Differentially interacting effects between lifetime and acute stress on striatal prediction error signals and their relation to symptoms in patients with schizophrenia

Teresa Katthagen[1], Jacob Nudelman[2], Olivia Hutchinson[2], Florian Schlagenhauf[1], James Waltz[2]

[1]Charité-Universitätsmedizin Berlin, [2]University of Maryland School of Medicine

ABSTRACT

Both the emergence of psychotic illness (at first break) and the exacerbation of symptoms in chronic psychotic illness are commonly associated with stressful life events. Adverse childhood events (ACEs) have been linked to an increased risk of conversion to psychotic illness in those at clinical high-risk and has been shown to compound the effects of acute stressors on psychotic symptom severity. There is also evidence that acute stress can exacerbate the negative symptoms of psychotic illness, such as anhedonia and avolition. Our goal was to investigate how neural circuits for stress reactivity, reward processing, and salience signaling interact in mediating the effects of cumulative and acute stress on both the positive and negative symptoms of psychotic illness. We hypothesized that ACEs impact salience attribution and motivation by altering neural mechanisms of learning.

Participants consisted of a sample of individuals between 18 and 64 years old (inclusive) with diagnosed schizophrenia or schizoaffective disorder (collectively termed SZ; N = 58; mean age = 39.3; 70.7% male) and a healthy volunteer (HV) group comprised of individuals with no diagnosed psychiatric condition (N = 37; mean age = 42.2; 56.8% male). Participants performed a 3-choice reversal learning task twice, once after being administered an acute stressor (the Socially-evaluated Cold Pressor Task/SECPT), and once after not being stressed. The SECPT involved the participant submerging his/her left hand up to the wrist in water just above freezing (1º-4º C) until the pain became unbearable (up to for 3 minutes), while being filmed by an unsympathetic confederate. In the reversal learning task, choices were rewarded probabilistically, with a choice of the optimal deck (i.e., the one with the highest expected value) leading to a 100-point gain on 90% of trials (and a loss of 50 points on 10% of trials). Choices of two non-optimal decks led to 100-point gains on 50% and 10% of trials (and losses of 50 points on 50% and 90% of trials), respectively. Participants were instructed to try to identify the optimal deck as quickly as possible; they were also informed that, occasionally, a new deck would become the optimal one. Participants achieved as many stages as possible in 240 total trials (4 runs of 60 trials). To quantify task performance, we concatenated all trials within subjects and modeled choices with a Hierarchical Gaussian Filter (HGF) with decision noise. Via Bayesian Model Comparison, we tested whether computational parameters remained stable or changed across conditions (stress vs. control). To assess ACEs in participants, we used the 28-item Childhood Trauma Questionnaire (CTQ), which quantifies 3 kinds of abuse and 2 kinds of neglect. To assess anhedonia and avolition in SZ patients, we used the Clinical Assessment Interview for Negative Symptoms (CAINS). We examined brain responses to precision-weighted prediction errors (PEs) at the second level of the learning hierarchy in a priori volumes of interest (VOIs) in the anatomically defined bilateral ventral striatum (VS).

As revealed by model comparison, we observed no effect of the acute stress condition on any model parameter (protected exceedance probability for model with stable parameters = 1). This was mirrored in the brain findings, which showed only weak main effects for acute stress on the precision weighted PE signal across all subjects [left PCC (-8, -34, 36): F=15.6, p<0.001 uncorrected, right putamen (24, 8, -6): F= 12.5, p<0.001]. Across conditions and subjects, precision weighted PEs were accompanied by BOLD response within the salience network (ACC/vmPFC, striatum, and insula) at pFWE for the whole brain<0.05. Overall, we observed a between-group difference (HV > PSZ) in responses to PEs in right [(6, 8, -8), F=12.48, p=0.015] and left [(-10, 10, -12), F=5.53, p=0.02] VS (small volume corrected). There were no significant interactions between Group and Stress condition within the clusters of the main effect for PEs. However, we observed interacting effects of group, acute stress condition, and the severity of childhood trauma on VS PE signals [for Condition*Group*CTQ total score interaction: β(SE)=-0.3 (0.11), t=-2.63, p=0.01; for Condition*Group*CTQ emotional neglect interaction: β(SE)=-0.75 (0.25), t= 3, p=0.003]. In controls, CTQ Total Scores predicted VS PE responses in the stress condition [β(SE)=-0.21 (0.09), t=-2.44, p=0.02]. In people with SZ, CTQ Emotional Neglect scores predicted VS PE responses in the non-stress condition [β(SE)=-0.24(0.08), t=-2.85, p=0.008]. Additionally, Motivation and Pleasure (MAP) scores from the CAINS interacted with CTQ Emotional Neglect scores in predicting attenuated VS PE responses in the non-stress condition, in SZ patients [β(SE)=-0.009(0.003), t= 2.69, p=0.01].

These results replicate prior findings of attenuated reward prediction error signaling in people with schizophrenia, especially those with more severe motivational deficits. In addition, these findings demonstrate differential effects of ACEs on brain responses to reward PEs in people with schizophrenia and healthy volunteers. Further research is required to identify specific pathways from childhood trauma to schizophrenia symptoms, by way of brain mechanisms of learning and motivation.

REFERENCES

Teresa Katthagen: Nothing to declare.
Jacob Nudelman: Nothing to declare.
Olivia Hutchinson: Nothing to declare.
Florian Schlagenhauf: Nothing to declare.
James A. Waltz: Nothing to declare.

DISCLOSURES

Teresa Katthagen: Nothing to declare.
Jacob Nudelman: Nothing to declare.
Olivia Hutchinson: Nothing to declare.
Florian Schlagenhauf: Nothing to declare.
James A. Waltz: Nothing to declare.

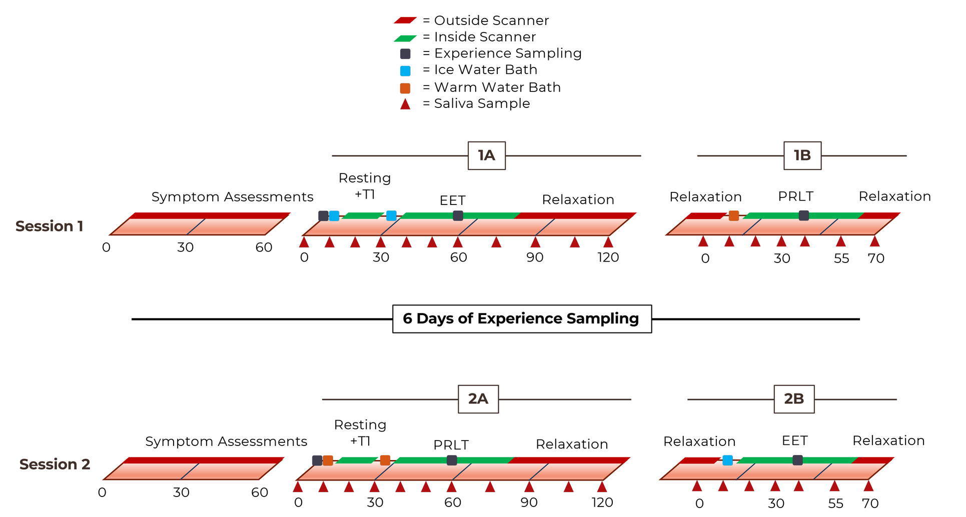
CONTACT

James A. Waltz, PhD
Maryland Psychiatric Research Center
P.O. Box 21247
Baltimore, MD 21228
jwaltz@som.umaryland.edu

INTRODUCTION

- Both the emergence of psychotic illness (at first break) and the exacerbation of symptoms in chronic psychotic illness are commonly associated with stressful life events.
- Adverse childhood events (ACEs) have been linked to an increased risk of conversion to psychotic illness in those at clinical high-risk and has been shown to compound the effects of acute stressors on psychotic symptom severity.
- There is also evidence that acute stress can exacerbate the negative symptoms of psychotic illness, such as anhedonia and avolition.
- Our goal was to investigate how neural circuits for stress reactivity, reward processing, and salience signaling interact in mediating the effects of cumulative and acute stress on both the positive and negative symptoms of psychotic illness.
- We hypothesized that ACEs impact salience attribution and motivation by altering neural mechanisms of learning.

GENERAL METHODS



- Participants performed a 3-choice reversal learning task twice, once after being administered an acute stressor (the Socially-evaluated Cold Pressor Task/SECPT), and once after not being stressed.
- The SECPT involved the participant submerging his/her left hand up to the wrist in water just above freezing (1º-4º C) until the pain became unbearable (up to for 3 minutes), while being filmed by an unsympathetic confederate.
- To quantify task performance, we concatenated all trials within subjects and modeled choices with a Hierarchical Gaussian Filter (HGF) with decision noise.
- Via Bayesian Model Comparison, we tested whether computational parameters remained stable or changed across conditions (stress vs. control).
- To assess ACEs in participants, we used the 28-item Childhood Trauma Questionnaire (CTQ), which quantifies 3 kinds of abuse and 2 kinds of neglect.
- To assess anhedonia and avolition in SZ patients, we used the Clinical Assessment Interview for Negative Symptoms (CAINS).
- We examined brain responses to precision-weighted prediction errors (PEs) at the second level of the learning hierarchy in a priori volumes of interest (VOIs) in the anatomically defined bilateral ventral striatum (VS).

ACUTE STRESS MANIPULATION

The Socially Evaluated Cold Pressor Test (SECPT)

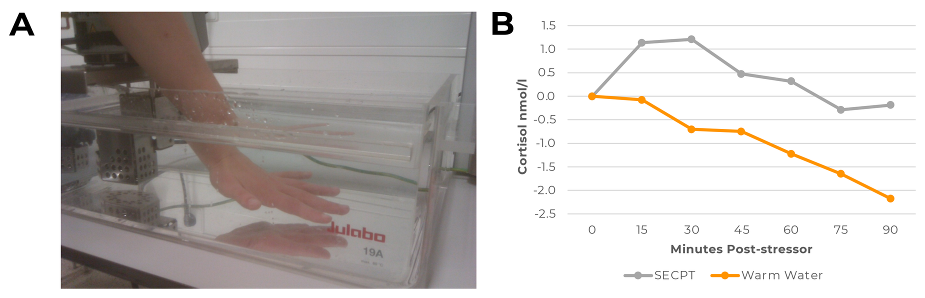


Figure 2. A. In the stress condition of the SECPT, participants submerged their non-dominant arm including the wrist joint, in a tub of ice water (0-4ºC) for up to three minutes, while being filmed by an unsympathetic confederate. They were told to not make a fist or place their hand on the bottom of the tub. The control condition used warm water. **B.** Performance of the SECPT was associated with clear elevations in salivary cortisol up to 45 minutes after administration of the stressor.

PARTICIPANTS

Table 1. Participant demographic information.

Domain/Measure	SZ	(N=58)	HV	(N=37)	Inferential Statistic	Significance
Demographics						
Age (Years)	39.28	(10.09)	42.30	(13.82)	$t_{93} = 1.148$	p = 0.255
Sex at Birth	18 F,	40 M	16 F,	21 M	$\chi^2 = 1.465$	p = 0.226
Race	28 W,	30 NW	25 W,	12 NW	$\chi^2 = 3.409$	p = 0.065
Ethnicity	1 Hispanic,	57 Non-Hisp.	7 Hispanic,	30 Non-Hisp.	$\chi^2 = 8.660$	p = 0.003
Tobacco User	14 Yes,	44 No	5 Yes,	32 No	$\chi^2 = 1.594$	p = 0.207
Education						
Subject Education	13.55	(2.09)	15.44	(2.02)	$t_{92} = 4.326$	p < 0.001
Mother's Education	14.86	(3.16)	14.46	(3.25)	$t_{84} = 0.578$	p = 0.565
Father's Education	15.08	(3.05)	14.63	(3.73)	$t_{83} = 0.613$	p = 0.542

Abbreviations.

BEHAVIORAL TASK

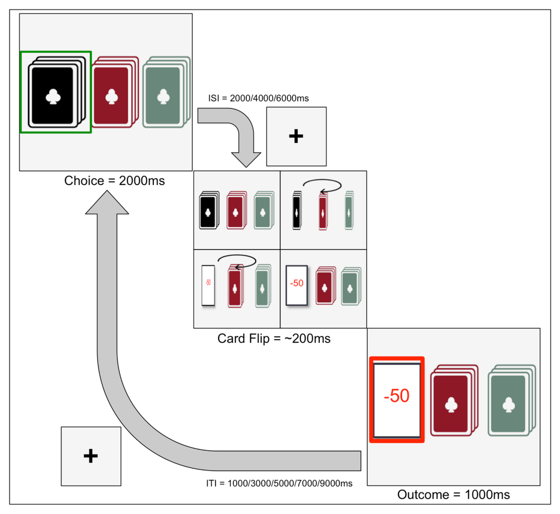


Figure 1. In the reversal learning task, choices were rewarded probabilistically, with a choice of the optimal deck (i.e., the one with the highest expected value) leading to a 100-point gain on 90% of trials (and a loss of 50 points on 10% of trials). Choices of two non-optimal decks led to 100-point gains on 50% and 10% of trials (and losses of 50 points on 50% and 90% of trials), respectively. Participants were instructed to try to identify the optimal deck as quickly as possible; they were also informed that, occasionally, a new deck would become the optimal one. Participants achieved as many stages as possible in 240 total trials (4 runs of 60 trials).

COMPUTATIONAL MODELING

The HGF is describes learning on various levels and approximates Bayesian updating via error-based learning rules. The most often used version contains three levels, whereas the first and second levels are transformations of each other in tasks as ours, where there is no visual ambiguity about cues and outcomes. Thus, in our task design, the second-level belief μ_2 describes the strength of the association between each of the cards and outcomes, being updated via prediction errors:

$$(1)\quad \Delta\mu_i^k \propto \frac{\hat{\pi}_{i-1}^{(k)}}{\pi_i^{(k)}}\,\delta_{i-1}^{(k)} \propto \varepsilon_i^k$$

The weight of the update (the equivalent to a dynamic learning rate) is determined by a precision ratio:

$$(2)\quad \frac{\hat{\pi}_1}{\pi_2^{(t)}} = \frac{\hat{\pi}_1}{\hat{\pi}_2^{(t)} + \hat{\pi}_1} = \frac{\hat{\pi}_1}{\frac{1}{\sigma_2^{(t-1)} + \exp\left(\kappa\mu_3^{(t-1)} + \omega_2\right)} + \hat{\pi}_1}$$

With the third-level belief μ_3 tracking the estimation of environmental volatility, a prediction error on the lower level is weighted more strongly when the volatility belief is currently high. For a more detailed explanation of the HGF, please see the original publications and our recent review (Mathys et al., 2011, 2014; Katthagen et al., 2022).

RESULTS

Analyses of Reinforcement Learning Behavior

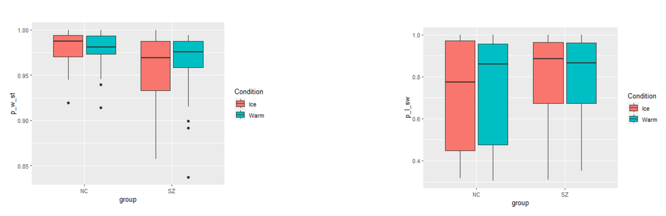


Figure X. For percent correct responses and achieved reversals, there were no significant main effects for Group and Condition, nor any interaction (p>0.11). PSZ showed less win-stay behavior (F(1,75)=7.3, p=0.008). Patients decreased win-stay strategy in the stress condition (Group x Condition interaction, F=6.6, p=0.012; within t-test control vs. stress in PSZ: t(47)=2.7, p=0.011), while NC did not differ between conditions (p=0.18). In contrast, NC showed higher lose-switch behavior in the control condition compared to stress, while there was no difference in patients (Group x Condition interaction, F=4.5, p= 0.038, within t-test control vs. stress in NC: t(28)=2.2, p=0.036).

Modeling Parameters

	Prior	Mean fitted parameter in PSZ	Mean fitted parameter in NC	Statistics
μ_0^2	0 (0)			
μ_0^3	1 (1)	1.0	1.0	t(57.5)=0.18, p=0.8
σ_0^2 (in log-space)	0.1 (0)			
σ_0^3 (in log-space)	1 (0)			
ϕ^2 (in logit-space)	0.4 (1)	0.39	0.43	t(56.8)=1.7, p=0.1
ϕ^3 (in logit-space)	0.05 (0)			
m^2	0 (0)			
m^3	1 (0)			
κ^2 (in log-space)	0.6 (1)	2.7	2.5	t(58.7)=0.56, p=0.58
ω^2	-2 (1)	-0.79	-0.98	t(57.4)=2.1, p=0.04
ω^3	-2 (1)	-2.11	-2.13	t(63.5)=0.24, p=0.8
β^{win} (in log-space)	1 (1)	23.0	23.6	t(62)=0.35, p=0.7
β^{loss} (in log-space)	1 (1)	0.6	0.46	t(70.3)=2.56, p=0.01

Notes. Priors and fitted parameters of the best fitting model (HGF with 2 inverse decision noise betas in softmax with same parameters across both conditions). Numbers in brackets in the prior column refer to variance, with 0 indicating fixed parameters and 1s indicating individual fitting for subjects. Hence, only these rows (variance = 1) have group parameters and statistics.

Effect of group on prediction error signal in brain

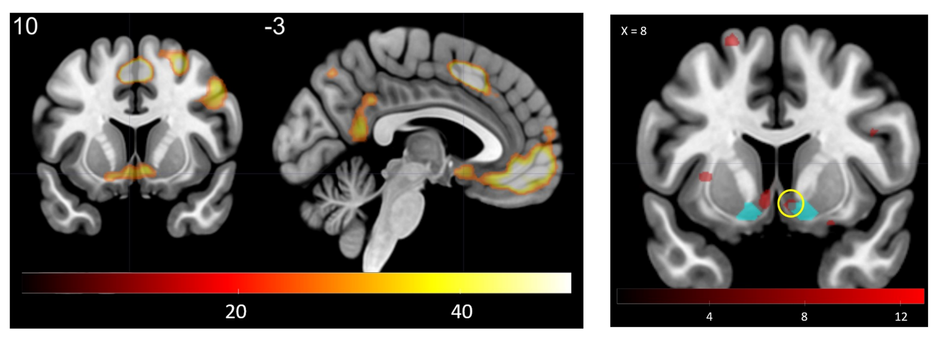


Figure 4. A. Regions activated by 2nd-level precision-weighted prediction error across stress conditions and groups (displayed at $p_{FWE}<0.05$). **B.** Between-group difference (HVs > PSZ) in 2nd-level precision-weighted PE signal, across conditions, in right VS [6, 8, -8; F=12.48, $p_{SVC\ for\ VS}=0.015$; displayed in red at F>10 and k>10; bilateral VS mask shown in cyan].

Effects of the acute stressor on VS PE signals

	Region	MNI Coordinates (X, Y, Z)	Cluster Size (voxels)	Statistic
Stress > NoStress for ε_2 (at $p_{uncorr.} < 0.001$)	Left middle temporal gyrus	-60, -52, 6	55	t=3.9
	Left middle occipital gyrus	-42, -72, 28	68	3.8
	Left posterior cingulate gyrus	-8, -34, 36	17	3.5
	Right middle occipital gyrus	40, -80, 36	12	3.5
	Left middle temporal gyrus	-50, -42, 2	16	3.5
	Left hippocampus	-26, -28, -4	1	3.2
NoStress > Stress for ε_2 (at $p_{uncorr.} < 0.001$)	Brainstem	-8, -12, -28	40	4.3
	Right cerebral white matter	18, -30, 4	19	3.9
	Left cerebral white matter	-30, -64, -6	30	3.7
	Right putamen	24, 18, 6	15	3.5
	Left middle cingulate gyrus	-10, 14, 44	5	3.5
	Right caudate	26, 2, 24	9	3.4
	Left lingual gyrus	0, -78, -4	12	3.4
	Left superior frontal gyrus	-16, 52, 14	1	3.2
	Right cerebral white matter	18, -70, 0	2	3.2
Stress x Group Interaction for ε_2 (at $p_{uncorr.} < 0.001$)	Left thalamus	-20, -8, 10	17	F=16.4
	Right anterior insula	28, 18, -16	10	15.5
	Right parietal operculum	38, -28, 28	15	15.3
	Left brainstem	-12, -10, -28	13	14.8
	Left anterior cingulate gyrus	-6, 20, -12	12	14.4
	Right precuneus	14, -54, 40	10	13.7
	Left thalamus	-24, -32, 16	18	13.5
	Right inferior frontal gyrus	58, 30, -6	6	13.3
	Right lateral orbital gyrus	50, 52, -12	2	12.9
	Right lateral orbital gyrus	40, 60, -8	12	12.4
	Right thalamus	20, -24, 2	1	11.9
	Right middle occipital gyrus	44, -86, 16	2	11.9
	Right angular gyrus	66, -48, 32	2	11.6

Abbreviations.

ACEs, VS PE signals, and Negative Symptoms

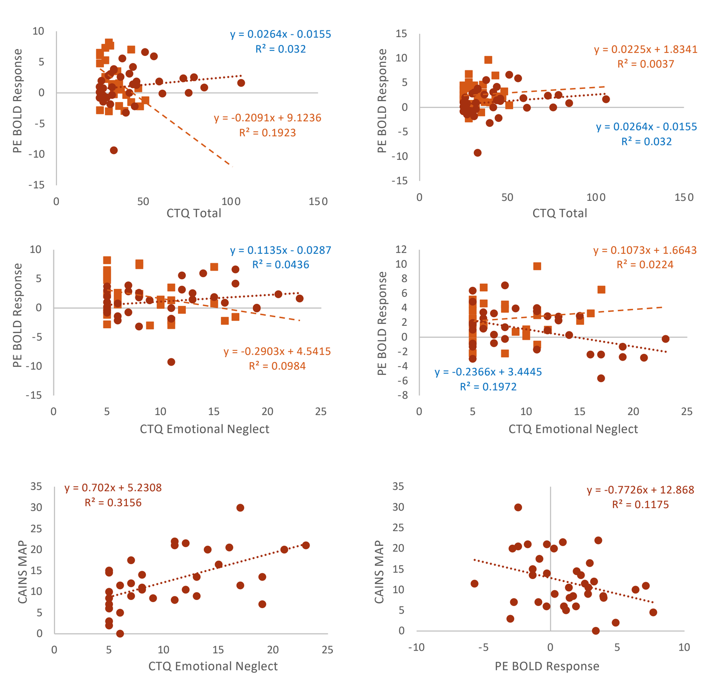


Figure 4.

DISCUSSION

- These results replicate prior findings of attenuated reward prediction error signaling in people with schizophrenia, especially those with more severe motivational deficits.
- In addition, these findings demonstrate differential effects of ACEs on brain responses to reward PEs in people with schizophrenia and healthy volunteers.
- Further research is required to identify specific pathways from childhood trauma to schizophrenia symptoms, by way of brain mechanisms of learning and motivation.