and HC administration during learning results in the pattern of memory impairment that is observed in healthy populations exposed to acute stress, but not the pattern (i.e., no impairment) that is expected when healthy participants are given HC. This suggests that while HC and acute psychosocial stress present during learning result in more normative memory impairments, they may be further detrimental to CAI patients'

already decreased memory performance as compared to healthy individuals (Henry & Thomas, 2014; Tiemensma et al., 2016).

Previous literature has suggested that the emotional valence attached to wordlists may increase or decrease learning and memory. To help explore the effect of valence on CAI patients' recall performance, participants were exposed to both negative and neutral wordlists 15 minutes after the cessation of the TSST. Findings were consistent with other published results (Zimmerman & Kelley, 2010; Majerus & D'Argembeau, 2011), with both CAI participant groups recalling more negative words than neutral words at both the immediate and delayed recall periods. While previous studies have found that stress just prior to learning emotionally valenced information facilitates memory consolidation (Schwabe et al., 2008) and subsequent delayed recall (Zoladz et al., 2011), the results of this study suggest that CAI patients' memory for emotional information is less affected by exposure to psychosocial stress and elevated cortisol.

Taken together, findings from this study suggest that contrary to what is expected in healthy individuals, a psychological stressor alone is not sufficient to alter memory performance in CAI patients, that the introduction of HC and an acute stressor during recall does not affect memory performance, and that the combination of a psychosocial stressor and HC during learning significantly impair delayed recall performance. The latter finding may have implications for CAI patients' treatment regimens, as their cortisol replacement therapy, while essential to survival, may be a contributory factor in their reported memory functioning. It seems that cortisol treatments further exacerbate memory deficits in an already disadvantaged population. Current treatment options result in large spikes in cortisol following HC administration resulting in fluctuating states between hyper and hypocortisolism, and have a high

potential for overtreatment (Peacey et al., 1997). Therapeutic options that avoid large dosages of HC and more closely mimic normal basal cortisol patterns may alleviate these additional detrimental effects on memory and learning.

Limitations

While this study has many strengths, several limitations must be acknowledged. First, there was no healthy control group. While other studies have examined CAI patients compared to healthy controls, our study focused on CAI patients treated with HC to mimic an acute stress response and NaCl treated patients. Including a group of healthy participants treated with NaCl would have allowed us to confirm that CAI patients have memory deficits relative to healthy individuals and whether the NaCl performs similarly or better than controls without the interference of cortisol. Secondly, the study design did not allow for assessing both learning and delayed recall under the same condition: neither wordlist was both learned and recalled with and without the stress interventions. It may that psychosocial stress only affects performance in CAI patients when both learning and recall occur under stress. This would further emphasize the role of psychosocial stress as an influential factor in CAI patients' cognitive performance. Third, as people afflicted with chronic adrenal insufficiency are rare, this study had relatively modest sample sizes, so generalizations should be made cautiously. Finally, the impairing effect of HC on immediate and delayed recall (aim 3) may be the result of long-term substitution therapy changing patients' sensitivity to the memory-impairing effects of cortisol rather than direct interference by HC itself.

Summary

Overall, this study found that when recall occurs either under stress or under stress in addition to HC, there is no difference in CAI patients' delayed recall performance. However,

when learning occurred under these conditions, patients treated with HC exhibited impaired immediate and delayed recall performance, suggesting that HC decrease recall performance (aim 3). Patients treated with HC also recalled fewer words overall, suggesting that HC treatment, and the subsequent abrupt elevations in cortisol, may contribute to an overall cognitive deficit in CAI patients, in addition to the potential cognitive impairments of having destroyed adrenal cortex cells. These findings provide insight into the cognitive functioning of CAI patients, particularly in that the relationship between cortisol, acute stress exposure, and memory in CAI patients seems to differ from what is expected in healthy populations. Future work should further explore the cognitive effects of long-term cortisol replacement therapy, particularly given the impairing effects of acute HC treatment we observed. These results may have implications for alterations in treatment regimen for CAI patients that could alleviate some of the memory difficulties they report.

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Tables

Table 1. Independent group t-tests and chi-square values comparing the placebo and the hydrocortisone group on variables that could influence differences in cortisol response and recall performance.

Variable		Placebo (*N*=15)	Hydrocortisone (*N*=13)		
		Mean (SD)/*n*	Mean (SD)/*n*	t/χ^2	p
Age		45.47 (8.81)	44.31 (9.22)	-.34	.74
Sex	Female	11	10	.05	.83
	Male	4	3		
Etiology	PAD	3	1	5.69	.13
	AD-Infection	1	.		
	AD-AI	8	12		
	Cushing's	3	.		
Cortisol substitution medication	Hydrocortisone	11	12	1.71	.19
	Cortisone Ciba	4	1		
Cortisol substitution/day(mg)		28.67 (7.78)	29.04 (10.88)	.11	.92

PAD = primary adrenal insufficiency AI = autoimmune AD = Addison's

Table 2. Summary of repeated-measures ANOVA comparing recall performance of the placebo and hydrocortisone patients (treatment) for the second wordlist recall time points by word type (valence).

Variable	Effect (*F*)
Time	37.54**
Valence	6.41*
Treatment	4.60*
Time*Treatment	.56
Valence*Treatment	.00
Time*Valence	8.40**
Time*Valence*Treatment	.35

*$p < .05$ **$p \leq .001$

Figures

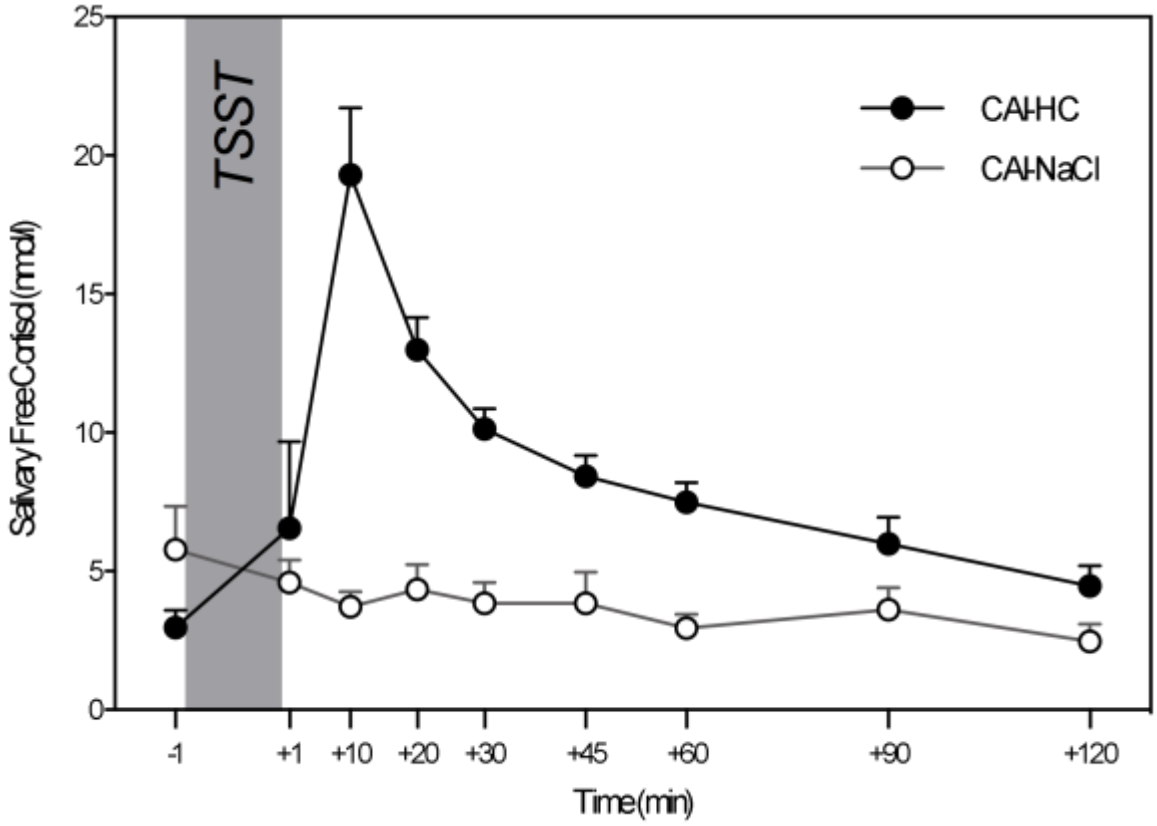

Figure 1. Cortisol profile of the placebo group versus the hydrocortisone group across testing time.

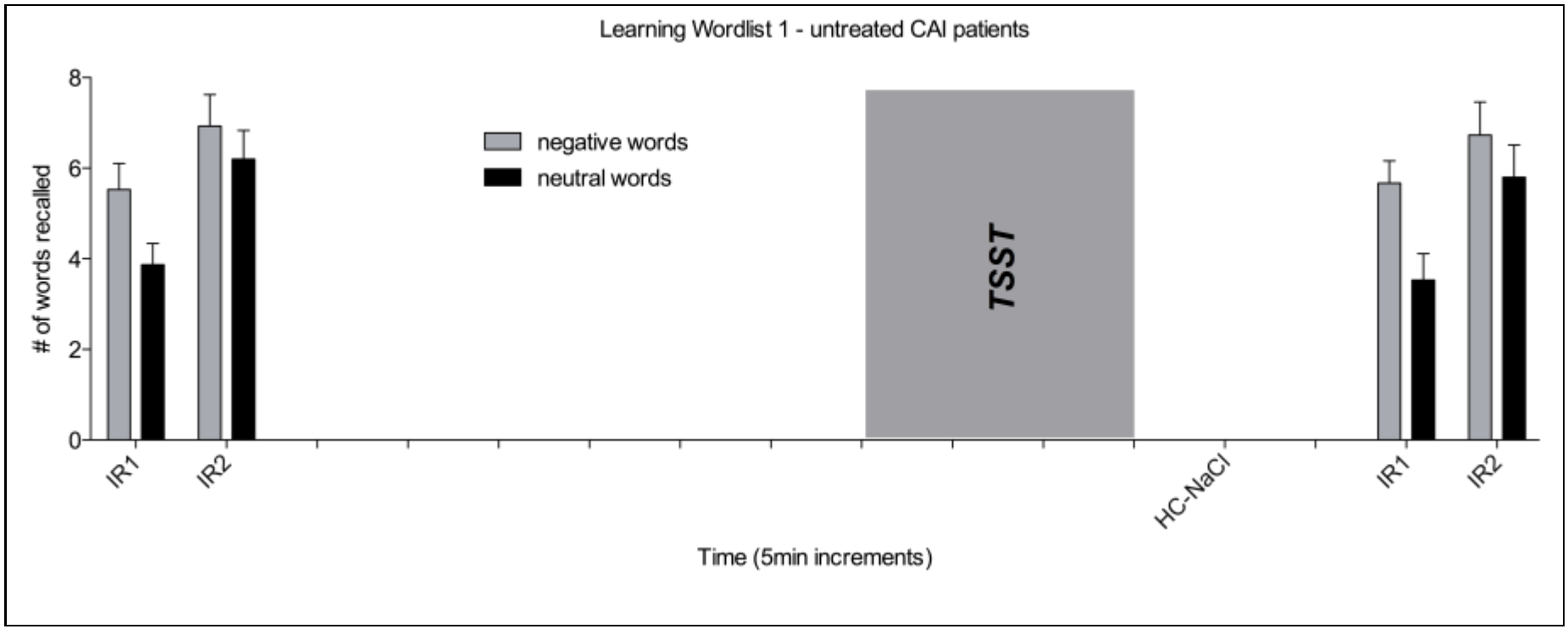

Figure 2. Immediate recall learning trials (IR1, IR2) of Wordlist 1(pre-stress) and Wordlist 2 (post-stress) negative and neutral words in NaCl patients.

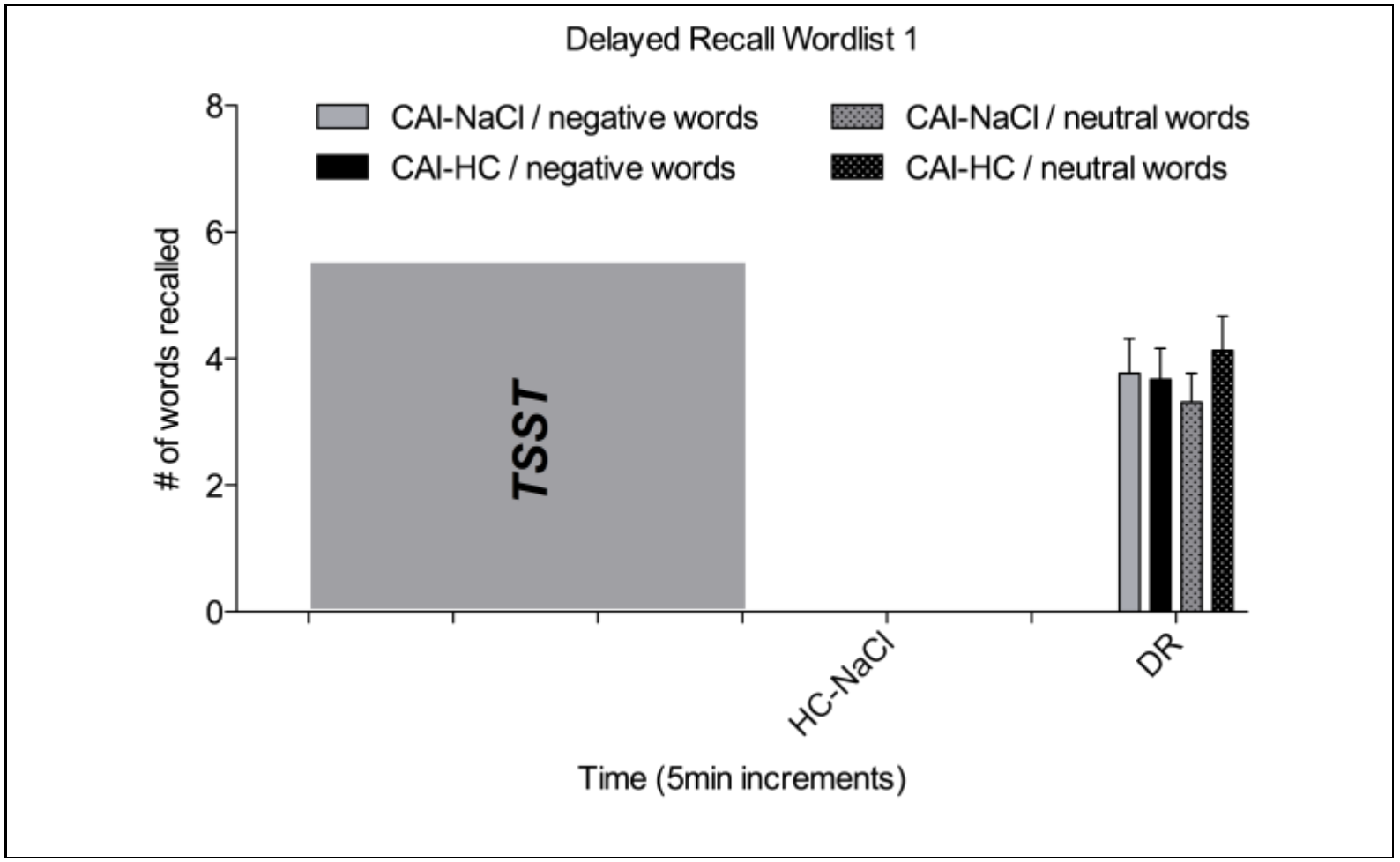

Figure 3. Post-stress delayed recall of Wordlist 1 negative and neutral words by treatment group.

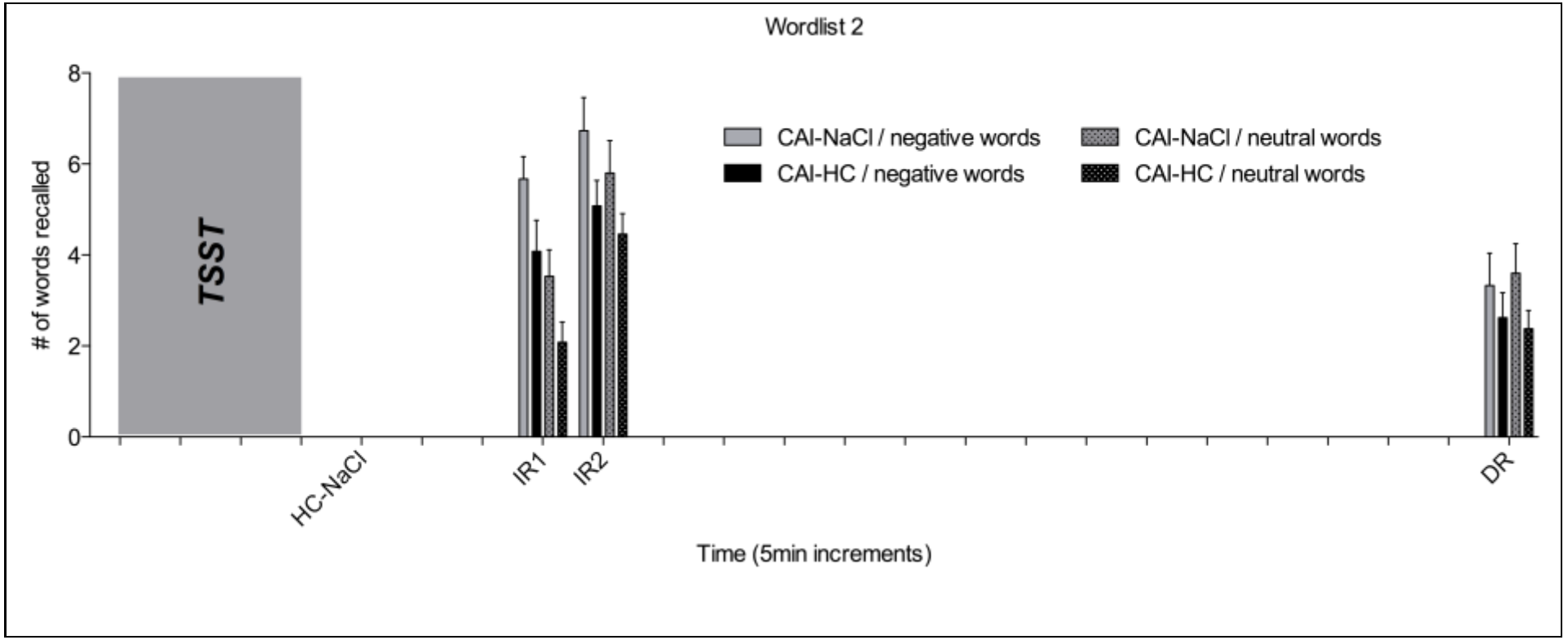

Figure 4. Recall of Wordlist 2 negative words and neutral words from the two learning trials (IR1, IR2) to delayed recall (DR) by treatment group.