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Original Articles

Sympathetic arousal, but not disturbed executive functioning, mediates the impairment of cognitive flexibility under stress

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ABSTRACT

Cognitive flexibility emerges from an interplay of multiple cognitive systems, of which lexical-semantic and executive are thought to be the most important. Yet this has not been addressed by previous studies demonstrating that such forms of flexible thought deteriorate under stress. Motivated by these shortcomings, the present study evaluated several candidate mechanisms implied to mediate the impairing effects of stress on flexible thinking. Fifty-seven healthy adults were randomly assigned to psychosocial stress or control condition while assessed for performance on cognitive flexibility, working memory capacity, semantic fluency, and self-reported cognitive interference. Stress response was indicated by changes in skin conductance, hearth rate, and state anxiety. Our analyses showed that acute stress impaired cognitive flexibility via a concomitant increase in sympathetic arousal, while this mediator was positively associated with semantic fluency. Stress also decreased working memory capacity, which was partially mediated by elevated cognitive interference, but neither of these two measures were associated with cognitive flexibility or sympathetic arousal. Following these findings, we conclude that acute stress impairs cognitive flexibility via sympathetic arousal that modulates lexical-semantic and associative processes. In particular, the results indicate that stress-level of sympathetic activation may restrict the accessibility and integration of remote associates and bias the response competition towards prepotent and dominant ideas. Importantly, our results indicate that stress-induced impairments of cognitive flexibility and executive functions are mediated by distinct neurocognitive mechanisms.

1. Introduction

Stress is a complex adaptive response that affects multiple brain areas responsible for cognitive functioning and modulates distinct cognitive systems, such as attention, memory, and problem solving (Arnsten, 2015; Byron, Khazanchi, & Nazarian, 2010; Hermans, Henckens, Joëls, & Fernández, 2014; Schwabe, 2017; Shields, Sazma, & Yonelinas, 2016). A handful of studies showed that one of the functions that seems to be overly sensitive to stress is cognitive flexibility (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Hillier, Alexander, & Beversdorf, 2006; Martindale & Greenough, 1973). Drawing upon these reports here we refer to cognitive flexibility as the flexibility to access and combine remote elements in lexical-semantic and associative networks in insightful problem solving, which has been most widely assessed by the Remote Associates Test (RAT; Mednick, 1962). In contrast to more constrained attentional set-shifting and multitasking paradigms so defined cognitive flexibility involves changing how we think about a problem (i.e., conceptual shifts and idea exploration) to overcome mental inertia formed by habitual structure of thought (see Ionescu, 2012 for a detailed discussion). In our study, the term "cognitive flexibility" thus refers to this form of lexical-semantic and associative flexibility, whereas "executive switching" is used to denote an executive function related to the attentional control component of the working memory system (see Engle & Kane, 2004).

Numerous findings have implied that cognitive flexibility depends on processes of activation, retrieval, and integration of distant memory representations (Abraham, 2014; Davelaar, 2015; Smith, Huber, & Vul, 2013) as well as the connectivity of lexical-semantic and associative networks in which such representations are stored (Kenett, Anaki, & Faust, 2014; Marupaka, Iyer, & Minai, 2012; Schilling, 2005). Research suggests that these processes are sensitive to acute stress. For instance, it has been shown that acute stress impairs memory retrieval (Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Schwabe & Wolf, 2013). In particular, acute stress decreases access to remote memory

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representations while biasing retrieval towards close associations (Harkins, 2006; Storbeck & Clore, 2008). This indicates that the impairment of cognitive flexibility under stress may result from modulations of lexical-semantic processes and networks.

On the other hand, flexible thought heavily relies on executive attentional functions of the working memory system (Beaty, Benedek, Barry Kaufman, & Silvia, 2015; Benedek, Jauk, Sommer, Arendasy, & Neubauer, 2014; Metuki, Sela, & Lavidor, 2012). Specifically, cognitive flexibility requires inhibition of prepotent associations (Gupta, Jang, Mednick, & Huber, 2012), attentional shifts to alternative retrieval candidates (Katz & Pestell, 1989; Radel, Davranche, Fournier, & Dietrich, 2015; White & Shah, 2006), and maintenance of relevant information in working memory (Chein & Weisberg, 2014; Lee, Huggins, & Therriault, 2014). Ample evidence also indicates that acute stress modulates executive functions. For instance, it has been shown that psychosocial stress decreases performance on working memory tasks (e.g., digit span task, Elzinga & Roelofs, 2005; reading span task, Luethi, Meier, & Sandi, 2009; operation Span task, Schoofs, Wolf, & Smeets, 2009; and n-back tasks, Schoofs, Preuss, & Wolf, 2008), impairs switching of attention (Elling et al., 2012), and overall "top-down" attentional control (Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011; Starcke, Wiesen, Trotzke, & Brand, 2016; Sänger, Bechtold, Schoofs, Blaszkewicz, & Wascher, 2014). This suggests that such stress-induced deterioration of executive functioning may play a major role in the impairment of cognitive flexibility under stress.

The motivation for our study was to better understand the mechanisms which underlie the impairing effects of acute stress on cognitive flexibility. To this aim we assessed the effects of acute stress on cognitive flexibility, working memory capacity, semantic fluency, and self-reported cognitive interference in the same individuals. While working memory capacity and interference control inherently employ the functionality of executive attention (Engle & Kane, 2004; Mccabe, Roediger, Mcdaniel, Balota, & Hambrick, 2010), semantic fluency is mainly related to lexical-semantic access, search and retrieval, and the involvement of executive functioning in semantic fluency is relatively minor (Henry & Crawford, 2004; Shao, Janse, Visser, & Meyer, 2014; Whiteside et al., 2015). With this selection of tasks, two alternatives could be tested. First, cognitive flexibility under stress may be impaired due to downregulation of executive functioning: i.e., stress dysregulates optimal cognitive control over information maintenance and retrieval that is required for flexible thinking. In such a case we would expect that working memory capacity and cognitive interference mediates the effect of stress on cognitive flexibility. Second, stress-induced potentiation of closely related associates could hinder access to remote concepts required for flexible thinking: i.e., stress restricts the "range" of accessible information within lexical-semantic and associative networks. In this case, we would expect that acute stress would decrease cognitive flexibility but would have no or even a facilitating effect on semantic fluency, for which typical and strongly associated category instances may be utilized. This prediction is also of interest given that in absence of stress semantic fluency and cognitive flexibility seem to be positively associated (Benedek, Könen, & Neubauer, 2012).

Importantly, the effect of stress on cognitive flexibility was observed early after the onset of stressors in previous studies (Alexander et al., 2007; Hillier et al., 2006), indicating that a rapid stress mechanism is involved in the impairment. We therefore used a modified psychosocial stress paradigm, in which the cognitive assessment was superimposed on the stressors early after their introduction and was carried out concurrently during their presence (Marko, 2016). This setup was advantageous because of two reasons. First, the presence of stressors imposed an ongoing threat and continuous distraction during the cognitive performance (this important feature is absent in paradigms in which cognitive tests are administered after the stressors have terminated). Second, since the cognitive tasks were completed before peak corticoadrenal activation (Droste et al., 2008; Hermans et al., 2014), this method enabled us to focus preferentially on the early neural rather than late hormonal stress effects. The magnitude of these rapid effects was estimated using the physiological measures of the sympathetic autonomic nervous system activation (skin conductance level and heart rate). We expected that the increase in sympathetic arousal would be associated with decreased flexibility and included sympathetic arousal in serial mediation models alongside the behavioral measures in order to disentangle the processes contributing to the impairment of cognitive flexibility under stress.

2. Method

2.1. Participants

Sixty healthy adults were sampled from a larger pool of volunteers to participate in the study following an a priori power analysis (5% Type I error rate, 20% Type II error rate, and effect size from Byron et al., 2010, were used for the calculation). Due to technical problems, data of three participants were excluded. The final group thus consisted of 57 participants (39 females and 18 males, mean age = 19.9 ± 1.3 years). All participants met the following inclusion criteria: age between 18 and 25 years, Slovak primary language, absence of a mental disorder, cardiovascular disease or chronic health problems, and no current pharmacological treatment (except contraceptives). The participants were asked to abstain from alcohol and intense physical exercise 24 h before testing and from caffeine 12 h before testing. A written informed consent was obtained from all participants. The protocol was approved by the appropriate ethics committee. Research has been conducted in accordance with the Declaration of Helsinki.

The participants were randomly divided into a group undergoing stress procedure (Stress, $N = 28$) and a control group ($N = 29$). The stress and the control group did not differ in the proportion of gender, $\chi^2(1, N = 57) = 0.230$, $p = .631$, mean age, $t(55) = -0.190$, $p = .850$, mean BMI, $t(55) = 0.209$, $p = .836$, or session time, $t(55) = -0.058$, $p = .954$. The groups were also equivalent in terms of trait anxiety level, $\chi^2(2, N = 57) = 0.026$, $p = .987$, initial state anxiety, $t(55) = 0.933$, $p = .355$, positive affect, $t(55) = -0.130$, $p = .897$, distress $t(48.5) = 1.630$, $p = .107$, self-confidence $t(55) = -0.522$, $p = .604$, and general self-efficacy, $t(55) = 0.324$, $p = .747$, prior to stress induction and cognitive assessment (see Section 2.6 for details of the used self-report methods). Finally, the control and the stress group did not differ in the frequency of the individual task sequences, $\chi^2(5, N = 57) = 0.230$, $p = .631$, nor in the administration order of individual cognitive tasks, $\chi^2(2, N = 57) < 0.846$, $p > .655$ (see Tables S1 and S2 in supplementary online material for the exact frequencies and further details).

2.2. Design and procedure

The experiment included two randomly assigned between-subjects factors, Stress (as a main factor of interest defining the testing conditions) and Task sequence (a control factor defining the assessment order of cognitive tests; 6 levels), and one fixed within-subjects factor, Time block (this factor was used to define specific time windows for repeated physiological measurements). Administation order of individual cognitive tests (administered as first, second, or third; 3 levels) was derived from Task sequence as a separate factor.

Experimental sessions were run between 9:00 and 17:00 and followed the procedure depicted in Fig. 1. Each session started with a brief interview followed by assessment of affective state and general self-efficacy (from −30 to −12 min with respect to stressor onset; see Section 2.5). Subsequent experimental procedures included 5 time blocks: baseline, 3 cognitive tests (administered in a random order), and recovery. Baseline (from −12 to −2 min) and recovery (from +35 to +45 min) were fixed to 10 min, during which participants were sitting alone in a quiet room and were instructed to relax. The cognitive testing lasted up to 30 min (from +3 to +30 min). Before cognitive

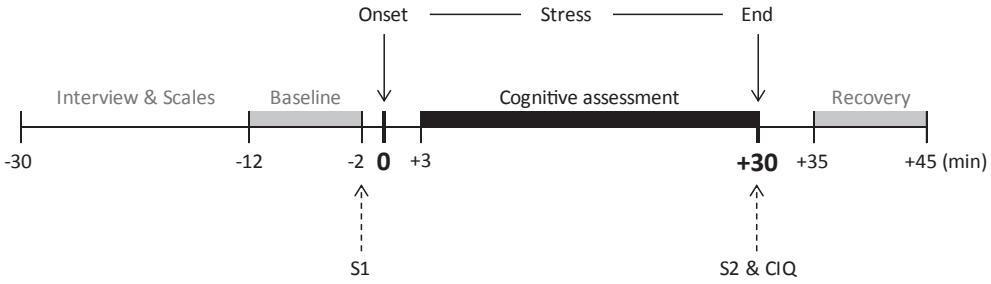

Fig. 1. Structure and timing of the experimental protocol. S1 – pre-test state anxiety assessment, S2 – post-test state anxiety assessment, CIQ – Cognitive interference questionnaire.

testing (following baseline and immediately before stress induction or control procedure; i.e. from −2 to 0 min), pre-test State Anxiety Inventory was administered (STAI-S; Spielberger, 1989). After cognitive testing (before recovery period; from +30 to +35 min), post-test State Anxiety Inventory and Cognitive Interference Questionnaire (CIQ; Sarason, Sarason, Keefe, Hayes, & Shearin, 1986) were completed. At the end of the experiment (following recovery period; +45 min), participants underwent final debriefing in a separate room.

2.3. Stress and control treatment

To induce stress, study participants were tested in front of an evaluating unfamiliar committee (Marko, 2016). The procedure utilized effective psychosocial and cognitive factors known to reliably elicit stress (Dickerson & Kemeny, 2004) and was in many aspects similar to the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993). At the beginning, the experimenter and three committee members dressed in white coats entered the laboratory. Within the first three minutes (0 to +3 in Fig. 1), the experimenter stationed the apparatus and introduced the committee members as experts trained in behavioral and psychological profiling (including the analysis of facial expressions, speech, voice modulation, gestures and body movements, accuracy of the answers, cognitive performance, and personality dimensions). The psychosocial stress was further enhanced by the use of several instruments: a proximal camera projecting participant's face on a feedback monitor, a distal camera recording whole body, a spotlight and a microphone on a stand placed in front of the seated participant. Participants were informed that the audio and video recordings would be subsequently subjected to an additional behavioral analysis. The committee was instructed to observe participant's behavior, responses and task progress (shown on a smaller screen), take notes, and provide no sign of positive reinforcement. After the committee was introduced and apparatus placed, the committee members described upcoming procedure and instructed the participant to introduce himself/herself on the camera. The transitions between cognitive tasks were filled by brief questions on general knowledge and/or cognitive estimation (e.g.: "What time is it now in Tokyo?") in a speeded manner to sustain testing dynamics.

In contrast to the Trier Social Stress Test, the anticipatory period was replaced by a shorter preparation (0 to +3 min) and cognitive assessment was superimposed on the stressors rather than administered in a post-stress period (Marko, 2016). These modifications were introduced to increase the relative influence of the rapid neuronal (i.e., sympathetic) over the slower hormonal (i.e., cortisol) stress effects and to enable the assessment of cognitive performance in the actual presence of the stressors rather than during their prolonged aftereffects. This protocol was also more consistent with the procedures of cognitive assessment used in previous studies (Alexander et al., 2007; Hillier et al., 2006).

In the control conditions, the specific stress-inducing procedures (such as the presence of committee members, recording apparatus, evaluative instructions, and questions) were not introduced and the participants underwent cognitive testing in the presence of the experimenter alone. In order to minimize his presence, the experimenter was seated on the left peripheral view of the participant. All other aspects of the testing situation were matched as much as possible.

2.4. Cognitive tests

Three cognitive tests were administered in a random order. Each test was displayed on a screen placed in front of the participant and one smaller screen placed in front of the committee. In order to enhance the evaluative environment, participants were instructed to respond verbally to the committee in each task.

Cognitive flexibility was assessed by the Remote Associates Test (RAT; Mednick, 1962). This test requires participants to generate a word meaningfully associated with three simultaneously presented words within 30 s. The test consisted of 22 items ordered by increasing difficulty. Each item was scored for accuracy (binary values). Cognitive flexibility was estimated as a continuous, latent variable by reflective item response model using the Item Response Theory approach. Each item was calibrated by a 2-parameter model, which was assessed in a comparable sample of 202 healthy students prior to this experiment and showed an acceptable fit, χ^2 (72) = 79.19, p = .289, RMSEA = 0.022, and internal consistency (Cronbach's alpha α = 0.81).

Working memory capacity (WMC) was assessed by the Operation Span Task (OSPAN; Turner & Engle, 1989), a measure assumed to recruit executive attentional control (Engle & Kane, 2004; Mccabe et al., 2010) and shown to have several psychometric advantages over other tasks used to assess individual differences in WMC (Klein & Fiss, 1999). Moreover, among other span tasks, OSPAN was reported to be most strongly correlated with cognitive flexibility in previous research (r = 0.43; Lee et al., 2014). In each trial, participants had to solve an arithmetic problem and then remember a word provided by a committee member (stress condition) or experimenter (control condition). After 4 to 8 trials, participants were asked to recall as many words as possible. The test contained 9 blocks of trials. As previously recommended, the length of blocks was not predictable and at least 75% of correct arithmetic problems were explicitly required. As an index of task performance the sum of correctly recalled words was calculated.

Lexical-semantic retrieval was assessed using semantic fluency tasks. Although included among executive measures by some scholars (for instance Diamond, 2013), behavioral and neuroimaging evidence indicates that semantic fluency tasks predominantly employ lexical-semantic abilities whereas the executive involvement is minor (Henry & Crawford, 2004; Shao et al., 2014; Whiteside et al., 2015). In our study, semantic fluency was assessed by asking participants to name as many words belonging to a certain category as possible within 60 s. After a training trial ("*Plants*") three other categories were administered in the following fixed order: "*Animals*", "*Supermarket products*" and "*Occupations*". Each participant was administered all three categories. Participants were instructed that duplicated instances were not accepted. The total number of retrieved words in the three categories was used as the performance index.

2.5. Physiological measures and signal processing

Physiological data were acquired using Neurobit Optima 4 (Neurobit Systems, Gdansk, Poland) with a sampling rate of 1000 Hz and processed using Labchart 7 (ADInstruments, Otago, New Zealand). Electrodermal activity (EDA) was measured using Ag/AgCl electrodes placed on medial phalanxes of the index and ring fingers of the non-dominant hand. Skin conductance level (SCL) was used as a marker of tonic sympathetic activity (Boucsein, 2012). SCL was preferred over phasic skin conductance responses (SCR) due to the prolonged duration of the stressor and the fact that speech interferes with SCR (Boucsein, 2012). EDA signal was digitally low-pass filtered at 0.1 Hz. To eliminate distortion by SCR, SCL was derived from minima assessed within a 10-s moving window shifted along the signal.

Electrocardiogram (ECG) was assessed by using two disposable 80 mm Ag/AgCl electrodes placed over the right clavicula and the left hypochondrium (an approximate of Einthoven's lead II). ECG was digitally filtered in the range 5–35 Hz and the heart rate was assessed from R-R intervals. In each experimental block, the physiological measures were averaged within a 4-min period (assessment windows). In the blocks of cognitive tasks, the assessment window was centered at the middle of the block. In the baseline and the recovery block, last 4 min of the blocks were analyzed. To eliminate individual variability in absolute values of the physiological parameters, relative values (denoted rSCL, rHR) were calculated with respect to the baseline (i.e., resting level). Relative rather than absolute change values were used due to better statistical properties (i.e., both the values and model residuals more closely approximated the normal distribution and yielded less outlying values) and stronger mutual associations.

Principal component analyses (PCA) were performed in two steps to aggregate the levels of rSCL and rHR into a single index of sympathetic activation (SYM). First, composite change scores were aggregated separately from rSCL and rHR scores across the blocks. Subsequently, an additional PCA merged these two first-order composites into the SYM index.

2.6. Self-reported measures

Trait and state anxiety were assessed using the State and Trait Anxiety Inventory (Müllner, Ruisel, & Farkaš, 1980; Spielberger, 1989). Based on the trait anxiety scores, participants were divided into three groups: low (scores below 35, $N = 23$), medium (35–43, $N = 18$), high (above 43, $N = 16$). Cognitive interference (CogI) was assessed by the Task-related Worries subscale of Cognitive Interference Questionnaire (CIQ; Sarason et al., 1986). The subscale assesses the frequency of intrusive thoughts related to the evaluative conditions (e.g. "I thought about what the experimenter would think of me", "I thought about how poorly I was doing", "I thought about my level of ability") and thus provides a rough estimate of attentional control. Cognitive interference was indicated by 10 items with a 5-point scale from 0 (never) to 4 (very often). Cronbach's α was 0.87 for our sample.

Furthermore, current affective state was assessed using 20 adjectives selected on the basis of a priori PCA of items from the Positive and Negative Affect Schedule – Extended (PANAS-X; Watson & Clark, 1994), Tellegen Mood Terms (Tellegen, 1985), and additional adjectives commonly associated with stress (e.g., "*Anxious*", "*Tense*", and "*Worried*"). This approach was adopted to shorten the scale format and select the most indicative mood terms that are particularly associated with stress ("*Distressed*", "*Nervous*", "*Afraid*", "*Frightened*", "*Shaky*" "*Jittery*", "*Anxious*", "*Tense*", and "*Worried*"), positive emotionality (e.g. "*Happy*", "*Cheerful*", "*Joyful*", "*Excited*", "*Enthusiastic*", and "*Energetic*"), or self-confidence ("*Strong*", "*Bold*", "*Confident*", "*Fearless*", and "*Proud*"), which are most relevant for the purpose of the current research. Participants assessed the overlap between the adjectives and their feelings using a 7-point Likert scale. Subsequently, three orthogonal composites with acceptable internal consistency were extracted by means of PCA. These composites were labeled as *Distress* (9 adjectives; $\alpha = 0.92$), *Positive affect* (6 adjectives; $\alpha = 0.89$), and *Self-confidence* (5 adjectives; $\alpha = 0.81$), respectively.

The General Self-Efficacy Scale (Jerusalem & Schwarzer, 1992) was utilized to access general belief in own ability to perform well on novel or difficult tasks. The scale refers to successful coping and an internal-stable attribution of success. The scale has 10 items scored in a 4-point range ($\alpha = 0.86$).

2.7. Statistical analysis

The general linear model was applied to analyze the data using SPSS (version 23.0) software. Serial multiple mediator models were computed by PROCESS Macro (model 6, Hayes, 2013) and AMOS (version 23.0). The models test a hypothesized causal structure including multiple mediators with a specified direction. As recommended, indirect effect were assessed by bias-corrected 95% bootstrap confidence intervals based on 10,000 bootstrap samples (Preacher & Hayes, 2008).

3. Results

Using Lilliefors significance correction, Kolmogorov-Smirnov statistic verified that all measures approximated normal distribution (for complete sample or each group separately, $p > .176$). Table 1 shows descriptive statistics for both groups and zero-order Pearson correlations among the measures for the whole sample. The linear model was appropriate for all tested associations except for the relationship between self-reported cognitive interference and cognitive flexibility, which could be described by both linear and inverted "U" (quadratic) relationship, $r_{linear} = –0.405$, $p = .002$, $r_{quadratic} = –0.484$, $p = .001$. Adding the quadratic component (CogI-squared values) into the linear model significantly enhanced the model fit, $R^2_{(quadratic–linear)} = 0.070$, ΔF (1,54) = 4.970, $p = .03$, indicating that the inverted U-shape was a better approximation of the relationship between cognitive interference

Table 1
Group means, group standard deviations, and zero-order correlations for the total sample. *Notes*: Values above diagonal of the correlation table show Pearson correlation coefficients. RAT – Remote associate test; WMC – Working memory capacity; CogI – Self-reported cognitive interference; FLU – Semantic fluency; SYM – the index of sympathetic arousal.

Measure	Control group [N = 29]		Stress group [N = 28]		Zero-order correlations [N = 57]				
	X	*SD*	*X*	*SD*	RAT	WMC	CogI	FLU	SYM
RAT	0.386	0.998	−0.423	0.842	1	0.15	−0.41**	0.29*	−0.51***
WMC	36.14	4.29	31.61	4.80		1	−0.51***	−0.001	−0.33*
CogI	18.45	6.58	26.96	9.45			1	−0.20	0.38**
FLU	68.83	9.73	67.11	9.66				1	0.13
SYM	−0.341	0.297	0.341	0.385					1

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 2
Effect of stress on physiological and affective measures. *Notes*: rSCL – relative (%) change in skin conductance level with respect to baseline, rHR – relative (%) change in heart rate with respect to baseline, SYM –the index of sympathetic activity.

Measure	Control Group [N = 29]		Stress Group [N = 28]		Difference (95% CI)	ANOVA model			
						F	*df*	η_p^2	*p*
	X	*SE*	*X*	*SE*					
rSCL	166.97	8.45	231.66	8.72	64.7 (39.8, 89.6)	33.39[a]	1,28	0.544	< 0.001
rHR	99.56	1.18	112.94	1.20	13.4 (9.9, 16.8)	48.97[a]	1,28	0.636	< 0.001
SYM	−0.378	0.051	0.413	0.053	0.791 (0.641, 0.941)	110.8[a]	1,28	0.798	< 0.001
State anxiety	41.51	1.70	54.71	1.69	13.2 (8.4, 18.0)	29.98[b]	1,5	0.375	< 0.001

[a] ANOVA model was controlled for Task sequence and Trait anxiety.
[b] ANOVA model was controlled for Trait anxiety and the pretest score of state anxiety.

and cognitive flexibility. Following this finding, quadratic model was considered where appropriate.

3.1. Stress response

First, the level of sympathetic activation and state anxiety was compared between the stress group and the control group. As for physiological measures, related analysis of variance (ANOVA) models (controlled for Task sequence and Trait anxiety) revealed a significant main effect of stress on skin conductance level (rSCL) and heart rate (rHR). Compared with the control condition, both sympathetic measures were significantly and strongly elevated under stress (Table 2). Next, using a two-step PCA procedure (see Section 2.4), rSCL and rHR values were merged into a single index of sympathetic activation (SYM). SYM explained 68.3% of variance of rSCL and rHR composite scores. An ANOVA (controlled for Task sequence and Trait anxiety) confirmed a strong and statistically significant effect of stress on SYM. Notably, the effect size of stress was higher for SYM than for either rSCL or rHR individually, indicating higher robustness and sensitivity of the aggregate measure. Stress also elevated state anxiety. An ANOVA (controlled for Trait anxiety and baseline state anxiety score) confirmed that state anxiety ratings were significantly higher in the stress group compared with the control group (Table 2).

3.2. The effect of stress on cognitive performance

First, we assessed the effect of stress on each of the behavioral measures (i.e., cognitive flexibility, working memory, semantic fluency, and self-reported cognitive interference) with separate ANOVAs. The effects on the behavioral measures were controlled for task Administration order (this does not apply for self-reported cognitive interference, which was assessed after the cognitive testing). These analyses revealed that stress significantly impaired cognitive flexibility, $F(1,51) = 9.893$, $p = .003$, $\eta_p^2 = 0.162$, working memory capacity, $F(1,51) = 22.417$, $p < .001$, $\eta_p^2 = 0.305$, and increased self-reported cognitive interference, $F(1,55) = 15.687$, $p < .001$, $\eta_p^2 = 0.222$. The effect of stress on semantic fluency was not significant, $F(1,51) = 0.080$, $p = .779$, $\eta_p^2 = 0.002$ (see Fig. 2). For working memory capacity, the effect of stress significantly interacted with order of task administration, $F(2,51) = 5.422$, p = .007, $\eta_p^2 = 0.175$, indicating that the effect of stress was highest when working memory task was administered as first. Such an effect was not observed for other measures.

Next, in order to investigate their effect on cognitive flexibility, the executive measures (working memory capacity and self-reported cognitive interference) and semantic fluency were separately added into the previous ANOVA model for cognitive flexibility. Consistently with the zero-order correlations, these ANCOVAs showed that RAT score was significantly predicted by self-reported cognitive interference, $F(1,51) = 4.937$, $p = .031$, $\eta_p^2 = 0.088$, and semantic fluency, $F(1,51) = 8.668$, $p = .005$, $\eta_p^2 = 0.144$, but not working memory capacity, $F(1,51) = 0.144$, $p = .663$, $\eta_p^2 = 0.004$. In order to account for the inverted U-shape relationship between RAT and self-reported cognitive interference, squared score values were added into the model, resulting in significant quadratic component, $F(1,50) = 4.874$, $p = .032$, $\eta_p^2 = 0.089$, and non-significant linear component, $F(1,50) = 2.685$, $p = .108$, $\eta_p^2 = 0.051$. Importantly, neither of the covariate accounted for the negative effects of stress on cognitive flexibility (i.e., the main effect of stress remained stable and statistically significant).

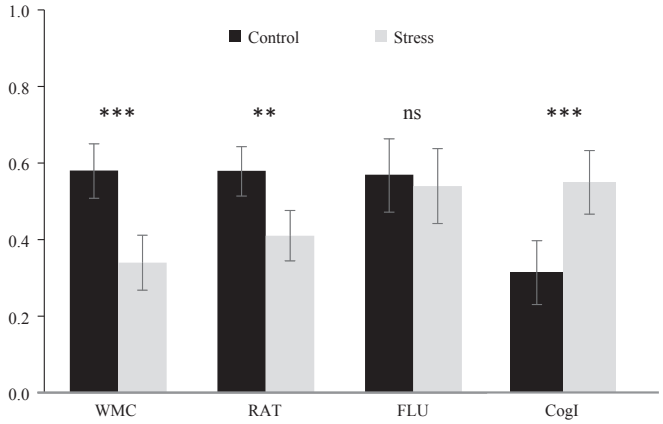

Fig. 2. Estimated group means (± 2 SEM) for each cognitive task (ordered by the effect size) and self-reported cognitive interference. The stress group showed lower working memory capacity (WMC) and cognitive flexibility (RAT), but higher self-reported cognitive interference (CogI), i.e., increased distractibility, than the control group. The groups did not significantly differ in semantic fluency (FLU). For a better visualization of the effects, original scales of the variables were transformed into a common range from 0 to 1. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; ns: not significant.

3.3. Serial multiple mediation models

Finally, we used mediation analysis to investigate the role of sympathetic activation in stress-related changes in cognitive performance. Due to the significant relation with RAT score, semantic fluency was included in the first mediation model (see Fig. 3A and Table 3). On the other hand, since the relationship between RAT and self-reported cognitive interference was nonlinear this variable was not included. The analysis indicated that the negative effect of stress on cognitive flexibility was mediated by the increased sympathetic activation (red path shown in Fig. 3A; parameter $a_1 \times b_1$ in Table 3). However, an opposite effect of stress on cognitive flexibility via sympathetic activation and semantic fluency was also disclosed (green path shown in Fig. 3A; parameter $a_1 \times d_{21} \times b_3$ in Table 3). The model also showed a non-zero negative effect of stress on cognitive flexibility via semantic fluency ($a_2 \times b_2$), but the link between stress and semantic fluency was not reliable (see parameter a_2). In order to exclude a possible effect of self-

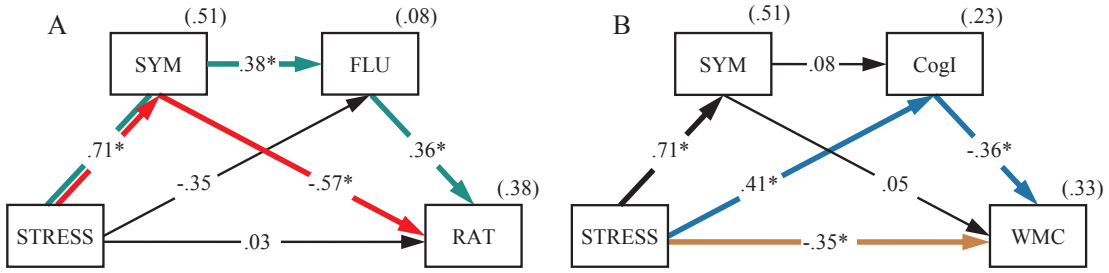

Fig. 3. Standardized estimates of regression weights of serial multiple mediator models for (A) cognitive flexibility and (B) working memory capacity. In model A, colored paths indicate the indirect effect of stress on cognitive flexibility through sympathetic activation (red – $a_1 \times b_1$, Table 3) and via both sympathetic activation and semantic fluency (green – $a_1 \times d_{21} \times b_2$). In model B, colored paths indicate the indirect effect of stress on working memory capacity through cognitive interference (blue – $a_2 \times b_2$, Table 4), and the direct effect of stress on working memory capacity (orange – c'). Asterisks and thick lines indicate significant regression paths; parenthesis show multiple squared correlations; SYM – the index of sympathetic activity; FLU – semantic fluency; RAT – Remote Associates Test; CogI – self-reported cognitive interference; WMC – working memory capacity.

reported cognitive interference on the model parameters, we calculated residuals of RAT in a linear regression model with CogI and CogI-squared as predictors. The residual RAT scores were subsequently used as the dependent variable in the same mediator analysis yielding very similar results (the model parameters remained stable and the indirect effects significant).

A separate mediation model focused on the relationship between stress, sympathetic activation and working memory capacity, since our analysis indicated no significant relationship between this executive function and cognitive flexibility (see Fig. 3B and Table 4). As a linear predictor of working memory capacity, self-reported cognitive interference was also implemented in the model. This analysis revealed that the effect of psychosocial stress on working memory capacity was not mediated by sympathetic activation (parameter $a_1 \times b_1$ in Table 4). Instead, a part of the effect was mediated by cognitive interference (blue path; parameter $a_2 \times b_2$ in Table 4). A significant portion of the effect of stress on working memory capacity remained unexplained (orange path; parameter c' Table 4).

Introducing the Administration order of RAT and WMC as a covariate in the respective mediation models did not change the results (see Tables S3 and S4 in supplementary online material for further details), and post hoc zero-order and partial correlations did not show a significant association between RAT and WMC at any particular time point. However, more complex time-related interactions among the cognitive and physiological measures must be considered with caution due to low statistical power of these analyses.

4. Discussion

The main goal of the present study was to determine the processes mediating stress-related impairment of cognitive flexibility. In particular, we investigated whether the negative effect of stress on cognitive flexibility could be explained by impaired executive functioning or compromised lexical-semantic retrieval. For this purpose, we assessed concurrent effects of stress on cognitive flexibility, executive functioning (complex working memory capacity task recruiting attentional control functions), self-reported cognitive interference, and lexical-semantic retrieval (semantic fluency). In line with previous reports, stress impaired cognitive flexibility (Alexander et al., 2007; Hillier et al., 2006; Martindale & Greenough, 1973; Renner & Beversdorf, 2010), working memory capacity and interference control (Elling et al., 2012; Luethi, 2008; Schoofs et al., 2009; Sänger et al., 2014). However, the disrupted executive functioning did not explain the stress-induced decline of cognitive flexibility and our analyses indicate that stress impairs cognitive flexibility and executive functions, respectively, via different neurocognitive mechanisms. In particular, the mediation analyses revealed that cognitive flexibility and working memory capacity were differently related to sympathetic arousal and self-reported cognitive interference. Whereas the sympathetic arousal accounted for the entire effect of stress on cognitive flexibility (Fig. 3A, red and green path), it was not associated with the stress-related dysregulation of working memory capacity and self-reported cognitive interference. On the other hand, cognitive interference explained a substantial part of the stress-induced impairment of working memory (approximately one third of the total effect of stress, see Fig. 3B blue path) but not cognitive flexibility.

4.1. Stress-induced modulation of cognitive flexibility

Interestingly, while the stress-induced sympathetic activation was negatively associated with cognitive flexibility, it was positively related to semantic fluency. This finding indicates that the modulation of lexical-semantic processing under stress is not uniform. Specifically, this pattern suggests that the increased sympathetic tone is associated with a downregulation of complex (i.e., “multiply-constrained”, Smith et al., 2013) retrieval of remote associates but with a facilitated simple access to and retrieval of closer associates in the semantic fluency task. Although similar complexity-dependent effects of arousal have been

Table 3
Unstandardized parameters for the serial multiple mediator model for cognitive flexibility. *Notes*: the estimation of standard errors and lower level and upper level confidence intervals (LLCI and ULCI) for indirect effects are based on bias-corrected 95% bootstrap method (10,000 bootstrap samples); SYM – the index of sympathetic activity; FLU – semantic fluency; RAT – Remote Associates Test.

$Effect_{(path/mediators)}$	Parameter	Estimate	*SE*	*t*	*p*	LLCI	ULCI
$Antecedent_{(STRESS \rightarrow SYM)}$	a_1	0.682	0.091	7.501	< 0.001	0.500	0.864
$Antecedent_{(STRESS \rightarrow FLU)}$	a_2	−6.617	3.556	−1.808	0.068	−13.747	0.512
$Consequent_{(SYM \rightarrow RAT)}$	b_1	−1.190	0.331	−3.598	< 0.001	−1.853	−0.527
$Consequent_{(FLU \rightarrow RAT)}$	b_2	0.038	0.012	3.228	0.021	0.014	0.061
$Total_{(STRESS \rightarrow RAT)}$	c	−0.810	0.245	−3.304	0.002	−1.301	−0.319
$Direct_{(STRESS \rightarrow RAT)}$	c'	0.059	0.315	0.186	0.853	−0.574	0.691
$Intermediate_{(SYM \rightarrow FLU)}$	d_{21}	7.481	3.710	2.018	0.048	0.496	14.925
$Indirect_{(SYM)}$	$a_1 \times b_1$	−0.811	0.237	–	–	−1.321	−0.399
$Indirect_{(SYM\ \&\ FLU)}$	$a_1 \times d_{21} \times b_2$	0.193	0.125	–	–	0.018	0.539
$Indirect_{(FLU)}$	$a_2 \times b_2$	−0.250	0.150	–	–	−0.630	−0.024

Table 4
Unstandardized parameters for the serial multiple mediator model for working memory capacity. Notes: the estimation of standard errors and lower level and upper level confidence intervals (LLCI and ULCI) for indirect effects are based on bias-corrected 95% bootstrap method (10,000 bootstrap samples); SYM – the index of sympathetic activity; CogI – self-reported cognitive interference; WMC – working memory capacity.

$Effect_{(path/mediators)}$	Parameter	Estimate	*SE*	*t*	*p*	LLCI	ULCI
$Antecedent_{(STRESS→SYM)}$	a_1	0.682	0.090	7.569	< 0.001	0.506	0.858
$Antecedent_{(STRESS→CogI)}$	a_2	7.457	3.024	2.466	0.014	1.530	13.384
$Consequent_{(SYM→WMC)}$	b_1	0.517	1.524	0.339	0.743	−2.470	3.504
$Consequent_{(CogI→WMC)}$	b_2	−0.187	0.064	−2.899	0.004	−0.312	−0.062
$Total_{(STRESS→WMC)}$	c	−4.531	1.109	−4.084	< 0.001	−6.754	−2.308
$Direct_{(STRESS→WMC)}$	c′	−3.293	1.578	−2.087	0.042	−6.458	−0.128
$Intermediate_{(SYM→CogI)}$	d_{21}	1.553	3.155	0.484	0.622	−4.631	7.737
$Indirect_{(SYM)}$	$a_1 \times b_1$	0.352	0.910	–	–	−1.483	2.151
$Indirect_{(SYM\ \&\ CogI)}$	$a_1 \times d_{21} \times b_2$	−0.198	0.439	–	–	−1.337	0.500
$Indirect_{(CogI)}$	$a_2 \times b_2$	−1.393	0.755	–	–	−3.385	−0.300

previously demonstrated in some cognitive processes (Beilock & DeCaro, 2007; Schwabe & Wolf, 2009, 2013; Yerkes & Dodson, 1908), to our knowledge, this is the first study showing such a phenomenon within the domain of lexical-semantic processing.

The stress-related activation of the sympathetic nervous system is a marker of the activation of the central noradrenergic system (Bremner, Krystal, Southwick, & Charney, 1996; Samuels & Szabadi, 2008a, 2008b) indicating that these effects might be mediated by noradrenaline (NA). This account is also consistent with the evidence showing that antagonism of β-adrenergic receptors reverses the effects of stress on cognitive flexibility (Alexander et al., 2007). Converging evidence suggests that NA enhances transmission of dominant neural signals and inhibits noise (i.e., weaker and diffuse neural signal) to adjust cognitive processing in threatening situations (e.g., resulting in enhanced vigilance and faster threat detection; Aston-Jones & Cohen, 2005; Hermans et al., 2014). According to a recent model (Clewett, Sakaki, Huang, Nielsen, & Mather, 2017; Mather, Clewett, Sakaki, & Harley, 2016), the stress-induced release of NA in the brain modulates mental representations as a function of their activation strength so that NA enhances prioritized representations even further, while simultaneously attenuates noisy or weak inputs. As a result, higher NA tone reduces the variability and spreading of activation within neural networks and promotes stereotyped responding (Hasselmo, Linster, Patil, Ma, & Cekic, 1997; Servan-Schreiber, Printz, & Cohen, 1990). In the context of semantic retrieval, this arousal-induced functional modulation would be manifested in a restricted accessibility and integration of weakly and diffusely represented information (i.e., remote associates) within lexical-semantic and associative networks but an enhanced conductivity of well-structured and strong associative connections. By such means, elevated arousal would impair cognitive flexibility, but enhance the speed of retrieving closer and habitual associates during the semantic fluency task, which is in line with our data. Furthermore, this neurocognitive account is also consistent with the behavioral evidence showing that evaluation stress strengthens fixation of close and frequent associates (Harkins, 2006), which hinders the search for a more unusual solutions (Gupta et al., 2012), but also with pharmacological evidence showing that solving more difficult RAT problems (i.e., more "remote") is more sensitive to modulation of the noradrenergic system (Campbell, Tivarus, Hillier, & Beversdorf, 2008).

It should be noted that, after accounting for the facilitative effect mediated by sympathetic arousal, stress tended to reduce semantic fluency (p = .068, see Fig. 2A and Table 4), indicating concurrent positive and negative effects of stress on the performance. Given the hybrid nature of semantic fluency (Shao et al., 2014), stress may simultaneously increase the accessibility of close category instances but decrease the executive control over the retrieval (e.g., switching to a less exploited subcategory, see Hills, Todd, & Jones, 2015). Although consistent with the present account that stress affects lexical-semantic and executive functioning via distinct mechanisms, this explanation requires future empirical support from studies employing finer-grained analyses of fluency responses.

4.2. Stress-induced modulation of working memory capacity

The results of the second mediator model (Fig. 3B, blue path) showed that the impairment of working memory under stress was mediated by the elevated self-reported cognitive interference, but was unrelated to sympathetic arousal. The relationship between cognitive interference and working memory capacity is in line with previous research showing that stress impairs the control over intrusive thoughts and concerns and decreases the focus on task-relevant stimuli, which has a negative impact on the working memory system (Coy, O'Brien, Tabaczynski, Northern, & Carels, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007; Sarason et al., 1986). The missing links between modulations of working memory capacity and self-reported cognitive interference on the one hand and sympathetic arousal on the other hand indicate that the effects of stress on these functions were not mediated by the activation of the noradrenergic system, but were probably conveyed by a different neurophysiological mechanism. This possibility is also supported by the observations that the β-adrenergic antagonist propranolol was able to reverse the effects of stress on cognitive flexibility (Alexander et al., 2007) but had no effect on stress-related decrease in working memory performance (Ernst, Lago, Davis, & Grillon, 2016; Murphy, Arnsten, Jentsch, & Roth, 1996).

Numeorous reports linked the stress-related impairment of executive attentional functions with the activation of the hypothalamo-pituitary-adrenal axis and hence the effects of elevated levels of corticosteroids (see Shields, Bonner, & Moons, 2015; Shields et al., 2016). Although we did not assess cortisol levels in the participants, it seems unlikely that the observed effects could be driven by an increased cortisol release. Firstly, in contrast to the activity of the sympathetic autonomic nervous system, the cortisol response is substantially delayed with respect to stressor onset and its neurobiological effects occur in a later time period than those choosen for the testings (Droste et al., 2008). Secondly, if cortisol played a significant role, due to a gradual increase over time, the effects on working memory would be stronger in the last testing block than in earlier blocks, which is contrary to our observation (the working memory impairment was strongest when tested first). Nevertheless, the extent to which cortisol could contribute to the impairment of working memory capacity was not addressed in the present study and future research is therefore required.

A more likely mediator of the observed effects on working memory seems to be the dopaminergic system, which is also activated in stress (Vaessen, Hernaus, Myin-Germeys, & van Amelsvoort, 2015). It is well known that dopamine (DA) plays role in working memory and executive control (Cools & D'Esposito, 2011). In particular, a moderate DA level (ensuring moderate activation of DA D1 receptors) is optimal for maintenance of sustained prefrontal neuronal activity during working memory tasks (Arnsten, Wang, & Paspalas, 2015). In such a state, interference is reduced, and neural representations are stabilized in

prefrontal circuits during working memory engagement (Durstewitz, Seamans, & Sejnowski, 2000). An excessive release of DA during stress is associated with an attenuated neural activity in the prefrontal cortex and a decreased working memory performance (Arnsten, 2009; Arnsten et al., 2015). Furthermore, humans with a less active variant of catechol-O-methyltransferase, an enzyme involved in DA metabolic degradation, are more vulnerable to stress-induced impairment of working memory and dysfunction of the prefrontal cortex (Qin et al., 2012). Pharmacological studies have shown that stress-induced working memory deficits were ameliorated by administration of DA receptor antagonists (Arnsten & Goldman-Rakic, 1998; Murphy et al., 1996). Altogether, this evidence supports the possibility that the observed effects of stress on working memory and cognitive interference might be due to an increased dopaminergic activity.

4.3. Conclusions

The present findings indicate that acute stress may impair cognitive flexibility via concomitant neural activation that modulates lexical-semantic and associative processes. This was demonstrated by arousal-dependent decrease in access and integration of remote associates but facilitated retrieval of well-established associative links during semantic fluency. Following these results, we conclude that the stress-induced arousal may restrict the accessibility and integration of remote associates and bias the response competition towards prepotent and dominant associative elements. Importantly, these results also indicate that the stress-induced modulations may not be uniform but depend on complexity of the lexical-semantic and associative relations employed in the task (e.g., search constraints, remoteness). Interestingly, stress concurrently dysregulated executive working memory system, but this effect was not correlated with the impairment of cognitive flexibility and sympathetic arousal. Our findings suggest that the impairment of cognitive flexibility and working memory capacity under stress might be mediated by distinct neurocognitive mechanisms. The precise nature of this dissociation awaits further investigation.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cognition.2018.02.004.

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