Neural Computations as Markers of Stress, Anxiety and Trauma

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter John Krystal

Affiliation Yale University School of Medicine

Affiliate Type Member

Gender Male

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

SUBMISSION DETAILS

Secondary Category Anxiety Disorders/PTSD

Research Area Integrative

Request for Proposals No

Presenter Affiliations No

Attestation and Affirmation John H. Krystal

Neuroscience Based Nomenclature

Overall Panel Abstract Computation, the fundamental function of the brain, enables adaptation to the environment by transforming the stream of multisensory information into a tractable problem. Resolving the rules and regularities of dynamic multifaceted environments enables forecasting and preparation for future scenarios. Psychiatric illness may thus cause or result from distorted computations. Computational psychiatry is a young and burgeoning field attempting to theorize parameters and algorithms that produce good enough solutions, explain how they go awry, and unveil neurocomputational networks that may underlie psychiatric illness. This symposium will describe the utilization of computational modeling within the realm of stress, anxiety and post-traumatic stress disorders.
Candace Raio (NYU) will describe how stress modulates learning and decision making under uncertainty. Using associative threat learning protocols, she will show that stress biases predictions toward more dire consequences, and slows value updating by disrupting the adjustment of learning rates. Ifat Levy (Yale University) will then directly examine decision making in combat soldiers, who face high levels of uncertainty in the battlefield. The talk will demonstrate how the use of paradigms inspired by behavioral economics allows identifying variations in decision making under

uncertainty and devising objective diagnostic tools for trauma-related psychopathology. Daniela Schiller (Mt. Sinai) will further show that a specific learning parameter, the value of threat-predictive cues, is tracked by the amygdala; and the structure of function of this brain region is predictive of PTSD symptoms. Finally, Rony Paz (Weizmann Institute) will describe two models for anxiety - over-generalization and exploration - revealing computations linked to anxiety levels. Together, these talks will provide a compelling demonstration of the utility of computational models in delineating specific computations and their underlying neural substrates, which may lie at the heart of psychiatric illness. We will discuss the use of behavioral and neural proxies of such computations as transdiagnostic markers, and the path forward for computational psychiatry.
The panel is gender-balanced, representing various seniority levels and geographic locations.

Unique Data Unique data will be presented in each of the four talks as follows:
In the first talk, unique data will show that higher stress reactivity is associated with a bias toward negative evaluation of emotionally ambiguous stimuli; and more severe exposure to stress, particularly early in life, is selectively related to economic preferences to avoid ambiguous but not risky decisions. The second talk will include unique data using a behavioral economics fMRI task and a dimensional approach to PTSD symptoms. The results will show that trauma-related symptoms are predicted both by economic behavior and by activation in vmPFC. The third talk will present unpublished data using threat discrimination and reversal task with fMRI, showing that amygdala function (value computation) and morphology both predict PTSD symptom severity. The last talk will include unpublished data showing that people have a higher tendency for exploration in a decision-making task that is correlated with their anxiety baseline levels, and that changes as a function of the outcome valence. The underlying brain networks will also be described.

Keywords

Keywords
Computational Neuroscience
computational psychiatry
mood and anxiety disorders
Combat PTSD

Participant Diversity Yes

Previously Published Material I attest that the information submitted has not been previously published.

DISCLOSURE

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Neural Computations as Markers of Stress, Anxiety and Trauma

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter Daniela Schiller

Affiliation Icahn School of Medicine at Mount Sinai

Affiliate Type Member

Gender Female

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

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Neural Computations as Markers of Stress, Anxiety and Trauma

Stress Modulates Learning and Decision-Making Under Uncertainty

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter Candace Raio

Affiliation New York University

Affiliate Type Non Member

Gender Female

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

SUBMISSION DETAILS

Affirmation and Attestation I agree and affirm.

ACNP Role Limit Policy Candace M. Raio

Neuroscience Based Nomenclature

Background Stress is pervasive in daily life and can promote maladaptive behavioral responses, particularly under conditions of uncertainty. Yet we still know surprisingly little about how stress shapes learning and decision-making under uncertainty. Identifying how stress alters the computations that give rise to these processes is critical to gaining a more mechanistic understanding of how they may be altered both in healthy individuals as well as those with stress or trauma-related disorders.

Methods Across two studies, we used an aversive-learning paradigm to test how stress affects the evaluation (Study 1: n=52) and flexible updating (Study 2: n=75) of aversive value under uncertainty. In both studies, healthy participants first underwent an aversive learning task in which visual stimuli were probabilistically associated with an aversive (electric shock) or safe (no shock) outcome while physiological arousal (skin conductance) was measured continuously. The acquisition phase was either followed by extinction training—in which reinforcement was omitted—and an extinction test a day later (Study 1), or reversal learning a day later where stimulus-outcome contingencies unexpectedly switched (Study 2). Directly before the extinction test or reversal, participants completed a physiological stressor or matched control task; salivary cortisol and perceived stress were measured to verify stress responses.

In a third study (n=58), we extended our investigation to a decision-making context, where we explicitly quantified how stress exposure relates to individuals' tolerance for uncertainty. Healthy participants completed a well-validated experimental economic paradigm where they chose between a certain and uncertain monetary options. Choice behavior was fit with computational models to estimate uncertainty attitudes. Given that uncertainty preferences are thought to develop over time, we measured cumulative stress exposure using the Stress and Adversity Inventory for Adults (STRAIN), which quantifies a broad range of stressors that may have occurred over an individual's lifetime, and examined how this index related to individuals' estimated choice parameters.

Results In Study 1, stress led to significantly higher threat arousal during the extinction test relative to controls ($t(50) = -2.34$, $p = .02$), suggesting that stress biases individuals to predict aversive outcomes when the associated value of a cue is uncertain. In Study 2, stress exposure led to marked deficits in reversal learning. Fitting arousal data to a computational reinforcement-learning model revealed that the reversal-learning deficits in the stress condition emerged from reductions in the weight (ρ) assigned to prediction error signals (ρ: $t(73) = -2.46$; $p = 0.01$), slowing the adjustment of learning rates. Finally, in Study 3, we found a significant association between lifetime stress and ambiguity tolerance ($r = -0.33$, $p = 0.01$; Spearman's rho), such that individuals with the highest exposure to lifetime stress were the most averse to ambiguity.

Conclusions These results point to stress as playing a causal role in altering selective computations involved in learning and decision-making processes in healthy adults by promoting negative predictions of ambiguous cues, disrupting the ability to track changes in aversive reinforcement and shaping uncertainty preferences. These findings have implications for understanding maladaptive behavior and affective dysregulation in healthy populations as well as clinical disorders marked by affective psychopathology.

Unique Data Study 1 & 2: Published (Neurobio of Stress & PNAS)
Study 3: Unpublished

Keywords

Keywords
stress
uncertainty
anxiety

Research Type Human Subjects Research

Other Research Type The submitted abstract or portions of the work has been published, however, I would still like the opportunity to present at the 2018 ACNP Annual Meeting.

Previously Published Material <blank>

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Neural Computations as Markers of Stress, Anxiety and Trauma

Decision Making Under Uncertainty in Post-Trauma Psychopathology

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter Ifat Levy

Affiliation Yale University

Affiliate Type Non Member

Gender Female

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

SUBMISSION DETAILS

Affirmation and Attestation I agree and affirm.

ACNP Role Limit Policy Ifat Levy

Neuroscience Based Nomenclature

Background Traumatic events are often associated with high levels of uncertainty, yet the role of individual uncertainty attitudes in the development of trauma-related psychopathology has hardly been examined. We have recently used a paradigm inspired by behavioral economics, and identified variations in decision making under uncertainty that were associated with posttraumatic stress disorder (PTSD; Ruderman et al., 2016). Here, we use the same task to explore neural markers of trauma-related symptoms.

Methods We used a monetary task to assess uncertainty attitudes of 78 male combat veterans. Subjects chose between a certain gain (or loss), and playing a lottery which offered a larger gain (or loss) but also chance of zero outcome. Outcome probabilities for half of the lotteries were precisely known (“risk”), and were ambiguous for the other half (“ambiguity”). Functional MRI was used to track neural activation while subjects completed 240 decisions. One choice was randomly picked for payment. The choice behavior of each subject was used to fit a computational model, which provided estimates of individual risk and ambiguity attitudes in the gain and loss domains. We evaluated PTSD symptoms with the Clinician-Administered PTSD Scale (CAPS), and used additional measures to assess trauma exposure and other psychiatric symptoms, including depression, anxiety and addiction.

Results Using a dimensional approach, we replicated our recent behavioral results, and found that veterans suffering from more severe trauma-related symptoms (higher CAPS) were more averse to ambiguous losses (Pearson's correlation r=0.25, p<0.05), but not to ambiguous gains. In addition, this approach revealed increased risk aversion in veterans with higher CAPS scores, when these veterans were making choices between gains (r=0.3, p<0.05), but not between losses. A whole-brain analysis highlighted the ventromedial prefrontal cortex (vmPFC), an area involved in both value-based decision making and fear learning. General activation in this area during the decision phase was negatively correlated with CAPS (p<0.05). Interestingly, when controlling for correlations between symptom clusters, emotional numbing remained the only significant cluster. Severity of this symptom cluster predicted activation when making choices between gains, but not losses (p<0.05), emphasizing the significance of studying reward, in addition to punishment, processing in post-trauma psychopathology.

Conclusions Our results demonstrate the potential of neuroeconomics techniques for studying the neural basis of psychopathology in a transdiagnostic manner, and for devising objective diagnostic tools that compensate the categorical diagnoses of the DSM.

Unique Data All of the results are new and unpublished.

Keywords

Keywords
Posttraumatic stress disorder
uncertainty
Functional MRI (fMRI)
combat veteran
computational models of decision-making

Research Type Human Subjects Research

Other Research Type I attest that the information submitted has not been previously published.

Previously Published Material <blank>

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Neural Computations as Markers of Stress, Anxiety and Trauma

Neural Computations of Threat Value after Combat Trauma

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter Daniela Schiller

Affiliation Icahn School of Medicine at Mount Sinai

Affiliate Type Member

Gender Female

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

SUBMISSION DETAILS

Affirmation and Attestation I agree and affirm.

ACNP Role Limit Policy DS

Neuroscience Based Nomenclature

Background Although abnormal threat conditioning features prominently in theoretical accounts of post-traumatic stress disorder (PTSD), the manner in which learning becomes dysfunctional is less clear. Moreover, it is possible that PTSD abnormalities are not observable in overt behavior but rather reside in latent parameters of learning, such as learning rate and expected value, which could only be estimated from observable behavior. Another key issue in the field is the specific role that the amygdala plays in PTSD: we do not know what is the relationship between amygdala structure and function in relation to PTSD symptoms, and we do not know what exactly is computed in the amygdala in response to negative stimulation. To address these issues here, we used the Rescorla-Wagner (RW) learning model to estimate learning rate and expected value in a threat conditioning and reversal paradigm, in a population of 54 combat veterans with varying degrees of psychopathology.

Methods The experiment began with an acquisition stage, in which participants were presented with two visual stimuli, one of which co-terminated with an aversive outcome on some of the trials, and the other was never paired with the shock. The acquisition phase was immediately followed by an unsignaled reversal stage, in which the contingencies were flipped. Skin conductance response (SCR) served as the index of conditioned defensive responses. To estimate the learning rate, the free parameter in the RW model, we fitted a Hierarchical Bayesian RW model to the recorded SCR data. Using the RW model and the estimated learning rate, we created parametric predictors comprised of the expected value in each trial for each participant. We then used these parametric predictors to examine the degree of value tracking in the amygdala, and to what extent amygdala value-dependent activity corresponds to PTSD symptoms (CAPS).

Results We found a structure-function relationship with CAPS in the right amygdala, where both volume ($\beta = -0.50$, $t(46) = -2.73$, $P = 0.009$) and neural activity ($\beta = -0.33$, $t(46) = -2.52$, $P = 0.015$) independently predicted the total CAPS score. No other factors, including learning rate, showed a significant relationship with PTSD symptoms.

Conclusions This study provides evidence for independent structural and neurocomputational contributions of the amygdala to combat-related PTSD symptoms. Higher levels of PTSD symptoms in combat veterans related to lower fidelity of value representation in the amygdala during threat learning, and smaller amygdala volume. Thus, the combined power of computational, morphological, and functional analytic tools enable us to relate latent markers of learning and morphological indices to overt symptoms, as specific targets for investigating trauma related psychopathology and its potential treatment.

Unique Data All data are unique and unpublished.

Keywords

Keywords
Combat PTSD
computational modeling
Threat Conditioning

Research Type Human Subjects Research

Other Research Type I attest that the information submitted has not been previously published.

Previously Published Material <blank>

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Neural Computations as Markers of Stress, Anxiety and Trauma

Neurocomputational Correlates of Exploratory Decision in Anxiety

Submission ID 3010319

Submission Type Panel

Topic Other

Status Submitted

Submitter Rony Paz

Affiliation Weizmann Institue of Science

Affiliate Type Non Member

Gender Male

Participant(s) John Krystal (Chair), Daniela Schiller (Co-Chair), Candace Raio (Presenter), Ifat Levy (Presenter), Daniela Schiller (Presenter), Rony Paz (Presenter)

SUBMISSION DETAILS

Affirmation and Attestation I agree and affirm.

ACNP Role Limit Policy ronypaz

<u>Neuroscience Based Nomenclature</u>

Background An appropriate balance between exploiting what is known and exploring what is largely unknown is relevant for everyday-life decision making. The extent of exploration biases may be governed by how an individual processes uncertainty. Yet, how these biases relate to anxiety trait is not completely known. Moreover, the effects of gain vs. loss on uncertainty processing was not examined. It is therefore unclear if anxious individuals would confront short-term uncertainty and perform exploratory decision in order to reduce uncertainty in the environment, and how it differs across loss or gain contexts.

Methods Subjects (n=28) participated in a three-armed bandit task. Exploration was promoted by varying the outcome in each machine across trials. Each participant performed both a Gain condition, where all outcomes were positive and a loss condition where all outcomes were negative and participants had to avoid.
Sine-wave functions described the outcomes associated with each slot machine. The magnitude and mean of each sine-wave was always 20 and 50 points respectively. The period lengths of the three sine-waves were different in each session, and the sine-waves were phase-shifted.
Individual trait anxiety scores were estimated via Spielberger's State-Trait Anxiety Inventory (STAI).

The tasks were performed while subjects underwent model-based fMRI scans. We used computational modeling to determine whether a decision was exploratory or exploitation. A second model examined the contribution of the expected value, outcome uncertainty, change uncertainty (time-dependent), and random switching. Models were fitted to each individual.

Results Participants were more likely to explore when trying to avoid losses as compared to acquiring gains, yet more anxious individuals showed increased exploration independent of the Gain/Loss condition (repeated measures ANOVA). The computational modelling (see methods) revealed that anxious individuals show i) a reduced motivation to exploit the best option, and ii) increased intolerance to uncertainty in the decision making environment. Both of these tendencies contribute and increase the proportion of exploratory decisions.
The same model was used to examine neural activations, with separate repeated measures ANOVAs conducted for each of ROIs derived from exploration-exploitation contrasts, with within-subject factor Condition (Gain, Loss) and Trait anxiety as continuous covariate, to identify how decision-related BOLD signal is modulated by differences in expected outcome and change uncertainty (the main factors revealed by behavior). The main findings were:
1. Neural activations for difference in expected outcomes was significantly and positively correlated with Trait anxiety in the dACC.
2. Neural activations for change-uncertainty were significant and negatively correlated with Trait anxiety bilaterally in the anterior-insula.

Conclusions Individuals with higher levels of trait anxiety showed increased exploration in both Gain and Loss conditions, associated with two distinct mechanisms. First, decisions made by more anxious individuals were less influenced by expected outcomes and associated with a less efficient recruitment of the dACC. Second, trait anxiety increased the motivation to reduce change uncertainty, associated with a more rapid engagement of the anterior-insula as uncertainty increased. Thus, high levels of trait anxiety boosted exploration via a combination of a reduced focus on value-based decision making and an increased intolerance of uncertainty in the environment.

Unique Data all data are unpublished and new

Keywords

Keywords
anxiety state
uncertainty
exploration
decision-making
dACC

Research Type Human Subjects Research

Other Research Type I attest that the information submitted has not been previously published.

Previously Published Material <blank>

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