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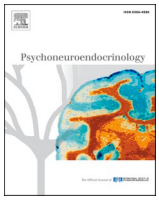

The influence of a glucose administration on stress responsivity and memory after a socially evaluated cold pressor test

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ABSTRACT

The nutritional state of participants prior to stress induction via a laboratory stressor has been demonstrated to influence reactivity of the Hypothalamus-Pituitary-Adrenal axis. So far, either primarily psychosocial or primarily physiological stressors have been utilized investigating this effect. In the present study, we aimed to fill this gap in the existing literature by utilizing a stressor that combines both elements, namely the Socially Evaluated Cold Pressor Test. Furthermore, we investigated how glucose consumption and subsequent stress induction influence long-term memory retrieval as well as working memory. In a 2 × 2 design, half of the 72 participants (36 women, 36 men) participated in the laboratory stressor while the other half participated in a control condition after having fasted for at least six hours. Thirty minutes prior to stress or control treatment, fasted participants consumed either 75 g of glucose or stevia-sweetened water. Salivary cortisol levels, systolic and diastolic blood pressure, as well as affect did not significantly differ between participants consuming glucose or the placebo beverage. Acute stress impaired working memory but had no effect on long-term memory retrieval. Glucose consumption did not significantly influence memory. Our results suggest that the intensity of a stressor might be important when determining the effects of a glucose administration on stress reactivity. The nutritional state of participants taking part in studies investigating the effects of acute stress on memory might be less decisive than previously assumed.

1. Introduction

Acute stress activates the Hypothalamic-Pituitary-Adrenal (HPA) axis, which subsequently releases the glucocorticoid cortisol (Foley and Kirschbaum, 2010). Cortisol has a multitude of functions in the body, one of which is the mobilization of energy in the form of glucose (Peters et al., 2004). This is accomplished by an increase in gluconeogenesis, the metabolic pathway by which glucose is generated (Dallman et al., 1995). The nutritional state of participants prior to being exposed to a laboratory stressor has been pointed out as one important factor influencing cortisol reactivity (Strahler et al., 2017). In a study by Kirschbaum et al. (1997) male participants were confronted with a Trier Social Stress Test (TSST; Kirschbaum et al., 1993) after having fasted for 8–11 h. Participants consumed either glucose or water before being exposed to the stressor. Salivary cortisol only increased in stressed participants that had consumed glucose prior to stress induction, but not in stressed participants that had consumed water. Thus, the absence of readily available energy appears to lead to a blunted stress response which can be restored by glucose intake (Kirschbaum et al., 1997). A follow-up study demonstrated that modulation of stress reactivity is specific to glucose load and does not depend on energy availability in general (Gonzalez-Bono et al., 2001). Energy in the form of fat or proteins was not able to restore a blunted stress response after fasting.

Four recent studies investigated the effects of fasting and energy availability on HPA-axis reactivity further. Zänkert et al. (2020) compared the effects of glucose administration with consumption of grape juice and maltodextrin, a rapidly absorbed polysaccharide. Participants took part in a TSST after having fasted for 3 h. There was a significant increase in cortisol in participants that consumed either glucose or grape juice, but not maltodextrin (Zänkert et al., 2020). The study by von Dawans et al. (2021) compared not only the effects of three different drinks (glucose, sweetened water, and plain water) but also two different stressors, namely the TSST and the Cold Pressure Task (CPT; Lovallo, 1975). Participants fasted 4 h before being exposed to either stressor. Results demonstrated a significantly stronger stress response after glucose consumption. This effect was more prominent in response to the TSST as compared to the CPT (von Dawans et al., 2021). Bentele et al. (2021) had women consume either grape juice or water

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before exposing them to the TSST for groups. Their results showed that women consuming grape juice had higher increases in cortisol over time (Bentele et al., 2021).

In a study by Meier et al. (2021) women participated in the TSST for groups after an 8 h fast. Prior to stress induction, they consumed either a drink containing simple sugar, a sweetened, non-caloric placebo drink that had been matched for sweetness, or plain water. Although participants consuming the drink containing sugar and participants consuming the sweetened drink had higher cortisol increases than participants consuming the water, the sugar-containing drink had a significantly higher impact on cortisol trajectories than the other two drinks. Taken together, it seems that counteracting a blunted stress response after a period of fasting with glucose administration is only effective when utilizing a potent psychosocial stressor like the TSST. It remains unclear whether this is due to the intensity of the stressor or depends on it being of physical or psychological nature.

While the underlying mechanisms leading to the effect of glucose on HPA stress reactivity are not well understood, four potential explanations have been provided. First, it has been proposed that a central mechanism, namely glucose-dependent insulin release, is responsible for the boost in stress reactivity in response to glucose administration (Ulrich-Lai, Ryan, 2014). Glucose or insulin release might modulate activity in the ventromedial nucleus (VMN) which in turn activates the paraventricular nucleus (PVN) of the hypothalamus (Choi et al., 1996). Insufficient blood glucose levels might inhibit activity in the PVN which negatively affects HPA-axis functioning. Second, it has been argued that the effect might take place on a more basic level. Insulin receptor signaling in hypothalamic neurons may be of importance for the cross-talk between energy status and stress reactivity (Chong et al., 2015). Third, it has been suggested that sweet taste irrespective of actual caloric load might have an influence on stress reactivity in fasted women (Meier et al., 2021). The exact nature of the underlying mechanism requires further investigation. Lastly, neuropeptides regulating appetite and satiety might play a role in HPA-axis responsivity (Rohleder and Kirschbaum, 2007). While orexigenic peptides primarily activate the HPA-axis, anorexic peptides have been shown to depress as well as stimulate HPA-axis activity. Thus, while the regulation of energy homeostasis by neuropeptides might moderate the effects of glucose availability on stress reactivity, results are still inconclusive.

Blood glucose levels have been shown to influence cognitive performance (Riby, 2004). This effect, which is more pronounced in cognitively demanding tasks, has been termed *Glucose Memory Facilitation Effect* (Smith et al., 2011). Numerous studies have found that a glucose administration can positively affect episodic memory (Meikle et al., 2005; Messier, 2004; Riby et al., 2006), as well as working memory (Sünram-Lea et al., 2002). Fasting, on the other hand, hampered working memory (Martin and Benton, 1999).

In the present study, we wanted to further test the relationship between energy availability and HPA-axis functioning. We investigated the effects of glucose consumption on stress reactivity after a fasting period of at least 6 h. Since research has shown that it might take up to 5 h after ingestion of calories for blood glucose to return to fasting levels (Moebus et al., 2011) we decided to choose a longer fasting window than some of the previous studies on this topic (see von Dawans et al., 2021; Zänkert et al., 2020). Because all existing studies utilized either a primarily psychosocial or a primarily physiological stressor, we made use of a laboratory stressor that combines both elements, namely the Socially Evaluated Cold Pressor Test (SECPT; Schwabe et al., 2008). Because the SECPT is a comparatively easy to conduct and resource efficient stress test, our study provides strategies on how to investigate glucose effects with limited means. Because stress and specifically cortisol has been shown to impair working memory and long-term memory retrieval (Shields et al., 2016, 2017; Schoofs et al., 2008), we incorporated two memory tasks. The influence of stress and glucose on cognitive performance is a research question of many studies. Testing the potential interaction of these two manipulations makes our study a valuable addition to the existing literature. Next to saliva samples to analyze cortisol levels, we took blood pressure measurements and assessed subjective stress as secondary stress response markers. Our hypotheses were tested with a 2 × 2 design consisting of the variables stress (stress vs no stress) and drink (glucose vs. placebo). We hypothesized a higher increase of the stress hormone cortisol as well as of systolic and diastolic blood pressure values in stressed participants compared to non-stressed participants. Also, we expected an increase in negative affect in stressed, but not in non-stressed participants and hypothesized stressed participants to find it more difficult to keep their hand in the water, feel more uncomfortable and stressed, and perceive the water immersion as more painful than non-stressed participants. Moreover, we hypothesized blood glucose levels to increase in participants consuming glucose while not changing in participants consuming the control beverage. Considering our main hypothesis, we expected stressed participants consuming glucose to have a higher increase of cortisol than stressed participants consuming the control beverage. Regarding the effects on memory, we expected improved performance on the working and long-term memory task in participants consuming glucose, compared to participants consuming the control beverage. Also, we expected stressed participants to have worse long-term retrieval and working memory performance than non-stressed participants. Lastly, we investigated the interaction between glucose consumption, stress levels, and cognitive performance. We considered two possibilities: (1) Because glucose has the potential to boost stress reactivity and increased cortisol levels lead to impaired working memory and long-term memory retrieval, participants consuming glucose have worse cognitive performance than participants consuming the placebo. (2) Due to its potential to enhance memory, glucose might buffer the negative effects of acute stress on memory performance. Consequently, stressed participants consuming glucose perform better on the cognitive tasks than stressed participants consuming the placebo.

This study has been preregistered at the Open Science Framework (https://osf.io/wg4p5?view_only=6a91877ccf5d4b2788c1481652c5ae27).

2. Materials and methods

2.1. Participants

We recruited 72 healthy men and women (sex ratio 50%) from Ruhr University Bochum through posters, handouts, social media, and online advertisement. We determined our target sample size based on past relevant work (Kirschbaum et al., 1997; Zänkert et al., 2020) by averaging the effect sizes of the interaction between blood glucose level and HPA-axis reactivity. By conducting an a priori power analysis using G*Power (Faul et al., 2007) for an Analysis of Variance (ANOVA) for fixed effects, special effects, main effects, and interactions (4 groups; 3 degree of freedom) with 80% power, an alpha of.05, and a medium to large effect size (f =0.41), a target sample size of N = 69 was determined.

Participants were between 18 and 35 years old (M = 24.5, SD = 4.33). Their Body-Mass-Index (BMI) ranged between 18.5 kg/m^2 and 25 kg/m^2 (M = 23.11, SD = 2.5). They underwent a standardized screening procedure via email or telephone before being invited to the laboratory. Participants were excluded from the study if their BMI was below 18 or above 30 kg/m^2, if they were younger than 18 or older than 35 years old, reported current use of medication, suffering from a chronic disease, using drugs or smoking. Further exclusion criteria were exceptional familiar or occupational stress, shift work four weeks leading up to the testing session, recent blood donation, and consumption of more than 15 alcoholic drinks per week. In addition, participants had not participated in the SECPT before. Because sex hormones can influence stress reactivity (Kirschbaum et al., 1999; Kudielka et al., 2009) and its effect on memory (Merz and Wolf, 2017), female participants were not using hormonal contraceptives and were tested preferably in the luteal phase

of their menstruation cycle. By having women report the date of their last and next expected menstruation, we were able to determine their respective cycle phase. Four of the 36 women (11,11%) were in the follicular phase when being tested, the remaining 32 (88,89%) in the luteal phase. The distribution of cycle phase between the groups was identical, with one women of each group being in the follicular phase. This was also statistically tested; results are reported in the results section under subheading 3.1.

Participants received either 15 € or 1.5 study credits for 75 min of their time. The study had been approved by the local ethics committee of the Faculty of Psychology and was conducted in accordance with the Declaration of Helsinki.

2.2. Design and procedure

In the 2 × 2 design, participants were randomly assigned to four groups (Glucose + Stress, Stevia + Stress, Glucose + noStress, and Stevia + noStress). Additionally, we counterbalanced for sex, so that the same number of participants of either sex was exposed to each of the four conditions.

At the time of their arrival at the lab, participants were blind to the condition they had been assigned to (stress or control) as well as to which of two beverages they were going to consume (glucose or sweetened water). Testing sessions took place between 13:00 pm and 17:50 pm to account for circadian fluctuations in cortisol levels (Maheu et al., 2005). Participants did not consume food or drinks other than water at least six hours prior to the start of the testing session. Next to a demographic questionnaire, participants filled in the State-Trait Anxiety Inventory (STAI; Laux et al., 1981) to control for symptoms of anxiety. After consuming either the glucose or placebo drink, participants were provided with the word list and were instructed to memorize as many words as possible in two minutes. Salivary cortisol and blood glucose levels were measured five times over the course of the testing session. Blood pressure was measured before, during, and after participants took part in either the stressful or non-stressful warm water variant of the SECPT. The Positive and Negative Affect Scale (PANAS; Krohne et al., 1996) was filled in before and after either condition, while the four questions about their subjective experience were answered only afterwards. Before taking the last saliva samples and blood glucose measurements, participants were asked to write down as many of the words they had previously learned as possible. Afterwards, they performed the digit span backwards task. After taking the last saliva sample and blood glucose measurement, participants were debriefed and paid. Details regarding the timing of each measurement are provided in Fig. 1.

2.3. Materials

2.3.1. Stress induction

The SECPT is a validated laboratory psychosocial stressor that has been shown to reliably activate the HPA axis (Schwabe et al., 2008). Participants immersed their dominant hand up to and including the wrist in ice cold water (0–2 °C) while being videotaped. Additionally, participants were observed by a person standing behind the camera. The person kept a neutral facial expression and did not provide any supportive social feedback. Participants were instructed to look at the camera and hold their hand in the water for as long as possible. They were not beforehand informed about the duration of immersion. After three minutes, participants were instructed to remove their hand from the water (Schwabe et al., 2008).

The warm water variant functioned as a control version. Here participants immersed their dominant hand in lukewarm water (37 °C). They were not being videotaped or observed by a third person.

2.3.2. Stress assessment

Systolic and diastolic blood pressure values were taken as autonomic stress markers. Measurements were taken via an Omron M700 Intelli IT device. As an endocrine stress marker, saliva samples were collected at multiple timepoints to measure salivary cortisol. The samples were taken via Salivettes® (Sarstedt, Nümbrecht, Germany). Salivettes® were stored at − 20 °C until assayed. Saliva samples were analyzed at the Genetic Psychology Lab of Ruhr University Bochum with a time-resolved fluorescence immunoassay (IBL; Hamburg, Germany). All intra- and inter-assay coefficients of variations were below 8,70%.

Subjective stress was assessed via the German version of the PANAS. Additionally, measurements of subjective pain and stress perception were taken by having participants answer four questions. The questions in free translation to English were: (1) How hard was it for you to keep your hand in the water? (2) How uncomfortable was the situation for you? (3) How stressed did the situation make you feel? (4) How painful was it for you to keep your hand in the water? Participants were asked to answer these questions on a decimal scale from 0 (“not at all) to 100 (”a lot”).

2.3.3. Blood glucose manipulation

Two of the groups consumed a 300 ml drink with 75 mg diluted glucose (Accu-Chek Dextrose O.G-T., F. Hoffmann-La Roche AG, Basel, Schweiz). This amount has been utilized in previous studies investigating the influence of glucose availability on HPA-axis reactivity (e.g. Gonzalez-Bono et al., 2002; von Dawans et al., 2021; Zänkert et al., 2020). The other two groups consumed 300 ml of still water sweetened with stevia (Stevia rebaudiana). Stevia is a natural sweetener which does

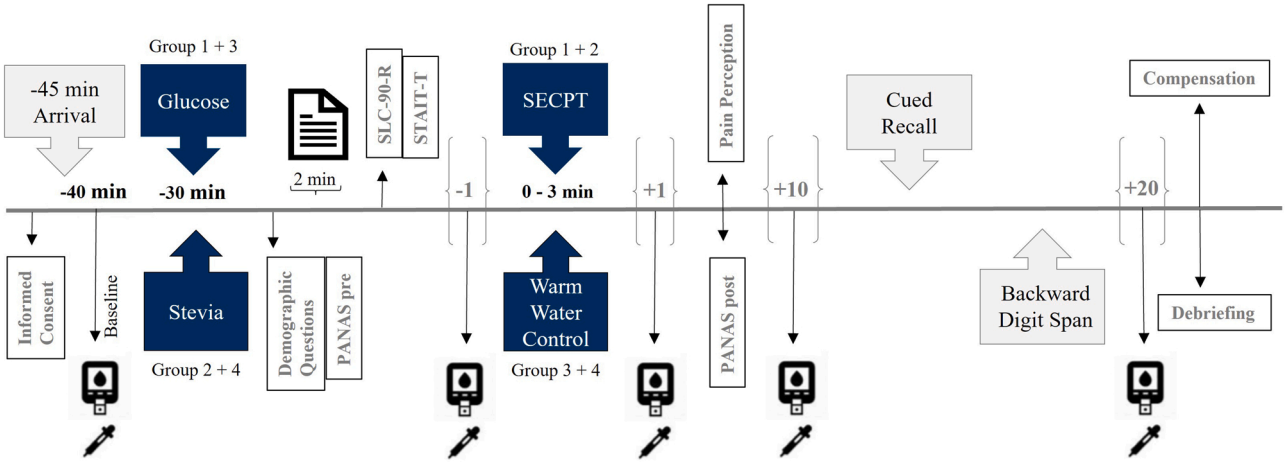

Fig. 1. Experimental procedure.

not contain any calories and therefore does not influence blood glucose levels. We used ten drops of a liquid stevia, which was equivalent to one tablespoon of sugar. The sweetness of the placebo drink was matched to that of the glucose drink by having three experts judge the subjective level of sweetness of both drinks. Capillary blood samples were taken which were subsequently analyzed via the MediTouch 2® (Medisana GmbH) blood glucose monitor.

2.3.4. Memory

Participants´ memory was assessed via two separate tests. First, 32 min prior to the SECPT or the warm water control they memorized a list of 30 words (ten negative, ten neutral and ten positive words; Merz et al., 2019), which were presented on a sheet of paper. Participants had two minutes for memorization. Fifteen minutes after the SECPT or the warm water control their memory retrieval for the words was assessed via a cued recall. Participants received a list with the first two letters of each previously presented word as a cue. Second, 20 min after the SECPT or the warm water control participants working memory performance was assessed via a digit span backward task (DSBT; Wechsler Adult Intelligence Scale [WAIS-IV]; Wechsler, 2008). A sequence of numbers was read to the participants by the instructor, after which participants were instructed to repeat the numbers in reverse order. Each round had two trials, participant received one point for each correct trial, thus, participants could score from zero to two points in each round. The sequence of numbers got longer each round, thus making the challenge increasingly difficult as the test progressed. The test was discontinued if participants failed to recite the correct sequence of numbers twice in one round. Performance on both tests has been shown to be impaired by acute stress (Merz et al., 2019; Schoofs et al., 2009).

2.4. Statistical analysis

We performed all statistical analyses in IBM SPSS Statistics for Windows 21.0. The significance level was set to $\alpha = 0.05$; all post hoc tests were Bonferroni-corrected. In case the sphericity assumption was not met, Greenhouse-Geisser corrected values were reported. Due to violation of the normality assumption, cortisol and blood glucose data were log-transformed. One participant had to be removed from all analyses because his baseline cortisol level was more than three times higher than the mean. Analyses of variance (ANOVA) always included the between-subject factors stress (stress vs. control), glucose (glucose vs. stevia), and sex (male vs. female). Our hypothesis regarding the endocrine stress manipulation as well as our hypothesis regarding blood glucose levels and the influence of blood glucose levels on the stress response were tested with repeated measures ANOVAs which additionally included the within-subject factor time (baseline, −1, +1, +10, +20). For the autonomic stress response, the factor time had three (before, during, after), for the subjective stress response two (before vs. after) levels. Lastly, our hypothesis regarding the effects of stress and blood glucose levels (as well as their interaction) on memory performance as well as our hypothesis regarding subjective stress and pain perception were tested with three-way ANOVAs. For analysis of word list recall performance, the additional within-subject factor valence (positive vs. neutral vs negative) was included.

3. Results

3.1. Sample characteristics

The four groups did not differ significantly in age, BMI, or symptoms of anxiety.

A chi-square test indicated that there was no significant difference in distribution of cycle phase between the four groups ($\chi^2[df = 3] < 0.01$, $p = 1$).

3.2. Blood glucose levels

In the 5 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on blood glucose levels, the main effect of time ($F_{[2.57,\ 162.19]} = 79.97$, $p < .001$, $\eta_p^2 = .56$) as well as the time x glucose interaction ($F_{[2.57,\ 162.19]} = 108.5$, $p < .001$, $\eta_p^2 = .63$) were significant. All other effects were not significant (all $F < 2.16$, all $p > .104$). Post hoc analyses revealed that participants consuming glucose had significantly higher blood glucose levels at timepoints − 1, + 1, + 10, and + 20 than participants consuming stevia (all $p < .001$, Fig. 2).

3.3. Cortisol response

In the 5 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on cortisol levels, the main effect of time ($F_{[1.67,\ 103.62]} = 31.21$, $p < .001$, $\eta_p^2 = .36$), as well as the time x stress ($F_{[1.67,\ 103.62]} = 44.12$, $p < .001$, $\eta_p^2 = .42$), time x sex ($F_{[1.67,\ 103.62]} = 3.65$, $p = .037$, $\eta_p^2 = .06$) and time x stress x sex ($F_{[1.67,\ 103.62]} = 3.66$, $p = .037$, $\eta_p^2 = .06$) interactions were significant. All other effects were not significant (all $F < 0.94$, all $p > .381$). Post hoc analyses indicated that stressed participants had significantly higher cortisol levels at + 10 and + 20 min than non-stressed participants (all $p < .001$). Stressed male participants had significantly higher cortisol levels at + 10 ($p = .007$), and + 20 ($p = .009$) than stressed female participants (Table 1; Fig. 3).

We calculated the correlation coefficient between the individual blood glucose increase and total salivary cortisol output (area under the curve with respect to ground; AUCg). The individual blood glucose increase did not predict the individual cortisol response ($F_{[1,68]} = 0.15$, $p = .697$, $R^2 < 0.01$). Next, the correlation coefficient between the individual blood glucose increase and salivary cortisol increase (area under the curve with respect to increase; AUCi) was calculated. Again, the individual blood glucose increase did not predict the individual cortisol response ($F_{[1,68]} = 0.15$, $p = .703$, $R^2 < 0.01$).

According to the cortisol response criterium of 1.5 nmol/l baseline to peak increase proposed by Miller et al. (2013), participants were classified as either cortisol responders or non-responders. In both stress groups 13 (72,22%) participants could be classified as responders. A chi-square test indicated that there was no significant difference in responder rates between stressed participants that consumed glucose and stressed participants that consumed the placebo drink ($\chi^2[df = 1] < 0.06$, $p = .812$).

3.4. Blood pressure

In the 3 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on systolic blood pressure values, the main effect of time ($F_{[2128]} = 44.40$, $p < .001$, $\eta_p^2 = .41$) as well as the time x stress interaction ($F_{[2128]} = 51.19$, $p < .001$, $\eta_p^2 = .44$) were significant. All other effects were not significant (all $F < 0.64$, all $p > .531$). Post hoc analyses revealed that stressed participants had significantly higher systolic blood pressure values during stress induction than non-stressed participants ($p < .001$). In the 3 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on diastolic blood pressure values, the main effect of time ($F_{[2128]} = 81.63$, $p < .001$, $\eta_p^2 = .56$) as well as the time x stress interaction ($F_{[2128]} = 87.90$, $p < .001$, $\eta_p^2 = .58$) were significant. All other effects were not significant (all $F < 2.55$, all $p > .082$) Post hoc analyses revealed that stressed participants had significantly higher diastolic blood pressure values during stress induction than non-stressed participants ($p < .001$, Table 2).

3.5. Subjective stress response

In the 2 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on positive PANAS scores, the time x stress interaction ($F_{[1,64]} = 5.22$, $p = .026$, η_p^2

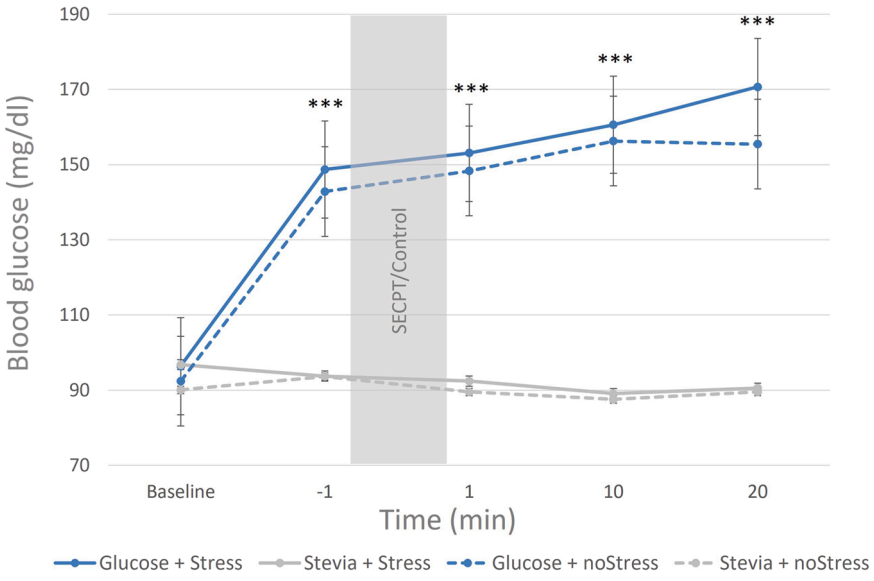

Fig. 2. Mean blood glucose levels over the course of the testing session; SECPT = Socially Evaluated Cold Pressor Task; error bars represent standard errors of the mean; *** p < .001 compared to groups consuming the placebo.

Table 1
Mean (+ SD) cortisol levels (in nmol/l) over the course of the testing session.

		Glucose + Stress n = 18		Stevia + Stress n = 18		Glucose + noStress n = 18		Stevia + noStress n = 18	
		M	SD	M	SD	M	SD	M	SD
Women									
	Baseline	3.57	± 2.69	3.83	± 3.17	2.85	± 1.13	3.88	± 2.18
	-1	2.96	± 1.87	2.86	± 2.15	2.71	± 1.23	3.92	± 2.14
	+1	2.64	± 1.70	2.54	± 1.69	3.12	± 1.99	3.33	± 1.42
	+10	4.45	± 2.53	4.34	± 3.21	2.67	± 1.18	3.22	± 1.42
	+20	7.21	± 5.19	6.31	± 4.63	2.61	± 1.36	3.10	± 1.02
Men									
	Baseline	3.29	± 1.63	3.09	± 2.04	3.25	± 2.29	5.60	± 2.89
	-1	4.25	± 2.55	2.58	± 2.81	3.08	± 1.59	4.42	± 1.81
	+1	4.69	± 3.12	3.42	± 2.89	2.85	± 1.16	3.53	± 1.36
	+10	7.91	± 4.70	6.22	± 3.10	2.92	±.85	3.50	± 1.60
	+20	12.70	± 7.51	9.81	± 6.03	3.30	±.79	3.50	± 1.38

Note. M = Mean; SD = Standard Deviation.

=.08) was significant. All other effects were not significant (all $F < 1.22$, all $p > .274$). A post hoc test was not significant anymore (all $p > .235$). In the 2 (time) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on negative PANAS scores, the time x stress interaction ($F_{[1,64]} = 7.06$, $p = .01$, η_p^2 =.1) was significant. All other effects were not significant (all $F < 3.07$, all $p > .085$). Post hoc analyses indicated that stressed participants had significantly higher negative PANAS scores after stress induction than non-stressed participants ($p < .034$, Table 2).

In the 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on the subjective pain and stress perception, the main effect of stress ($F_{[4,61]} = 91.74$, $p < .001$, η_p^2 =.86) was significant. All other effects were not significant (all $F <$ 1.85, all $p > .130$). Stressed participants perceived the procedure as being more difficult, uncomfortable, and painful, and reported being significantly more stressed than non-stressed participants (Table 2).

3.6. Digit span backward task

In the 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on the digit span backward task scores, the main effect of stress ($F_{[1,64]} = 7.05$, $p = .01$, η_p^2 =.10) was significant. All other effects were not significant (all $F <$0.66, all $p > .419$). Stressed participants performed significantly worse on the digit span task than non-stressed participants. This effect was not modulated by glucose (Fig. 4).

3.7. Word list recall

In the 3 (valence) x 2 (stress) x 2 (glucose) x 2 (sex) ANOVA on word list recall, the main effect of valence ($F_{[2128]} = 4.22$, $p = .017$, η_p^2 =.06) as well as the valence x sex ($F_{[2128]} = 3.32$, $p = .039$, η_p^2 =.05) and valence x glucose x sex interaction ($F_{[2128]} = 5.12$, $p = .007$, η_p^2 =.07) were significant. All other effects were not significant (all $F < 2.18$, all $p > .117$). Exploratively, we conducted separate repeated measures ANOVAs for each of the two sexes. In male participants, the valence x glucose interaction was significant ($F_{[1.62,\ 55.19]} = 4.94$, $p = .016$, η_p^2 =.13). A subsequent post hoc test was not significant anymore (all $p < .103$). Male participants consuming glucose tended to remember more negative words (4.33) than male participants consuming the placebo (3.5). In female participants, the main effect of valence ($F_{[2,68]} =$ 6.29, $p = .003$, η_p^2 =.16) was significant. The valence x glucose interaction was not significant ($F_{[2,68]} = 1.56$, $p = .218$, η_p^2 =.04). Compared to neutral words (3.56), women significantly better remembered positive (4.56, $p = .007$) and negative (4.5, $p = .012$) words (Fig. 5).

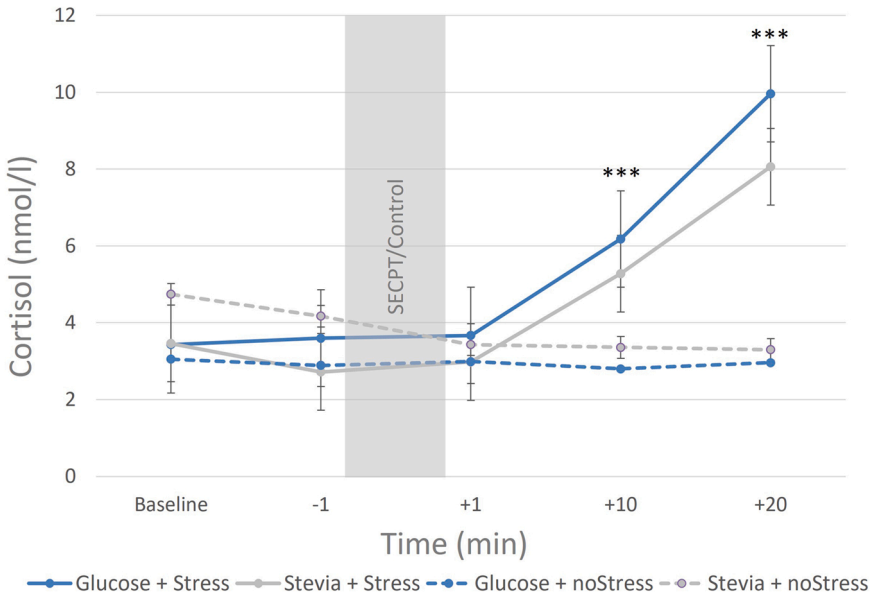

Fig. 3. Mean cortisol levels over the course of the testing session; SECPT = Socially Evaluated Cold Pressor Task; error bars represent standard errors of the mean; * ** $p < .001$ compared to non-stressed participants.

Table 2
Mean (+ SD) systolic and diastolic blood pressure values (in mg/dl), positive and negative PANAS scores, and subjective stress ratings over the course of the testing session.

		Glucose + Stress n = 18		Stevia + Stress n = 18		Glucose + noStress n = 18		Stevia + noStress n = 18	
		M	SD	M	SD	M	SD	M	SD
Systolic BP									
	pre	117.97	± 11.74	113.86	± 14.58	113.67	± 15.81	113.78	± 15.34
	during	135.53	± 12.82	131.56	± 12.09	110.17	± 14.33	113.53	± 12.50
	post	118.92	± 10.78	114.47	± 11.30	109.19	± 13.03	112.89	± 12.64
Diastolic BP									
	pre	72.31	± 8.46	74.78	± 7.64	74.33	± 6.84	73.75	± 6.98
	during	90.50	± 12.21	92.00	± 9.62	73.50	± 7.14	73.44	± 4.29
	post	76.31	± 9.45	77.33	± 6.59	73.47	± 8.16	73.08	± 7.16
PANAS pos.									
	pre	28.06	± 6.46	30.00	± 7.21	30.56	± 6.23	31.11	± 5.54
	post	28.21	± 7.15	32.39	± 7.48	29.50	± 6.29	29.83	± 6.11
PANAS neg.									
	pre	24.06	± 10.29	25.17	± 9.33	26.39	± 13.17	21.67	± 9.52
	post	24.33	± 9.09	26.22	± 10.22	23.06	± 8.08	18.50	± 7.94
4 Questions									
	difficult	71.11	± 24.47	71.11	± 27.63	0.00	± 0.00	2.22	± 7.32
	uncom.	62.78	± 30.45	62.22	± 35.24	1.11	± 3.23	0.56	± 2.36
	painful	55.00	± 30.15	47.78	± 34.40	2.22	± 5.48	1.11	± 3.23
	stressful	76.11	± 23.55	75.00	± 22.30	0.00	± 0.00	0.00	± 0.00

Note. M = Mean; SD = Standard Deviation; BP = blood pressure; pos. = positive; neg. = negative; pre = before stress induction; during = during stress induction; post = after stress induction; uncom. = uncomfortable.

4. Discussion

The present study investigated the interaction between energy availability and HPA-axis functioning. In fasted participants, glucose consumption prior to stress exposure did not increase the subsequent cortisol response. While stress impaired working memory, glucose consumption did not moderate this effect. Neither stress nor glucose moderated long-term memory retrieval.

Blood glucose level manipulation as well as stress induction on an autonomic and psychological level were successful. Participants consuming glucose had substantially higher blood glucose levels throughout the testing session, compared to participants consuming stevia-sweetened water. Stressed participants responded with higher increases in salivary cortisol than non-stressed participants. Also, their systolic and diastolic blood pressure was higher during stress induction. Furthermore, they reported feeling more stressed and uncomfortable.

Contrary to our hypothesis, glucose consumption did not affect stress reactivity. Participants consuming glucose prior to stress induction did not react with a higher cortisol release than participants consuming the placebo drink. Prior research had investigated stress reactivity after glucose consumption utilizing either psychosocial or physiological stressors. By utilizing the SECPT, a laboratory stressor combining these elements, we aimed to fill a gap in the existing literature. A study by von Dawans et al. (2021) compared a primarily psychosocial stressor, the TSST, with a primarily physiological stressor, the CPT. There was a stronger increase in stress reactivity after stress induction via the TSST. These results suggest that counteracting a blunted stress response via glucose administration is only feasible when using a potent,

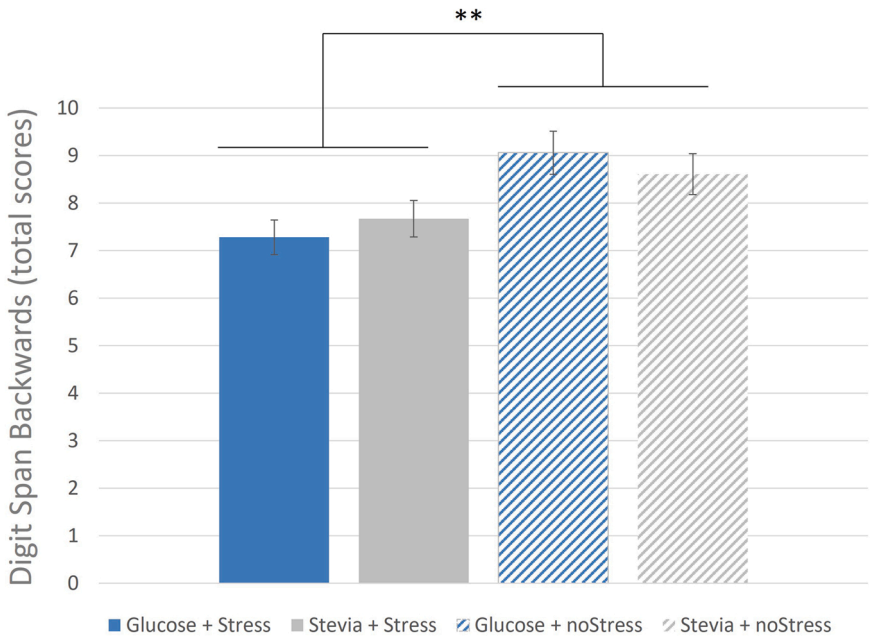

Fig. 4. Digit Span Backward Task mean scores; error bars represent standard errors of the mean; * * p < .01.

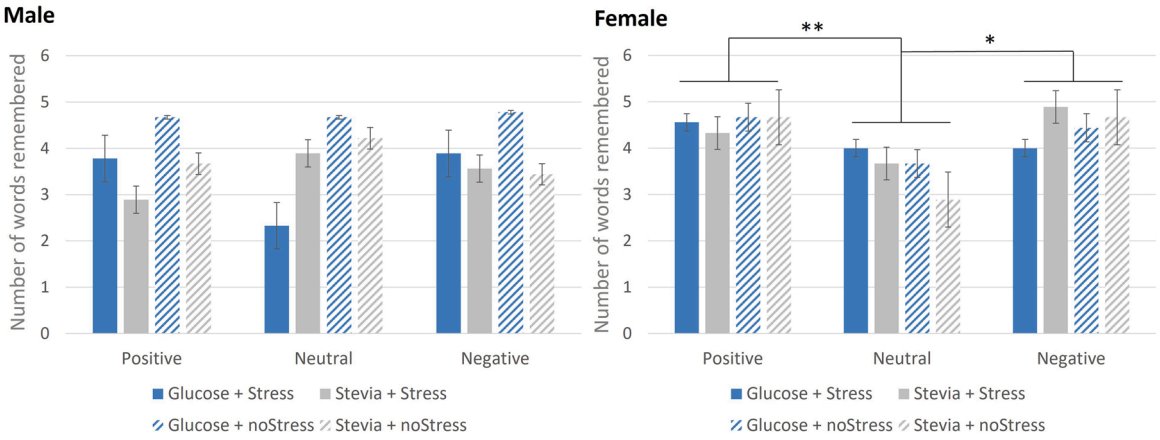

Fig. 5. Mean number of words remembered per valence (positive, neutral, and negative) and sex; error bars represent standard errors of the mean; * * p < .01; * p < .05.

psychosocial stressor. It has been shown that compared to the CPT, the TSST leads to higher plasma cortisol levels (McRae et al., 2006). The effect might only be detectable if stress levels reach a specific threshold. The difference in stress induction between the CPT and SECPT might not be sufficiently large. Since the SECPT combines psychosocial and physiological elements, we argue that the intensity of a stressor is of central importance when trying to detect a restorative effect of glucose on stress reactivity.

Participants consuming the placebo beverage did not react with abnormally low cortisol levels. Furthermore, responder rates were equal in stressed participants consuming glucose and stressed participants consuming the placebo drink. Thus, our data do not support the notion that the nutritional state of participants prior to stress induction is a prerequisite for normal stress reactivity to take place. In case no blunted stress reaction in control participants is provable, we argue that it is not appropriate to speak of restorative mechanisms. The combination of a relatively normal cortisol increase in control participants and the moderate stress reaction induced by the SECPT might explain the absence of the expected difference in stress reactivity. Future studies might provoke blunted stress responses in control participants by incorporating even longer fasting periods. Other popular stress tests, for instance the Maastricht Acute Stress Test (MAST; Smeets et al., 2012) might be incorporated and compared to the stress tests investigated so far. Like the SECPT, the MAST combines psychological and physiological elements. Thus, the results should be comparable when utilizing this stress test.

As expected, acute stress impaired working memory performance. On the Digit Span Backward Task stressed participants performed worse than non-stressed participants. Existing literature supports these findings, demonstrating a negative effect of acute stress on working memory (Lupien et al., 2007; Shields et al., 2016; Schoofs et al., 2009). Contrary to our expectations, acute stress did not impair long-term memory retrieval. Stressed participants remembered as many words as non-stressed participants. Valence did not moderate the results. The effects of acute stress on long-term memory differ regarding the timing of the stressor. While acute stress at encoding has been shown to enhance memory, it impairs memory retrieval (Shields et al., 2017; Wolf, 2017). Since the time between encoding and retrieval was comparatively short, consolidation processes were not complete. This potentially masked the effects of acute stress on retrieval. Previous

studies, however, had been able to demonstrate negative effects of acute stress on long-term memory retrieval, despite applying a comparatively short retention interval (Buchanan et al., 2006; Merz et al., 2019). Compared to neutral words, women recalled more positive and negative words. This is in line with existing research showing improved memory for emotional words, regardless of them being positively or negatively connoted (Adelman and Estes, 2013). It has been reported that women rely more strongly on emotional content when processing information (Bremner et al., 2001; Cahill, 2003). Compared to men, women have a greater overlap of brain regions processing current emotions and regions contributing to subsequent memory formation (Canli et al., 2002). These differences in the underlying neural mechanism could explain gender specific effects in memory for emotional words.

Neither working memory nor long-term memory were influenced by glucose consumption. Due to its comparatively short duration, the Digit Span Task might not be sufficiently sensitive to be affected by blood glucose levels. It has been suggested that the likelihood of glucose to enhance cognitive performance increases if the task is more cognitively demanding (Smith et al., 2011). Since the Digit Span Backward Task is already more demanding than the regular Digit Span Task (Schoofs et al., 2009) and only four participants reached the maximum score, this explanation seems unlikely. An alternative explanatory approach might come from the theory that cognitively demanding tasks are associated with more depletion of circulating blood glucose (Scholey et al., 2006). Several studies found a drop in blood glucose levels after engagement in cognitively demanding tasks (Fairclough and Houston, 2004; Scholey et al., 2006). While the Digit Span Backward Task is challenging enough, it might be too short of duration for this effect to have an influence on performance. This might also explain that glucose did not affect performance on the word list recall task. Meikle et al. (2005) found enhancing effects of glucose on long-term memory only for longer, but not comparatively shorter word lists. While, compared to other studies (see Meikle et al., 2005), our word list was relatively long, the actual recall lasted only a few minutes. This might have been too short for glucose to make a significant difference in performance. Future studies could incorporate memory tasks requiring longer, more continuous focus, for instance the *n*-back task (Jaeggi et al., 2010). Other fields have studied the effects of glucose availability on cognitive performance with a difference focus. It has been suggested that self-control requires certain amounts of energy, and that depletion of energy resources negatively affects self-control mechanisms (Gailliot and Baumeister, 2007). If self-control is depleted due to a lack of quickly available energy, performance on subsequent tasks might be impaired. More recently this theory, which has been termed *glucose hypothesis* (Gailliot et al., 2007), has been, however, disproven (Vadillo et al., 2016). The relationship between glucose availability, self-control, and cognitive performance remains controversial and needs to be further investigated.

Regarding the interaction between glucose consumption, stress levels, and cognitive performance, we considered two alternative explanations. Because glucose had been shown to increase cortisol levels, we hypothesized that glucose consumption might exacerbate the negative effects of acute stress on working and long-term memory. Since glucose did not moderate stress levels, we cannot elaborate on this possibility. Alternatively, we argued that glucose might buffer the negative effects of acute stress on memory. In regards to working memory, glucose did not buffer the hampering effects of acute stress. The negative effects of acute stress on working memory have often been replicated and constitute an established result in the literature (Shields et al., 2017). Thus, the effect might be too robust to be influenced by glucose consumption. Moreover, as argued before, the Digit Span Task might not be sensitive enough to be influenced by a glucose administration. Our data do not allow assumptions about the interaction between glucose and stress regarding long-term memory, since neither stress nor glucose had a significant influence on our participants´ long-term memory performance.

The present study has several limitations. First, there was no assessment of insulin levels. Glucose-dependent insulin release has been considered as one potential underlying factor in stress reactivity after glucose consumption (Ulrich-Lai, Ryan, 2014). Data on insulin levels in response to glucose consumption and stress induction could help to characterize the underlying mechanisms. Second, participants´ sex might have had a significant influence on stress reactivity after glucose consumption. It has been suggested that estradiol changes how carbohydrates are metabolized and utilized in the body (Wismann and Willoughby, 2006). In the study by Zänkert et al. (2020) men consuming grape juice had a stronger increase in cortisol than women consuming the same beverage. Although not moderated by glucose, men in our study had higher cortisol increases than women. This is in line with the existing literature (Kudielka et al., 2009) and further stresses the importance of considering general differences in stress reactivity between men and women. Although the majority of women were tested in the same phase of their menstrual cycle, it is nevertheless possible that differences in the hormonal profile influenced our results. Concentration of sex hormones varies substantially over the course of the menstrual cycle (Ecochard and Gougeon, 2000). This in turn influences stress reactivity and its effect on cognitive performance (Shields, 2020; Merz and Wolf, 2017). Our study does not have sufficient power to adequately investigate sex specific effects. Future studies with larger sample sizes are needed to further investigate the relationship between sex specific hormone levels and stress reactivity after glucose consumption. Optimally, these studies would assess levels of sex steroids, like progesterone and testosterone. Third, because our design does not entail control groups consuming plain water, it is not possible to rule out the possibility that the sweet taste of the stevia-sweetened water did influence cortisol levels. It had been suggested by previous work that the psychological experience of tasting sweet food affects stress reactivity irrespective of caloric load (Meier et al., 2021). This effect, however, had only been shown in women and is not supported by other studies (see van Dawans et al., 2021; Zänkert et al., 2020). As we did not check whether participants were able to tell which of the two drinks they consumed, it is possible that some participants could tell whether they received the glucose or placebo drink. This might have influenced our participants´ behavior.

5. Conclusion

Taken together, our results suggest that the stress induced by the SECPT might not suffice to detect a boost in HPA-axis reactivity after glucose consumption. Since the SECPT combines elements of a psychosocial and physiological stressor, we suspect the intensity of the stressor is one factor underlying these results rather than the presence or absence of a psychosocial stress component. Also, a blunted stress response seems necessary for a restorative process to occur. Since glucose administration did not moderate the effects of acute stress on cognitive performance, the nutritional state of participants taking part in studies investigating the effects of acute stress on memory may not be of primary importance. When studying the effects of blood glucose on memory, longer, more sensitive memory tasks might have to be utilized. Considering that the sex of the participants influenced stress reactivity, future studies should characterize sex specific effects. The influence of different periods of the menstrual cycle and usage of oral contraceptives might also be further investigated. Furthermore, the underlying mechanism of glucose metabolism and its effects on stress reactivity as well as the role of insulin should be an area of further research.

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Conflict of interest

All authors declare no conflict of interest.

Disclosure of sample, conditions, measures, and exclusions

We report how we determined our sample size, all data exclusion (if any), all manipulations, and all measures in the study.

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