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Glucocorticoid response to stress induction prior to learning is negatively related to subsequent motor memory consolidation

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ABSTRACT

Hippocampal activity during early motor sequence learning is critical to trigger subsequent sleep-related consolidation processes. Based on previous evidence that stress-induced cortisol release modulates hippocampal activity, the current study investigates whether exposure to stress prior to motor sequence learning influences the ensuing learning and overnight consolidation process. Seventy-four healthy young adults were exposed to a stressor (i.e., the socially evaluated cold pressor test, SECPT) or a control procedure before initial training on a bimanual motor sequence learning task. Participants were retested on the motor task 24 h (including a night of sleep) after training to assess memory consolidation. Our results indicate that the SECPT, as compared to the control condition, induced significant physiological stress responses as evidenced by increased heart rate and blood pressure as well as elevated salivary cortisol concentrations. Cortisol concentration in the stress group reached peak levels immediately before and stayed significantly elevated for the full duration of initial motor learning before returning to baseline during the consolidation period. Stress induction prior to learning did not, on average, influence initial performance nor subsequent motor memory consolidation as indicated by similar overnight gains in performance in both groups. However, higher levels of stress-induced cortisol prior to training were correlated to smaller overnight gains in performance speed. These results indicate that the glucocorticoid response to a stressful encounter experienced prior to hippocampal-mediated motor learning is negatively related to subsequent memory consolidation processes.

1. Introduction

Retaining newly acquired skills is a fundamental capacity that underlies the elaborate and complex set of motor behaviours in humans. This capacity is supported by the process of memory consolidation, which allows newly acquired motor memory traces to be transformed into more stable, long-term representations (Robertson, Pascual-Leone, & Miall, 2004). Motor memory consolidation has extensively been studied using motor sequence learning tasks during which a series of movements is gradually acquired and transformed into a unitary well-rehearsed sequence. Accordingly, both the behavioural and neural correlates of motor sequence memory consolidation are comprehensively described in the literature (e.g., Albouy, King, Maquet, & Doyon, 2013; Doyon, Bellec, et al., 2009).

Motor sequence memory acquisition is first triggered during initial task practice, but the memory trace continues to develop over time after initial task exposure. During this post-acquisition phase, taking place in the absence of any further task practice, the memory trace undergoes a slow offline process that is thought to support motor memory consolidation (Albouy, King et al., 2013; Robertson et al., 2004). At the behavioural level, consolidation can be reflected by offline performance maintenance or improvements as well as by increased resistance to interference from competing material (Robertson et al., 2004). Sleep, as compared to wakefulness, plays a unique role in this offline mnemonic process, as it not only protects motor memory traces against interference but also facilitates performance enhancement (e.g. Robertson, 2005; Korman et al., 2007; Albouy et al., 2015; Albouy et al., 2016). At the neural level, numerous studies have converged towards the view that motor sequence memory processes are mediated by differential recruitment of *cortico-cerebellar, cortico-striatal* and *cortico-hippocampal* circuits (see Albouy, King et al., 2013; Doyon, Bellec, et al., 2009; Doyon, Korman, et al., 2009; Penhune & Steele, 2012 for various

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models). Interestingly, while initial motor memory acquisition is supported by both striatal and hippocampal networks, sleep-related motor memory consolidation is described to be more particularly linked to hippocampal functioning (Albouy, King et al., 2013). Specifically, task-related brain activity in the hippocampus and the strength of its competitive interaction with the striatal system during initial training forecast subsequent overnight performance gains (Albouy et al., 2008; Albouy, Sterpenich, et al., 2013). While these specific cerebral patterns have been described as crucial pre-requisites to trigger sleep-related consolidation processes (Albouy, King et al., 2013; King, Hoedlmoser, Hirschauer, Dolfen, & Albouy, 2017), it remains unknown whether factors that can modulate hippocampal activity and its functional connectivity with the striatal system can influence the motor memory process.

Accumulating evidence suggests that experimentally-induced stress or administration of cortisol, a major stress hormone, can rapidly modulate hippocampal activity (Albert, Pruessner, & Newhouse, 2015; De Quervain et al., 2003; Kim & Diamond, 2002; Lovallo, Robinson, Glahn, & Fox, 2010; Pruessner et al., 2008) and modify the relative engagement of the hippocampal and striatal system during both declarative and procedural learning (Schwabe, Tegenthoff, Höffken, & Wolf, 2013; Schwabe & Wolf, 2012; Wirz, Wacker, Felten, Reuter, & Schwabe, 2017; Vogel et al., 2017; Packard & Goodman, 2012; Quaedflieg & Schwabe, 2017; Wirz, Reuter, Wacker, Felten, & Schwabe, 2017). More specifically in the procedural domain, acute stress prior to training on a probabilistic learning task reduced the use of hippocampal strategies in favour of dorsal striatum-dependent strategies (Schwabe & Wolf, 2012, Schwabe et al., 2013; Wirz, Reuter et al., 2017). In these studies, the stress-induced behavioural shift was paralleled by reduced hippocampal activity during task performance. Based on the evidence that the hippocampus and the striatum competitively interact during classification learning (Poldrack et al., 2001), it was recently proposed that stress-induced reduction in hippocampal recruitment may allow the striatum to dominate learning under stress (Schwabe, 2017). Thus, based on the evidence that stress modulates hippocampal activity as well as its connectivity with the striatum and that these specific neural patterns are crucial for motor sequence memory consolidation, we argue that stress will influence motor memory processes.

To the best of our knowledge, the effect of stress on motor memory has only been studied with non-hippocampal-mediated motor tasks (Hordacre, Immink, Ridding, & Hillier, 2016; Lawrence et al., 2014; Marteniuk & Wenger, 1970; Oudejans & Pijpers, 2009; Sage & Bennett, 1973; Wegner, Koedijker, & Budde, 2014). This is surprising given the large body of evidence suggesting that stress alters neural processing in the hippocampus (see Kim & Diamond, 2002 for a review) which is known to play an important role in motor sequence memory (Albouy, King et al., 2013). The aim of this study was therefore to investigate the effect of stress on the acquisition and consolidation of a hippocampal-mediated motor sequence memory task. To do so, participants were exposed to the Socially Evaluated Cold Pressor test (SECPT (Schwabe, Haddad, & Schachinger, 2008)) or to a non-stressful control intervention prior to initial training on a motor sequence learning task. According to studies showing that not only the hippocampal but also the striatal system is involved in initial motor memory acquisition (see Albouy, King et al., 2013 for a review), we hypothesized that stress prior to learning would *not* compromise initial memory acquisition, presumably due to compensatory mechanisms supported by the striatum (and favored by stress induction, Schwabe, 2017). Importantly, based on the evidence that (a) cortisol release in response to stress can modulate the recruitment of the hippocampus and the interaction between hippocampal and striatal networks (De Quervain et al., 2003; Schwabe et al., 2013, Schwabe & Wolf, 2012; Wirz, Reuter et al., 2017), and (b) activity in and interaction between these structures during initial motor learning is a pre-requisite for subsequent sleep-related consolidation (Albouy et al., 2015; Albouy, King et al., 2013), we hypothesized that exposure to stress prior to initial memory acquisition will hinder subsequent overnight motor memory consolidation processes. Furthermore, the physiological stress response prior to learning, assessed with salivary cortisol concentration, was expected to be negatively associated with overnight gains in performance.

2. Material and methods

2.1. Participants

Eighty-six young (mean age: 23.6 years, SD: 3.1 years, 42 females), right-handed (Edinburgh Handedness Inventory; Oldfield, 1971), healthy participants gave their written informed consent to take part in the study, which was approved by the Medical Ethics Committee UZ KU Leuven. Participants received a monetary compensation for their participation. They did not present any current or previous neurological or psychiatric diseases and were free of medications. Participants showed no evidence of chronic pain (Pain Catastrophizing Scale; Sullivan, Bishop, & Pivik, 1995), extreme stress (Perceived Stress Scale; Cohen, Kamarck, & Mermelstein, 1983), excessive daytime sleepiness (Epworth Sleepiness Scale; Johns, 1991), anxiety (Beck Anxiety Inventory; Beck, Epstein, Brown, & Steer, 1988) or depression (Beck Depression Inventory; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). None of the participants were extreme morning or evening chronotypes (Circadian Rhythm Questionnaire; Horne & Ostberg, 1976) or shift-workers. All participants reported normal sleep quality and quantity during the month prior and during the study as assessed using the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the St Mary's Hospital Questionnaire (Ellis et al., 1981), respectively. None of the participants received formal training on a musical instrument or as a professional typist. None of the participants were smokers or currently taking oral contraceptives, as these factors can affect the reactivity of the hypothalamus pituitary adrenal (HPA) axis (Kirschbaum, Pirke, and Hellhammer, 1993; Rohleder & Kirschbaum, 2006).

Of the 86 participants recruited, 12 were discarded from the analyses. One participant in the stress group was excluded because of incomplete data on the motor sequence learning (MSL) task. Four participants (one in the stress group and three in the control group) were excluded due to non-compliance to their sleep/wake schedule. In the stress group, 7 participants were excluded from further analyses because they were classified as cortisol non-responders, i.e., the stress-induced increase in cortisol concentration from baseline to T25′ was below 15.5% and 1.5 nmol/l (Miller, Plessow, Kirschbaum, & Stalder, 2013; baseline to T25′ change in cortisol concentration in stress-non-responders (nmol/l): M = −1.85, SD = 3.15, range = [−8.36, 1.43]). All the participants in the control group were non-responders (baseline to T25′ change in cortisol concentration (nmol/l): M = −1.91, SD = 2.22, range [−10.54, 1.30]). A total of 74 participants were included in the analyses (Control group, N = 38, 19 females; Stress group, N = 36, 17 females). Participant characteristics are summarized in Supplementary Table 1.

2.2. Experimental procedure

The experimental procedure is depicted in Fig. 1. Participants were instructed to respect a regular sleep/wake schedule (according to their own schedule ± 1 h) starting three days before the first experimental session and until the end of the study (four nights in total). Compliance to this schedule was assessed using sleep diaries and wrist actigraphy (ActiGraph wGT3X-BT, Pensacola, FL). All participants completed two experimental sessions spread across two days and separated by a 24 h interval including a full night of sleep spent at home. Subjective sleep quality during the night before each experimental session was assessed using the St. Mary's Hospital Sleep Questionnaire. Participants received the instruction to wake up at the latest 1 h before the start of each

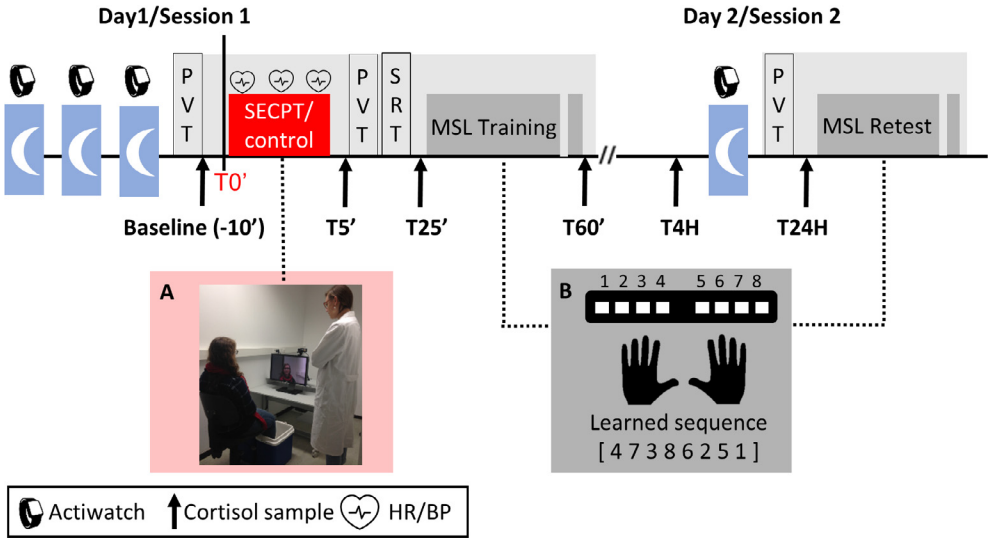

Fig. 1. Experimental Design. All participants respected a constant sleep/wake schedule for 4 nights starting 3 days before the first experimental session (Session 1). Participants were trained on a motor sequence learning (MSL) task (bimanual finger-tapping task) at 2 different occasions, referred to as Training and Retest. The task required participants to learn an 8-element sequence (using 8 fingers, no thumbs) through repeated practice (subpanel B). On day 1 (Session 1), subjects were randomly assigned to one of two groups according to whether they were exposed to the stress (SECPT, subpanel A) or control intervention before the MSL Training session. Participants were retested 24 h after initial training (Session 2, Retest). Between sessions, participants went back home for a full night of sleep. Salivary samples were collected before (−10′, Baseline) and immediately after the stress/control intervention (T5′), immediately before (T25′), immediately after (T60′), 4 h after (T4h) and 24 h after (T24h) the initial Training on the MSL task. Heart rate (HR) and blood pressure (BP) were measured before, during and after the stress/control intervention. PVT = Psychomotor Vigilance Testing. SECPT = Socially Evaluated Cold Pressor Task. SRT = Serial Reaction Time task.

experimental session to account for the cortisol awakening response (Fries, Dettenborn, & Kirschbaum, 2009). They were also instructed to not brush their teeth, eat and drink (apart from water) for 1 h before each experimental session to ensure adequate saliva sampling for cortisol assessment (see below). Excessive exercise and intake of alcohol, nicotine or caffeine (and other vigilance-altering substances) was prohibited the day before as well as the day of the experimental sessions. All testing sessions took place between 10 am and 3 pm with the number of participants tested in the PM and the AM being comparable between experimental groups. As previous evidence suggests that the time of testing (AM vs. PM) influences the effect of glucocorticoids on cognition (Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005), additional control analyses using time of testing as a between-subjects factor were performed. Results showed that this factor did not influence the results reported in the main text (see Supplementary Materials).

During the first session (Session 1/Day 1), participants were randomly assigned to one of two groups according to whether they were exposed to a control or a stress intervention (i.e. Socially Evaluated Cold Pressure Test, SECPT) **before** practice on a MSL task (referred to as MSL Training) (Fig. 1). Practice on the MSL task started on average 30 min (range: 25–40 min) after the control/stress intervention. This timing was chosen because SECPT-induced secretion of cortisol is known to reach peak levels after 25 min (Schwabe et al., 2008). In order to investigate whether the delay between SECPT and task influenced our results, delay (min) was entered as a confounding factor in additional control analyses presented in the Supplementary Materials. Importantly, no effect of delay was observed on the results presented in the main text. After Session 1, participants were allowed to leave the lab and go back to their daily activities (with the instruction to avoid finger tapping and napping) and returned to the lab 24 h later for a second practice session on the MSL task (referred to as MSL Retest) (Session 2/Day 2).

Immediately before and after the control/stress intervention, as well as before the MSL Retest, vigilance was measured objectively using the Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985) and subjectively with the Stanford Sleepiness Scale (Maclean, Fekken, Saskin, & Knowles, 1992). The effect of the control/stress intervention on general motor execution was assessed using a Serial Reaction Time (SRT) task taking place after the intervention (i.e., before the MSL Training). Practice on the SRT task started on average 20 min (range: 18–21 min) after the control/stress intervention. To measure the time course of cortisol concentration, a total of six salivary samples were collected throughout the study (see below for details).

2.3. Stress induction method

In the stress condition, participants were exposed to a modified version of the socially evaluated cold pressor test (SECPT, see Fig. 1 subpanel A) (Larra, Schilling, Röhrig, & Schachinger, 2015; Schwabe et al., 2008; Schwabe & Schachinger, 2018). The task required participants to immerse their feet (up to and including the ankles) in ice water (0–2 °C) while they were videotaped for pretended analysis of facial expression and monitored by a rather unsociable and non-reinforcing experimenter. During feet immersion, participants were asked not to move or speak, to keep their eyes focused on the camera and to keep their feet in the water until the experimenter gave the instruction to withdraw (after 3 min). No information was given with respect to the duration of the cold water stimulation in order to increase the unpredictability of the intervention. In contrast to the stress condition, participants in the control condition submerged their feet up to and including the ankles for 3 min in warm water (35–37 °C). They were neither monitored by an unsociable experimenter nor videotaped.

To measure the effectiveness of the stress induction by the SECPT, subjective and physiological responses were repeatedly measured during the experiment. Participants were asked to rate their subjective feeling of stress, pain and unpleasantness on a visual analogue scale from 0 (“Not at all”) to 100 (“Very much”) immediately following the control/stress manipulation. Heart rate and blood pressure (systolic and diastolic) were assessed using an automatic upper arm blood pressure monitor (BP6000, Braun) before (pre), during and immediately following (post) feet immersion during the control/stress manipulation.

Finally, for each participant, a total of six salivary cortisol samples were collected using Salivette collection devices (Sarstedt Salivette). The start of the control/stress manipulation is referred to as time point 0 (T0′). Samples were collected before (T0 – 10 min; baseline) and after (T0 + 5 min; T5′) the start of the control/stress manipulation, as well as before (T0 + 25 min; T25′) and after (T0 + 60 min; T60′) the MSL Training session. Supplemental samples were taken at home (T0 + 4 h; T4h) and in the lab at the start of the MSL Retest session (T0 + 24 h; T24h). All samples were collected while participants were seated. After collection, the samples were stored at −20 °C until analysed using immunoassay in the laboratory for clinical chemistry and radio-immunology (UZ Brussels).

Table 1
Subjective, autonomic (heart rate, systolic and diastolic blood pressure) and endocrine (cortisol) responses to the intervention.

	Control	Stress	Control vs. Stress
Subjective response (%)			
Pain	0.76 ± 1.74	70.20 ± 21.90	***p* < .001**[a]
Stress	2.77 ± 5.63	58.92 ± 23.13	***p* < .001**[a]
Unpleasantness	2.60 ± 5.61	75.20 ± 18.44	***p* < .001**[a]
HR (bpm)			
Pre	69.61 ± 12.97	72.69 ± 9.94	*p* = .260
During	69.63 ± 11.54	93.51 ± 16.49	***p* < .001**
Post	71.34 ± 12.91	75.19 ± 14.97	*p* = .242
SBP (mmHg)			
Pre	129.76 ± 14.71	129.08 ± 13.08	*p* = .905
During	123.58 ± 14.88	151.94 ± 20.12	***p* = .000**
Post	125.21 ± 11.49	133.53 ± 16.89	***p* = .019**
DBP (mmHg)			
Pre	78.55 ± 11.66	75.97 ± 8.81	*p* = .343
During	76.39 ± 8.22	95.34 ± 22.67	***p* = .000**
Post	74.24 ± 7.59	85.33 ± 17.31	***p* = .001**
Cortisol (nmol/l)			
Baseline	7.41 ± 4.51	6.64 ± 3.11	*p* = .461
T5′	6.74 ± 4.12	6.68 ± 3.57	*p* = .936
T25′	5.50 ± 3.01	15.31 ± 7.09	***p* < .001**
T60′	5.61 ± 3.49	10.40 ± 5.41	***p* < .001**
T4H	4.02 ± 1.81	4.59 ± 2.55	*p* = .265
T24H	6.36 ± 3.83	6.52 ± 3.10	*p* = .721[a]

Notes: Values are means ± SD. Note that cardiovascular measures of one participant and a cortisol measure (at the T4H time point) of another participant (both in the stress group) are missing due to measurement error. Significance tests based on planned pairwise comparisons corrected for multiple comparisons using Bonferroni correction. *p*-values in bold represent significant group differences.

[a] Significance test based on unpaired t-tests. HR = heart rate. Bpm = beats per minute. SBP = systolic blood pressure. DBP = diastolic blood pressure.

2.4. Motor sequence learning task

To probe motor learning and memory consolidation processes, all participants performed a bimanual finger-tapping task implemented in Matlab Psychophysics Toolbox version 3 (Kleiner et al., 2007) at two different occasions, referred to as MSL Training and Retest. Participants were positioned supine in a mock scanner during both practice sessions. The task required participants to tap an eight-element finger sequence (8 fingers, no thumbs, see Fig. 1 panel B) on a specialized keyboard as rapidly and accurately as possible. The sequence to perform (4-7-3-8-6-2-5-1, where 1 and 8 correspond to the little finger of the left and right hand, respectively) was explicitly taught to the participants prior to initial training. Similar to previous research (Albouy, Fogel, et al., 2013; Debas et al., 2014; Doyon, Korman, et al., 2009; Fogel et al., 2014; Robertson, 2005), all participants were trained on the same sequence. To ensure that participants memorized the sequence, each session included a brief pre-training phase during which participants were instructed to perform the sequence repeatedly and slowly until they reproduced three consecutive correct sequences. Both the Training and Retest sessions consisted of 16 practice blocks followed by an immediate post-test (after a 2-min break) of 4 practice blocks in order to minimize the confounding effect of fatigue on end-training performance (Pan & Rickard, 2015). Each practice block was indicated by a green cross displayed in the middle of the screen and included 64 keypresses (ideally corresponding to 8 correct sequences) after which the cross automatically turned red, indicating a rest block (duration 20 s). During rest blocks, participants were instructed to keep their fingers still and look at a red fixation cross. During the last 5 s of each rest block, the sequence of numbers appeared on the screen as a reminder.

Motor performance was measured in terms of speed (mean time to perform a correct transition in s) and accuracy (% of correct transitions). To investigate the effect of stress on consolidation processes, offline gains in performance speed and accuracy were computed as the percent change from the end of Training (average 4 blocks immediate post-Training test) to the beginning of the MSL Retest (average first 4 blocks). To investigate the relationship between offline gains in performance and the physiological response to stress prior to learning, correlations were calculated separately within each group. Performance variables of interest were offline gains in speed and accuracy. Physiological measure of interest was cortisol concentration at T25′.

2.5. Assessment of general motor performance

A random SRT task (Nissen & Bullemer, 1987), implemented in Matlab Psychophysics Toolbox version 3, was used to assess general motor execution after the control/stress intervention but prior to the MSL Training. During this task, eight squares were presented on the screen, each corresponding to one of the eight keys on the specialized keyboard and to one of the 8 fingers (no thumbs). The colour of the outline of the squares alternated between red and green, indicating rest and practice blocks, respectively. During the practice blocks, participants had to press as quickly as possible the key corresponding to the location of a green filled square that appeared on the screen. After a response, the next square changed to green (response-stimulus interval = 0 ms) following a random order. After 64 presses, the practice block automatically turned into a rest block and the outline of the squares changed from green to red. The task included four practice blocks, separated by 15 s rest intervals. Performance was measured in terms of speed (response time in ms) and accuracy (number of correct key presses).

2.6. Statistical analyses

Statistical analyses were performed using SPSS Statistics 24 (IBM). For all analyses, the probability level was set at $p < 0.05$. In case of violation of the sphericity assumption, Greenhouse-Geisser corrections were applied. Results of planned pairwise comparisons were corrected using Bonferroni correction for multiple comparisons.

3. Results

Results related to measures of sleep and vigilance prior to and during the experiment are reported in Supplementary Table 2.

3.1. Stress induction by the SECPT

Participants in the control and stress group submerged their feet on average 180 s (SD = 0) and 153 s (SD = 48.7) in the water, respectively. With respect to the subjective response to the intervention, the SECPT was rated as significantly more stressful, unpleasant and painful as compared to the control manipulation (unpaired t tests, all *ps* < .001, Table 1).

To investigate the autonomic response, heart rate (bpm) and (systolic and diastolic) blood pressure (mmHg) were analysed using 3 (time: pre vs. during vs. post) × 2 (groups) repeated-measures ANOVAs. Results are detailed below and follow-up between-group comparisons are reported in Table 1. With respect to heart rate (HR), there was a significant effect of time [$F_{(2,128.71)} = 34.907$, $\eta_p^2 = 0.33$, $p < .001$], group [$F_{(1,71)} = 14.224$, $\eta_p^2 = 0.167$, $p < .001$] as well as a time by group interaction [$F_{(1.813,\ 128.713)} = 39.974$, $\eta_p^2 = 0.36$, $p < .001$] (see Fig. 2A, left panel). During the intervention, HR was significantly higher in the stress than in the control group whereas no group differences were apparent pre- and post-intervention. In the stress group, HR returned to baseline levels post-intervention [Stress group, effect of time: $F_{(2,70)} = 77.123$, $\eta_p^2 = 0.688$, $p < .001$; pre vs. during, $p < .001$, during vs. post, $p < .001$, pre vs. post, $p = .202$], while HR remained stable over time in the control group [Control

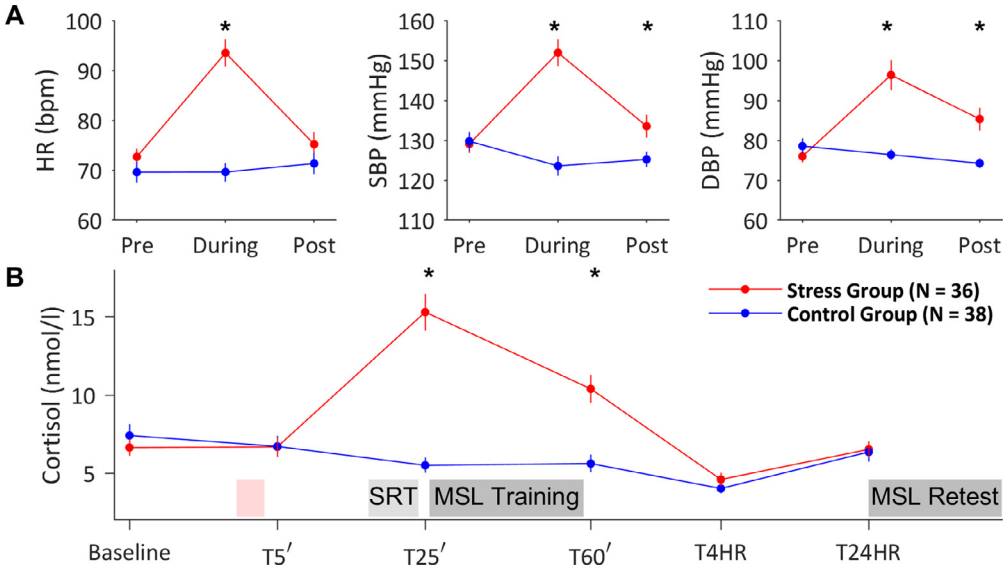

Fig. 2. (A) Heartrate (HR; beats per minute, bpm), systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) pre, during and post the control/stress intervention. The SECPT resulted in a significant increase in HR, SBP and DBP in the stress group. (B) Time course of salivary cortisol concentration (nmol/l). The red bar indicates the control/stress intervention. In the stress group, cortisol levels were significantly increased at the start of MSL Training (T25′) and remained elevated until the end (T60′). Cortisol concentration was significantly higher in the stress as compared to the control group at T25′ and T60′. *Represents significant between-group differences ($p < .05$). Error bars represent SEM. SRT = Serial Reaction Time task. MSL = Motor Sequence Learning.

group, effect of time: $F_{(2,70)} = 0.813$, $\eta_p^2 = 0.023$, $p = .448$]. The analysis on systolic blood pressure (SBP) revealed a main effect of time [$F_{(2,125.34)} = 19.636$, $\eta_p^2 = 0.217$, $p < .001$], group [$F_{(1,71)} = 14.626$, $\eta_p^2 = 0.171$, $p < .001$] and a time by group interaction [$F_{(1.765,125.340)} = 46.217$, $\eta_p^2 = 0.394$, $p < .001$] (see Fig. 2A, middle panel). SBP was significantly elevated in the stress as compared to the control group during and post-intervention. Within the stress group, SBP increased during the intervention and subsequently decreased but remained significantly higher post as compared to pre intervention [Stress group, effect of time: $F_{(2,70)} = 26.903$, $\eta_p^2 = 0.577$, $p < .001$; pre vs. during, $p < .001$, during vs. post, $p < .001$, pre vs. post, $p = .048$]. Within the control group, SBP decreased during the intervention before it stabilized post-intervention [Control group, effect of time: $F_{(2,70)} = 3.596$, $\eta_p^2 = 0.093$, $p = .033$; pre vs. during, $p = 0.015$, during vs. post, $p = .404$, pre vs. post, $p = .019$]. Similarly, the analysis on diastolic blood pressure (DBP) revealed a main effect of time [$F_{(2,142)} = 12.027$, $\eta_p^2 = 0.145$, $p < .001$], group [$F_{(1,71)} = 16.420$, $\eta_p^2 = 0.188$, $p < .001$] and a time by group interaction [$F_{(2,142)} = 17.5$, $\eta_p^2 = 0.198$, $p < .001$] (see Fig. 2A, right panel). DBP was significantly higher during as well as after the intervention in the stress as compared to the control group. Within the stress group, DBP increased during and remained significantly higher post- as compared to pre-intervention [Stress group, effect of time: $F_{(2,70)} = 26.903$, $\eta_p^2 = 0.435$, $p < .001$; pre vs. during, $p < .001$, during vs. post, $p < .001$, pre vs. post, $p = .002$]. Within the control group, DBP remained stable over time [Control group, effect of time: $F_{(2,70)} = 1.307$, $\eta_p^2 = 0.036$, $p = .277$].

Finally, a 5 (time: baseline vs. T5′ vs. T25′ vs. T60′ vs. T4H) × 2 (groups) repeated measures ANOVA on cortisol concentration (nmol/l) was conducted to analyse the endocrine response to the SECPT. The analysis revealed a significant main effect of time [$F_{(2.889,205.118)} = 40.359$, $\eta_p^2 = 0.362$, $p < .001$], group [$F_{(1,71)} = 17.760$, $\eta_p^2 = 0.2$, $p < .001$] and a time by group interaction [$F_{(2.889,205.118)} = 40.431$, $\eta_p^2 = 0.363$, $p < .001$]. As shown in Fig. 2B, cortisol was significantly elevated in the stress group as compared to the control group at T25′ and T60′ but there were no significant group differences at any other time points (see Table 1 for between-group comparisons). Within the stress group, peak levels of cortisol were reached approximately 25 min after the stressor and cortisol concentration remained significantly elevated as compared to all other time points for the full duration of MSL Training, i.e. up to and including T60′ [Stress group, effect of time: $F_{(4,68)} = 47.887$, $\eta_p^2 = 0.738$, $p < .001$; T25′ vs. all other time points, all $ps < 0.001$, T60′ vs. all other time points, all $ps < 0.001$]. Within the control group, the time effect [$F_{(4,68)} = 8.972$, $\eta_p^2 = 0.345$, $p < .001$] was driven by decreased cortisol levels at T4H [T4H vs. Baseline, $p < .001$; T4H vs. T5′, $p < .001$; T4H vs. T25′, $p = .002$; all other $ps \geq 0.088$]. Importantly, similar cortisol concentrations were observed in both groups at the start of the Retest session (see T24H in Table 1). Altogether, results indicate that the SECPT effectively triggered subjective, autonomic and endocrine responses.

3.2. General motor performance

To investigate whether the stress intervention influenced general motor execution, all participants performed a random SRT task after the intervention. A 4 (blocks of practice) × 2 (groups) repeated measures ANOVA was performed on performance speed (response time) and accuracy (number of correct key presses). The analysis yielded a main effect of block [$F_{(2.570,185.028)} = 35.162$, $\eta_p^2 = 0.328$, $p < .001$], whereby performance was slower in block 1 as compared to blocks 2 to 4 (all $ps < .001$). No main effect of group, nor an interaction between group and block was observed for performance speed, indicating similar speed in both groups [main effect of group: $F_{(1,72)} = 1.704$, $\eta_p^2 = 0.023$, $p = .196$; block × group interaction: $F_{(2.570,185.028)} = 0.740$, $\eta_p^2 = 0.01$, $p = .510$]. Performance accuracy remained stable across blocks [main effect of block: $F_{(3,216)} = 0.879$, $\eta_p^2 = 0.012$, $p = .453$] and was comparable in both groups [main effect of group: $F_{(1,72)} = 1.33$, $\eta_p^2 = 0.018$, $p = .253$; time × group interaction: $F_{(3,205)} = 0.539$, $\eta_p^2 = 0.007$, $p = .656$]. Altogether, these results indicate that the stress and control interventions did not differently influence general motor execution.

3.3. Motor sequence learning task

Statistical analyses were conducted on performance speed (mean time to perform a correct transition) and accuracy (% of correct transitions per block).

3.3.1. MSL training

To test the effect of the stress intervention on initial motor learning, a 16 (blocks of practice) × 2 (groups) repeated measures ANOVA was conducted on performance speed and accuracy. Analyses on speed revealed a significant main effect of block [$F_{(3.541,\ 254.961)} = 67.475$, $\eta_p^2 = 0.484$, $p < .001$], indicating that speed improved with practice. Performance improvement was comparable in both groups [main effect of group: $F_{(1,72)} = 0.642$, $\eta_p^2 = 0.009$, $p = .426$; block × group interaction: $F_{(3.541,254.961)} = 0.94$, $\eta_p^2 = 0.013$, $p = .433$] (Fig. 3A, left

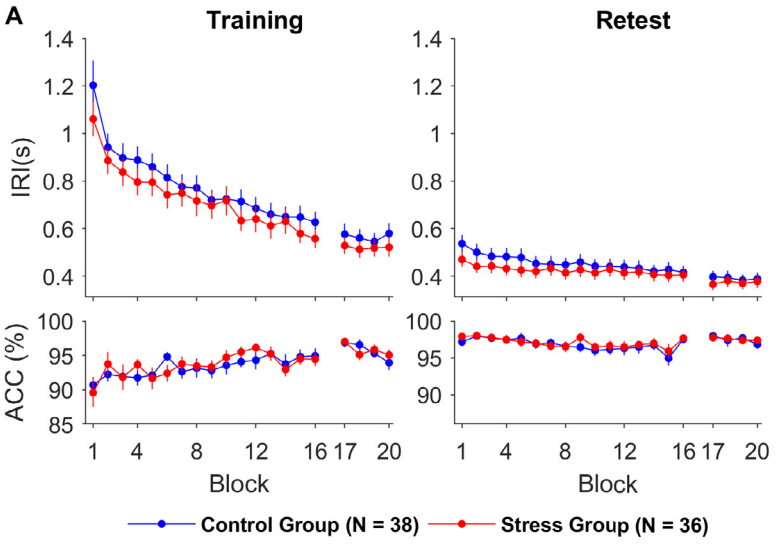

Fig. 3. (A) Performance speed (inter response interval, IRI) (upper panel) and accuracy (lower panel) plotted as a function of blocks of practice during Training and Retest for the control and stress groups. Performance speed and accuracy improved with practice during Training and reached similar levels in both groups during the immediate post-test. During Retest, performance speed further improved to the expense of accuracy. Performance reached stable levels at the post-test and did not differ between groups. (B) Offline gains (% change) in performance speed (upper panel) and accuracy (lower panel) between the end of Training (4 blocks of the immediate post-test) and the start of the Retest (first 4 blocks). There were no group differences in offline gains in performance speed and accuracy. Error bars represent SEM.

upper panel). Performance accuracy also increased with practice during the Training session and similarly in both groups (main effect of block: $F_{(9.115,\ 656.263)} = 3.789$, $\eta_p^2 = 0.050$, $p < .001$; main effect of group: $F_{(1,72)} = 0.066$, $\eta_p^2 = 0.001$, $p = .797$; block × group interaction: $F_{(9.115,\ 656.263)} = 0.713$, $\eta_p^2 = 0.010$, $p = .699$] (Fig. 3A, left lower panel). In order to investigate whether the level of performance reached at the end of Training differed between groups, a 4 (blocks of practice) × 2 (group) repeated measures ANOVA was conducted on performance speed and accuracy during the immediate post-test. Results show that performance speed further improved during the immediate post-test, which was reflected by a main effect of block [$F_{(2.66,\ 191.514)} = 2.944$, $\eta_p^2 = 0.039$, $p = .040$], and to a similar extent in both groups [main effect of group: $F_{(1,72)} = 0.679$, $\eta_p^2 = 0.009$, $p = .413$; block × group interaction: $F_{(2.660,191.514)} = 1.221$, $\eta_p^2 = 0.017$, $p = .302$]. In contrast, performance accuracy decreased as a function of practice in both groups [main effect of block: $F_{(3,216)} = 5.330$, $\eta_p^2 = 0.069$, $p = .001$; main effect of group: $F_{(1,72)} = 0.013$, $\eta_p^2 = 0.0$, $p = .91$; block × group interaction: $F_{(2.904,209.099)} = 1.589$, $\eta_p^2 = 0.022$, $p = .195$]. Altogether, these results indicate that stress induced prior to training had no influence on motor performance during initial motor sequence learning.

3.3.2. MSL Retest

The 16 (block of practice) × 2 (group) repeated measures ANOVA on performance speed at Retest yielded a main effect of block [$F_{(4.694,\ 337.995)} = 16.512$, $\eta_p^2 = 0.187$, $p < 0.001$], indicating further performance improvements. A trend for a block by group interaction [$F_{(4.694,\ 337,995)} = 2.258$, $\eta_p^2 = 0.030$, $p = 0.052$] but no significant effect of group was observed [$F_{(1,72)} = 0.56$, $\eta_p^2 = 0.008$, $p = 0.457$] (see Fig. 3A, right upper panel). It is worth emphasizing that the stress group was slightly, albeit not statistically, faster at the beginning of the Retest. The repeated measures ANOVA performed on performance accuracy showed no difference between groups at Retest [main effect of group; $F_{(1,72)} = 0.204$, $\eta_p^2 = 0.003$, $p = .653$] and that accuracy decreased with practice [main effect of block: $F_{(10.658,\ 767.361)} = 2.72$, $\eta_p^2 = 0.037$, $p = .002$] to a similar extent in both groups [block × group interaction; $F_{(9.934,715.265)} = 0.335$, $\eta_p^2 = 0.005$, $p = .971$] (see Fig. 3A, lower right panel). Both groups reached asymptotic performance speed and accuracy during the post-test [repeated measures ANOVA block (4) × group (2); all Fs ≤ 1.547, all $\eta_p^2 \leq 0.021$, all *ps* ≥ *0.209*]. In sum, stress applied before initial training did not significantly influence performance during a 24 h retest.

3.3.3. Offline gains in performance and the relationship to physiological stress responses

To investigate the effect of the stress intervention on overnight consolidation processes, offline changes in performance were calculated as the percent change from the end of Training (average 4 blocks of the immediate post-Training test) to the beginning of the Retest (average first 4 blocks). Both groups showed significant and comparable overnight gains in speed [one sample *t*-test; control: $t_{(37)} = 6.233$, $p < .001$; stress: $t_{(35)} = 8.536$, $p < .001$; unpaired *t*-test: $t_{(72)} = -0.805$, $p = .423$] and accuracy [one sample *t*-test; control: $t_{(37)} = 3.295$, $p = .002$; stress: $t_{(35)} = 4.179$, $p < .001$; unpaired *t*-test: $t_{(72)} = -0.120$, $p = .905$] (see Fig. 3, panel B). In line with these results, a 2 (session; 4 blocks of post-Training test vs. 4 first blocks of Retest) × 2 (groups) repeated measures ANOVA on speed and accuracy showed a significant effect of session [speed: $F_{(1,\ 72)} = 61.825$, $\eta_p^2 = 0.462$, $p < 0.001$; accuracy: $F_{(1,\ 72)} = 27.423$, $\eta_p^2 = 0.276$, $p < 0.001$] but no significant effect of group nor any interaction [all Fs < 1 all $\eta_p^2 \leq 0.014$, all *ps* ≥ *0.332*].

To assess the hypothesis that the physiological stress response prior to learning modulates motor memory consolidation, we conducted correlational analyses between offline gains in performance and cortisol concentration at T25′ (i.e. immediately before training). We observed a negative correlation between overnight gains in speed and T25′ salivary cortisol levels within the stress group ($r = -0.43$, $p = .009$) (see Fig. 4A). Thus, the higher the stress-induced cortisol concentration before initial training, the smaller the overnight gains in performance speed. For the sake of completeness, the correlation was tested again while excluding the participant with a relatively high cortisol concentration at T25′ and results remain similar albeit weaker ($r = -0.323$, $p = .058$, see Supplemental Fig. S1). Note that this participant is not a statistical outlier. No significant correlation was found in controls ($r = -0.126$, $p = .450$) (see Fig. 4B). Noteworthy, pre-training cortisol levels were not related to performance during initial training. Specifically, there was no correlation between T25′ cortisol levels and average performance speed during Training (computed across 16 blocks of practice, $r = -0.14$, $p = .449$) or online performance gains during Training (computed between the first 2 blocks of training and the post-training test, $r = 0.08$, $p = .977$). These results suggest that stress-induced cortisol levels have no immediate effect on initial motor learning, but relate to subsequent offline changes in performance speed tested 24 h later. Offline gains in accuracy in the stress group were not correlated with cortisol levels at T25′, and again no significant correlation was observed in the control group (both rs < 0.01 and *ps* ≥ 0.724).

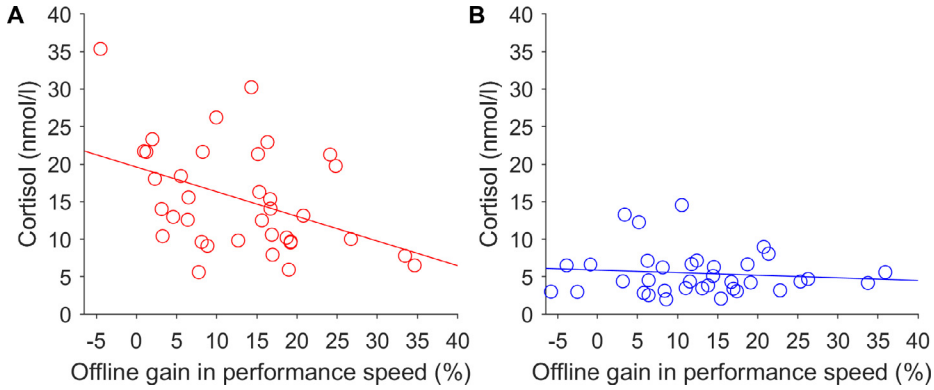

Fig. 4. Correlation between cortisol concentration at T25′ and offline gains in performance speed in the stress (A) and control group (B).

4. Discussion

The goal of the present study was to test whether stress modulates the consolidation of hippocampal-mediated motor sequence memory. Our results show that although stress induced experimentally before initial motor learning triggered significant physiological responses, it did not influence, on average, the overnight consolidation process as compared to the control intervention. However, correlation analyses indicated that higher levels of stress-induced cortisol concentration prior to training were associated with smaller overnight gains in performance speed. These results indicate that the stress-induced cortisol response prior to hippocampal-mediated motor learning is negatively related to subsequent memory consolidation processes.

The majority of the studies on stress and motor learning have used conditioning paradigms in which anxiety-inducing or stressful stimuli (e.g., electric shocks, negative feedback) were associated with task performance. Overall, these studies show that stress-related arousal during task performance is beneficial for motor performance and learning (e.g., Lawrence et al., 2014; Marteniuk & Wenger, 1970; Oudejans & Pijpers, 2009; Sage & Bennett, 1973) (but see Calvo, Alamo, & Ramos, 1990; Carron & Morford, 1968 for no effect on motor learning). These results are in line with evidence of improved motor memory retention when the material to learn is tagged as relevant during initial learning (e.g. by expectancy of a retest in Wilhelm et al., 2011; by expectancy of teaching it to another person in Daou, Buchanan, Lindsey, Lohse, & Miller, 2016; Daou, Lohse, & Miller, 2018). Importantly, however, in the studies cited above, stress/anxiety was introduced in association to the task to investigate whether this factor reinforces learning. It is crucial to note that we used a different approach in the present study, as stress was applied prior to and independent of the motor task. Our goal was to assess how stress-induced physiological responses can modulate motor memory consolidation while controlling for the direct arousing effect of stress on performance. With this approach, we observed that while stress induced experimentally before initial motor training did not differentially influence consolidation relative to controls, the stress-induced cortisol response was negatively related to the magnitude of subsequent overnight gains in performance speed.

To the best of our knowledge, only two studies in the motor domain have used an approach similar to ours and induced stress prior to and independent of the motor task (Hordacre et al., 2016; Wegner et al., 2014). It is important to note that in contrast to our study, these studies did not assess the physiological response to the intervention and the effectiveness of the stress induction was determined based on subjective experience only. Results of these studies indicate a positive effect of stress on motor performance across the learning period (pinch grip task in Hordacre et al., 2016; manual dexterity test in Wegner et al., 2014). Our behavioural results are therefore not in line with the available but limited literature. We suggest that the discrepancy in findings might be attributed to the different nature of the task and in particular to the distinct neural networks supporting these tasks (King et al., 2017). More specifically, none of the studies cited above investigated the effect of stress on hippocampal-mediated motor memory tasks.

We propose that the negative relationship between the glucocorticoid response to a stressful event and motor sequence memory consolidation is mediated by a stress-induced modulation of hippocampal functioning. Motor sequence memory acquisition and consolidation is indeed thought to depend on dynamical interactions between striato-cortical and hippocampo-cortical networks (Albouy, King et al., 2013). Specifically, during initial acquisition, motor sequence learning is characterized by a competitive interaction between hippocampal and striatal networks (Albouy et al., 2008; Albouy, King et al., 2013). Activity in the hippocampal network typically decreases as a function of practice, while activity in the striatal network increases with practice (Albouy et al., 2008; Albouy, King et al., 2013). These early interactions are thought to not only support optimal initial learning but also to tag the optimally-encoded memory traces for subsequent sleep-related consolidation (Albouy et al., 2008; Albouy, King et al., 2013). Moreover, the amplitude of the responses in the hippocampal system and the strength of its competitive interaction with the striatal system during acquisition forecast overnight performance enhancements and are therefore necessary to optimize consolidation (Albouy, King et al., 2013; King et al., 2017). We speculate that our behavioural results can be explained by a cortisol-mediated *disruption* of hippocampal functioning during initial motor sequence learning. This hypothesis is in line with evidence that cortisol administration can impair hippocampal dependent memory processes through a stress-related impairment in hippocampal activity (De Quervain et al., 2003 and see Oei et al., 2007 for reduced hippocampal activity without impaired memory processes). Beyond these modulatory effects within the hippocampus, stress has been shown to promote striatal-related behaviour (also called 'rigid') at the expense of more 'flexible' behaviour supported by the hippocampus (for a review, see Wirz, Bogdanov, & Schwabe, 2018). This shift might arise from impaired hippocampal and/or enhanced striatal activity (Schwabe et al., 2013; Vogel et al., 2015, 2017; Wirz, Reuter et al., 2017 in Wirz et al., 2018) and is thought to critically depend on cortisol binding to MR receptors in the brain (Schwabe, Schachinger, Kloet, & Oitzl, 2010; Schwabe et al., 2013; Vogel, Fernández, Joëls, & Schwabe, 2016; Wirz, Reuter et al., 2017). In the light of these findings, it is tempting to speculate that intact motor performance observed in our study during initial learning might be supported by a compensatory recruitment of the striatal system, which is known to parallel motor performance automatization (see Albouy, King et al., 2013; Doyon, Bellec, et al., 2009; Doyon, Korman, et al., 2009; Penhune & Steele, 2012 for various models). Based on our previous work, we argue that the potential increase in striatal contribution during learning does not trigger sleep-related consolidation as this process is rather predicted by hippocampal function (Albouy et al., 2015; Albouy, King et al., 2013).

Accordingly, we propose that the reduced overnight gains in performance speed observed in our study in individuals showing a high physiological stress-response are attributable to impaired hippocampal functioning during initial stages of acquisition. We argue that the presumable stress-induced decrease in hippocampal activity and shift in hippocampal-striatal balance during initial learning might have compromised the "tagging" of the memory trace and therefore hinder the subsequent overnight consolidation process (Albouy, King et al., 2013).

It must be acknowledged that there is evidence in the literature for stress-related *enhancement* of hippocampal functioning within this time window (20–60 min post-intervention). For example, studies in rodents suggest that noradrenergic responses and glucocorticoids effects rapidly increase activity in the hippocampus after stressor onset (Joels, Krugers, & Karst, 2008). Recent findings suggest a similar pattern of changes in the resting human brain (Quaedflieg et al., 2015) and during task performance (van Stegeren, Roozendaal, Kindt, Wolf, & Joëls, 2010). This enhancing effect is thought to be reversed only in later stages, resulting in reduced hippocampal activity (Henckens et al., 2012). Accordingly, and in the context of our study, an alternative possibility is that smaller overnight gains in performance speed in high cortisol responders is attributable to a cortisol-induced increase in hippocampal activity. It can be hypothesized that stress-related increase in hippocampal activity during initial learning might alter or delay the hippocampus-striatum antagonistic interplay known to condition sleep-related consolidation (Albouy, Sterpenich, et al., 2013) and therefore compromise the emergence of overnight gains in performance speed. Altogether, the direction of stress-induced effects on hippocampal activity (increase vs. decrease) and the precise timing of these effects is still debated (Joëls, Fernandez, & Roozendaal, 2011; Oitzl, Schwabe, & Aggleton, 2012; Quaedflieg & Schwabe, 2017) and future neuroimaging studies are warranted.

It is worth noting that the negative relationship between cortisol concentration and offline gains in performance speed was only observed in the stress group, while no association was found in the control group. A lack of association in the control group suggests that only reactive cortisol, e.g. released in response to a stressor, is linked to impaired consolidation. These results are in line with evidence that reactive, as compared to basal, levels of cortisol differentially affect the regulation of the hypothalamus pituitary adrenal (HPA) axis and associated structures (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Henckens et al., 2016). Our results are also in line with the study of Hodyl et al. (2016) in which no relationship between basal cortisol levels pre-training and overnight changes in performance on a serial reaction time task was found (note that only basal, but not reactive, cortisol was investigated in this study). Furthermore the correlation between cortisol concentration at T25′ and performance gains was observed for performance speed only but not for accuracy. This is in line with the MSL literature showing that speed is an outcome usually more modulated by experimental interventions than accuracy, especially in these tasks – like the one used in the present study – in which accuracy levels are high (see Albouy et al., 2015, 2016; Borragán, Urbain, Schmitz, Mary, & Peigneux, 2015; Brown & Robertson, 2007; Cohen, Pascual-Leone, Press, & Robertson, 2005; Debas et al., 2010; Fogel et al., 2014; Hallgató, Gyori-Dani, Pekár, Janacsek, & Nemeth, 2013 for examples of studies in which speed but not accuracy was modulated by the experimental intervention). Last, we acknowledge that the strength of the correlation decreased after exclusion of an extreme participant. However, as this participant was not a statistical outlier, he/she was kept in the sample.

Even though our data show a negative link between stress-induced cortisol release and overnight gains in performance speed, it remains unclear why no effect of stress was observed at the group level. First, one could argue that the stress induction protocol used in the present study was not effective. Our data speaks against this hypothesis as our results indicated that the stress intervention (SECPT) activated two prominent stress response systems, (a) the hypothalamus pituitary adrenal (HPA) axis and (b) the autonomic nervous system (ANS) with a time course that is consistent with the available literature (see Schwabe & Schachinger, 2018 for a review). Specifically, with respect to the ANS response, the significant increases in heart rate and blood pressure during stimulation was short lived as indicated by the quick return to baseline levels after the intervention. Regarding the HPA response, cortisol concentration was significantly elevated 25 to 60 min post-intervention (for the complete duration of initial training) and returned to pre-stress levels within four hours. Importantly, evidence indicates that both fast noradrenergic and long-lasting corticosteroid effects critically mediate stress-induced changes in memory functioning (McGaugh & Roozendaal, 2002; Roozendaal, De Quervain, & McGaugh, 2004; Schwabe et al., 2009). Furthermore, not only the timing but also the magnitudes of stress-induced cortisol increases and cardiovascular responses observed in our study are in line with the SECPT literature (e.g., Schwabe et al., 2008, 2013, Vogel et al., 2015, 2017). Second, and as highlighted above, the effect of stress on brain activity appears to be highly diverse and stress-induced modulation of hippocampal activity with the timing used in the present study is not observed in every individual. Specifically, recent findings indicate that common genetic variations (of the noradrenergic system or mineralocorticoid receptors) modulate the impact of stress on the balance between hippocampal and striatal memory systems (Wirz, Reuter et al., 2017; Wirz, Wacker et al., 2017), suggesting that not all individuals are susceptible to the stress-induced shift in neural processing. Such high inter-subject variability in the neural response to stress might have weakened our results at the group level. Last, the lack of an effect at the group level could be attributed to the time window during which sleep occurred after learning. It is possible that potential interference during the delay between the end of training and the sleep episode (8–10 h delay) might have masked potential group differences in consolidation (Cai & Rickard, 2009; Fischer, Hallschmid, Elsner, & Born, 2002; Holz et al., 2012; van der Werf, Van Der Helm, Schoonheim, Ridderikhoff, & Van Someren, 2009). This interference might be circumvented in future studies by providing a sleep opportunity immediately after the learning episode. It is also worth acknowledging that the specific effect of sleep (as compared to wakefulness) on the consolidation of memory traces subjected to stress warrants further investigation.

5. Conclusions

In conclusion, this is, to the best of our knowledge, the first study to investigate the effect of experimentally-induced stress on the acquisition and consolidation of hippocampal-mediated motor memory. Our results indicate that cortisol release in response to a stressor prior to motor sequence learning is negatively related to the subsequent memory consolidation process. The present study opens unexplored horizons in which the hippocampal system is a cerebral target of interest to modulate motor memory processing. However, future neuroimaging studies are certainly necessary to reveal the interaction among stress, hippocampal functioning and motor learning processes.

Declarations of interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2019.01.009.

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