Antecedents and Clinical Implications of Blunted Neural Response to Social and Monetary Rewards

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Abstract

Depression is a leading cause of death and disability on a global scale. Despite its prevalence, much remains to be understood in terms of the etiology and biological underpinnings of depression. Accordingly, we are still unable to prospectively predict with sufficient accuracy who will develop depression, making it difficult to intervene before the disorder's onset. In part, this is because depression is a highly heterogeneous syndrome, and may have multiple causes across individuals. Focusing on specific, quantifiable, neurobiological endophenotypes as proximal indicators of risk may advance our understanding of who is most likely to become depressed.

One promising endophenotype for depression is impaired reward response. Blunted neural responses to reward have been found to precede the onset of depression in some samples and may relate specifically to anhedonia, the loss of interest or pleasure in previously enjoyed activities. The present thesis aimed to advance our understanding of how other known risk factors for depression, including stress and family history of depression, might predict blunted neural response to social or monetary reward. A second objective was to investigate whether neural responses to social or monetary incentives might be more relevant to predicting depression risk under conditions of stress. Throughout this thesis, neural reward responses were measured using the Reward Positivity (RewP), an event-related potential sensitive to rewarding feedback.

In Study 1, we found, using a quasi-experimental design, that exposure to the stress of the COVID-19 pandemic led to a striking reduction in neural response to monetary reward. Further, we did not observe a significant change in the RewP in our demographically similar pre-pandemic control group. This suggested that experiencing the prolonged, real-world stress of the

pandemic induced potentially maladaptive changes in reward response that could not be attributed to the mere passage of time.

Study 2 investigated whether other known risk factors for depression, personal or maternal depression history and chronic interpersonal stress, were independently associated with a blunted RewP to social reward in a mother-daughter sample. We found a numerically smaller social RewP in adult women with a past history of depression and a significantly blunted social RewP in their never-depressed adolescent daughters. We also found that recent chronic interpersonal stress was associated with a smaller social RewP in the mother sample but not in the daughter sample. This study strengthens the evidence that neural response to social reward is a potentially useful risk marker for depression and highlights the fact that associations between risk factors for depression can vary across groups.

While the first two studies examined predictors of blunted neural reward response, Study 3 examined blunted reward response as a predictor of depressive symptoms. We tested whether baseline neural response to monetary or social reward was a better prospective predictor of depressive symptoms measured during a period of stress. We found that neural response to social but not monetary incentives predicted increased depressive symptoms during the first six months of the COVID-19 pandemic. These findings suggest that social reward response may be a better indicator of depression risk, especially during times of stress.

The quasi-experimental, case-control, and longitudinal designs of these three studies elucidate temporal associations between different risk factors for depression, improving our model of who is most at risk. Although most of the existing literature has explored how response to monetary reward is related to depression, these studies highlight the potentially greater

relevance of social reward response. Together, these findings may improve our ability to guide depression prevention interventions, reducing the overall burden of this difficult disorder.

Résumé

La dépression est l'une des principales causes de décès et d'handicap à l'échelle mondiale. Malgré sa prévalence, il reste encore beaucoup à comprendre en termes d'étiologie et de fondements biologiques de la dépression. Par conséquent, nous ne sommes toujours pas en mesure de prédire prospectivement avec suffisamment de précision qui développera une dépression, ce qui rend difficile toute intervention avant l'apparition du trouble. Cela s'explique en partie par le fait que la dépression est un syndrome très hétérogène, dont les causes peuvent être multiples d'un individu à l'autre. En se concentrant sur des endophénotypes neurobiologiques spécifiques et quantifiables en tant qu'indicateurs proximaux de risque pour la dépression, nous pourrons mieux comprendre qui est plus susceptible de devenir dépressif.

Un endophénotype prometteur pour la dépression est l'altération de la réponse à la récompense. Il a été constaté que l'affaiblissement des réponses neuronales à la récompense précède l'apparition de la dépression dans certains échantillons et peut être lié spécifiquement à l'anhédonie, la perte d'intérêt ou de plaisir dans des activités précédemment appréciées. La présente thèse visait à mieux comprendre comment d'autres facteurs de risque connus pour la dépression, notamment le stress et les antécédents familiaux de dépression, pourraient prédire une réponse neuronale émoussée à la récompense sociale ou monétaire. Un deuxième objectif était d'étudier si les réponses neuronales aux récompenses sociales ou monétaires pouvaient être plus pertinentes pour prédire le risque de dépression dans des conditions de stress. Tout au long de cette thèse, les réponses neuronales à la récompense ont été mesurées à l'aide du Reward Positivity (RewP), un potentiel évoqué (ERP ou PE) sensible aux récompenses. Dans la première étude, nous avons constaté, à l'aide d'un modèle quasi-expérimental, que l'exposition au stress de la pandémie de COVID-19 entraînait une réduction frappante de la réponse neuronale à la

récompense monétaire. En outre, nous n'avons pas observé de changement significatif dans le RewP dans notre groupe de contrôle démographiquement similaire avant la pandémie. Cela suggère que l'expérience du stress prolongé et réel de la pandémie a induit des changements potentiellement néfastes dans la réponse à la récompense qui ne peuvent pas être attribués au simple passage du temps.

La deuxième étude visait à déterminer si d'autres facteurs de risque connus pour la dépression, les antécédents de dépression personnelle ou maternelle et le stress interpersonnel chronique, étaient associés de manière indépendante à un affaiblissement de la réponse à la récompense sociale dans un échantillon mère-fille. Nous avons observé un RewP social numériquement plus faible chez les femmes adultes ayant des antécédents de dépression et un RewP social significativement émoussé chez leurs filles adolescentes n'ayant jamais souffert de dépression. Nous avons également constaté que le stress interpersonnel chronique récent était associé à un RewP social plus petit dans l'échantillon de mères, mais pas dans celui de leur filles. Cette étude renforce les preuves que la réponse neuronale à la récompense sociale est un marqueur de risque potentiellement utile pour la dépression et souligne le fait que les associations entre les facteurs de risque pour dépression peuvent varier d'un groupe à l'autre.

Alors que les deux premières études ont examiné les prédicteurs de la réponse neuronale émoussée à la récompense, la troisième étude a examiné la réponse émoussée à la récompense en tant que prédicteur des symptômes dépressifs. Nous avons testé si la réponse neuronale de base à une récompense monétaire ou sociale était un meilleur prédicteur prospectif des symptômes dépressifs mesurés pendant une période de stress. Nous avons constaté que la réponse neuronale aux récompenses sociales, mais pas aux récompenses monétaires, permettait de prédire l'augmentation des symptômes dépressifs au cours des six premiers mois de la pandémie de

COVID-19. Ces résultats suggèrent que la réponse à la récompense sociale pourrait être un meilleur indicateur du risque de dépression, en particulier en période de stress.

Les modèles quasi-expérimentaux, cas-témoins et longitudinaux de ces trois études élucident les associations temporelles entre différents facteurs de risque pour la dépression, améliorant ainsi notre modèle de détermination des personnes les plus à risque. Bien que la plupart des études existantes aient exploré la manière dont la réponse à une récompense monétaire est liée à la dépression, ces études soulignent la pertinence potentiellement plus grande de la réponse à une récompense sociale. Ensemble, ces résultats peuvent améliorer notre capacité à guider les interventions de prévention de la dépression, réduisant ainsi le fardeau global de ce trouble difficile.

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Contribution to Original Knowledge

The three empirical studies presented in this thesis constitute original work and provide novel contributions to the scientific literature on neural processing of reward. Study 1 used a quasi-experimental design to evaluate the impact of the COVID-19 pandemic, a naturally occurring large-scale stressor, on neural responses to monetary reward. Relatively few previous studies have tested the impact of chronic or prolonged real-world stress on neural reward processing in adulthood. Fewer still have done so using a more rigorous design that allows for both within-person (pre- and post-stress) and between-group (affected individuals vs. unaffected controls) comparisons. Therefore, to our knowledge, this study was the first to show, using a quasi-experimental design, that experiencing a major prolonged stressor leads to significant reductions in the Reward Positivity, our index of neural reward responses, in an adult sample. This change was not seen in a demographically similar control group, strengthening our conclusion that the COVID-19 pandemic was directly related to this reduction in neural reward responses. Study 1 also provides novel contributions to the literature by demonstrating how the COVID-19 pandemic specifically impacted brain function.

Study 2 evaluated how three important risk factors for depression, a personal depression history, a maternal depression history, and interpersonal stress, were associated with neural responses to social reward in a mother-daughter sample. This was the first paper to show, using event-related potentials, that a maternal history of depression was associated with a relatively blunted neural response to social reward in adolescent girls. While a small number of existing studies has shown that a parental history of depression is linked to smaller neural responses to monetary reward, only one previous study had found this with social reward. This previous study used different methodology to measure neural reward response and had a much smaller sample.

Importantly, not only did the present study evaluate how a maternal history of depression or a personal history of depression was associated with neural response to social reward, but it also included interpersonal stress as a simultaneous predictor. This had the unique advantage of assessing whether clinical or family history risk variables and interpersonal stress had independent effects on reward function. Another novel aspect of Study 2 was that we measured neural responses in daughters at risk for first-onset depression and in their mothers at risk for recurrence in the same study. This allowed us to conduct supplemental analyses assessing the degree of correlation between mother and daughter social reward response.

Study 3 also provided valuable and original contributions to the literature on reduced reward processing as a risk factor for depression. This study was the first, to our knowledge, to directly compare event-related potential markers of monetary and social reward response as prospective predictors of depressive symptoms measured during a time of stress in the same sample. Though previous studies had speculated that responses to social rewards might be more relevant to depression risk than responses to monetary rewards, this study showed that neural responses to social rewards significantly predicted future depressive symptoms, but monetary rewards did not. Another novel advantage of this study was the method of statistical analysis. Rather than measure depressive symptoms only once during the COVID-19 pandemic, we measured depressive symptoms at eight different timepoints from March 2020 to August 2020. This enhanced the reliability of our depressive symptom measurement and increased the generalizability of our findings to a longer period of time. This design also allowed us to dissociate vulnerability to chronic stress from vulnerability to acute stress at each timepoint. Overall, these three studies deliver important advances in our understanding of how impaired

processing of monetary and social rewards relates to depression risk. This may improve our ability to target early interventions for the disorder.

Contribution of Authors

The present thesis contains three original manuscripts from my (CF) doctoral research, supervised by Dr. Anna Weinberg (AW). Citations for these manuscripts and a description of each co-author's contribution are listed below.

Study 1

Freeman, C., Carpentier, L., & Weinberg, A. (2023). Effects of the COVID-19 pandemic on neural responses to reward: A Quasi-experiment. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.

AW conceptualized the design for the parent study from which a part of these data were drawn. CF conceived and designed the analysis for the present study. CF and LC collected data. CF performed the data analysis. CF wrote the manuscript with help from LC and AW edited it. All authors provided revisions and approved the final version of the manuscript for submission.

Study 2

Freeman, C., Ethridge, P., Banica, I., Sandre, A., Dirks, M. A., Kujawa, A., & Weinberg, A. (2022). Neural response to rewarding social feedback in never-depressed adolescent girls and their mothers with remitted depression: Associations with multiple risk indices. *Journal of Psychopathology and Clinical Science*, *131*(2), 141.

AW and CF developed the study concept and contributed to the study design. Testing and data collection were performed by PE, AS, IB and CF. AW and MAD supervised clinical interviews. AK designed the original version of the social reward task. CF performed the data analysis and interpretation under the supervision of AW. CF drafted the paper, and all authors provided critical revisions. All authors approved the final version of the paper for submission.

Study 3

Freeman, C., Panier, L., Schaffer, J., & Weinberg, A. (2022). Neural response to social but not monetary reward predicts increases in depressive symptoms during the COVID-19 pandemic. *Psychophysiology*, e14206.

AW conceptualized the design for the parent study from which a part of these data were drawn. CF conceived and designed the analysis for the present study under the supervision of AW. CF collected data. CF performed the data analysis. JS assisted with literature review. CF wrote the manuscript. LP and JS made figures and tables. AW edited the manuscript. All authors provided revisions and approved the final version of the manuscript for submission.

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List of Abbreviations

ACC……Anterior cingulate cortex
ANOVA…….Analysis of variance
BOLD…….Blood oxygenation level-dependent
CBT……Cognitive behavioral therapy
CSDS……..Chronic Social Defeat Stress
dB/oct……Decibels per octave
dmPFC……Dorsomedial prefrontal cortex
EEG……Electroencephalogram
EOG……Electrooculogram
ERP…….Event-related potential
fMRI……Functional magnetic resonance imaging
HR……..Relatively high risk for depression
Hz……Hertz
ICA…….Independent component analysis
IDAS-II……..Inventory of Depression and Anxiety Symptoms - II
LR……...Relatively low risk for depression
MDD……...Major depressive disorder
MDE……Major depressive episode
MFQ……...Mood and Feelings Questionnaire
µV……...Microvolts
MINI……...Mini International Neuropsychiatric Interview
mPFC……..Medial prefontal cortex
ms……...milliseconds
NAc……Nucleus accumbens
PAT……Positive Affect Therapy
PCA……Principal component analysis
PDS……Pubertal Development Scale
PET……Positron emission tomography
PSQ……Pandemic Stress Questionnaire
RDoC…….Research Domain Criteria
RewP……..Reward Positivity
SCID-5……Structured Clinical Interview for DSM-5
SD……...Standard Deviation
SSRI……Selective Serotonergic Reuptake Inhibitor
T1, T2, etc…..Time 1, Time 2, etc.
UCLA LSI…..UCLA Life Stress Interview
vmPFC……Ventromedial prefrontal cortex
VS……...Ventral Striatum
VTA……Ventral Tegmental Area

General Introduction and Literature Review

Depressive disorders[1] are highly prevalent and have an immense impact on functioning and quality of life on a global scale. As of the most recent data from the Global Burden of Disease study, depressive disorders are the thirteenth leading cause of death and disability for people of all ages; for age groups 10 to 24 and 25 to 49 they are the fourth and sixth leading causes, respectively (Diseases & Injuries, 2020). Even though depressive disorders are almost twice as prevalent in women than men, they are the top contributor to disability among mental disorders for both men and women (Rehm & Shield, 2019). While infrequent, children as young as preschool age may develop depression (Luby, 2010). Rates of depression remain low throughout childhood, but begin to increase markedly in adolescence, at which point the stark gender difference in prevalence emerges with women roughly twice as likely to receive a depression diagnosis as men (Kessler et al., 2001; Nolen-Hoeksema, 2002).

Despite its prevalence, much is yet to be understood in terms of the etiology and biological signatures of depression (Pizzagalli, 2014). Still, many significant risk factors for depression have been identified. To name a few, female gender (Nolen-Hoeksema, 2002), family history of depression (Levinson, 2006), and stress (Kessler, 1997; Mazure, 1998), particularly interpersonal stress (Kendler et al., 2003; Monroe et al., 1999), are all reliably linked with increased prevalence of depression. However, even these well-established risk factors do not account for all the variance in depressive outcomes. For example, a slight majority of those with an immediate family history of depression will not develop the disorder (Levinson, 2006). Similarly, not everyone experiencing significant stressors will become depressed (Mazure,

[1] These include major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, depressive disorder due to another medical condition, substance-induced depressive disorder, and other or unspecified depressive disorder American Psychiatric, A. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

1998). This suggests a need for ongoing refinement of risk factors, including an understanding of how they culminate in depression.

One complication to understanding the etiology of depression is the immense heterogeneity even within Major Depressive Disorder (MDD; Monroe & Anderson, 2015), the most common of the depressive disorders (National Comorbidity Survey). Major Depressive Disorder is diagnosed, using the DSM-5 criteria, based on the presence of at least five of nine symptoms, one of which must be low mood or anhedonia, for a period of at least two weeks (American Psychiatric, 2013). Many of the remaining symptoms contain opposites within them such as heightened *or* diminished appetite and excessive sleep *or* insomnia. Furthermore, there is significant variability in the course of MDD. Approximately 50% of those diagnosed with a depressive episode will experience a recurrence and the likelihood of a future recurrence increases with each subsequent episode (Burcusa & Iacono, 2007). This means that for some, MDD is a fairly time-limited problem while for others it is a lifelong episodic disorder. Because of the vast heterogeneity within the syndrome, both in terms of symptom presentation as well as severity, episode duration, age of onset, and recurrence, it is likely that MDD has many different risk factors and biological underpinnings that vary across individuals (Monroe & Anderson, 2015).

In an effort to uncover the relevant risk mechanisms for depression amongst this heterogeneity, many studies have focused on identifying neurobiological endophenotypes as more proximal indicators of risk (Pizzagalli, 2014). Endophenotypes are intermediary, quantifiable phenotypes that lie on the path between genetics and a disorder or syndrome (Gottesman & Gould, 2003). Studying more specific and homogenous phenotypes may improve our ability to elucidate the genetic or biological mechanisms of a given disorder. To qualify as an

endophenotype, a biological trait must be heritable, state-independent (i.e. still present in the absence of an active episode of the disorder of interest), and specifically associated with the disorder of interest (Gottesman & Gould, 2003). It must co-segregate with the disorder of interest in families and be present at higher rates in non-affected family members compared to the general population (Gottesman & Gould, 2003). Focusing on more specific biological traits is congruent with dimensional approaches to understanding mental disorders like the Research Domain Criteria framework (RDoC; Insel et al., 2010).

Many different biological processes at different levels of analysis have been investigated as candidate endophenotypes for depression. These include increased stress sensitivity, impaired cognitive control, impaired reward function, and others (Hasler et al., 2004; Hasler & Northoff, 2011; Webb et al., 2016). Of particular interest here, impaired reward function refers to deficits in responding to rewarding stimuli at the neural and/or behavioral level. Such decreased reward sensitivity is hypothesized to map specifically onto anhedonia (Foti et al., 2014; Liu et al., 2014; Stringaris et al., 2015; Weinberg & Shankman, 2017), clinically defined as the loss of interest or pleasure in typically enjoyed activities.

Impaired reward function appears to meet the conditions for an endophenotype (Pizzagalli, 2014), with varying degrees of evidence supporting each criterion. To start, many studies have linked diagnosed MDD or depressive symptoms (including anhedonia) with impaired or blunted reward processing, captured through a variety of methods including behavioral tasks, functional magnetic resonance imaging (fMRI), and electroencephalogram (EEG; Belden et al., 2016; Borsini et al., 2020; Foti et al., 2014; Halahakoon et al., 2020; Hall et al., 2014; Henriques & Davidson, 2000; Klawohn, Burani, et al., 2021; Knutson et al., 2008; Kumar et al., 2018; Pizzagalli, 2014; Pizzagalli et al., 2008; Robinson et al., 2012; Whitton et al.,

2016). Studies on the heritability of reward responsivity are more limited but existing data from twin studies suggest that behavioral (Bogdan & Pizzagalli, 2009), self-report, and striatal anticipatory reward sensitivity (Li et al., 2019) are all moderately heritable (h^2 = .30 - .61). A larger body of evidence supports the state-independence of impaired reward. Blunted reward responsiveness has been found in euthymic individuals who later developed an initial depressive episode (Bress et al., 2013; Nelson et al., 2016; Stringaris et al., 2015) and in individuals with remitted depression (Dichter et al., 2012; McCabe et al., 2009; Pechtel et al., 2013; Weinberg & Shankman, 2017; Whitton et al., 2016), suggesting that this phenotype does not track only actively depressed states. Finally, impaired reward response does appear to be familial and elevated in unaffected first-degree relatives of individuals with a depression history (Ethridge et al., 2021; Gotlib et al., 2010; Kujawa et al., 2014; Liu et al., 2016; McCabe et al., 2012; Olino et al., 2014; Weinberg et al., 2015). Therefore, although more research is needed on several of the criteria for an endophenotype (e.g. heritability, co-segregation), blunted reward responsiveness does appear to be a likely candidate endophenotype for depression, or at least anhedonic depression.

Given that impaired reward functioning has been implicated in the pathophysiology of depression, this raises the important question of whether and how reward functioning might be put to use in a clinical context. For example, identifying those with impaired reward function could help direct prevention interventions for depression. However, risk for depression is highly multifaceted and one risk factor alone is not sufficiently sensitive to accurately predict depression onset (Garber, 2006). Therefore, multiple risk factors must be taken into account. Although many risk factors for depression have been identified, less work has examined whether they are independent predictors or potentially redundant when considered together (Michelini et

al., 2021). Not only has blunted reward processing been linked with depression, it has also been associated with other prominent risk factors for depression such as stress (Admon et al., 2013; Ethridge et al., 2018; Rappaport et al., 2019) and family history (Gotlib et al., 2010; Kujawa et al., 2014; McCabe et al., 2012; Olino et al., 2014; Olino et al., 2015). More work is needed to address the question of how these risk factors might impact each other and come together to produce a depressive episode. Furthermore, if markers of reward sensitivity are to become clinically useful (Nielson et al., 2021), we need to understand how and under what circumstances reward functioning becomes impaired and for whom it might be clinically relevant. This relies on a foundational understanding of the reward system.

The Reward System

Reward functioning can be parsed into related but separable constructs including reward wanting, liking, and learning (Berridge et al., 2009). These processes are supported by a network of brain regions referred to as the reward system (Kelley & Berridge, 2002). It should be noted, however, that referring to this network as "the reward system" is a simplification intended to aid interpretation and is not meant to imply that this network or the constituent regions are only responsive to reward and not active in other processes. For example, many of these same regions are also implicated in the processing of pain and stress (e.g., Leknes & Tracey, 2008; Robinson et al., 2013).

The neural circuitry comprising the reward system includes the nucleus accumbens (NAc), anterior cingulate cortex (ACC), orbitofrontal cortex, insula, ventral pallidum, ventral tegmental area (VTA), amygdala, and mesocorticolimbic dopamine projections (Berridge et al., 2009; Russo & Nestler, 2013). Multiple neurotransmitter systems are involved in the motivation to obtain rewards and the pleasure derived from receiving them. While the 'liking' of rewards is

mediated mainly by opioid, endocannabinoid, and GABAergic neurotransmitters (Berridge et al., 2009; Kelley & Berridge, 2002), 'wanting' rewards, or incentive salience, is mediated primarily by dopamine (Berridge et al., 2009).

Mesolimbic dopamine neurons, which receive inputs from many areas of the brain including the striatum and the ACC, project from the VTA to the nucleus accumbens, as well as prefrontal regions (Beier et al., 2015; Fields et al., 2007; Kelley & Berridge, 2002). These neurons encode reward salience and value with increased phasic firing to unexpected rewards and decreased firing to unexpected non-rewards (Schultz, 2016b). This phenomenon is known as the reward prediction error and underlies reinforcement learning (Schultz, 2016a). In cases where rewards are consistently preceded by a sensory cue, mesolimbic dopamine neurons will begin firing in response to the cue, signaling the availability of a reward (Fields et al., 2007). Therefore, mesolimbic dopamine neurons respond to both reward receipt and reward-predictive cues, mediating reinforcement learning and appetitive behavior (Cox & Witten, 2019).

The mesocortical pathway, another important part of the reward system, includes dopaminergic neurons that originate in the VTA and project to the medial prefrontal cortex (mPFC), including the ACC. The ACC, which receives the most dopaminergic innervation in the prefrontal cortex, also helps encode the reward prediction error and the outcome of choices in reward tasks (Wallis, 2019). Accordingly, patients with ACC lesions demonstrate deficits in adjusting behavior based on reward or non-reward feedback (Wallis, 2019; Williams et al., 2004).

Whereas preclinical studies have been invaluable in mapping this reward circuitry, studies investigating the human reward system have allowed a deeper understanding of how reward processes are implicated in clinical disorders. The human reward system is sensitive to

both primary rewards (e.g., palatable food, drugs; Simon et al., 2014; Tang et al., 2012; Volkow & Morales, 2015) and secondary rewards (e.g., money; Knutson et al., 2001; Proudfit, 2015) as well as rewarding social stimuli (e.g., a smiling face, social acceptance feedback; Ait Oumeziane et al., 2017; Banica et al., 2022; Bhanji & Delgado, 2014). Even rewarding music activates these same brain regions (Blood & Zatorre, 2001). Reward system activity in response to these incentives in humans can be probed with a variety of non- or minimally invasive methods. These include positron emission tomography (PET; Dubol et al., 2020; Hirvonen et al., 2008; Wiers et al., 2017), fMRI (Keren et al., 2018; Knutson et al., 2000), and EEG (Proudfit, 2015; Weinberg et al., 2021).

While each of these methods has advantages and disadvantages, one particularly useful, economical, and well-tolerated method for quantifying reward responses is event-related potentials (ERPs). ERPs are task-based measures derived from ongoing EEG recordings (Luck, 2014). EEG activity reflects a direct measurement of neuronal activity: post-synaptic potentials from large populations of neurons firing together. When neurons are oriented in the same direction and activated synchronously, their post-synaptic potentials sum together and the voltage of this activity can be measured at the scalp with high temporal precision (milliseconds; Luck, 2014). EEG activity in response to a specific stimulus or event can be calculated using the ERP technique. EEG data time-locked to an identical stimulus (e.g. rewarding feedback) from multiple trials of a task are averaged together to yield an ERP waveform from which ERP components of interest can be measured (Luck, 2014). Multiple trials are typically required to enhance the signal of interest relative to noise in the data and extract a reliable measurement of the ERP, though single-trial analyses are possible (Blankertz et al., 2011). In the case of reward

processing, a primary ERP component of interest is the Reward Positivity (RewP; Proudfit, 2015).

The Reward Positivity

The RewP is a positive-going deflection in the ERP waveform that is heightened to rewarding feedback (e.g. winning money) and absent to non-rewarding feedback (e.g. losing money). It is typically maximal at frontocentral electrodes 250 to 350ms after reward receipt. Based on the RDoC framework (Insel et al., 2010), the RewP can be considered an Initial Response to Reward, part of the Positive Valence System.

Originally, the RewP was conceptualized as a negative-going ERP component enhanced to negative feedback (e.g. monetary loss) and was calculated as the neural response to negative feedback minus the neural response to positive feedback (Krigolson, 2018). This component was referred to as the Feedback-Related Negativity or the Feedback Negativity (among others; Krigolson, 2018). However, studies found that the conditional waveform to positive feedback, rather than the conditional waveform to negative feedback, was sensitive to feedback valence (Foti et al., 2011b; Holroyd et al., 2008; Proudfit, 2015). This suggested that the component was better understood as a positivity in response to rewards rather than a negativity in response to losses. This new understanding led to the reconceptualization of the component as the Reward Positivity or RewP, which is simply the inverse of the Feedback Negativity (i.e., response to positive feedback minus response to negative feedback). It should be noted that the polarity of an ERP component does not tell us whether it is the result of excitatory or inhibitory neuronal activity (Luck, 2014). While some of the studies cited here used Feedback Negativity terminology, all future mentions of this component in this document will refer to the RewP to avoid further confusion.

Source localization studies suggest that the RewP is generated by activity in the ACC, a brain region implicated in effort-based decision making and computing reward prediction errors (Krigolson, 2018; Wallis, 2019), and in the putamen, part of the dorsal striatum (Carlson et al., 2011; Foti et al., 2011b), which is active in response to behavior-contingent rewards (Delgado, 2007). Event-related potentials must be generated by large populations of neurons that are aligned in parallel and fire together (e.g. pyramidal neurons in the cortex) so that their post-synaptic potentials sum together and become measurable at the scalp (Luck, 2014). Because the striatum is a non-laminar structure fairly deep in the brain, there is some controversy surrounding the assertion that the putamen is the most likely generator of the RewP (Cohen et al., 2011; Foti et al., 2011a). Nonetheless, other studies examining correlations between RewP and fMRI activation (measured separately or concurrently) show clear positive associations between the magnitude of the RewP and Blood Oxygen Level Dependent (BOLD) response in the ventral striatum (VS), caudate, and anterior cingulate cortex (Becker et al., 2014; Carlson et al., 2011; Foti et al., 2014). Further evidence suggests that the RewP is related to dopaminergic neurotransmission as it is enhanced to unexpected rewards (Holroyd et al., 2011; Mulligan & Hajcak, 2018) and modulated by drugs impacting dopamine activity (Cavanagh et al., 2022; Santesso et al., 2009; Schutte et al., 2020). Taken together, these findings indicate that the RewP reflects, at least in part, activation of the mesocorticolimbic dopaminergic reward system and can be used as an index of neural reward sensitivity.

Furthering its utility as an index of neural reward sensitivity, the RewP demonstrates favorable psychometric properties. It is internally consistent (Ethridge & Weinberg, 2018; Levinson et al., 2017; Szenczy et al., 2021) and demonstrates good test-retest reliability (Bress et al., 2015; Levinson et al., 2017; Szenczy et al., 2021). The RewP also appears to be externally

valid as not only is it associated with fMRI measures of reward response (Becker et al., 2014; Carlson et al., 2011; Foti et al., 2014), it is also correlated with behavioral and self-report indices of reward sensitivity (Bress & Hajcak, 2013). While most studies have elicited the RewP using monetary reward tasks, it can also be elicited by food and social rewards (Ait Oumeziane et al., 2017; Banica et al., 2022), meaning that it can be used to measure responsiveness to multiple domains of rewards. Importantly, many studies have found links between the RewP and clinically relevant outcomes like anhedonia and depression (Foti et al., 2014; Keren et al., 2018; Klawohn, Burani, et al., 2021; Weinberg & Shankman, 2017).

Given its good psychometric properties and relative cost effectiveness, the RewP is an excellent tool to study neural responses to reward. Many studies have used the RewP to study how impaired reward response relates to risk for depression (e.g., Belden et al., 2016; Burani et al., 2021; Klawohn, Brush, et al., 2021; Kujawa, Hajcak, et al., 2019; Mackin et al., 2019; Novak et al., 2016; Proudfit, 2015). However, in order to fully understand pathways of depression risk, we need to not only understand the circumstances in which blunted reward response leads to depression, but also the mechanisms by which reward processing becomes blunted (Kujawa, Klein, et al., 2020).

Predictors and Mechanisms of Impaired Reward Response

Genetic and family factors

Both genetic and environmental factors play a role in reward responsiveness and anhedonia. As discussed, reward responses, behavioral or neural, tend to be moderately heritable based on twin studies (Bogdan & Pizzagalli, 2009; Li et al., 2019), highlighting the genetic component of impaired reward function. Another body of literature has examined the extent to which reward responses in youth are associated with a parental history of depression (Freeman et

al., 2022; Gotlib et al., 2010; Kujawa et al., 2014; Luking et al., 2016a, 2016b; McCabe et al., 2012; Olino et al., 2014; Olino et al., 2015; Sharp et al., 2014). These studies have helped establish that family history of depression, one of the strongest risk factors for depression (Lieb et al., 2002; Van Dijk et al., 2021; Weissman et al., 2005), is typically associated with blunted neural reward response in adolescence. While such studies do not capture only genetic influences, they do suggest that there is a significant familial effect on reward responses. However, the mechanisms of the intergenerational transmission of reward responses are likely complex, as some studies testing correlations between parent and child reward responses have found null or negative correlations (Colich et al., 2017; Ethridge et al., 2021; Moser et al., 2018). Further, in one study, these correlations were moderated by child pubertal development, indicating that the degree of correspondence between parent and child reward response may change as the child matures (Ethridge et al., 2021).

Stress

Beyond genetic and family factors, stress is an important and highly studied predictor of impaired reward response. Stress is a heterogeneous construct and can be used to refer to the subjective experience of stress (i.e. stress response) and the objective stressors themselves (i.e. stress exposure; Harkness & Monroe, 2016). Stressors can be acute, chronic, physical, interpersonal, severe, and/or mild. All these domains may determine the impact of a stressor on an individual's response. Stress responses can be measured with self-report, behavioral, physiological, and/or hormonal measures (e.g. cortisol). Therefore, while stress appears to be both a robust predictor of depression (Aneshensel, 1982; Hammen, 2005; Kessler, 1997; Mazure, 1998; Monroe et al., 2019) and of impaired reward function (Berghorst et al., 2013; Bogdan & Pizzagalli, 2006; Ethridge et al., 2018; Hanson et al., 2016; Kujawa, Klein, et al., 2020;

Pizzagalli, 2014; Stanton et al., 2019), these effects may vary somewhat based on the operationalization of stress being used (Anisman & Matheson, 2005).

Preclinical studies have been instrumental in identifying the conditions under which stress exposure leads to impaired reward function as well as the mechanisms underlying this association. For example, studies with rodents have found divergent effects of acute and chronic stress exposure on reward responses and dopamine activity (Baik, 2020; Pizzagalli, 2014; Stanton et al., 2019; Valenti et al., 2012). Acute stress administration, often in the form of acute restraint, foot shock, tail pinch, short-term handling, or short-term exposure to threat (e.g. predator odor, aggressive conspecific), reliably leads to increased dopaminergic firing in the mesolimbic pathway (Baik, 2020). This dopamine boost seems to allow for active coping and may promote learning (Baik, 2020; Cabib & Puglisi-Allegra, 2012). An increase in striatal dopamine release after acute psychosocial or pain stress exposure has also been observed in humans using PET imaging (Mather & Lighthall, 2012; Pruessner et al., 2004; Scott et al., 2006). However, human studies using other methods (fMRI, ERPs) have often found the opposite result wherein the administration of acute stress causes a reduction in reward responses (Berghorst et al., 2013; Bogdan & Pizzagalli, 2006; Ethridge et al., 2020; Porcelli et al., 2012). Possibly this discrepancy stems from the fact that different methods capture different aspects of reward processing (i.e. dopamine release versus overall brain activation in a given region or network).

The translational literature seems to be more aligned when examining associations between chronic stressors and reward function in humans and rodents, though again findings may vary based on the methods used. Preclinical studies have consistently shown that chronic stressors, especially when uncontrollable (Pizzagalli, 2014), lead to impaired reward-related behavior (Baik, 2020; Stanton et al., 2019). In fact, administering a protocol of chronic stress

(e.g. chronic uncontrollable mild stress, chronic social defeat stress) is a common method used to induce a rodent model of depression characterized by anhedonia and validated by observations of reduced reward-seeking behavior or motivation to obtain rewards (e.g. reduced sucrose preference, fewer level presses in a progressive ratio task; Bergamini et al., 2016; Dieterich et al., 2021; Russo & Nestler, 2013). However, the mechanisms by which chronic stress exposure leads to anhedonic behaviors appears to depend, in part, on the type of stressor used.

While there is promising evidence that changes in the mesolimbic dopamine system mediate the effect of chronic stress on reward functioning, the nature of that change seems to differ by the type of chronic stress administered. Chronic social defeat stress (CSDS) is a paradigm in which a male mouse is attacked by a large aggressive mouse for ten minutes and then kept in the aggressor's cage for the rest of the day, separated by a clear, perforated divider. This is repeated daily for 10 days (Wang et al., 2021). Across studies, CSDS has been associated with increased firing rates in dopaminergic VTA neurons (Baik, 2020). Interestingly, just as not all humans exposed to a major stressor will develop depression or another form of psychopathology, only a subset of mice who undergo this stressful procedure will actually develop depressive-like behaviors (Krishnan et al., 2007); these susceptible mice are the ones that show increased dopamine firing (Baik, 2020; Krishnan et al., 2007). One important limitation of this model is that it can only be used with male mice, inherently limiting its translatability given that depression is twice as prevalent in women than men (Lopez & Bagot, 2021). Modifications to the CSDS paradigm to allow its use with female mice are possible, though they may involve non-naturalistic behavior or be more logistically difficult to use compared to the traditional CSDS model (Lopez & Bagot, 2021).

Another commonly used chronic stress paradigm that causes anhedonic behavior in rodents is chronic (uncontrollable) mild stress (Lamontagne et al., 2018; Willner, 1997). Rats or mice undergoing this procedure are exposed to variable stressors (e.g. overnight illumination, periods of food and/or water deprivation, cage tilt, wet bedding, swapping cage-mates, etc.) that change every few hours but together last for a period of weeks or months[2] (usually at least four to six weeks; Willner, 1997; Willner, 2017). While this paradigm also reliably induces anhedonic behaviors, unlike CSDS, it leads to *decreased* dopaminergic VTA neuron activity (Baik, 2020; Tye et al., 2013). One hypothesis for why these two models both induce anhedonic and depressive-like behaviors yet have differing impacts on mesolimbic dopamine functioning is that chronic mild stress paradigms tend to be considerably longer (four weeks or more rather than ten days; Baik, 2020). This further supports the idea that stressor duration matters for the impact on reward system functioning (Hollon et al., 2015).

These studies, and others, suggest that while the specific impact on dopamine may differ, chronic stress causes maladaptive changes in mesolimbic dopamine activity, which in turn cause anhedonia and reduced reward motivation (Pizzagalli, 2014; Tye et al., 2013). These effects can be reversed by antidepressant medication (Bergamini et al., 2016; Pizzagalli, 2014) or optogenetic stimulation of VTA dopamine neurons (Tye et al., 2013), further highlighting the mesolimbic dopamine system as a mechanistic pathway. However, altered mesolimbic dopamine functioning is not the only potential mechanism mediating the effects of stress on anhedonia. For example, increases in corticotropin releasing factor and stress hormones, immune

[2] It should be noted that while this paradigm is called chronic *mild* stress, the procedure would be considered unethical if administered to humans and is not particularly mild. The reason it is called mild stress seems to be that the stressor severity was considerably downgraded from the original paradigm, developed before the Animals Act of 1986, which increased ethical standards for animal research. In the original version, mice received intense foot shocks, were plunged into cold water, and were deprived of food for 48 hours at a time (Willner, 2017).

activation/inflammation, and homeostasis factors are also impacted by stress and in turn impact reward-related behavior (Bergamini et al., 2018; Stanton et al., 2019). Therefore, there are likely numerous ways that chronic stress can lead to anhedonia, though these many pathways largely seem to converge on the mesolimbic reward system (Stanton et al., 2019).

The human literature on chronic stressors and reward functioning is somewhat sparser and is inherently less controlled as it must rely on naturally occurring chronic stress rather than experimentally manipulated conditions. Nevertheless, a general pattern emerges from this literature wherein experiencing greater levels of chronic stress (e.g. peer victimization, early life stress) tends to correlate with blunted neural reward processing (Ethridge et al., 2018; Hanson et al., 2016; Hanson et al., 2015; Herzberg & Gunnar, 2020; Panier et al., 2022; Rappaport et al., 2019), though not always (Kujawa, Klein, et al., 2020). Because findings are mixed and because relatively few types of chronic stressors have been evaluated as predictors of reward functioning, more research is needed to better understand what qualities of real-world stressful conditions (e.g. duration, severity, domain, etc.) lead to impaired reward response.

Reward processing as a predictor of depression

As discussed above, blunted reward responsiveness is a promising candidate endophenotype for depression. However, given that depression is so heterogeneous, and its etiology likely varies across individuals, reward sensitivity may not always be a meaningful risk factor or mechanism for depression. Understanding the conditions under which impaired reward response is a relevant and useful predictor for depression is therefore essential for improving its clinical utility. Evidence for moderators of the association between reward responses and depressive outcomes is discussed below.

Development

One relevant factor for understanding links between reward processing and depression appears to be developmental timing. Not only is adolescence a period of time where risk for depression increases, but it is also a developmental stage marked by increased reward-seeking and risk-taking behaviors (Casey et al., 2008; Galvan, 2010; Steinberg, 2008; Urosevic et al., 2012). These behavioral changes are accompanied by important neural development wherein subcortical structures (e.g. ventral striatum, amygdala) mature relatively faster than prefrontal regions (Casey et al., 2016; Casey et al., 2008; Pfeifer & Allen, 2012). Some fMRI studies have found a relative hypersensitivity of the reward system during adolescence (Casey et al., 2008; Galvan, 2010; Galván, 2013; Urosevic et al., 2012), suggesting that the normative developmental pattern of reward system sensitivity follows an inverted U-shaped trajectory from childhood to adulthood. Unsurprisingly though, there is individual variability in this trajectory (Bjork & Pardini, 2015). One theory, outlined by Olino (2016), suggests that these individual differences in the developmental trajectory of reward responses are a more sensitive way to capture risk for depression rather than a cross-sectional "snapshot" of mean levels of reward sensitivity. Based on this theory, adolescents who fail to show the normative peak in reward response during adolescence may be at highest risk for developing depression.

Empirical evidence supporting this theory has shown that reward responsiveness may be more closely linked to depression during adolescence than at other ages. For example, although multiple studies have found that adolescents with a family history of depression exhibit reduced striatal reward processing (Gotlib et al., 2010; Olino et al., 2014; Olino et al., 2015; Sharp et al., 2014), a large study of 9-year-old children failed to replicate this (Freeman et al., 2022). Furthermore, a meta-analysis of the association between fMRI and EEG measures of reward processing and depression found larger (negative) effect sizes in samples under age 18 relative to

adult samples (Keren et al., 2018). Ethridge and colleagues found that unlike in a group of adolescent girls at low risk for depression, age was not associated with an increased RewP in a sample of adolescent girls at high risk for depression (2021). Another study by Luking and colleagues found that striatal and insular BOLD activation to reward peaked earlier in girls with a maternal history of anhedonia such that their reward responses were blunted by mid-adolescence (2019). Although both these studies were cross-sectional, they highlight the possibility that girls at risk for depression do not (or to a lesser extent) experience the normative trajectory of reward system development. Another study with a longitudinal design and a relatively gender-balanced sample found that reduced striatal activation to reward anticipation prospectively predicted depressive symptoms two years later, but only for adolescents in mid-late puberty and not earlier in development (Morgan et al., 2013). Together, these studies further support the premise that adolescence is a sensitive period for the link between reward system functioning and depression risk, though more work is needed to confirm this.

Reward type

In addition to age or developmental status, the type of reward in question has implications for the association between reward responses and depression risk. Much of the literature on reward system functioning and depression has used monetary rewards to elicit reward responses. Monetary reward has the advantage of being an easily operationalized and quantifiable incentive. However, while the same dopaminergic reward system responds to different incentive types (Izuma et al., 2008; Lin et al., 2012; Simon et al., 2014), correlations between the RewP to money and other rewards (e.g. food, positive social feedback) tend to be small to moderate (r's .17-.44; Ait Oumeziane et al., 2019; Ait Oumeziane et al., 2017; Banica et

al., 2022; Distefano et al., 2018; Ethridge & Weinberg, 2018). Therefore, monetary reward response does not reflect domain general reward processing.

Depression is often accompanied by impairment in social functioning and relationship quality, including decreased motivation to socialize and poorer social skills (Barkus & Badcock, 2019; Kupferberg et al., 2016; Zlotnick et al., 2000). Therefore, increased attention has been given of late to social reward responses in relation to depression, based on the premise that less responsiveness to social incentives may be more relevant to the pathology of depression than responsiveness to monetary incentives. In fact, associations between the RewP and depressive symptoms are larger for social compared to monetary reward when measured within the same sample (Banica et al., 2022; Distefano et al., 2018; Pegg et al., 2021; Zhang et al., 2020). Furthermore, a relatively blunted social RewP has been found to be specifically associated with increased self-reported social anhedonia, reflecting that this neural marker does map on to real-world interpersonal functioning (Banica et al., 2022). Some evidence indicates that the link between impaired social reward response and increased depressive symptoms may be strengthened by increased rejection sensitivity (Pegg et al., 2021) or by female gender (Distefano et al., 2018). Additional studies have found gender differences in neural responses to social reward with larger responses in women than men (Soutschek et al., 2017; Spreckelmeyer et al., 2009). Taken together, these studies suggest that social reward sensitivity may be particularly relevant to depression and perhaps especially so in women.

Stress

As previously discussed, stress is strongly associated with depression (Hammen, 2005) and with blunted reward processing (Kujawa, Klein, et al., 2020). There are multiple possible models for how stress, reward functioning, and depression are related. These include the

mediation model, the stress generation model, and the moderation/diathesis-stress model (Auerbach et al., 2014). The mediation model posits that stress leads to blunted reward sensitivity, which leads to depression (Hanson et al., 2015; Kujawa, Klein, et al., 2020; Pizzagalli, 2014). This model is consistent with pre-clinical models of depression that use stressors to induce anhedonia and other depressive-like phenotypes, which are mediated by impaired reward system functioning (Baik, 2020; Tye et al., 2013). Next, the stress generation model proposes the converse association between stress and reward; in this model, blunted reward sensitivity leads to the generation of stress, perhaps through maladaptive approach/avoidance behaviors (Auerbach et al., 2014), which then leads to depression (Liu & Alloy, 2010; Mackin et al., 2019). Lastly, the moderation/diathesis-stress model suggests that blunted reward and increased stress interact to produce depression (Eckstrand et al., 2022; Feurer et al., 2021; Pegg et al., 2019; Pizzagalli, 2014). As cited, there is evidence supporting all three of these models. Importantly, they are not mutually exclusive given the likelihood of bidirectional associations between reward and stress and multiple pathways to depression (Mackin et al., 2023). The diathesis-stress model in particular, however, may help answer the question of under what conditions is reward system functioning relevant to the development of depression.

Despite the many findings that impaired reward functioning is associated with depression (Halahakoon et al., 2020; Pizzagalli, 2014; Pizzagalli et al., 2008), a number of studies have reported null associations between neural reward responses and concurrent depressive symptoms (Banica et al., 2022; Distefano et al., 2018; Eckstrand et al., 2022; Pegg et al., 2021). This raises the possibility that lower reward sensitivity on its own is not sufficient to lead to increased risk for depression. The diathesis-stress model would explain these null findings based on the idea

that blunted reward sensitivity (the diathesis) needs to be "activated" by stress to produce the outcome of depression (Zuckerman, 1999). Supporting this theory, multiple studies have found that individuals with lower levels of neural reward sensitivity but greater levels of early and/or recent life stress report increased depressive symptoms (Burani et al., 2021; Corral-Frías et al., 2015; Feurer et al., 2021; Goldstein et al., 2020; Pegg et al., 2019). A similar interaction was found between reduced ventral striatal reactivity and recent life stress in predicting lower levels of positive affect (Nikolova et al., 2012), which are often seen in depression (Forbes & Dahl, 2005). Several of the aforementioned studies were conducted prospectively with depressive symptoms measured one to three years after the measure of reward response (Burani et al., 2021; Feurer et al., 2021; Goldstein et al., 2020). This study design increases our confidence that the interaction between stress and reward precedes depressive symptoms and not the other way around.

In sum, impaired reward response is not always linked to depressive outcomes. Instead, developmental timing, reward type, and stress exposure can all impact whether impaired reward functioning is associated with depressive symptoms. Still, more work is needed to improve our precision in understanding when and for whom reward functioning constitutes a clinically meaningful risk mechanism for the development of a depressive disorder.

Thesis Objectives

The present thesis has aimed to advance our understanding of how impaired reward response contributes to the etiology and pathophysiology of depression. Using the RewP as an index of neural reward sensitivity, the first two studies examined predictors of blunted reward response, namely stress exposure and family history of depression. These studies help identify how blunted reward response is associated with these other important predictors of depression,

contributing to a better model of how risk factors may converge to produce a depressive episode. The third study investigated when neural reward response may be useful in prospectively predicting depressive symptoms, exploring sensitivity to different incentive types and under conditions of stress. Together, these studies deepen our knowledge of how impaired reward responsiveness may contribute to the development of depression.

Study 1

Effects of the COVID-19 pandemic on neural responses to reward: A Quasi-experiment.

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Abstract

BACKGROUND: The COVID-19 pandemic has been a prolonged period of stress due to social isolation, illness, death, and other major life disruptions. Neural reward sensitivity, essential for healthy functioning, may become reduced under major naturalistic stressors, though few studies have examined this. The present study sought to test whether neural responses to rewards were significantly blunted by the stress of the pandemic.

METHODS: We compared two groups of young adult participants, who completed a monetary reward task while EEG was recorded, at two timepoints, one to three years apart. Our measure of reward sensitivity was the Reward Positivity (RewP), a neural marker enhanced to gain relative to loss feedback. The magnitude of the RewP is sensitive to stress exposure and can prospectively predict depression. The pre-pandemic group (N = 41) completed both timepoints before the pandemic while the pandemic group (N = 39) completed the baseline visit before the pandemic and the follow-up visit during its second year.

RESULTS: The pandemic group reported having experienced significant stressors over the course of the pandemic. We did not observe a significant decrease in the RewP from baseline to follow-up in the pre-pandemic group. In contrast, in the pandemic group, the RewP was significantly blunted at the follow-up visit to the extent that it no longer distinguished gain from loss feedback.

CONCLUSION: These results suggest that prolonged naturalistic stressors can result in adaptations in neural responses to rewards. Our findings also highlight a possible mechanism linking stress to the development of depression.

Introduction

The COVID-19 pandemic has been a prominent stressor for much of the world's population. While the specific impacts of the pandemic varied by individual, family, and geographic location, many people experienced illness and death, social isolation, and major life disruptions. Accordingly, rates of self-reported stress and stress-related psychopathology, such as depression, increased significantly compared to pre-pandemic levels (Barendse et al., 2022; Elmer et al., 2020; Hawes et al., 2021; Racine et al., 2021). However, the mechanisms by which stress increases risk for depression are not clear (McLaughlin et al., 2022). Identifying such mechanisms might allow for more tailored interventions aimed at disrupting the link between stress exposure and depression.

One proposed but understudied potential mechanism linking the stress of the pandemic to increased rates of depression is alterations in reward processing (McLaughlin et al., 2022). Being able to seek, learn from, and respond to rewards is essential for survival and wellbeing (Berridge & Robinson, 2003; Schultz, 2015). These behaviors are supported by neural circuitry including the striatum (Berridge & Robinson, 2003); this circuitry not only supports essential functions involving food, social affiliation, and reproduction, it also promotes resilience against stress and depression (Dutcher & Creswell, 2018; Telzer, 2016). However, the reward system is vulnerable to stress exposure, both laboratory-induced and naturalistic, leading to reduced neural and behavioral sensitivity (Admon et al., 2013; Bergamini et al., 2018; Bogdan & Pizzagalli, 2006; Ethridge et al., 2020; Porcelli et al., 2012). Blunted measures of neural responses to reward, in turn, have been prospectively associated with psychopathology, including major depressive disorder and depressive symptoms (Bress et al., 2013; Nelson et al., 2016; Stringaris et al., 2015).

Although previous research has demonstrated links between stress exposure and altered reward functioning (Kujawa, Klein, et al., 2020), there are important limitations to consider. For instance, in humans, the administration of acute laboratory stressors is typically associated with blunted neural and behavioral responses to reward (Bogdan & Pizzagalli, 2006; Ethridge et al., 2020; Porcelli et al., 2012). Yet these stressors may not fully resemble real world experience, where stressors are often lengthier and more complex (Weinberg, 2022). Although preclinical work has consistently demonstrated that exposure to chronic stressors leads to impairment in dopamine signaling and reward responsiveness (Baik, 2020; Bergamini et al., 2018; Cabib & Puglisi-Allegra, 2012; Ironside et al., 2018), results in humans have been more mixed. Though some studies have found that real-world stress exposure is associated with blunted reward response (Ethridge et al., 2018; Freeman, Ethridge, et al., 2022; Hanson et al., 2016; Panier et al., 2022; Rappaport et al., 2019), others have found evidence of heightened reward sensitivity (Kujawa, Klein, et al., 2020) or no association (Freeman, Ethridge, et al., 2022; Freeman, Panier, et al., 2022; Panier et al., 2022). This may depend on the type or severity of the stressor (Kujawa, Klein, et al., 2020). However, in the case of real-world stress exposure, it is often difficult to infer the directionality of associations, particularly given cross-sectional and/or retrospective designs (Olson et al., 2018).

Furthermore, there is a lack of research on how large-scale stressors (e.g. war, natural disasters, pandemic) impact reward processing (McLaughlin et al., 2022), especially when experienced in adulthood. One small study found that young adult survivors of an earthquake had less striatal response to donating money to the Red Cross compared to a group of unaffected healthy controls (Wei et al., 2013); however, this study lacked a pre-earthquake measure of neural reward responses against which to compare their results. Another study using a pre-post

design found that school-age children highly impacted by Hurricane Sandy had a reduced reward response after the hurricane compared to a pre-hurricane baseline, but only when accompanied by low levels of positive parenting (Kessel et al., 2019). This effect was not seen in a control group of participants who experienced low levels of hurricane-related stress. More work employing such quasi-experimental designs will be needed to understand how reward processing might be impacted by prolonged, major naturalistic stressors.

One index of reward sensitivity useful in investigating how reward processing is impacted by stress is the Reward Positivity (RewP; Burani et al., 2022; Ethridge et al., 2020; Ethridge et al., 2018). The RewP is an early event-related potential (ERP) that is enhanced following rewarding feedback compared to non-rewarding feedback (Proudfit, 2015). The RewP is thought to reflect dopaminergic reward signaling (Cavanagh et al., 2022) and to originate from the anterior cingulate cortex and striatum (Becker et al., 2014; Carlson et al., 2011; Foti et al., 2015; Foti et al., 2011). This component has good internal consistency and is relatively stable over time (Bress et al., 2015; Ethridge & Weinberg, 2018; Levinson et al., 2017) and development (Kujawa et al., 2018).

To examine whether neural responses to reward were blunted by the stress of the COVID-19 pandemic, we compared neural responses to reward measured during the pandemic (fall 2021) to a pre-pandemic baseline from those same participants. To investigate whether any changes observed in this pandemic group could more easily be attributed to the passage of time, we selected a demographically similar pre-pandemic "control" group. These participants had completed the same procedures to measure neural response to reward at two timepoints with a comparable time interval, but both visits were completed before the pandemic. We hypothesized that neural response to reward would be significantly blunted during the pandemic compared to

the pre-pandemic baseline, reflecting a decrease over and above any change observed in the pre-pandemic control group. If this hypothesis is supported, these findings will have important implications for understanding how major naturalistic stressors affect the brain's response to rewards. As a secondary aim, we evaluated whether change in the RewP across timepoints was associated with a corresponding change in depressive symptoms, hypothesizing that as the RewP decreased, depressive symptoms would increase. If both hypotheses were supported, this would suggest the possibility that neural response to reward could be a mediator of the effect of stress exposure on depressive symptoms.

Methods and Materials

Participants

All participants included in the present analyses were recruited from an ongoing longitudinal study of undergraduate students at McGill University. As part of this parent study, participants completed an in-person laboratory visit during their first semester and were invited to return to the lab each subsequent semester. This first lab visit served as the baseline for both groups. Multiple waves of the study had been enrolled; participants in the present analyses were first enrolled between 2016 and 2019.

For the present analyses, we included two groups, the pandemic group and the pre-pandemic group. For the pandemic group, any student who completed a baseline visit for the parent study, consented to being recontacted, and was still enrolled at McGill was invited to return to the lab in the fall of 2021. Forty-two participants returned for the pandemic follow-up visit. Three participants had not completed the monetary reward task at baseline leaving N = 39 participants in the pandemic group. For the pre-pandemic group, any participant in the parent study who had completed a baseline visit and a subsequent follow-up visit one to three years

later was included. One participant was excluded for poor data quality leaving a final sample of N = 41 in the pre-pandemic group. Two participants in the pre-pandemic group did not report their depressive symptoms at their first or second lab visit and were therefore excluded from the depressive symptom analysis.

Participants in the two groups did not significantly differ in baseline age, gender identity, or self-reported ethnicity. For demographic characteristics and descriptive statistics by group, see Table 1.

Procedure

Baseline and follow-up lab visits for both groups contained near-identical procedures. Before each visit, participants completed online surveys using Qualtrics software (SAP America Inc.). These surveys contained questionnaires covering demographic information, depressive symptoms from the general depression scale of the IDAS-II (Watson et al., 2012), and other measures relevant to mental health. Participants in the pandemic group also reported on their experience of stressful pandemic-related life events in the survey preceding their follow-up visit.

During each lab visit, participants completed four computer-based tasks in a randomized order while EEG was recorded. One of these tasks was the Doors Task (Figure 1), a monetary reward task in which participants win and lose money while guessing which of two doors is hiding a prize (Proudfit, 2015). Data from this task and others from the parent study have been published previously (Banica et al., 2020, 2021; Ethridge & Weinberg, 2018; Freeman, Panier, et al., 2022; Pegg et al., 2019; Sandre et al., 2019; Weinberg et al., 2021). At the end of each visit, participants were compensated with extra course credit or $20.

McGill University's Research Ethics Board approved all study procedures prior to data collection. All participants provided informed consent before taking part in any study procedures. All authors adhered to APA ethical standards in the treatment of participants.

Self-report measures

Participants in the pandemic group completed a modified version of the Pandemic Stress Questionnaire (Kujawa, Green, et al., 2020) to report stressful life events experienced between March 2020 and their follow-up visit. This 25-item measure contains a checklist of pandemic-related life events in the following domains: general life disruption, interpersonal, financial, educational, health (self), and health (close others). Participants indicated whether given events occurred, yielding a stress count, and how bad the events were on a scale of 1 to 5, yielding a severity score. We administered an expanded version of this questionnaire with 65 items (see supplement for full list); however, only those reflecting the original 25 items are reported here to be comparable to other studies using this measure (Table 2). In addition to the stressors captured in this survey, pandemic group participants experienced remote learning for two-and-a-half semesters and had to contend with provincial and international border closures, bans on gathering with members of other households, extended closures of public spaces (gyms, restaurants, etc.), delays in vaccination for SARS-CoV-2, and a mask mandate which was still in place at the time of the follow-up visit.

Participants in both groups completed the Inventory of Depressive and Anxiety Symptoms (IDAS-II; Watson et al., 2012) at both timepoints. This measure contains a 20-item General Depression Scale, which we used to assess changes in depressive symptoms from baseline to follow-up in both groups. The General Depression Scale demonstrated good internal consistency

reliability at the baseline visit (Cronbach's α = .79) and very good internal consistency at the follow-up visit (Cronbach's α = .83).

Reward Response

Participants completed the Doors Task (Figure 1) while EEG was recorded to measure the RewP. In each trial, participants selected one of two doors, one of which is hiding a prize. After selecting a winning door, participants received feedback indicating they won $0.50 and after a losing door, feedback indicating a loss of $0.25. After five practice trials, participants completed two 20-trial blocks with a short break between. Feedback was pseudo-randomized so that participants had 20 win and 20 loss trials. All participants received $3 in winnings immediately after task completion.

Electroencephalogram Recording

Continuous EEG was recorded with a BrainVision actiChamp system (Brain Products, Munich, Germany). Participants wore a 32-channel electrode cap with a standard 10/20 layout and the ground electrode at Fpz. Data were recorded at a 1000Hz sampling rate. No online filters were used.

EEG data was processed offline using Brain Vision Analyzer (Brain Products). All data were processed using an automatic pipeline. First, data were filtered using a Butterworth Zero Phase bandpass filter with a lower cutoff of 0.01 Hz, an upper cutoff of 30Hz, and a 24 dB/oct slope. Next, each trial was segmented from 1000ms before task feedback until 1500ms after feedback. Data were then referenced to the mastoids (TP9, TP10). Ocular correction was done using the Gratton & Coles method (Gratton et al., 1983) with electrode FT9 as the horizontal electrooculogram channel and FP1 as the vertical electrooculogram channel; Oz served as the reference channel for ocular corrections. Artifacts were removed from the data based on the

following criteria: a voltage step of >30.0 μV between sample points, a voltage difference >150.0 μV within 200 ms intervals, or a voltage difference <0.50 μV within 100 ms intervals. Channels were also removed from a trial if their amplitude exceeded 125 μV or fell below -125 μV. After artifact rejection, participants had an average of 19.5 (SD = 1.08, range = 13-20) usable gain trials and 19.35 (SD = 1.47, range = 12-20) usable loss trials at baseline and 19.38 (SD = 1.82, range = 13-20) usable gain trials and 19.28 (SD = 2.16, range = 9-20) usable loss trials at follow-up. The number of usable trials did not differ significantly by feedback type, timepoint, or group.

Next, data were baseline corrected with the 200ms before feedback. Finally, all gain trials and all loss trials were separately averaged. Data were checked visually after automatic processing. Channels with fewer than five trials contributing to the average for gain or loss were interpolated using linear derivation with the four surrounding channels, or three surrounding channels if at the edge of the cap. The RewP was scored as the mean activity 250ms-350ms following feedback at electrode Cz (Proudfit, 2015). Split-half reliability comparing the RewP from even and odd numbered trials for each timepoint was evaluated using the Spearman-Brown coefficient. At baseline, the Spearman-Brown coefficient was .84 for neural responses to gain and .85 for response to loss. At follow-up, the Spearman-Brown coefficient was .89 for neural responses to gain and .86 for response to loss. Test-retest reliability coefficients were .55 for response to gain and .63 for response to loss in the pre-pandemic group and .50 for gain and .44 for loss in the pandemic group. These are comparable to other studies examining similar ERPs over a two-year interval (Bress et al., 2015; Weinberg & Hajcak, 2011).

Data analyses

All analyses were conducted in SPSS version 27 (IBM Corp, Armonk NY). To test our hypothesis, neural response data were analyzed using a 3-way ANOVA with task feedback (gain vs. loss) and time (baseline vs. follow-up) as within-person factors and group (pre-pandemic group vs. pandemic group) as a between-person factor. Significant 3-way interactions were then broken down by separate time by feedback ANOVAs for each group. Significant 2-way ANOVAs in either group were broken down using paired t-tests.

We conducted additional analyses for our secondary aim of investigating whether change in the RewP was associated with a corresponding change in depressive symptoms. To do this, we calculated a standardized RewP residual for each timepoint. This residual is computed by regressing response to gain on response to loss such that the residuals capture any variance in neural response to gain not accounted for by response to loss. Then, we ran a regression with $RewP_{resid}$ from each timepoint and baseline depressive symptoms as predictors of depression symptoms at follow-up. This allowed us to test whether a smaller $RewP_{resid}$ at follow-up, adjusting for baseline $RewP_{resid}$ and depressive symptoms, was associated with greater depressive symptoms.

Bivariate correlations between all study variables and a supplementary regression testing the association between the change in RewP and PSQ stress count can be found in the supplemental material (Table S1, S2). Anonymized study data and SPSS syntax are available here: https://osf.io/4tgau/

Results

Validation of pandemic related stress

Participants in the pandemic group reported a mean number of 7.48 pandemic-related stressors (SD = 3.65). This is slightly higher than previous studies reporting PSQ data (Kujawa,

Green, et al., 2020), though we surveyed a longer time period. The most commonly endorsed stress domain was interpersonal (Table 2). Three participants reported receiving a COVID-19 diagnosis.

Interaction between feedback type, timepoint, and group on the RewP

Following the three-way ANOVA (Table 3, Figure 2), we observed a main effect of feedback such that the neural response to monetary gain was more positive than the response to loss. We also observed a main effect of time such that neural responses to both types of feedback were decreased at the follow-up visits compared to baseline across groups. The main effect of group was not statistically significant.

However, the main effects of time and feedback were qualified by the significant three-way interaction between feedback type, time, and group, which tested our main hypothesis. To decompose this interaction, we conducted two-way interactions between time and feedback type separately by group (Table 4). In the pre-pandemic group, there was a significant main effect of feedback (response to gain > loss), but no significant main effect of time and no significant feedback by time interaction. In contrast, in the pandemic group, we observed significant main effects of feedback and time. These main effects in the pandemic group were further qualified by a significant time by feedback interaction. Breaking this down using paired-sample t-tests, we found that neural response to gain decreased more significantly from baseline to follow-up ($t(38) = 4.51$, $p < .001$, $d = .72$) than neural response to loss ($t(38) = 2.23$, $p = .03$, $d = .36$). Furthermore, while the pandemic group had a larger neural response to gain versus loss feedback in the time-window of the RewP at baseline ($t(38) = 5.00$, $p < .001$, $d = .80$), the RewP no longer significantly distinguished between gain and loss feedback at the follow-up visit ($t(38) = 1.10$, p

= .28, *d* = .17). Spaghetti plots depicting individual trajectories for neural response to gain and loss from baseline to follow-up are found in supplemental Figure S1.

Because there was variation in the number of times participants had completed the Doors task between their baseline and follow-up visits, we reran the 3-way ANOVA with the number of task completions as a covariate. This covariate was not significant (p = .78) and did not change the significance or decrease the effect size of the 3-way interaction testing our main hypothesis. We also conducted an analysis to evaluate whether group differences in the interval between lab visits could be confounding the effect of pandemic stress exposure on the RewP. Because group and interval duration were much more closely associated than group and the number of task completions, adding interval as a covariate to the 3-way ANOVA would have resulted in a significant loss of power and made it difficult to interpret results. Instead, we computed separate bivariate correlations between the interval between lab visits (rounded to the half year) and the difference in $RewP_{resid}$ from baseline to follow-up for each group. These correlations were of small magnitude and nonsignificant (pre-pandemic group: $r(39) = -.07$, $p = .68$; pandemic group: $r(37) = .15$, $p = .36$) suggesting that interval between lab visits does not fully explain the group differences observed.

Associations between RewP and depressive symptoms

In line with our secondary aim, we tested whether a more blunted RewP was associated with higher depressive scores at follow-up, adjusting for baseline RewP and depressive scores. We found that, collapsed across groups, the $RewP_{resid}$ at follow-up was negatively but not significantly associated with depressive symptoms at follow-up ($b = -1.93$, $\beta = -.16$, $p = .16$). Full results from this model can be found in the supplement (Table S3).

Discussion

Our results suggest that experiencing the COVID-19 pandemic was associated with decreased neural response to reward compared to a pre-pandemic baseline. This decrease was so pronounced that the RewP no longer significantly discriminated between gain and loss feedback during the pandemic follow-up visit. The decrease was also significantly larger for neural response to gain than it was for response to loss, suggesting that reward response, rather than feedback processing in general, may be specifically impaired under this type of stress. These conclusions are bolstered by the fact that no such decrease in the RewP was observed in a demographically equivalent control sample who completed the same procedures entirely before the pandemic. This strengthens our confidence that any changes in the RewP were related to experiences during the COVID-19 pandemic, rather than the mere passage of time.

These findings are largely consistent with the animal literature, which shows that prolonged uncontrollable stressors lead to impaired dopamine signaling and can induce a depression-like phenotype (Baik, 2020; Bergamini et al., 2018; Cabib & Puglisi-Allegra, 2012; Ironside et al., 2018). However, the human literature is sparser and has been less consistent, possibly because naturalistic stressors are difficult to measure and standardize across individuals. The COVID-19 pandemic, while devastating, provided a unique opportunity to study how a pervasive and life-changing yet shared (e.g., timing of lockdowns, school policies) stressor impacted neural reward response.

Because blunted neural sensitivity to reward may be an important risk factor for depressive disorders (Bress et al., 2013; Kujawa et al., 2014; Proudfit, 2015), these results highlight a potential pathway by which the experience of stress leads to depression (Hammen, 2005; Kendler et al., 1999; Kessler, 1997; Mazure, 1998; McGonagle & Kessler, 1990). If pandemic stress leads to blunted reward sensitivity, which in turn predicts depression, this could

explain, at least in part, why rates of depression have increased globally during the pandemic (Arora et al., 2020; Barendse et al., 2022; Elmer et al., 2020; Hawes et al., 2021). However, in this sample, the change in the RewP did not significantly predict increased depressive symptoms although the association was in the expected direction. This could mean that the pandemic-related increase in depression is not mediated by change in reward sensitivity; however, we may also have been underpowered to detect a significant between-person effect.

Another possibility is that stress-related decreases in the RewP could lead to increased risk for depression on a different timescale. Though its magnitude is malleable, the RewP is thought to reflect, in part, a trait-like measure of reward sensitivity and depression proneness rather than a state-like index of depressive symptoms (Bowyer et al., 2019; Bress et al., 2015; Weinberg & Shankman, 2017). One limitation of our data is that because we measured the RewP over a year into the pandemic, it is unclear when the RewP changed and for how long the change will last. It is therefore an important future direction to establish how long such stress-related changes in the RewP persist. If the observed change in neural reward response is long-lasting, it may indicate heightened vulnerability to future stressors, triggering increased depressive symptoms under conditions of stress later on (Weinberg et al., 2022). Furthermore, evidence suggests that not only can stress lead to blunted reward response (Burani et al., 2022) but blunted reward response can lead to increased person-dependent stressors (Mackin et al., 2019). Accordingly, it is possible that participants whose neural sensitivity to reward decreased during the pandemic will prospectively experience even more stressors, further exacerbating their depression risk. Future research will need to prioritize determining whether these stress-related changes in neural reward sensitivity persist over time and whether they prospectively predict later depressive symptoms or enhanced vulnerability to future stressors.

Despite the global impact of the COVID-19 pandemic, stress exposure varied across individuals. For many people it was a chronic stressor (e.g., social isolation) punctuated by acute stressors (e.g., job loss). For this reason, the "active ingredient" responsible for the striking decreases in reward response is unclear. One recent study found that cumulative acute but not chronic lifetime stressors prospectively predicted a blunted RewP (Burani et al., 2022), suggesting that it takes more severe events and their aftermath to induce such adaptations in the brain's reward system. However, our sample, which did show striking changes in neural reward response, did not report many of the most severe stressors associated with the pandemic (e.g. death of loved ones), indicating that the most severe acute events were not required to induce these changes. Additionally, only three of our pandemic group participants tested positive for the SARS-CoV-2 virus, suggesting that the change in the RewP is not a neurobiological sequela of a COVID-19 infection (Bougakov et al., 2021; Douaud et al., 2022). Larger diverse samples with more power to test moderators would be helpful to identify whether these results generalize to a more demographically representative sample and which aspects of the pandemic were most impactful in altering reward response. Additionally, although there was a very pronounced group effect of the pandemic on the RewP, individual trajectories of reward response from baseline to follow-up varied by person (Figure S1). Therefore, studies addressing not only what type of stress is most impactful but what individual characteristics (e.g. baseline reward sensitivity) predict reductions in reward response will help determine who is most vulnerable to major stressors.

There are several additional limitations to these data that must be noted. First, the average interval between baseline and follow-up was significantly longer for the pandemic group than the pre-pandemic group, potentially confounding our results. However, because the RewP is

generally quite stable over time (Levinson et al., 2017), even over a two-year period (Bress et al., 2015), and because the association between interval duration and change in the RewP in each group was of small magnitude and not statistically significant, we do not believe this difference is the most likely explanation of our results. Replicating these findings with equivalent intervals across groups would help bolster these conclusions. Another limitation is that we do not have equivalent stress measures in the pandemic and pre-pandemic groups to compare non-pandemic-related stress exposure, or perceived stress, to further ensure that elevated COVID-19 stress was the main difference across groups. Therefore, we cannot demonstrate that the pandemic group had a greater overall burden of stress exposure, and that this was the direct cause of the reduction in the RewP.

To conclude, these findings suggest that living through the stress of the COVID-19 pandemic induced potentially maladaptive changes in the brain's processing of reward signals. These longitudinal data are some of the first to show how living through real-world stressors of this scale can impact brain function. It will be very important to evaluate whether these neural changes outlast the pandemic and have consequences for future development of depression and other psychopathology (Gotlib et al., 2022).

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Disclosures

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Table 1. *Demographic and study variables by group.*

	Pre-pandemic group N = 41	Pandemic group N = 39
	M (SD)	**M (SD)**
Baseline age	18.09 (0.32)	18.04 (0.18)
Follow-up age[d]	19.59 (0.89)	20.50 (0.60)
N Doors[a,d]	3.10 (1.06)	2.62 (0.91)
Interval between timepoints (years)[d]	1.35 (0.59)	2.40 (0.49)
PSQ Stressor Count	————	7.48 (3.65)
Baseline depressive symptoms[b]	44.40 (11.46)	46.97 (9.92)
Follow-up depressive symptoms[b,d]	43.70 (11.15)	49.79 (12.28)
Baseline response to gain	15.27 (7.13)	15.51 (7.52)
Baseline response to loss	11.70 (6.56)	11.67 (6.04)
Follow-up response to gain[d]	13.75 (7.93)	10.43 (6.40)
Follow-up response to loss	10.38 (7.67)	9.51 (5.32)
	Median range	**Median range**
Household income [c]	$100,000 - $149,999	$90,000 - $99,999
	N (%)	**N (%)**
Gender: Female	35 (85.4%)	30 (76.9%)
Gender: Male	6 (14.6%)	8 (20.5%)
Gender: Prefer not to answer	0 (0%)	1 (2.6%)
Ethnicity: Chinese	12 (29.3%)	9 (23.1%)
Ethnicity: Hispanic	1 (2.4%)	1 (2.6%)
Ethnicity: Korean	0 (0%)	2 (5.1%)
Ethnicity: South Asian	2 (4.9%)	1 (2.6%)
Ethnicity: Southeast Asian	1 (2.4%)	1 (2.6%)
Ethnicity: White	22 (53.7%)	16 (41.0%)
Ethnicity: Other	3 (7.3%)	7 (17.9%)
Ethnicity: Prefer not to answer	0 (0%)	2 (5.1%)

Note. Descriptive statistics for demographic variables and other continuous variables of interest in each group. [a.] Number of times participants completed the Doors task over the course of the parent study from which participants were drawn for this analysis. [b.] Depressive symptoms measured from the general depression scale of the Inventory of Depression and Anxiety. [c.] 15 individuals in the pre-pandemic group (36.6%) and 15 individuals in the pandemic group

(38.5%) did not report on income. Symptoms (IDAS-II). [d.] Indicates a significant group difference ($p < .05$) based on an independent samples t-test.

Table 2. Frequency and severity of items endorsed on the Pandemic Stress Questionnaire by subscale.

Pandemic Stress Questionnaire	**Endorsed >= 1 stressor in this category**	**Items endorsed**	**Severity of endorsed events**
	N (%)	**M (SD)**	**M (SD)**
General life disruption (6 items)	31 (79.5%)	1.68 (1.14)	2.68 (0.90)
Interpersonal (5 items)	34 (87.2%)	1.86 (0.99)	3.07 (0.99)
Financial (3 items)	12 (30.8%)	0.46 (0.80)	3.14 (1.12)
Education/professional goals (3 items)	23 (59.0%)	0.87 (0.88)	3.06 (0.99)
Health - self (5 items)	32 (82.1%)	1.61 (0.95)	2.27 (0.91)
Health - close others (3 items)	20 (51.3%)	0.87 (0.99)	2.42 (1.22)

Note. Table indicating the number of pandemic group participants who endorsed at least one item in each stress domain on the Pandemic Stress Questionnaire (PSQ), the average number of items in each category, and the average severity of items endorsed in each category.

Table 3.
Three-way ANOVA results for the effects of feedback, time, and group on RewP

Predictor	***df***	***F***	***p***	η^2p
(Intercept)	(1, 78)	369.70	**<.001**	.83
Feedback	(1, 78)	45.02	**<.001**	.37
Time	(1, 78)	13.93	**<.001**	.15
Group	(1, 78)	0.62	.44	.01
Feedback x Time	(1, 78)	6.39	**.01**	.08
Feedback x Group	(1, 78)	1.53	.22	.02
Time x Group	(1, 78)	2.65	.11	.03
Feedback x Time x Group	(1, 78)	4.85	**.03**	.06

Note. Feedback represents the contrast between gain and loss, time represents the contrast between the baseline visit and follow-up visit, and group represents the contrast between the pre-pandemic group and pandemic group. P-values < .05 have been emphasized in bold.

Table 4.
Two-way ANOVA results for the effects of feedback and time on the RewP, separated by group

	Pre-pandemic group				Pandemic group			
Predictor	***df***	***F***	***p***	η^2_p	***df***	***F***	***p***	η^2_p
(Intercept)	(1, 40)	171.95	**<.001**	.81	(1,38)	208.60	**<.001**	.85
Feedback	(1, 40)	33.33	**<.001**	.46	(1,38)	14.19	**.001**	.27
Time	(1, 40)	2.10	.16	.05	(1,38)	15.38	**<.001**	.29
Feedback x Time	(1, 40)	0.07	.79	<.01	(1,38)	8.49	**.01**	.18

Note. Separate two-way ANOVAs for each group with feedback and time as within-person factors decompose the three-way feedback by time by group interaction in Table 3. Feedback represents the contrast between gain and loss, time represents the contrast between the baseline visit and follow-up visit. P-values < .05 have been emphasized in bold.

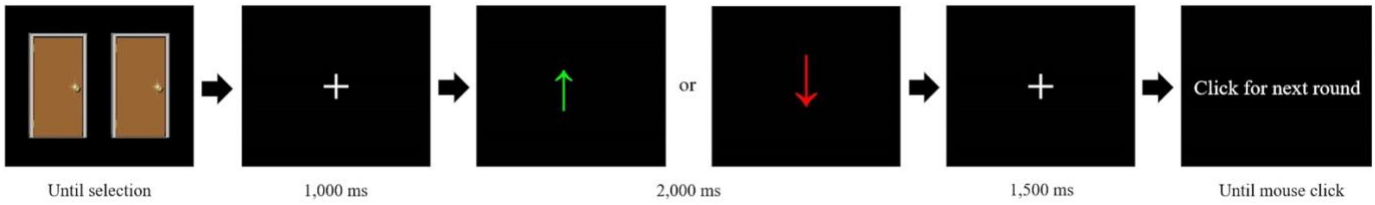

Figure 1. *Task schematics for the Doors task.*

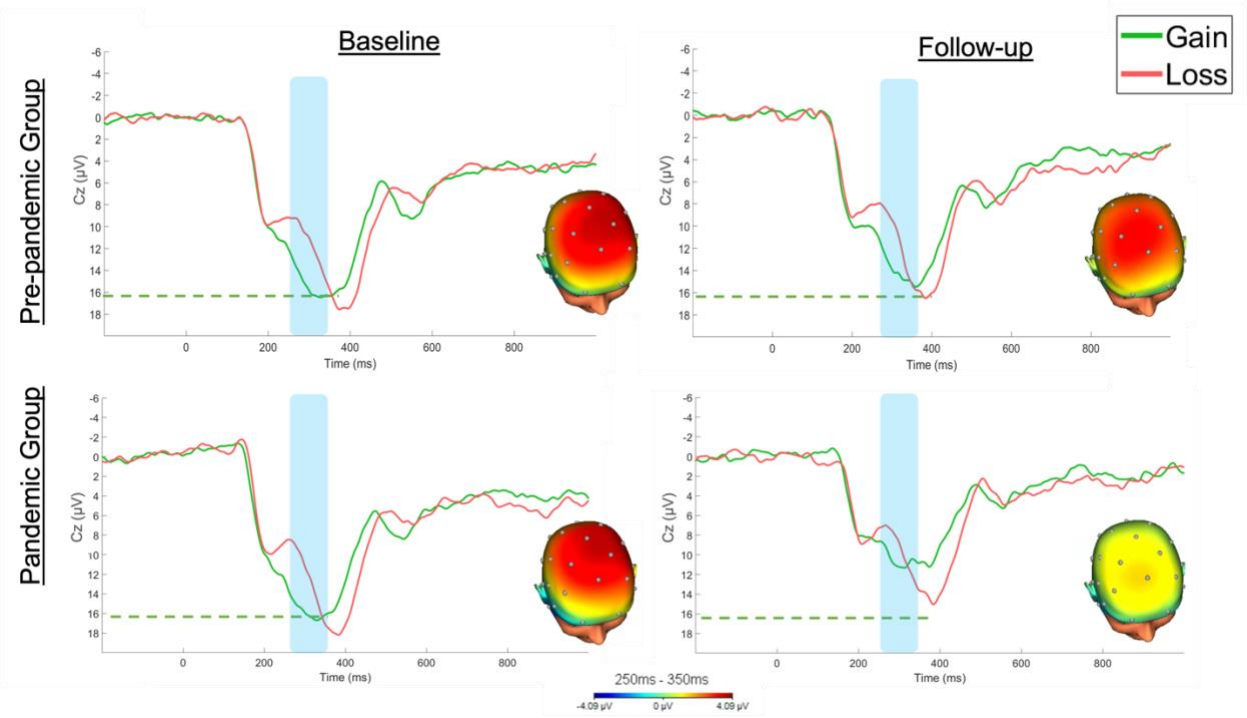

Figure 2. RewP waveforms at electrode Cz and topographic maps by group and time. Panels, divided by group (pandemic vs. pre-pandemic) and time (baseline visit vs. follow-up visit), display event-related potential waveforms following gain and loss feedback from the Doors Task at electrode Cz. Each panel also includes a topographic head map showing the average difference in μV between response to gain and response to loss in the time window of the RewP, 250ms – 350ms. This time window is highlighted in blue over the waveforms. Dashed lines reflect the peak of the gain waveform from the baseline visit for each group. It is reproduced in the follow-up visit panels to allow visual comparison of waveforms from baseline to follow-up within each group.

Study 1: Supplemental Material

Measuring pandemic-related stress exposure.

An expanded version of the Pandemic Stress Questionnaire (Kujawa et al., 2020) was given to participants in the pandemic group at their follow-up visit. The full list of items is listed below. Items reflecting the original 25 PSQ items, whose sum is used in the supplemental analyses below, are in bold.

1. My family or I have had a hard time finding food due to COVID-19.
2. **My family or I have had a hard time finding supplies (e.g., toilet paper, cleaning supplies) due to COVID-19.**
3. My family or I have had troubles with money due to COVID-19.
4. **I had difficulty accessing or paying for physical or mental health care due to COVID-19**
5. My work/school has been disrupted due to COVID-19.
6. My friendships have suffered due to COVID-19.
7. Political differences related to COVID-19 have been causing conflict with my family and friends (e.g., differing opinions on mask-wearing, vaccination).
8. **I had other conflicts or arguments not related to political differences with family members due to COVID-19 (e.g., conflicts about living arrangements, shared work space, schedule expectations).**
9. Political differences related to COVID-19 have been causing conflict in my neighborhood or city (e.g., differing opinions on mask-wearing, vaccination).
10. People around me have been more frightened than usual due to COVID-19.
11. People around me have been complaining more than usual due to COVID-19

12. I had to move when I did not plan to because of the coronavirus pandemic.

13. I was unexpectedly separated from family, friends, or others close to me because of the coronavirus pandemic (e.g., due to moves, travel restrictions).

14. I was unable to go outside for long periods of time because of the coronavirus pandemic.

15. I was unable to be with close family, friends, or partners because of the coronavirus pandemic.

16. I had less contact with good friends because of the coronavirus pandemic.

17. I had to cancel travel or experienced a major disruption in travel plans because of the coronavirus pandemic.

18. I had to cancel travel or postpone important events because of the coronavirus pandemic (e.g., events for a club, sporting events, major celebrations, prom, graduation ceremonies).

19. I had to take on additional responsibilities caring for others (e.g., siblings, other family members) due to the coronavirus pandemic.

20. My workload increased substantially due to COVID-19

21. Someone I rely on for financial support (e.g., parent) temporarily or permanently lost a job or had their work hours greatly reduced because of the coronavirus pandemic

22. I temporarily or permanently lost a job or had my work hours greatly reduced due to COVID-19

23. I was unable to complete important requirements for my education due to the coronavirus pandemic.

24. I had problems with online courses and/or remote work (e.g., slow connection, no computer or internet access, major differences in time zone).

25. I had to stop doing extra-curricular activities that I enjoy due to the coronavirus pandemic.

26. I had problems with my visa or study permit due to COVID-19

27. I was able to get vaccinated without any issues

28. My family and friends were able to get vaccinated without any issues

29. I experienced racism or discrimination due to COVID-19 (e.g., emotional abuse, verbal or physical assault)

30. Because of my race or ethnicity, I experienced psychological abuse due to COVID-19 (e.g., exclusion/isolation, blaming, name-calling)

31. Because of my race or ethnicity, I was verbally assaulted due to COVID-19 (e.g., told to "go back to where I came from")

32. Because of my race or ethnicity, I was physically assaulted due to COVID-19

33. Because of my race or ethnicity, I was targeted with vandalism due to COVID-19

34. My friend(s)/family of the same race or ethnicity experienced racism or discrimination due to COVID-19 (e.g., emotional abuse, verbal or physical assault)

35. My friend(s)/family of the same race or ethnicity experienced psychological abuse due to COVID-19 (e.g., exclusion/isolation, blaming, name-calling)

36. My friend(s)/family of the same race or ethnicity were verbally assaulted due to COVID-19 (e.g., told to "go back to where I came from")

37. My friend(s)/family of the same race or ethnicity were physically assaulted due to COVID-19

38. My friend(s)/family of the same race or ethnicity were targeted with vandalism due to COVID-19
39. My ethnic/racial group experienced racism or discrimination due to COVID-19 (e.g., emotional abuse, verbal or physical assault)
40. People of my ethnic/racial group experienced psychological abuse due to COVID-19 (e.g., exclusion/isolation, blaming, name-calling)
41. People of my ethnic/racial group was verbally assaulted due to COVID-19 (e.g., told to "go back to where I came from")
42. People of my ethnic/racial group was physically assaulted due to COVID-19
43. People of my ethnic/racial group was targeted with vandalism due to COVID-19
44. I was frequently at risk of exposure to COVID-19 (e.g., worked as an essential worker, volunteer position in a high-risk environment)
45. I am immunocompromised or at higher risk for complications related to COVID-19
46. **I had symptoms of COVID-19 (e.g., cough, fever, trouble breathing) but was unable to get tested.**
47. **I was tested for COVID-19.**
48. **I was quarantined for 2 weeks or longer.**
49. **I was diagnosed with COVID-19.**
50. Did you experience 'long-hauler' symptoms of COVID-19? (i.e., experiencing COVID-19 symptoms such as loss of taste & smell, shortness of breath, etc. for longer than two weeks?)
51. I was hospitalized due to COVID-19.
52. I was in the intensive care unit (ICU) due to COVID-19.

53. I was on a ventilator due to COVID-19.
54. I was exposed to someone who was diagnosed with COVID-19
55. Someone close to me was frequently at risk of exposure to COVID-19 (e.g., worked as an essential worker, volunteer position in a high-risk environment)
56. Someone close to me is immunocompromised or is at higher risk for complications related to COVID-19
57. Someone close to me was exposed to someone who was diagnosed with COVID-19
58. **Someone close to me had symptoms of COVID-19 (e.g., cough, fever, trouble breathing) but was unable to get tested.**
59. Someone close to me had to get tested for COVID-19 more than once
60. **Someone close to me was quarantined for 2 weeks or longer.**
61. **Someone close to me was diagnosed with COVID-19.**
62. Did someone close to you experience 'long-hauler' symptoms of COVID-19? (i.e., experiencing COVID-19 symptoms such as loss of taste & smell, shortness of breath, etc. for longer than two weeks?)
63. **Someone close to me was hospitalized due to COVID-19.**
64. Someone close to me was in the intensive care unit (ICU) due to COVID-19.
65. Someone close to me was on a ventilator due to COVID-19.

Bivariate associations between variables of interest

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. T1 Gain										
2. T1 Loss	.76**									
3. T2 Gain	.50**	.40**								
4. T2 Loss	.51**	.56**	.76**							
5. T1 RewP Residual	.65**	<.01	.31**	.13						
6. T2 RewP Residual	.18	-.04	.65**	<.01	.33**					
7. T1 Depressive Sx	-.06	-.05	-.03	.05	-.04	-.10				
8. T2 Depressive Sx	-.01	-.03	-.06	.08	.02	-.18	.39**			
9. Δ Depressive symptoms[a]	-.05	-.01	.02	-.06	-.07	.07	.48**	-.62**		
10. Δ RewP residual[a]	.40**	.03	-.29**	.11	.58**	-.58**	.06	.17	-.12	
11. PSQ Stressor Count	<.01	.15	.15	.34*	-.16	-.11	.09	.23	-.14	-.04

Table S1. Pearson correlations between variables of interest. [a]Measures of change in depressive symptoms and the RewP residuals were calculated with a simple difference score (T1 – T2) where a more positive score indicates a larger decrease.

*Significant at p <.05
**Significant at p<.01

Visualizing Change in the RewP

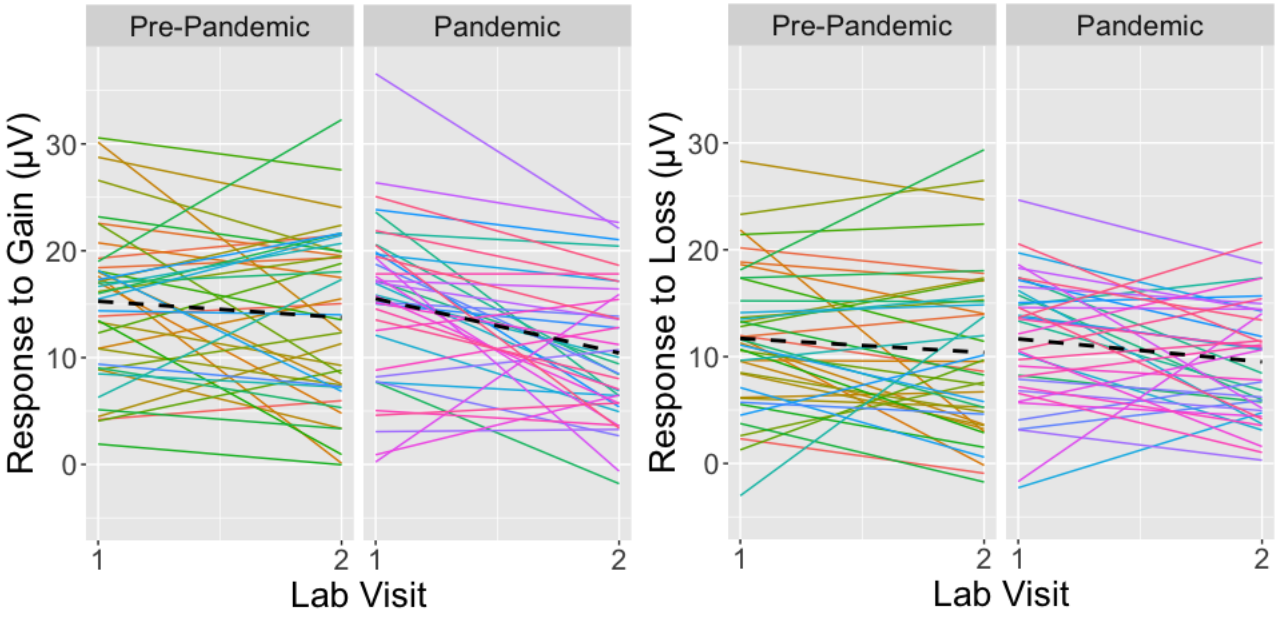

Figure S1. Spaghetti plots depicting individual trajectories of change in neural responses to gain and loss from baseline to follow-up. Each line represents a participant with 1 on the axis reflecting the baseline visit and 2 reflecting the follow-up visit.

Testing association between the degree of stress exposure and change in the RewP.

Previous studies have shown that those most impacted by the COVID-19 pandemic have shown the greatest increase in depressive symptoms (Hertz-Palmor et al., 2021; Venanzi et al., 2022; Watson et al., 2022; Zheng et al., 2021). Therefore, we sought to test whether stress exposure impacted the RewP in a dose-dependent manner such that those who reported the greatest number of pandemic-related stressors experienced the steepest decrease in the RewP from baseline to follow-up. We focused on stress exposure, rather than perceived stress severity, to limit confounds with other constructs that may be related to reward processing (e.g. depression; Harkness & Monroe, 2016).

We regressed the RewP residual measured during the COVID-19 pandemic on the baseline RewP residual and PSQ stressor count (Table S1). We found that PSQ stress count did not significantly predict the RewP residual measured during the COVID-19 pandemic, although the coefficient was in the expected direction (i.e. negative). It may be that we are underpowered to test between-person differences in this sample of 38 participants. It may also be that the PSQ, which was developed during the early months of the pandemic (Kujawa et al., 2020), was not the most sensitive measure to capture the stress experienced through the fall of 2021. Future research with a larger sample and perhaps a more in-depth assessment of stress is required to understand the nature of how naturalistic stressors impact neural reward processing.

Predictor	*B (SE)*	*β*	*p*
(Intercept)	-.13 (.39)		.74
Baseline RewP Residual	.28 (.17)	.27	.11
PSQ Count	-.02 (.05)	-.07	.67

Table S2. Regression results predicting the RewP residual measured during the pandemic

Associations between RewP and depressive symptoms

Full regression results from the model predicting follow-up depressive symptoms from baseline depressive symptoms, baseline RewP residual, and follow-up RewP residual.

Predictor	*B (SE)*	*β*	*p*
(Intercept)	27.41 (5.58)		<.001
Baseline depressive symptoms	0.42 (0.12)	.38	.001
Baseline RewP Residual	1.24 (1.36)	.10	.36
Follow-up RewP Residual	-1.93 (1.35)	-.16	.16

Table S3. Regression results predicting depressive symptoms measured at follow-up

Supplemental References

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Preface to Study 2

The results of Study 1 indicated that exposure to a prolonged multifaceted naturalistic stressor, in the form of the COVID-19 pandemic, was associated with a significant blunting of neural responses to monetary incentives. This finding supports the premise that chronic stressors can have a deleterious impact on reward sensitivity in humans. A major strength of this study was that it employed a quasi-experimental design. Although this does not afford the same degree of control as an experimental laboratory study, it does a better job of isolating the variable of interest (i.e. COVID-19 stress exposure) than a purely correlational study and has the advantage of studying naturally occurring conditions. Therefore, this study fills a critical gap in the literature by showing that prolonged, real-world stressors can prospectively lead to substantially impaired reward response, an outcome that was not seen in an unaffected control group.

While this study yielded strong evidence of the impact of stress exposure on reward response, it did not take into account other potential predictors of blunted reward response. This is important to consider as stress exposure is far from the only determinant of reward sensitivity and risk for depression. We therefore do not know the relative contribution of stress in predicting the RewP compared to other factors such as family history of depression. Furthermore, although we did collect a measure of neural response to social reward at baseline in our Study 1 participants, the social reward task involves a degree of deception and then debriefing. Accordingly, we were unable to take a second measure of social reward response during the pandemic. This made it impossible to evaluate the impact of real-world stress exposure on the social RewP, which may be more relevant to depression risk. Study 2 helps address some of these remaining questions by investigating the extent to which multiple known risk factors for depression were associated with smaller neural responses to social reward. More specifically, we

recruited for this study a sample of adult women with and without a past history of depression and their never-depressed adolescent daughters. We then tested whether a personal past history of depression and recent chronic interpersonal stress were independently associated with social reward response in the mothers. Similarly, we tested whether a maternal history of depression and recent chronic interpersonal stress were independently associated with social reward response in the daughters. This multigenerational case-control study allowed us to evaluate whether neural responses to social reward are blunted in individuals at risk for depression and to test the extent to which different factors (i.e. maternal depression history or personal depression history, interpersonal stress) might be independently related to impaired social reward response when considered together.

Study 2

Neural response to rewarding social feedback in never-depressed adolescent girls and their mothers with remitted depression: Associations with multiple risk indices

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Abstract

Prevention of depression requires a clear understanding of etiology. Previous studies have identified reduced neural responses to monetary reward as a risk factor for depression, but social reward processing may be particularly relevant to depression. This study investigated associations between neural responses to social reward and three well-established risk factors for depression: personal history, family history, and interpersonal stress. We examined the reward positivity (RewP), an event-related potential sensitive to rewarding feedback, in a sample of 85 women with and without remitted depression and their never-depressed adolescent daughters. In never-depressed daughters, maternal history of depression predicted a blunted social RewP, but interpersonal stress did not. In the mothers, greater interpersonal stress predicted a blunted RewP, but personal depression history was not significant. Combined, these data suggest that personal history, family history, and interpersonal stress may converge on social reward sensitivity, which may advance future research to understand the development of depression.

Keywords: social reward, depression, risk marker, adolescence, reward positivity

General Scientific Summary

This study examined whether individuals at elevated risk for depression had blunted neural responses to rewarding social feedback (i.e. acceptance) in a sample of mothers with a past history of depression at risk for a recurrent depressive episode, and their never-depressed adolescent daughters at risk for a first episode of depression. We found that mothers who experienced more interpersonal stress in the three months leading up to the study had less neural response to acceptance. Daughters whose mothers had had depression also had less brain activation to social acceptance. These results suggest that less neural response to social acceptance may be a risk marker for depression in some individuals.

Introduction

Major depressive disorder (MDD) is one of the most widespread mental health disorders and a primary contributor to the global burden of disease. In 2017 alone, over 163 million people worldwide experienced MDD, and the syndrome has become increasingly prevalent over the past twenty years (James et al., 2018). Because of the widespread and impairing impact of this disorder, it is important to identify risk markers that can identify those most vulnerable to developing MDD in order to intervene before the disorder progresses.

A significant barrier to these efforts is that MDD is both diagnostically and etiologically heterogeneous (Saveanu & Nemeroff, 2012). Despite this complexity, several potent risk factors for the disorder have been identified, each of which predicts the onset, maintenance, and severity of depressive episodes. These include personal history of depression (Burcusa & Iacono, 2007), family history of depression (Levinson, 2006), and stress (Kessler, 1997; Mazure, 1998), particularly interpersonal stress (Kendler et al., 2003; Monroe et al., 1999). However, even these well-established predictors, considered alone, do not account for all the variance in depressive outcomes. For example, a slight majority of those with a personal or immediate family history of depression will not experience a future depressive episode (Levinson, 2006; Monroe et al., 2019; Williamson et al., 2004), nor will all individuals experiencing significant stressors (Mazure, 1998), suggesting the need for ongoing research on how and when these risk factors culminate in depression.

Research on neural responses to reward may help to elucidate the pathways and mechanisms involved in the development of depression. Each of these risk factors for depression (personal history, family history, and stress) has shown independent associations with atypical neural responses to reward (Kujawa et al., 2020; Kujawa & Burkhouse, 2017; Pizzagalli et al.,

2008). An extensive body of research indicates that many depressed individuals show decreased neural responses to reward (Alloy et al., 2016; Keren et al., 2018). Reduced reward response has also been observed in individuals with remitted depression, who are at heightened risk for relapse (McCabe et al., 2009; Pechtel et al., 2013; Weinberg & Shankman, 2017; Whitton et al., 2016). Similarly, individuals with a family history of depression—particularly maternal history—have shown the same deficits, even before they show clinically-significant symptoms themselves (Foti et al., 2011; Kujawa, Proudfit, et al., 2014; Luking et al., 2016; Sharp et al., 2014).

Stress is also associated with blunted reward sensitivity. Experimentally controlled studies have observed decreased reward sensitivity following acute physical and psychosocial stressors (Bogdan & Pizzagalli, 2006; Ethridge et al., 2020). Naturally-occurring, interpersonal, and chronic life stress also predict blunted neural reward response and anhedonia (Berenbaum & Connelly, 1993; Hanson et al., 2016; Pizzagalli et al., 2007; Rappaport et al., 2019). Thus, each of the aforementioned risk factors appears to converge on neural responses to reward, suggesting the possibility that neural reward response may represent a final common pathway for depressive states (Auerbach et al., 2014), at least for some patients (Williams, 2017). Because these risk factors tend to cooccur, it is important to investigate how personal history of depression, family history of depression, and stress might predict reward response when considered together.

In addition, previous studies examining the associations between reward sensitivity and depression risk or stress have primarily focused on responses to monetary incentives. However, reward sensitivity is not a monolithic construct. Previous research has documented overlapping but non-redundant neural activation patterns to different rewards (Izuma et al., 2008; Lin et al., 2012; Rademacher et al., 2010). Similarly, work using the reward positivity (RewP), an event-

related potential derived from electroencephalogram (EEG) that is sensitive to rewarding feedback, has found only moderate correlations between the RewP elicited by monetary and social rewards (*r*s from .16 - .28; (Ait Oumeziane et al., 2017; Banica et al., under review; Ethridge et al., 2017; Pegg et al., 2021).

Moreover, given that deficits in social functioning play a critical role in the etiology and maintenance of MDD, careful study of neural responses to *social* rewards may be useful in understanding pathways to depression (Ait Oumeziane et al., 2019; Allen & Badcock, 2003; Kendler et al., 2003; Kupferberg et al., 2016). Consistent with this, MDD has been associated with less motivation to pursue social rewards (Brinkmann et al., 2014) and reduced endogenous opioid release in the nucleus accumbens after social acceptance (Hsu et al., 2015) while a blunted social RewP has been associated with depressive symptoms (Distefano et al., 2018; Kujawa et al., 2017). Consistent with work using monetary reward (Olino et al., 2014; Sharp et al., 2014), adolescents at familial risk for depression exhibited less neural activation to social reward in the ventral striatum and anterior cingulate cortex than low-risk adolescents (Olino et al., 2015). However, more research is needed to determine whether blunted social reward sensitivity shows similar associations with stress, personal history, and family history of depression, as does monetary reward responsiveness.

The present study aims to address this gap in the literature by assessing whether neural response to social reward, measured with the RewP, is associated with previous depressive episodes, family history, and life stress. We examined neural responses to social reward in women with remitted depression and their never-depressed adolescent daughters (relatively high risk for depression; HR) as well as women with no history of depression and their never-depressed daughters (relatively low risk; LR). Because the present study measured both

daughters' and mothers' RewPs, we were able to test social reward sensitivity in the context of risk for first-onset depression in adolescents (family history positive) and in the context of risk for relapse in adults (personal history positive). Additionally, by measuring interpersonal stress, we were able to assess the degree to which stress is associated with social reward response independently of personal or family history of depression. We hypothesized that women with a past history of depression would exhibit a blunted neural response to positive social feedback compared to never-depressed women, and that we would see the same effect in their high-risk but unaffected adolescent daughters. Finally, we expected that greater levels of interpersonal stress would be associated with a smaller RewP across groups, independently of personal or family history of depression.

Method

Participants

One hundred and nine dyads were recruited from the community through fliers and postings on social media. Eligibility was determined by phone interview using an adapted version of the MINI Neuropsychiatric Interview (Sheehan et al., 1998) for mothers' history of psychopathology. A head injury resulting in loss of consciousness was exclusionary. Mothers were recruited for the high-risk group if they had a past history of MDD and no history of mania, psychosis, or current substance abuse (Baskin-Sommers & Foti, 2015; Whitton et al., 2015). Mothers were recruited for the low-risk group if they had no history of any psychiatric diagnosis; however, specific phobia was not exclusionary for this group as it is less heritable, impairing, and predictive of children's internalizing risk compared to other disorders (Kendler et al., 1992). Maternal eligibility was updated post-enrollment based on the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2016) conducted during the lab visit.

Eighty-five mothers met inclusion criteria for the depression risk analyses. Of the 54 mothers recruited for the low-risk group, three were excluded from analyses for diagnoses other than specific phobia, and two did not complete the reward task, leaving 49 LR mothers. Of the 55 mothers recruited for the high-risk group, two were excluded from analyses due to current substance abuse, one for a past subthreshold manic episode, three for not meeting full criteria for a past MDE, nine for current depression, and four for not completing the task, leaving 36 mothers in the HR group.

Adolescent daughters (ages 10 – 19) were not screened for psychopathology at enrollment, but were excluded from analyses based on diagnoses from the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid; Sheehan et al., 2010) conducted during their lab visit. Daughters were excluded if they met criteria for current substance use disorder (n = 2). Additionally, because we are interested in understanding risk for first-onset depression, we excluded daughters with their own history of MDD (n = 25). The prevalence of lifetime depression in the daughters did not differ between the high- (n = 13) and low-risk (n = 14) groups (χ^2 = .077, p = .782). Daughters were excluded if their mother did not meet diagnostic criteria for the HR group (subthreshold depression, n = 2; manic symptoms, n = 1) or the LR group (DSM diagnosis other than specific phobia; n = 1). One daughter was excluded for not understanding the task, two for not completing it, and three for missing self-report questionnaire data. This left a final sample of 35 HR daughters and 37 LR daughters.

As reported by mothers given the following options, 76.5% of the eligible sample identified as “Caucasian”, 2.4% as “Chinese”, 2.4% “African-American”, 1.2% “Native/First Nations/Aboriginal”, 1.2% as “Arab/West-Asian”, 2.4% as “Hispanic”, 1.2% as “Japanese”, 8.2% as “Other”, and 4.7% not reported. The reported median household income was $90,000-

$99,999 CAD (range = <$10,000 - >$250,000), approximately $13,000 CAD greater than the median household income for families in the Montreal metro area (Statistics Canada, 2018). Additional demographics are reported in Table 1.

Mothers completed written informed consent for themselves and parental consent for daughters under age 18. Daughters under 18 provided assent and daughters over 18 provided consent. Each family received between $200–$225 CAD ($25/hour per individual) for participation. All procedures were pre-approved by McGill University's Research Ethics Board.

Procedure

Before their lab visit, participants completed an online questionnaire using Qualtrics online survey software (SAP America Inc.). During the lab visit, participants completed several computer-based tasks in a counterbalanced order while continuous EEG was recorded; one of these was the Island Getaway task. Results from other tasks are reported elsewhere (e.g., Ethridge et al., 2021). Mothers and daughters completed diagnostic interviews (SCID-5 and MINI-Kid respectively) and the UCLA Life Stress Interview (UCLA LSI; Hammen, 2004).

A full list of measures completed by participants, the task code, and deidentified data can be found at the following link: https://osf.io/zks9e/?view_only=f92d8c5c5eb342018e1b041e62281d2b.

Tasks and Measures

Self-Report. Daughters completed the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988). Because some did not answer every item, we computed individual averages out of the number of completed items for each daughter (Ethridge et al., 2021). Using this method, the mean PDS score was 3.30 (range = 1.20 - 4); the mean number of completed items was 4.78 (*SD* = 0.70).

To measure current depressive symptoms from the past two weeks, daughters completed the Mood and Feelings Questionnaire (MFQ; Angold et al., 1995). This 32-item scale demonstrated excellent internal consistency in our sample (Cronbach's alpha = .95). Mothers completed the Inventory for Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). To measure current depression, we used the General Depression Scale, a 20-item scale that demonstrated high internal consistency in our sample (Cronbach's alpha = .91).

Diagnostic Interviews. DSM diagnoses for mothers and daughters were obtained through interviews conducted by trained graduate students under the supervision of clinical psychology faculty members (AW or MD) and supported by monthly review meetings. Mothers were assessed using the SCID-5 (First, Williams, Karg, & Spitzer, 2016) for current and lifetime mood, anxiety, substance use, trauma and stressor-related, obsessive-compulsive, and psychotic disorders. Daughters were screened for the same disorders using the MINI-Kid (Sheehan et al., 1998). Inter-rater reliability for diagnoses was assessed with a subset of interviews, 20 each for SCIDs and MINIs. Four of the primary interviewers (CF, PE, IB, AS), blind to original diagnoses, watched recordings of interviews and recoded diagnoses. Inter-rater reliability was high for MDD, the primary disorder of interest to the study (Kappa = .88 in mothers, Kappa = .70 in daughters; Landis & Koch, 1977).

The UCLA Life Stress Interview. The UCLA Life Stress Interview (UCLA LSI; Hammen, 2004) was conducted by trained graduate students with both mothers and daughters to obtain a measure of chronic stress over the past three months. The UCLA LSI is a semi-structured interview and gold-standard measure for objectively assessing stressful life events and chronic stress in various domains. The adult version of this interview, administered to the mothers, included the domains of romantic relationships, close friendships, family relationships,

and target child relationship (the daughter participating in the study). Each domain was rated for objective chronic stress on a scale of 1-5. Individual domain scores were summed together to give an estimation of chronic interpersonal stress over the last three months such that a larger number indicates greater stress.

An adolescent version of the UCLA LSI was administered to the daughters, following procedures detailed above. Chronic stress ratings from the domains of romantic relationships, close friendships, social life, and family relationships were summed together to create a composite of chronic interpersonal stress from the last three months.

Social Reward Response. A modified version of the Island Getaway Task (Kujawa, et al., 2014) was used to elicit neural responses to acceptance and rejection feedback. In the task, participants are told that they will be playing a game against age-matched mothers and daughters in other laboratories. Participants create a profile including a picture. On each trial, participants are presented with a co-player's profile and vote to keep them in or kick them out of the game. After voting, they view a 1000ms fixation cross and then either a green thumbs up indicating acceptance or a red thumbs down indicating rejection from that co-player for 2000ms. Then, participants rate how much they like the co-player on a 9-point Likert scale and the next trial begins. Participants complete 51 trials over six rounds, receiving approximately 50% acceptance and 50% rejection feedback. For a more detailed description of this version of the task, please see the supplemental material and Weinberg and colleagues (2020).

Electroencephalogram Recording

We recorded continuous EEG using a BrainVision actiCHamp system (Brain Products, Munich, Germany) while participants completed Island Getaway. Participants wore a 32-electrode cap with the standard 10/20 layout and ground electrode at Fpz. We collected

electrooculogram (EOG) data with vertical electrodes placed one cm above and below one eye and horizontal electrodes placed one cm on the outside of both eyes in order to correct for eye movements during EEG recording. All electrode impedances were less than 20 kΩ prior to recording. The sampling rate for EEG collection was 1000Hz.

Offline analyses were conducted with Brain Vision Analyzer software (Brain Products, Munich, Germany). First, data were band-pass filtered with a Butterworth Zero Phase Filter using half-power cutoffs of 0.01 and 30 Hz and 24 db/oct slopes. Then, trials were segmented from 500ms preceding feedback to 1000ms post-feedback. Next, data were referenced to an average of the left and right mastoids. Eye movements and blinks were then corrected using vertical and horizontal EOG and a modification of Gratton, Coles, and Donchin's algorithm (1983). Additional artifacts were identified through a semi-automatic process: individual channels within trials were automatically rejected if they contained a voltage step of >50.0 μV between sample points, a voltage difference >175.0 μV within 400 ms intervals, or a voltage difference <0.50 μV within 100 ms intervals. Any remaining artifacts were identified then eliminated through visual inspection. Next, any channels with fewer than five usable trials were interpolated from three to four surrounding channels. Trials were averaged separately for acceptance and rejection feedback and were baseline corrected using the 200ms preceding feedback.

Principal Component Analysis

The component used to measure reward sensitivity in Island Getaway was the Reward Positivity (RewP), a frontocentral positivity maximal to positive relative to negative feedback, typically peaking between 325–375ms in this task (Ethridge et al., 2017; Kujawa et al., 2017; Pegg et al., 2019). Because the waveforms elicited by feedback in this task are complex and

involve overlapping componentry (Ethridge et al., 2017), we used a temporospatial principal component analysis (PCA) to empirically isolate the RewP from overlapping components (Ethridge et al., 2017; Weinberg et al., 2020). Please see the supplemental material for further information about the PCA.

Data analyses

We conducted robust analyses of variance (ANOVA; Keselman, Wilcox, & Li, 2003) on the PCA-derived ERP components to determine whether they significantly differentiated between acceptance and rejection feedback.

Pearson correlations were computed within the mother and daughter samples for all variables included in the regression analyses. To evaluate whether the RewP to social feedback was related to risk for depression and interpersonal stress in the mother and daughter samples, we ran a set of regression models predicting the RewP to acceptance feedback. These regression models included risk status (depression history for mothers, maternal depression history for daughters) and chronic interpersonal stress (UCLA LSI) as predictors while controlling for the neural response to rejection. By including neural response to rejection, we adjust for variance shared across both types of feedback, leaving the variance unique to neural response to acceptance as our outcome variable. This method has exhibited better psychometric properties than a simple difference score and is commonly used with this task (Ethridge & Weinberg, 2018; Meyer et al., 2017). The regression model for the daughter sample also controlled for pubertal development status (Forbes et al., 2010; Ladouceur et al., 2019).

We conducted supplementary analyses to investigate the extent to which mothers' and daughters' RewPs are correlated. These analyses can be found in the supplementary material under the heading "Familiality Analyses." We also included a number of sensitivity and

specificity analyses on neural response to rejection, daughter depressive symptoms, interpersonal stress domains, and depression recurrence in the supplement.

Results

Demographic variables from mothers and daughters at high and low risk for depression recurrence and onset respectively are presented in Table 1. While HR mothers reported significantly higher levels of current depressive symptoms than LR mothers, HR and LR daughters reported equivalent levels of depressive symptoms. There were no group differences in chronic interpersonal stress for mothers and daughters, nor were there group differences in pubertal status for daughters.

Reward Positivity

Figure 1A. depicts waveforms and scalp distributions for the PCA-derived RewP for high- and low-risk mothers and daughters. According to the results of the robust ANOVAs, the PCA-derived RewP did not significantly differentiate acceptance from rejection for either mothers ($t_{WJt/c}(1,89) = 1.45$, $p = 0.23$) or daughters ($t_{WJt/c}(1,93) = 3.63$, $p = 0.055$). In each case, the lack of a significant main effect of feedback appeared to be because the HR group had a larger neural response to rejection than acceptance.

RewP, depression risk, and interpersonal stress

Bivariate associations between variables included in the regression analyses are in Table 2. Regression results are presented in Table 3 with partial regression plots in Figure 1B. In the mother sample, greater interpersonal stress predicted a smaller neural response to social reward. The effect of depression history was not statistically significant ($p = .063$), but the effect ($\beta = -.11$) was in the hypothesized direction, and similar in magnitude to the effect of interpersonal stress ($\beta = -.12$).

In contrast, in the daughter sample, we observed a main effect of risk status, such that HR daughters had a significantly smaller RewP to acceptance, controlling for neural responses to rejection and pubertal status, compared to LR daughters. Interpersonal stress did not significantly predict the RewP.

Discussion

The present study examined whether established risk factors for depression, namely personal history of depression, maternal history of depression, and interpersonal life stress, predicted a blunted neural response to social reward in a sample of mothers and their adolescent daughters. We were particularly interested in whether these risk factors showed independent associations with social reward response when considered in tandem, which could suggest that they converge on maladaptive reward response on the pathway to depression. In a sample of never-depressed adolescent girls and their mothers with and without a personal history of depression, all with varying levels of interpersonal stress, we were able to test how these risk factors, taken together, predicted neural reward response to social feedback.

In the daughter sample, our hypothesis that adolescent girls at risk for first-onset depression would exhibit a blunted neural response to social reward was supported. Adolescents at higher risk due to a maternal history of depression exhibited a significantly blunted neural response to social acceptance compared to lower risk adolescents. This was evident despite the fact that the high- and low-risk daughters had equivalently low levels of depressive symptoms and no history of a depressive disorder. These findings are consistent with previous work observing abnormal monetary reward processing in non-depressed adolescents at risk for depression (Kujawa & Burkhouse, 2017; Michelini et al., 2020). Our findings advance the field

by demonstrating that neural reward sensitivity to social stimuli also appears to be a viable trait-like indicator of depression risk in adolescent females that may precede the onset of the disorder.

Our second hypothesis, that chronic interpersonal stress would be independently associated with a blunted social reward response, was not borne out in the daughter sample. The lack of a significant association between the social RewP and interpersonal stress in the daughter sample suggests the possibility that in adolescence, life stress may be an independent but parallel risk factor for depression alongside blunted social reward sensitivity. The absence of group differences in chronic interpersonal stress also implies that interpersonal stress may operate independently of family history, though this contradicts previous work finding greater stress in daughters of depressed mothers (Adrian & Hammen, 1993; Feurer et al., 2016). However, in previous work, greater stress in daughters was primarily associated with current depression in mothers (Feurer et al., 2016); because the high-risk mothers in our sample were in remission, we might expect less disparity in chronic stress between high- and low-risk daughters, though this is an issue for further research.

In the mother sample, we observed a different pattern of risk factors converging on the RewP. We found a negative effect of chronic interpersonal stress on the social RewP and a similarly-sized but nonsignificant effect of personal depression history. While the association between personal depression history and the social RewP did not reach significance, it was in the expected direction. Consistent with our predictions, however, greater interpersonal stress in mothers was associated with a smaller RewP to social reward, over and above personal depression history. This is consistent with previous findings that greater levels of acute psychosocial stress causally blunt neural and behavioral reward sensitivity (Bogdan & Pizzagalli, 2006; Ethridge et al., 2020) while chronic social stress is associated with reduced reward

sensitivity (Ethridge et al., 2018; Rappaport et al., 2019). Our results demonstrate that in this sample, recent chronic interpersonal stress also relates specifically to a blunted social reward response, which is overlapping but non-redundant with neural response to other rewards (Ethridge et al., 2017; Ethridge & Weinberg, 2018).

Although our hypotheses were supported in some instances, taken together, these results present mixed evidence for the overall hypothesis that personal depression history, family depression history, and life stress converge on social reward response. Family history had an independent effect on the social RewP in the never-depressed daughters but interpersonal stress did not. Interpersonal stress had an independent effect on the social RewP in the mothers, and the association was stronger than that observed for personal history, which was not statistically significant. These mixed findings should be considered in a broader sense. Depression is a highly heterogeneous disorder (Saveanu & Nemeroff, 2012), so while considering the interplay between different risk factors is important, we would expect that different risk factors will matter more for different people. There are many pathways to depression (Hasler et al., 2004; Levinson, 2006; Monroe et al., 2019; Williams, 2017) and to blunted reward sensitivity (Kujawa et al., 2020). Only some of those in our sample with a blunted social RewP will develop depression, just as only some of those with other key risk factors will become depressed (Levinson, 2006; Mazure, 1998; Monroe et al., 2019; Williamson et al., 2004). Therefore, it is possible that our hypothesized model of personal or family history and stress converging on neural response to social reward is part of the pathway to depression for *some* but not *all* people. It is also plausible that different risk factors matter more for first onset versus recurrence of depression (Lewinsohn et al., 1999). Furthermore, it is certain that there are other important neural and behavioral mediators not investigated here that help transform these risk factors into depressive

symptomology. In addition to determining how independent risk factors for depression relate to one another, it is increasingly important to determine which constellations of risk factors matter for which people, and when.

For example, it is not entirely clear why abnormal processing of social rewards might relate to social stress in adult women but not adolescent girls. The social ecology of adults and adolescents is very different – social life with peers becomes increasingly important to adolescents while they still remain dependent on their parents and family (Nelson et al., 2005; Spear, 2000; Steinberg, 2005). In that sense, it is surprising that the association between stress and social reward sensitivity is only apparent in adults due to the centrality of the social sphere in adolescence. We might expect that because developing strong social connections is so important in adolescence (Blakemore, 2018; Kandel, 1986), threats to social connection might be perceived as more important and stressful in adolescence compared to other time periods across the lifespan. Future research is required to understand developmental effects on the association between life stress and social reward sensitivity and why it might differ between adolescents and adults.

Importantly, although we observed a negative association between the social RewP and interpersonal stress in mothers, we cannot confidently establish the directionality of this association due to the cross-sectional nature of our data. Stress may impact neural processing of social rewards, but it is also possible that attenuated neural processing of social rewards impacts social behavior in a way that generates stress. Maladaptive monetary reward processing (measured by the RewP) has prospectively predicted increased dependent stressors over a period of 18 months, which in turn partially mediated the association between the RewP and future depression symptoms (Mackin et al., 2019), suggesting that blunted reward sensitivity may be a

mechanism for stress generation in depression (Hammen, 1991, 2005). A blunted social reward response might specifically predict interpersonal stress if it disincentivizes social interactions, facilitates social withdrawal, and impedes the ability to maintain healthy relationships (Auerbach et al., 2014; Davey et al., 2008). Social skills may suffer in those with low social reward sensitivity if they are less attuned to social cues (Auerbach et al., 2014), and there is evidence that those with a smaller social RewP engage with others in a less reciprocal manner (Weinberg et al., 2021). Therefore, the cross-sectional association between the RewP and stress observed in the mother sample should be examined as a dynamic association in future longitudinal studies.

In order to extend these findings, prospective longitudinal studies must be conducted using the risk factors investigated here with depression outcomes. It remains to be seen whether depressogenic effects of interpersonal stress are mediated by blunted social reward sensitivity (Pegg et al., 2019), at least in adult women at risk for depression recurrence. Similarly, we do not yet know to what extent the association between maternal depression history and offspring depression is mediated by social reward response. Investigating these questions will better contextualize these risk markers on the pathway to depression and also help identify when social reward response matters for future depression outcomes. Such longitudinal study designs will allow for more mechanistic investigations of *how* risk factors may together or separately lead to depression. For example, it will be important to explore the practical consequences of having blunted social reward sensitivity at the neural level in terms of social behavior, relationship quality, and interpersonal stress. Because social connection is so essential to human health and wellbeing (Diener & Seligman, 2002; Helliwell & Aknin, 2018; Inagaki, 2018), it is vital to continue to research social functioning deficits in depression (Hirschfeld et al., 2000; Kupferberg et al., 2016). It will also be important to assess whether, perhaps due to its increased relevance to

depression, a blunted social reward response may increase our ability to prospectively predict depression onset over and above other well-established risk factors like family history as well as neurobiological risk factors including monetary reward sensitivity (Freeman et al., under review; Michelini et al., 2020). Lastly, more work is needed to elucidate how a blunted social reward response develops in children of mothers with a depression history and whether it can be targeted for therapeutic intervention.

A notable limitation of the present study is that although we started with relatively large samples, due to various exclusions, our final samples for assessing depression risk were smaller, potentially resulting in some analyses being underpowered. However, the effect size observed for maternal history of depression in the daughters is similar in magnitude to that found in larger studies (e.g. Kujawa, Proudfit, et al., 2014). This research is still in an early discovery stage with little previously published on neural response to social reward in adolescents and adults (Olino et al., 2015), and future research with larger samples will be necessary to substantiate these findings.

Conclusion

Refining our understanding of risk factors for depression remains an important priority in the field of clinical science. This study adds evidence to the possibility that blunted social reward response may be a useful risk marker for depression in adolescents and adults, but also suggests that the nature of associations between neural response to social reward and other established risk factors are complex and may vary across individuals or subpopulations. Future research is needed to understand how and for whom these different risk factors come together to predict depression across the lifespan.

Author Note

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	Mothers			Daughters		
	Low-risk n = 49	High-risk n = 36		Low-risk n = 37	High-risk n = 35	
	M(SD)	M(SD)	p^*	M(SD)	M(SD)	p^*
Age	46.59(4.81)	45.78(7.29)	.56	13.76(2.42)	13.63(2.58)	.83
UCLA LSI	9.77(2.05)	9.51(2.01)	.57	8.20(1.57)	8.56(1.89)	.37
RewP acceptance[a]	5.48(5.74)	4.36(7.29)	.43	7.77(9.68)	0.30(9.37)	<.01
RewP rejection[a]	4.56(6.10)	4.86(8.22)	.85	6.71(10.77)	0.96(9.92)	.02
Depression symptoms[b]	34.19(9.67)	40.37(10.89)	.01	11.16 (10.14)	14.03(10.79)	.25
PDS				3.12(.69)	3.57(.82)	.69
	Median(IQR)	Median(IQR)	$p^\dagger$	Median(IQR)	Median(IQR)	$p^\dagger$
Household[c] Income	$125,000 ($122,500)	$80,000 ($90,000)	.03			
N depressive episodes	0(0)	2(1.75)		0(0)	0(0)	
	N(%)	N(%)	$p^\ddagger$	N(%)	N(%)	$p^\ddagger$
Psychotropic medication	0(0)	12(33.3)	<.01	0(0)	2(5.7)	.14
Lifetime anxiety diagnosis	3(6.1)	13(36.1)	<.01	3(8.1)	8(22.9)	.08
Past SUD	0 (0)	4(11.1)	.02	0(0)	0(0)	

Table 1. Demographic and study variables in the mother and daughter samples. UCLA LSI = sum score of chronic interpersonal stress from the UCLA Life Stress Interview. PDS = Pubertal Development Scale. Lifetime anxiety diagnosis includes anyone meeting lifetime specific phobia, social anxiety disorder, generalized anxiety disorder, panic disorder, separation anxiety disorder, and/or anxiety-related disorders such as PTSD and OCD. Any lifetime anxiety disorder in LR mothers is specific phobia. Past SUD indicates participant meeting criteria for past alcohol or substance use disorder. [a]PCA-derived RewP scores. [b]The IDAS-II general depression scale for mothers, the Mood and Feelings Questionnaire for daughters. [c]Data exclude 11 LR mothers and 5 HR mothers who declined to provide family income information. Income in CAD. *P-

value reflects result of a t-test. †P-value reflects result of a Mann-Whitney U-test. ‡P-value reflects result of a χ^2 test.

Mothers	1.	2.	3.	4.	5.	6.	7.
1.RewP Acceptance							
2.RewP Rejection	.83**						
3.Depression Hx[a]	-.09	.02					
4.Interpersonal stress	-.07	.05	-.06				
Daughters							
5.RewP Acceptance	.12	.25*	-.37**				
6.RewP Rejection	.17	.30**	-.27*		.83**		
7.PDS[b]			-.05		.25*	.30*	
8.Interpersonal Stress			.11	.33*[c]	.07	.02	.23*

Table 2. Bivariate associations between variables included in the regression analyses for the mother and daughter samples. * p <.05 , ** p <.01. [a]Maternal depression history, coded as 0 (LR) and 1 (HR). [b]Pubertal development scale. [c]Mother and daughter interpersonal stress included in this correlation are not independent as mothers' and daughters' report of their relationship with each other is factored into the interpersonal stress measure. When interpersonal stress is recalculated to exclude the mother-daughter relationship, the correlation is attenuated to $r = .08$, $p = .56$.

	Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
Mothers						.72	69.46	<.001
	Intercept	**5.69(1.90)**	**[1.91, 9.47]**		**.001**			
	RewP rejection	**0.77(0.05)**	**[0.66, 0.88]**	**.84**	**<.001**			
	Depression Hx[a]	-1.44(0.76)	[-2.95, 0.79]	-.11	.06			
	Interpersonal Stress	**-0.38(0.19)**	**[-0.75, -0.01]**	**-.12**	**.05**			
Daughters						.72	42.17	<.001
	Intercept	-0.50(3.90)	[-8.30, 7.29]		.90			
	RewP rejection	**0.75(0.07)**	**[0.62, 0.89]**	**.79**	**<.001**			
	Depression risk[a]	**-3.35(1.38)**	**[-6.10, -0.60]**	**-.17**	**.02**			
	PDS[b]	-0.25(0.95)	[-2.15, 1.66]	-.02	.80			
	Interpersonal stress	0.49(0.40)	[-0.31, 1.28]	.08	.22			

Table 3. Regressions for mothers and daughters predicting the RewP to acceptance from the RewP to rejection, depression risk status (past depression hx for mothers and maternal depression hx for daughters), interpersonal stress and, for daughters, pubertal status. Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (LR) and 1 (HR). [b]Pubertal development scale.

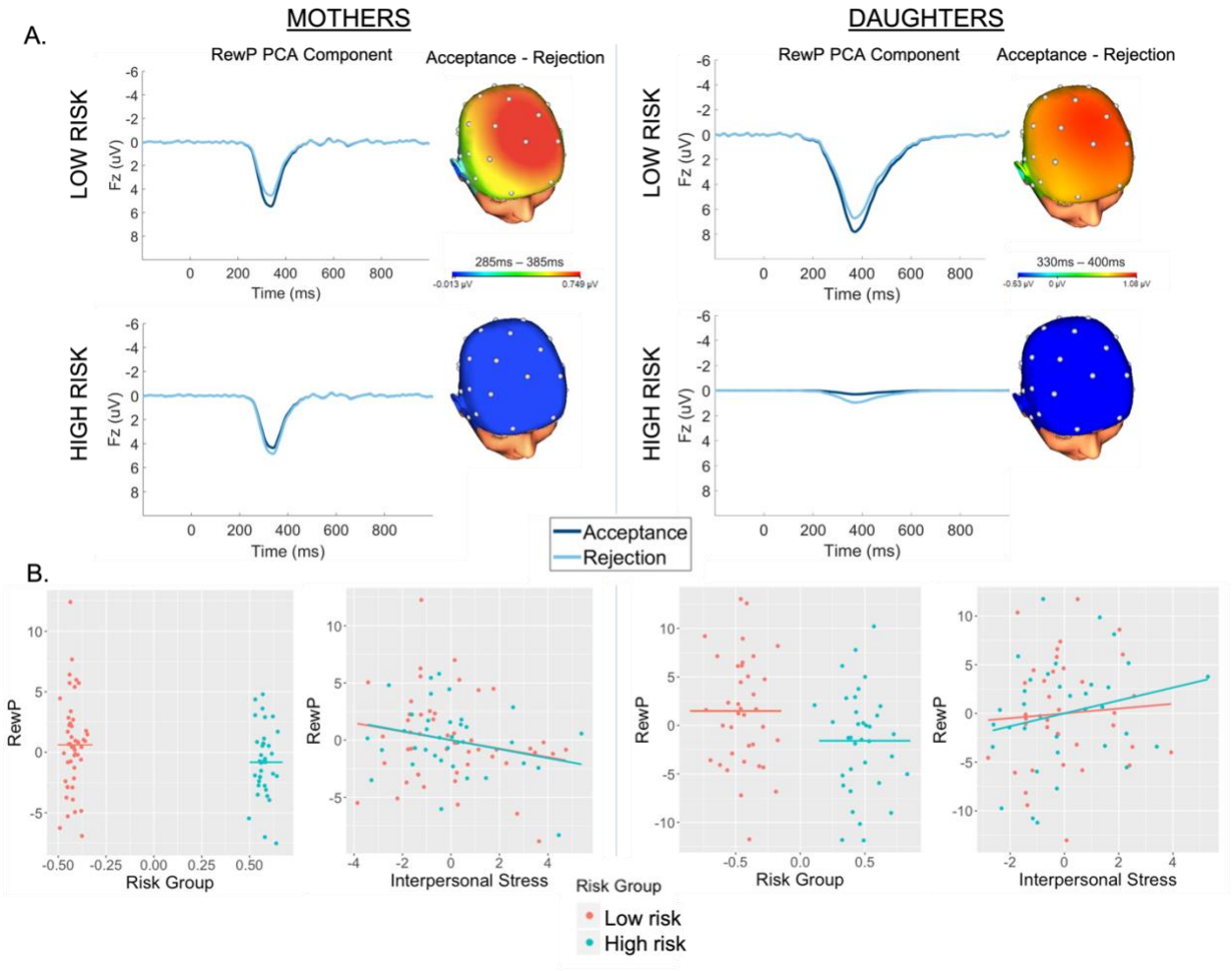

Figure 1. A. The PCA-derived RewP component waveform to acceptance and rejection at Fz in the low-risk mothers (top left), high-risk mothers (bottom left), low-risk daughters (top right), and high-risk daughters (bottom right) followed by the respective scalp distributions of response to acceptance minus response to rejection in the indicated time window. Time windows for depicting the difference were selected by centering a 100ms window around the peak of the component. B. Partial regression plots for mothers and daughters, depicting the associations between risk group and RewP to acceptance and interpersonal stress and RewP to acceptance, holding all other variables constant. Red dots represent LR mothers and daughters. Blue dots represent HR mothers and daughters.

Study 2: Supplemental Material

Island Getaway Task Description

The Island Getaway Task is a "Survivor"-style social interaction task compatible with EEG originally developed by Kujawa and colleagues (2014). The task involves voting computerized co-players on and off virtual islands and receiving such feedback in return. This allows us to collect neural response to acceptance and rejection in real time. The task involves minor deception in that participants are led to believe that they are playing against real people in real time rather than computerized peers. For more detail about the specific version of the task used in the present study, please see Weinberg and colleagues (2020).

Participants were told that they would be playing a game against other mothers and daughters in laboratory studies around the east coast. Four versions of the task were created: one for mothers, one for daughters ages 10 – 12, one for ages 13 – 15 and one for ages 16 – 19, so that they played against virtual female peers close in age. Participants created a profile with a picture and basic demographic information (e.g. name, hometown, interests) that would be visible to their co-players. They then proceeded through 51 trials divided into six rounds of the game. On each trial, the participant would be presented with a co-player's profile and would have to vote to accept or reject them, thereby choosing to keep or kick them off the virtual island. After voting on a co-player, they would view a 1000ms fixation cross followed by either a green thumbs up indicating acceptance from that co-player or a red thumbs down indicating rejection from that co-player for 2000ms. After receiving this feedback, participants would rate how much they liked the co-player on a 9-point Likert scale and the next trial would begin. At the end of each round, the co-player who received the fewest acceptances would be voted off the island and

the next round would begin. Participants always made it through to the sixth and final round. Participants received approximately 50% acceptance and 50% rejection feedback over the course of the game. Out of 51 trials, mothers had a mean of 26.86 (*SD* = 0.95) usable trials in the accept condition and 24.08 (*SD* = 1.07) in the reject condition while daughters had a mean of 26.98 (*SD* = 2.61) usable accept trials and 24.5 (*SD* = 2.66) reject trials.

After completing the task, participants were asked by an experimenter, "How much did you believe that you were playing against real players in real time?" and answered on a scale from one to five (five being believed fully). The median believability rating for mothers was 3 (IQR = 3) while the mode was 5. For the daughters, the median believability rating was 4 (IQR = 2) and mode was 5. Participants were debriefed following the task.

Principle Components Analysis

Method

We used the ERP PCA Toolkit in MATLAB (Dien, 2010b) to conduct a PCA to empirically isolate ERP components generated by the Island Getaway Task. Separate PCAs were conducted for the mother and daughter samples. Within each group, a data matrix was created for each participant including both accept and reject trials, and data at all timepoints and channels. First, we conducted a temporal PCA using a Promax rotation (Dien, 2010a; Dien et al., 2007). Based on a parallel test (Horn, 1965) after the first rotation, 25 temporal factors were retained in the mother sample accounting for 95.6% of the variance. In the daughter sample, 22 factors were retained, accounting for 96.7% of the variance. Using the covariance matrix and Kaiser normalization (Dien et al., 2005), scores were derived for each factor using all combinations of electrode, participant, and trial type.

Following the temporal PCA, a spatial ICA was conducted on each temporal factor to assess the spatial distribution of factor scores. All channels, trial types, and temporal factor scores for all participants were included. An infomax rotation was used to enforce independence between spatial factors (Dien, 2010a; Dien et al., 2007). A parallel test identified three spatial factors in both the mother sample and the daughter sample. Therefore, for the mothers, the combined temporospatial PCA resulted in 75 factor combinations that accounted for 81% of variance in the data. In the daughter sample, 64 factor combinations accounted for 79.9% of variance in the data.

Factor loadings from the final PCA results were converted back into voltages to analyze timing and spatial distributions. Separate robust analyses of variance (ANOVA; Keselman, Wilcox, & Li, 2003) were then conducted to assess which of the factors accounting for > 0.5% of variance significantly differentiated between acceptance and rejection. In both the mother and daughter samples, five factor combinations were similar in timing and spatial distribution to known ERP components. This judgement was made by examining grand averages collapsed across risk groups (Luck & Gaspelin, 2017). In the mother sample, a frontocentral positivity greater to acceptance than rejection feedback and maximal at Fz at 337ms was recognized as the RewP. In the daughter sample, this component peaked at 370ms and was also maximal at Fz. Other identified ERP components from the respective PCAs for mothers and daughters are presented in the supplementary material.

Results

In order to identify ERP components of interest, we conducted separate robust analyses of variance (ANOVA; Keselman, Wilcox, & Li, 2003) for mothers and daughters, and assessed which factors, out of the 22 in each sample that accounted for > 0.5% of variance, significantly

differentiated between acceptance and rejection. The results of these ANOVAs for components that resembled known ERPs in space and time are presented in table S1 below.

Temporospatial Factor Combination	Component	Temporal Peak	Peak channel	Spatial Distribution of accept-reject difference	T_{WJt}/c (1,89)	*P*
Mother Sample						
TF10SF1	N1	155 ms	Fz	Fronto-central negativity	0.01	.93
TF7SF1	P2	251 ms	Cz	Central positivity enhanced to accept	63.19	<.001
TF3SF1	RewP	337 ms	Fz	Fronto-central positivity enhanced to accept	1.45	.23
TF2SF2	P3	464 ms	P4	Parietal positivity enhanced to accept	36.66	<.001
TF1SF3	LPP	836 ms	Pz	Parietal positivity enhanced to accept	3.25	.08
Daughter Sample					T_{WJt}/c(1,93)	
TF6SF1	N1	188 ms	Cz	Central negativity enhanced to reject	49.42	<.001
TF5SF1	P2	230 ms	Cz	Central positivity enhanced to accept	24.10	<.001
TF2SF1	RewP	370 ms	Fz	Fronto-central positivity enhanced to accept	3.63	.06
TF3SF2	P3	584 ms	Pz	Parietal positivity enhanced to accept	21.54	<.001
TF1SF3	LPP	842 ms	O1	Occipital positivity enhanced to accept	28.12	<.001

Table S1. Temporospatial factor combinations that resembled known ERP components and accounted for more than 0.5% of the variance.

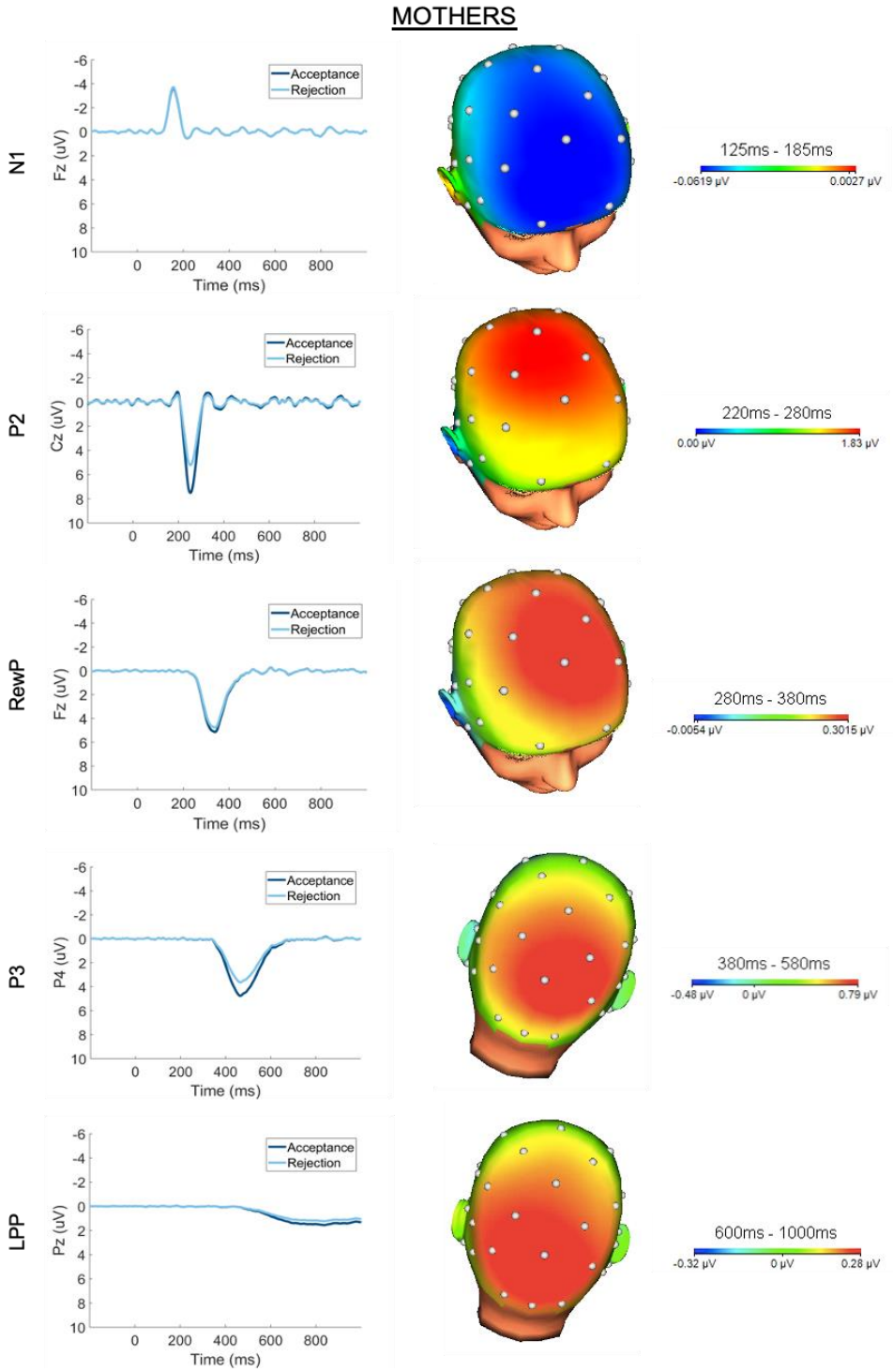

Figure S1. The results of the Principal Components Analyses (PCA) from the mother sample. PCA-derived waveforms and scalp distributions are collapsed across risk groups and therefore represent the whole sample. Waveforms on the left-hand side depict the responses to acceptance

and rejection and scalp distributions on the right-hand side depict the difference in neural response based on feedback in the time-window of the component. The scalp distribution for the N1 reflects the response to rejection minus the response to acceptance while the scalp distributions for the remaining components represent the response to acceptance minus the response to rejection.

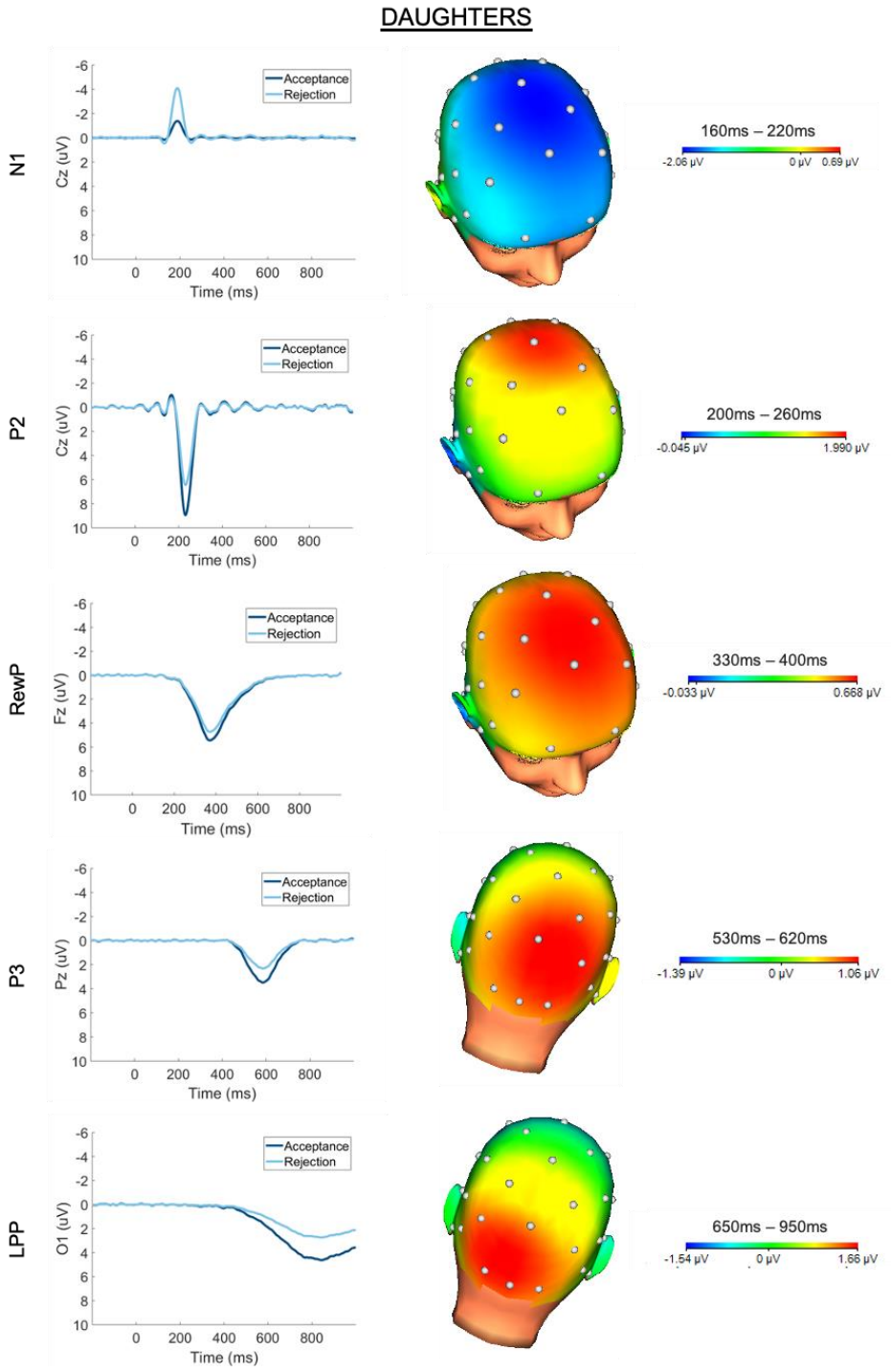

Figure S2. The results of the Principal Components Analyses (PCA) from the daughter sample. As with the mother sample, PCA-derived waveforms and scalp distributions are collapsed across both risk groups and therefore represent all daughters. Waveforms on the left-hand side depict

the responses to acceptance and rejection and scalp distributions on the right-hand side depict the difference in neural response based on feedback in the time-window of the component. The scalp distribution for the N1 reflects the response to rejection minus the response to acceptance while the scalp distributions for the remaining components represent the response to acceptance minus the response to rejection.

Familiality analyses

Method

For the analysis of the familiality of the social RewP, we removed all exclusion criteria other than not completing or understanding the task. This is because we are interested in whether mother and daughter RewPs are correlated independent of diagnostic factors. Therefore, this analysis included 96 dyads. The breakdown of ethnicities as reported by the mothers for the full sample included in the familiality analysis was 77.7% Caucasian, 2.1% Chinese, 2.1% African-American, 1% Caribbean, 1% Native/First Nations/Aboriginal, 2.1% Arab/West Asian, 2.1% Hispanic, 1% Japanese, and 9.4% other with 3.1% not reporting on their ethnicity. Additional demographics for the participants included in this analysis are presented in supplementary table S2.

We tested correlations between mothers' and daughters' residualized RewP difference scores. This residualized difference score is computed from a regression predicting the PCA-derived response to acceptance from response to rejection and captures variance in the RewP unique to acceptance processing. It will be referred to as $RewP_{resid}$. We also controlled for daughters' pubertal status using the PDS because of the wide developmental span in our sample and evidence that pubertal status moderates the relationship between mother and daughter

response to monetary reward (Ethridge et al., 2021). The partial correlation between mother and daughter $RewP_{resid}$ controlling for PDS included only 92 dyads due to missing PDS scores.

Results

A Pearson correlation between mothers' and daughters' $RewP_{resid}$ was calculated to examine the familiality of this component. There was no statistically significant association between mother and daughter $RewP_{resid}$ ($r(94) = -.14$, $p = .17$). We repeated this correlation controlling for daughter-reported PDS. Again, we did not observe a significant association between mother and daughter $RewP_{resid}$ controlling for daughter PDS ($r(90) = -.12$, $p = .24$).

Discussion

In our primary analyses, the high-risk adolescents had a significantly blunted RewP and their previously-depressed mothers had a numerically smaller RewP than their low-risk counterparts. Therefore, we might expect that one way in which mothers confer risk of depression to their daughters is through the transmission of abnormal social reward processing. It is believed that though depression is moderately heritable (Sullivan et al., 2000), intergenerational transmission of depression occurs not through a single gene but rather through the inheritance of a number of hereditary traits or endophenotypes relevant to depression (e.g. neuroticism, stress reactivity, negative affect; Gotlib & Colich, 2014). While impaired neural reward response to social feedback could theoretically be such a hereditary trait, in the present study we observed no significant association between mother and daughter RewP with or without controlling for daughter pubertal status. Instead, we observed a small negative correlation, though this was not statistically significant. However, two prior studies of the familiality of the monetary RewP have observed a significant negative association between mother and child RewP (Moser, Fisher, Hicks, Zucker, & Durbin, 2018; Ethridge et al., 2021),

which is moderated by the pubertal status of the child (Ethridge et al., 2021). The lack of a positive association between mother and daughter social RewP in the present study, in conjunction with these previous findings, suggest that the way reward sensitivity develops in adolescents at high and low risk for depression is complicated. More work is warranted to understand what is transmitted from mothers with a depression history to their daughters, and how it is transmitted.

	Mothers n = 96	Daughters n = 96
	M (SD)	M (SD)
Age	45.83 (5.81)	14.4 (2.56)
Median household income[a]	$90,000	-
UCLA	9.77 (2.03)	8.74 (1.87)
RewP acceptance	5.18 (6.11)	6.09 (9.72)
RewP rejection	4.89 (6.76)	5.34 (9.83)
Symptoms of depression[b]	38.32 (12.28)	48.68 (14.93)
PDS	-	3.25 (0.71)
	%	%
Psychotropic medication	17	6.5
Lifetime anxiety diagnosis	26	25
Lifetime SUD	9.4	4.2

Table S2. Demographic and study variables in the full mother and daughter samples, who were included in the familiality analysis. UCLA refers to the sum score of chronic interpersonal stress from the UCLA LSI and PDS refers to the Pubertal Development Scale. Lifetime anxiety diagnosis includes anyone meeting past or present specific phobia, social anxiety disorder, generalized anxiety disorder, panic disorder, separation anxiety disorder, and/or anxiety-related disorders such as post-traumatic stress disorder and obsessive-compulsive disorders. Lifetime SUD indicates any participant meeting criteria for a past alcohol or other substance use disorder. [a]Median income in CAD displayed instead of mean. These data exclude 22 mothers who

declined to provide family income information. [b]The IDAS general depression scale is reported here for the mothers and the MFQ is reported for the daughters.

Supplementary Exploratory Analyses

Neural response to rejection

We conducted specificity analyses in order to understand whether the associations between personal history of depression, maternal history of depression, and interpersonal stress were specific to neural response to social acceptance compared to neural response to rejection. To do this, first we conducted the same regression analyses as in the manuscript, but instead used neural responses to rejection in the time-window of the RewP as the outcome variable and controlled for the RewP elicited by acceptance. We found that for mothers, neither past depression history nor interpersonal stress was a statistically significant predictor of the RewP to rejection; however, the effect of interpersonal stress on rejection was similarly sized to that found for acceptance in our previous analyses (Table S3). For daughters, neither maternal depression history nor interpersonal stress was significantly associated with the RewP to rejection. This suggests that the effect of maternal depression history on the social RewP is specific to acceptance rather than rejection in adolescent females. However, a caveat to these analyses is that the RewP is typically conceptualized as the relative difference between neural response to acceptance and rejection feedback, making interpretation of associations with neural responses to rejection in this time window difficult. An important future direction for this work will be to isolate neural response to acceptance and rejection in comparison to a valid "neutral" feedback condition so as to get independent measures of neural response in the time-window of the RewP to acceptance and rejection, to determine whether it is appropriate to include rejection as a comparison condition for acceptance.

		RewP						
	Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
Mothers						.72	68.44	<.001
	Intercept	**-4.49(2.15)**	**[-8.76, -0.22]**		**.04**			
	RewP acceptance	**0.93(0.07)**	**[0.80, 1.06]**	**.85**	**<.001**			
	Depression Hx[a]	-1.43(0.84)	[-2.40, 3.11]	-.10	.09			
	Interpersonal Stress	-0.41(0.21)	[-0.01, 0.82]	-.12	.05			
Daughters						.70	39.67	<.001
	Intercept	-1.35(4.19)	[-9.71, 7.01]		.75			
	RewP acceptance	**0.86(0.08)**	**[0.71, 1.02]**	**.82**	**<.001**			
	Depression risk[a]	1.00(1.54)	[-2.07, 4.07]	.05	.52			
	PDS[b]	1.68(1.00)	[-0.32, 3.68]	.12	.10			
	Interpersonal stress	-0.48(0.43)	[-1.33, 0.38]	-.08	.27			

Table S3. Regressions for mothers and daughters predicting the RewP to rejection from the RewP to acceptance, depression risk status (past depression hx for mothers and maternal depression hx for daughters), interpersonal stress and, for daughters, pubertal status. Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (low-risk) and 1 (high-risk). [b]Pubertal development scale.

We also conducted similar specificity analyses using the PCA-derived N1 component, an early ERP component that is elevated to rejection relative to acceptance feedback and has been studied as an index of rejection sensitivity (Harrewijn et al., 2018; Kujawa et al., 2017, 2020). This model was identical to the one described above but with the N1 to rejection as the outcome variable and the N1 to acceptance as a predictor variable. The results from these analyses suggest that in the mother sample, past depression history and interpersonal stress are not significantly associated with rejection sensitivity measured with the N1 (Table S4). Results from the daughter sample suggest similar findings, that maternal depression history and stress are not statistically significantly associated with the N1 to rejection. However, although the effect of maternal depression history on the N1 in daughters is not significant, the effect size suggests that maternal depression may have a modest blunting effect on the N1 (because the N1 is a negative-going component, a positive association suggests a *smaller* N1), which might emerge as a significant predictor in a larger sample. If this finding were to be replicated in a larger sample, taken together with our findings with the RewP, it may reflect an overall blunting of neural responsivity to social feedback in adolescents at risk for depression.

		N1						
	Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
Mothers						.20	6.73	<.001
	Intercept	**-3.99(1.6)**	**[-7.18, -0.80]**		**.02**			
	N1 acceptance	**0.47(0.11)**	**[0.25, 0.70]**	**.42**	**<.001**			
	Depression Hx[a]	0.44(0.61)	[-0.77, 1.65]	.07	.47			
	Interpersonal Stress	0.18(0.15)	[-0.12, 0.48]	.12	.22			
Daughters						.67	33.49	<.001
	Intercept	**-6.41(2.66)**	**[-2.41, 0.02]**		**.02**			
	N1 acceptance	**0.71(0.07)**	**[0.58, 0.84]**	**.82**	**<.001**			
	Depression risk[a]	1.79(0.97)	[-0.14, 3.72]	.14	.07			
	PDS[b]	1.13(0.63)	[-0.14, 2.39]	.13	.08			
	Interpersonal stress	-0.15(0.27)	[-0.69, 0.39]	-.04	.58			

Table S4. Regressions for mothers and daughters predicting the N1 to rejection from the N1 to acceptance, depression risk status (past depression hx for mothers and maternal depression hx for daughters), interpersonal stress and, for daughters, pubertal status. Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (low-risk) and 1 (high-risk). [b]Pubertal development scale.

Daughter depressive symptoms

We ran a sensitivity analysis to ensure that the effect of maternal depression history on the daughter's social RewP was not confounded by daughters' own depressive symptoms. To assess this, we regressed neural response to social acceptance on maternal depression history, interpersonal life stress, neural response to rejection, pubertal status, and depressive symptoms in the daughter sample. Our results indicated that the effect of maternal history of depression was still a significant predictor when the daughters' own depressive symptoms were added to the model (Table S5).

Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
					.72	33.28	<.001
Intercept	-0.18(4.10)	[-9.71, 7.01]		.97			
RewP rejection	**0.75(0.07)**	**[0.62, 0.89]**	**.79**	**<.001**			
Depression risk[a]	**-3.31(1.40)**	**[-6.10, -0.52]**	**-.16**	**.02**			
PDS[b]	-0.18(0.99)	[-2.16, 1.80]	-.01	.86			
Interpersonal stress	0.53(0.43)	[-0.32, 1.38]	.09	.22			
Depressive symptoms[c]	-0.02(0.07)	[-0.17, 0.13]	-.02	.79			

Table S5. Regressions for daughters predicting the RewP to acceptance from the RewP to rejection, depression risk status (maternal depression history), interpersonal stress, pubertal status, and depressive symptoms measured with the Mood and Feelings Questionnaire. Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (no maternal depression history) and 1 (maternal depression history). [b]Pubertal development scale. [c] Measured with the Mood and Feelings Questionnaire.

Stress domains

In order to determine whether different facets of interpersonal stress might be differentially associated with the social RewP, exploratory regression models were conducted separately in the mother and daughter samples. These models were similar to the regression models in the main text, but instead of including the UCLA Life Stress Interview as a sum score, the individual domains that comprise that sum score were added into the regression as separate predictors. For the mother sample, these individual domains included romantic, friend, family (excluding the daughter who participated in the study), and target child (i.e. the daughter who

participated in the study). For the daughter sample, these domains included close friend, social life, romantic, and family. These individual domains were all scored between 1-5, with 5 being the most objectively stressful and 1 being the least objectively stressful.

In the mother sample, the negative association between chronic interpersonal stress and the social RewP appears to be driven by stress in friendships and, to a lesser degree, the relationship with the daughter included in the study (Table S6). In the daughter sample, while there was no statistically significant association between the sum of interpersonal stress and the social RewP, when broken down by domain it appears that there is a positive association between social life stress (this excludes close friendships) and the social RewP that approaches significance ($\beta = .17$, $p = .051$; Table S6). The associations between the remaining three domains and social RewP were not statistically significant.

	Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
Mothers						.72	68.44	<.001
	Intercept	**-4.49(2.15)**	**[-8.76, -0.22]**		**.04**			
	RewP acceptance	**0.93(0.07)**	**[0.80, 1.06]**	**.85**	**<.001**			
	Depression Hx[a]	-1.43(0.84)	[-2.40, 3.11]	-.10	.09			
	Close friendships	**-1.12(0.49)**	**[-2.09, -0.14]**	**-.15**	**.03**			
	Romantic	0.29(0.51)	[-0.73, 1.32]	.04	.57			
	Family	0.35(0.47)	[-0.59, 1.28]	.05	.46			
	Target child	-1.35(0.70)	[-2.75, 0.05]	-.12	.06			
Daughters						.70	39.67	<.001
	Intercept	-1.35(4.19)	[-9.71, 7.01]		.75			
	RewP acceptance	**0.86(0.08)**	**[0.71, 1.02]**	**.82**	**<.001**			
	Depression risk[a]	1.00(1.54)	[-2.07, 4.07]	.05	.52			
	PDS[b]	1.68(1.00)	[-0.32, 3.68]	.12	.10			
	Close friendships	-1.17(1.34)	[-3.86, 1.51]	-.07	.39			
	Social life	2.31(1.16)	[-0.14, 4.63]	.17	.05			
	Romantic	0.94(1.28)	[-1.62, 3.49]	.06	.47			
	Family	-0.37(0.87)	[-2.11, 1.37]	-.03	.67			

Table S6. Regressions for mothers and daughters predicting the RewP to acceptance. In the mother sample, predictors include the RewP to rejection, depression risk status (past depression history), and the following chronic interpersonal stress domains from the UCLA Life Stress Interview: close friendships, romantic relationships, family relationships, and relationship with target child (i.e. the daughter who participated in the study. In the daughter sample, predictors include the RewP to rejection, depression risk status (maternal depression history), pubertal status, and the following chronic interpersonal stress domains from the UCLA Life Stress Interview: close friendships, social life, romantic relationships, and family relationships.

Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (low-risk) and 1 (high-risk).

[a]Coded as 0 (low-risk) and 1 (high-risk). [b]Pubertal development scale.

Depression recurrence

Several previous studies assessing reward processing in children with a family history of depression restricted their sample to children of parents with recurrent depression (Gotlib et al., 2010; McCabe et al., 2012; Olino et al., 2015; Sharp et al., 2014). Therefore, we conducted an additional sensitivity analysis to determine whether the effects of past depressive episodes and maternal depression on the social RewP were driven by women with recurrent depression. To do this, we reran our regression models from the main text, excluding mothers with only a single episode (n = 12) and their daughters (n = 7). In the mother sample, the effect size for past depression history was the same size as in the original analysis but was no longer statistically significant, presumably due to the decrease in sample size (Table S7). The effect of maternal depression history on daughters' social RewP remained significant (Table S7) and of a similar magnitude (β = -.18 vs -.17), suggesting that a maternal history of recurrent depression may not be a significantly stronger predictor than maternal depression history in general. This should be tested further with larger samples with adequate representation of daughters with a maternal history of non-recurrent depression compared to daughters with a maternal history of recurrent depression.

	Predictor	*b(SE)*	*95% CI*	*β*	*p*	R^2	*F*	*p*
Mothers						.70	57.59	<.001
	Intercept	**5.78(2.05)**	**[1.70, 9.86]**		**.01**			
	RewP rejection	**0.76(0.06)**	**[0.64, 0.88]**	**.84**	**<.001**			
	Depression Hx[a]	-1.47(0.87)	[-3.20, 0.25]	-.11	.09			
	Interpersonal stress	-0.39(0.20)	[-0.79, 0.02]	-.12	.06			
Daughters						.70	38.52	<.001
	Intercept	-2.20(4.31)	[-10.82, 6.42]		.61			
	RewP rejection	**0.74(0.07)**	**[0.60, 0.89]**	**.78**	**<.001**			
	Depression risk[a]	**-3.90(1.54)**	**[-6.98, -0.82]**	**-.18**	**.01**			
	PDS[b]	0.06(1.04)	[-2.01, 2.13]	<.01	.95			
	Interpersonal stress	0.59(0.43)	[-0.28, 1.45]	.10	.18			

Table S7. Regressions for mothers and daughters predicting the RewP to acceptance from the RewP to rejection, depression risk status (past depression hx for mothers and maternal depression hx for daughters), interpersonal stress and, for daughters, pubertal status. Mothers with a single depressive episode and their daughters were excluded from these models. Significant predictors (p-values < .05) are in bold. [a]Coded as 0 (low-risk) and 1 (high-risk).

[a]Coded as 0 (low-risk) and 1 (high-risk). [b]Pubertal development scale.

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Preface to Study 3

Study 2 found associations between risk factors for depression and blunted neural response to social rewards; however, the patterns of associations differed between the adolescent and adult samples. In the never-depressed adolescent daughters, a maternal history of depression but not chronic interpersonal stress was associated with significantly impaired social reward response. In contrast, recent chronic interpersonal stress was associated with reduced social reward responses in mothers while the association between a personal depression history and social reward response was in the hypothesized direction but not statistically significant. These findings highlight that both stress exposure and family factors can predict blunted social reward response, but that these associations vary across distinct groups.

Taken together, Studies 1 and 2 highlight multiple nuanced predictors of impaired neural reward response including real-world stress exposure and maternal history of depression. This helps advance our understanding of this candidate endophenotype for depression and how it is linked to other known risk factors for the disorder. Yet, the question remains as to when blunted or impaired reward responses actually culminate in depression. In Study 1, even though we saw a marked reduction in monetary reward response, contrary to our hypotheses, it was not accompanied by a corresponding increase in depressive symptoms. In Study 2, we observed that adolescent girls at elevated risk for depression had significantly blunted neural responses to social reward. However, because this study was cross-sectional, we cannot know for sure whether the participants with small social RewPs will actually go on to develop depression in the future. Therefore, Study 3 aimed to address this question of when blunted neural responses to reward are likely to lead to depression, considering reward type and stress exposure. In this study, we tested whether the monetary and social RewP measured before the COVID-19

pandemic prospectively predicted depressive symptoms over the first six months of the pandemic. This study allowed us to evaluate whether monetary or social reward response is a stronger predictor of depressive symptoms and whether the experience of stress heightened the association between blunted neural response to reward and depressive symptoms, consistent with a diathesis-stress model.

Study 3

Neural response to social but not monetary reward predicts increases in depressive symptoms during the COVID-19 pandemic

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Short title: Reward responses and pandemic depressive symptoms

Abstract

The prevalence of depressive symptoms has increased during the COVID-19 pandemic, especially among those with greater pandemic-related stress exposure; however, not all individuals exposed to pandemic stress will develop depression. Determining which individuals are vulnerable to depressive symptoms as a result of this stress could lead to an improved understanding of the etiology of depression. This study sought to determine whether neural sensitivity to monetary and/or social reward prospectively predicts depressive symptoms during periods of high stress. 121 participants attended pre-pandemic lab visits where they completed monetary and social reward tasks while electroencephalogram was recorded. Subsequently, from March to August 2020, we sent eight questionnaires probing depressive symptoms and exposure to pandemic-related stressors. Using repeated-measures multilevel models, we evaluated whether neural response to social or monetary reward predicted increases in depressive symptoms across the early course of the pandemic. Furthermore, we examined whether neural response to social or monetary reward moderated the association between pandemic-related episodic stressors and depressive symptoms. Pandemic-related stress exposure was strongly associated with depressive symptoms. Additionally, we found that blunted neural response to social but not monetary reward predicted increased depressive symptoms during the pandemic. However, neither neural response to social nor monetary reward moderated the association between episodic stress exposure and depressive symptoms. Our findings indicate that neural response to social reward may be a useful predictor of depressive symptomatology under times of chronic stress, particularly stress with a social dimension.

1. Introduction

For much of the world's population, the COVID-19 pandemic has been a chronic and uncontrollable stressor due to its far-reaching impacts on health, financial stability, and social connectedness (Arora et al., 2020; Jewell et al., 2020; Zheng et al., 2021). For many, this chronic stress has also been punctuated by acute episodic stressors such as job loss, illness, or death of a loved one (Kujawa, Green, Compas, Dickey, & Pegg, 2020). Both chronic and episodic stressors are prominent risk factors for depression (Hammen, 2005; Kendler, Karkowski, & Prescott, 1999; Kessler, 1997; McGonagle & Kessler, 1990). Accordingly, depressive symptoms have significantly increased in the general population compared to pre-pandemic levels (Arora et al., 2020; Elmer, Mepham, & Stadtfeld, 2020; Jewell et al., 2020), particularly for those exposed to greater pandemic-related stressors (Ettman et al., 2020; Kujawa, Green, et al., 2020; Zheng et al., 2021). Nonetheless, not all individuals will develop depression even under substantial stress (Mazure, 1998; Monroe, Anderson, & Harkness, 2019). Therefore, it is critical to be able to prospectively predict which individuals are most susceptible to depression when facing chronic or episodic stressors such as those implicated in the COVID-19 pandemic. This will allow for more targeted efforts at prevention and early intervention.

One potentially useful marker of vulnerability to stress is blunted neural reward sensitivity. Never-depressed individuals with a blunted reward response are more likely to develop depression (Luking, Pagliaccio, Luby, & Barch, 2016; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016; Stringaris et al., 2015); however, some studies do not observe this main effect of reward response predicting future depressive symptoms. Instead, there is evidence that individuals with a blunted neural response to rewards may show increased

depressive symptoms specifically following stress exposure (Burani et al., 2019; Feurer et al., 2021; Nikolova, Bogdan, Brigidi, & Hariri, 2012; Pegg et al., 2019; Sandre, Bagot, & Weinberg, 2019). This suggests that a potential mechanism by which low reward sensitivity leads to depression is through enhanced stress susceptibility (Auerbach, Admon, & Pizzagalli, 2014; Ethridge, Ali, Racine, Pruessner, & Weinberg, 2020; Pizzagalli, 2014).

Much of this research has focused on neural responses to monetary rewards though sensitivity to other incentive types may play an important role. In particular, social reward sensitivity may be a more relevant risk marker for depression due to the prominent social impairment associated with depression (Hirschfeld et al., 2000; Kupferberg, Bicks, & Hasler, 2016). There is evidence that a blunted neural response to social reward is present in those at risk for depression (Freeman et al., 2022; Olino, Silk, Osterritter, & Forbes, 2015) and in those with elevated depressive symptoms (Distefano et al., 2018; Kujawa, Kessel, Carroll, Arfer, & Klein, 2017) or major depressive disorder (Hsu et al., 2015). Some findings suggest that neural response to social reward is more closely correlated with depressive symptoms than neural response to monetary reward (Ait Oumeziane, Jones, & Foti, 2019; Banica, Schell, Racine, & Weinberg, 2022; Chan et al., 2015; Pegg, Arfer, & Kujawa, 2021; Zhang et al., 2020). Blunted neural response to social reward has also been found to moderate the association between lifetime interpersonal stress exposure and depressive symptoms; however, this study was conducted cross-sectionally (Pegg et al., 2019). The present study examined neural response to monetary and social reward as prospective predictors of depression in the context of both chronic and episodic stress.

To do this, we measured neural responses to reward using the Reward Positivity (RewP), an early frontocentral event-related potential (ERP) indexing initial response to

reward (e.g., monetary gain, social acceptance; Kujawa, Klein, Pegg, & Weinberg, 2020; Proudfit, 2015). The RewP is thought to originate from the anterior cingulate cortex and striatum, brain regions implicated in reward processing (Becker, Nitsch, Miltner, & Straube, 2014; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011; Foti, Weinberg, Bernat, & Proudfit, 2015; Foti, Weinberg, Dien, & Hajcak, 2011). Studies that have measured both the monetary and social RewP in the same sample have observed moderate correlations between them (Ait Oumeziane, Schryer-Praga, & Foti, 2017; Banica et al., 2022; Ethridge et al., 2017; Pegg et al., 2021), suggesting that they reflect overlapping but non-redundant valuation of rewards.

Though neural responses to both monetary and social reward have been shown to confer vulnerability to depressive symptoms, at least in part through increased stress susceptibility, reward sensitivity appears to be, to some degree, incentive-specific. To see whether each or both types of neural response prospectively predict depression in times of chronic and episodic stress, we conducted a longitudinal study. Participants who previously completed an in-person lab visit were sent eight online surveys from March through August 2020. We examined whether individuals with a blunted neural response to social and/or monetary reward at baseline experienced increased depressive symptoms during the early months of the pandemic, a time of heightened chronic stress. We then tested the relative strength of the associations between each RewP and depressive symptoms during the pandemic. Finally, we tested whether the social or monetary RewP moderated the association between episodic stress exposure and concurrent depressive symptoms. We hypothesized that blunted monetary and social reward response would predict increased depressive symptoms but blunted social reward response would be a stronger predictor. We also hypothesized that a blunted response to both types of

reward would strengthen the association between stress exposure and depression, but that this moderation would be stronger for social reward.

2. Methods and Materials

2.1. Participants

Participants were recruited for the present study from an ongoing longitudinal study of McGill University students that included an in-person laboratory visit during their first semester of university. Four independent waves of this study had been collected, with the first wave enrolled in the fall of 2016 (Wave 1) and the last wave enrolled in the fall of 2019 (Wave 4). All participants who had completed a baseline visit for this study (N = 351) were invited to participate in the present study by email in March 2020, shortly after the beginning of the COVID-19 pandemic in Canada. McGill University's Research Ethics Board approved all procedures prior to data collection and all authors adhered to APA ethical standards in the treatment of participants.

Participants eligible for the present analyses had completed at least one of the two reward tasks while electroencephalogram (EEG) was recorded at baseline, reported on their depressive symptoms at baseline, and completed at least one follow-up COVID-19 survey. This left a final sample of 121 eligible individuals (34% of the original sample). Seven of these participants completed only the social reward task while fourteen completed only the monetary reward task. An additional ten participants were not included in the moderation analyses because they did not report their stress exposure. The mean age of participants at baseline was 18.29 years (SD = 1.62) and 78.5% of the sample identified as female. 19% of participants had completed their baseline visit as part of Wave 1 in Fall 2016, 17.4% as part of Wave 2 in Fall 2017, 24.8% as part of Wave 3 in Fall 2018, and 38.8% as part of Wave 4 in Fall 2019. Self-reported ethnicity

was distributed as follows: 46.3% White, 27.3% Chinese, 5.8% South Asian, 2.5% Arab/West Asian, 3.3% South East Asian, 1.7% Hispanic, 0.8% Korean, 9.9% Other, and 2.5% declining to report ethnicity. The median family household income reported was $90,000-$99,000 CAD (range: <$10,000 - >$250,000) though 33% of the sample declined to report on household income.

2.2. Procedure

2.2.1. Baseline visit

Prior to the in-person baseline lab visit, participants completed online surveys using Qualtrics software (SAP America Inc.) covering demographic information, depressive symptoms, and other mental health measures. During their lab visit and after providing informed consent, participants completed four computer-based tasks in a randomized order while EEG was recorded. Tasks included the Doors Task (Proudfit, 2015) to measure neural response to monetary reward and the Island Getaway Task (Kujawa, Arfer, Klein, & Proudfit, 2014) to measure neural response to social reward. Data from these tasks from a subset of the participants included in the present study have been analyzed previously to address other research questions (in larger samples with additional participants not included here; see (Ethridge & Weinberg, 2018; Pegg et al., 2019; Weinberg et al., 2021); data from other tasks are reported elsewhere (Banica, Sandre, Shields, Slavich, & Weinberg, 2020, 2021; Sandre et al., 2019). Participants were compensated with extra course credit for a participating psychology course or $20.

2.2.2. Follow-up during the pandemic

Participants were sent eight online Qualtrics surveys by email beginning in March of 2020 and continuing through August 2020. Surveys 1-5 were sent two weeks apart and surveys 6-8 were sent four weeks apart. There was no time limit for submitting responses. These surveys

included measures of depressive symptoms and of pandemic-related stress; however, the pandemic-related stress measure was added starting at the 3rd follow-up survey (mid-April, 2020). Participants were compensated $5.00 for each completed survey. Mean time to completion across surveys ranged from 2.03 days (SD = 3.75) to 7.65 days (SD = 5.35) and the sample size for each survey ranged from 52 - 70. The median number of completed follow-up surveys was four (range = 1 – 8, IQR = 6), although 25.6% of respondents only completed a single survey. Exploratory analyses investigating the impact of number of surveys completed on depressive symptoms and stress have been included in the supplemental material.

2.3.Tasks and Measures

2.3.1. Self-Report

At baseline and in the follow-up surveys, participants completed the Inventory of Depression and Anxiety symptoms (IDAS-II; 55). From the IDAS-II, we used the General Depression Scale to measure depressive symptoms from the previous two weeks. This scale demonstrated good internal consistency reliability at baseline (Chronbach's α = .86) and good to excellent internal consistency in follow-up surveys (Chronbach's α's .86 - .94). To measure pandemic-related stress, participants completed the Pandemic Stress Questionnaire (PSQ; Kujawa, Green, et al., 2020), starting in the third follow-up survey. This checklist questionnaire measures exposure to stressful life events related to the pandemic that occurred in the past week and the perceived severity of these events. The questionnaire asks about events in the following domains: general life disruption, interpersonal, financial, educational, health of self, and health of close others. We used the count of events endorsed to collect a more objective measure of stress rather than perceived severity.

2.3.2. Monetary Reward Response

The Doors Task is a forced-choice guessing task that reliably elicits the RewP (Figure 1A; Proudfit, 2015). In each trial, participants view two doors, one of which they are told is holding a prize. They choose a door by clicking the left or right mouse button and, after a 1000ms fixation cross, receive feedback indicating monetary gain or loss. A green upward-pointing arrow indicates winning $0.50 while a red downward-pointing arrow indicates losing $0.25; this discrepancy in value allows rewards to accumulate and is meant to equalize the subjective value of gain and loss (Proudfit, Bress, Foti, Kujawa, & Klein, 2015; Tversky & Kahneman, 1992). Feedback is presented for 2000ms followed by a 1500ms fixation cross and then participants are prompted to click to proceed to the next trial. Participants complete five practice trials to ensure they understand the task and then complete two blocks of 20 trials each. Feedback is randomized such that each individual receives 50% gain and 50% loss feedback; participants are not informed about this. Participants are told that they are playing for real money and receive $3.00 immediately following the task (Weinberg, Riesel, & Proudfit, 2014).

2.3.3. Social Reward Response

A modified version of the Island Getaway task was used to elicit neural responses to acceptance (i.e. social reward) and rejection from computer-generated peers (Figure 1B; Kujawa et al., 2014). The task involves six rounds in which co-players vote each other on and off a series of virtual islands. The objective is to make it to the final island (i.e. round) of the game. Participants are led to believe that they will be playing against other real participants in other labs rather than computerized co-players. They create a profile for the task including a picture of themselves. On each trial, participants view a co-player's profile and vote to keep them in or kick them out of the game. After a 1000ms fixation cross, they then view how that co-player voted on them for 2000ms: either a green thumbs up indicating acceptance or a red thumbs down

indicating rejection. Participants then vote how much they liked that co-player on a 9-point Likert scale and proceed to the next trial. The task includes 51 trials divided over 6 rounds and feedback is approximately 50% acceptance and 50% rejection for each participant. For a more detailed description of this version of the task, please see Weinberg and colleagues (2021).

2.4. Electroencephalogram Recording

During the Doors and Island Getaway tasks, continuous EEG was recorded using a BrainVision actiCHamp system (Brain Products, Munich, Germany). Participants wore a 32-electrode cap with a standard 10/20 layout. The ground electrode was located at Fpz. Electrooculogram (EOG) data was collected to correct for eye movements using vertical electrodes one cm above and below one eye and horizontal electrodes one cm to the outside of each eye. Data were recorded with a sampling rate of 1000 Hz and no online filters were used.

Offline analyses were conducted using Brain Vision Analyzer software (Brain Products). First, we filtered the data with a band-pass Butterworth Zero Phase filter with half-power cutoffs of 0.01 and 30 Hz with 24 db/oct slopes. Next, data from Island Getaway were segmented from 500ms preceding feedback to 1000ms after feedback and data from Doors were segmented from 200ms pre-feedback to 1000ms post-feedback. Data were then referenced to an average of the left and right mastoids, TP9 and TP10. Eye-blinks were removed from the data using the EOG and a modification of Gratton, Coles, and Donchin's algorithm (1983). Remaining artifacts were removed with semi-automatic inspection followed by manual inspection. Criteria for artifact removal in the semi-automatic process were as follows: a voltage step of >50.0 μV between sample points, a voltage difference >175.0 μV within 400 ms intervals, or a voltage difference <0.50 μV within 100 ms intervals. Identification of an artifact, either automatically or manually, resulted in the elimination of the affected channel within a trial. This process resulted in an

average of 0.67% (SD = 3.31%, Median = 0%) of data removal in the Doors Task and 0.77% (SD = 2.77%, Median = 0%) of data removal in the Island Getaway Task for each participant. Any channels with fewer than five usable trials were interpolated from three to four surrounding channels. Interpolation was not required for the electrode of interest (Cz) for any participant in either task. After artifact rejection, participants who completed Island Getaway had an average of 24.26 usable reject trials (SD = 0.90, range = 22 – 26) and 26.65 usable accept trials (SD = 0.91, range = 25 – 29); participants who completed the Doors Task had an average of 19.75 usable loss trials (SD = 1.51, range = 10 – 20) and 19.69 gain trials (SD = 1.68, range = 8 – 20).

Trials were then averaged separately by feedback type and baseline corrected using the 200ms prior to feedback. In the Doors Task, the monetary RewP was scored as the average activity from 250ms – 350ms following feedback at electrode Cz. The social RewP from the Island Getaway task was scored as the average activity at Cz from 275ms to 375ms following feedback; this time window is consistent with previous research (Ethridge et al., 2017; Kujawa, Kessel, Carroll, Arfer, & Klein, 2017; Rappaport et al., 2019) and visual inspection of our data (Luck & Gaspelin, 2017).

2.5. Data analyses

All analyses were run in SPSS v.24 (IBM Corp, Armonk NY) or in R (R Core Team, 2020). Two repeated-measures ANOVAs were calculated to determine whether the RewP significantly differentiated between gain and loss feedback in the Doors Task and between acceptance and rejection feedback in the Island Getaway Task. Next, by regressing reward response (i.e. gain, acceptance) on loss response (loss, rejection) separately for each task, we calculated standardized residual RewP scores to isolate neural response unique to monetary and social reward. This residual RewP has better psychometric properties than simple difference

scores (Ethridge & Weinberg, 2018) and future references to the RewP will refer to the residualized RewP. However, to clarify that any results are being driven by reward response rather than non-reward response, we have also included a set of analyses in the supplement that includes each neural response as separate predictors rather than the residualized RewP.

Pearson's correlations were computed between all study variables to be included in further analyses: baseline depression, social RewP, monetary RewP, average depression across COVID-surveys, and average stressful event count across COVID surveys.

Five repeated-measures two-level multilevel models were computed in R using lme4 (Bates, Mächler, Bolker, & Walker, 2015) to address our research questions. We chose to use repeated-measures rather than growth models as we did not have a hypothesis about depressive symptom scores changing linearly from March to August 2020, and instead expected that they would fluctuate across this period. All models were estimated with REML and unstructured variance-covariance matrices. These models were structured so that COVID-19 surveys were nested within participants (level 1 = $survey_i$, level 2 = $participant_j$). Models 1 and 2 assessed whether the monetary RewP and the social RewP predicted increases in depression during the pandemic. These models included pandemic depressive symptoms as the dependent variable, level-2 fixed effects for the RewP (monetary RewP for model 1 and social RewP for model 2), mean-centered baseline depressive symptoms, study wave, and gender, and a random intercept for each participant.

Model 1:

Level 1: $Depression_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_monetary_j) + \gamma_{03}(Wave_j) + \gamma_{04}(gender_j) + u_{0j}$

Model 2:

Level 1: $Depression_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(\text{depression\_baseline}_j) + \gamma_{02}(\text{RewP\_social}_j) + \gamma_{03}(\text{Wave}_j) + \gamma_{04}(\text{gender}_j) + u_{0j}$

Next, we computed a similar model, model 3, with both the social RewP and the monetary RewP entered simultaneously to assess whether effects of the social RewP and monetary RewP were unique or additive.

Model 3:

Level 1: $\text{Depression}_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(\text{depression\_baseline}_j) + \gamma_{02}(\text{RewP\_monetary}_j) + \gamma_{03}(\text{RewP\_social}_j) + \gamma_{04}(\text{Wave}_j) + \gamma_{05}(\text{gender}_j) + u_{0j}$

Lastly, we ran models 4 and 5 to test whether either RewP (monetary RewP in model 4 and social RewP in model 5) moderated the effect of stress on depression at each pandemic timepoint. These interaction models built off of models 1 and 2 and added a level-1 fixed-effect of stress to assess the effect of episodic stress exposure on depressive symptoms at each survey timepoint. Stress represents the count of stressful pandemic-related life events reported on the PSQ at timepoint i for participant j, mean centered within-person. We also added a random slope for stress count, and a cross-level interaction term between the RewP and within-person centered stress to assess moderation by the RewP.

Model 4:

Level 1: $\text{Depression}_{ij} = \beta_0 + \beta_1(\text{Stress}_{ij}) + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(\text{depression\_baseline}_j) + \gamma_{02}(\text{RewP\_monetary}_j) + \gamma_{03}(\text{Wave}_j) + \gamma_{04}(\text{gender}_j) + u_{0j}$

$\beta_1 = \gamma_{10} + \gamma_{11}(\text{RewP\_monetary}_j) + u_{1j}$

Model 5:

Level 1: $\text{Depression}_{ij} = \beta_0 + \beta_1(\text{Stress}_{ij}) + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(\text{depression\_baseline}_j) + \gamma_{02}(\text{RewP\_social}_j) + \gamma_{03}(\text{Wave}_j) + \gamma_{04}(\text{gender}_j) + u_{0j}$

$\beta_1 = \gamma_{10} + \gamma_{11}(\text{RewP\_social}_j) + u_{1j}$

Model 4, testing the moderation of the monetary RewP on the association of stress and depressive symptoms, generated a singular fit due to difficulty estimating the covariance between the random slope and random intercept; the covariance between these parameters was removed and the resulting model is reported below. A detailed legend for the model equations can be found in the supplemental material. The R code for these models, and the deidentified data, can be found at the following link: https://osf.io/6zf7u/?view_only=295285284c0145ec903d11855fb1cdb6. Aggregated linear regression models testing whether the between-person association between pandemic stress and depressive symptoms is moderated by each RewP are included in the supplemental material.

3. Results

The count and frequency of pandemic-related stressful life events from the PSQ at each timepoint are reported in Table 1. Many of the most frequently endorsed events were social in nature (e.g. "Unable to be with close family, friends, partners", "Unexpectedly separated from family, friends, or close others") while financial and health-related events were less frequently endorsed in this sample.

A repeated-measures ANOVA indicated that in the Doors Task, the neural response to gain was significantly larger than the response to loss in the time window of the monetary RewP at Cz ($F(1) = 75.49$, $p < .001$, $\eta_p^2 = .40$; Figure 2). In the Island Getaway Task, the neural response to acceptance was significantly larger than the response to rejection in the time window of the social RewP ($F(1) = 16.21$, $p < .001$, $\eta_p^2 = .13$; Figure 2).

Table 2 includes a correlation matrix for all continuous study variables to be included in the multilevel models. Depressive symptoms at baseline were not significantly cross-sectionally correlated with either RewP. The positive correlation between the monetary and social RewP in

this sample was of small magnitude and did not reach statistical significance ($r(98) = .18$, $p = .08$).

Results from models 1, 2, and 3 assessing whether the monetary and social RewP predicted increased depressive symptoms during the pandemic when considered separately and together are presented in table 3. We did not observe a significant association between the monetary RewP and depressive symptoms during the pandemic (model 1, n = 114). However, a smaller social RewP significantly predicted higher reports of depressive symptoms during the pandemic after controlling for baseline depressive symptoms, gender, and cohort effects (model 2, n = 107). In model 3 (n = 100), the social RewP remained a significant predictor of depression symptoms over and above the monetary RewP (see Figure 3).

We assessed whether either RewP moderated associations between pandemic episodic stress exposure and depressive symptoms (model 4, n = 106, and model 5, n = 97, Table 4). Results from both these models indicated that while exposure to stressful events was a strong predictor of concurrent depressive symptoms, neither RewP moderated this association. Notably, the social RewP remained a significant predictor of pandemic depressive symptoms even after stress was included in the model.

4. Discussion

The present study examined whether neural response to monetary and social reward prospectively predicted depressive symptoms in the context of the COVID-19 pandemic and whether these associations were similar across incentive types. We further aimed to evaluate whether the RewP moderated the association between episodic stress and depressive symptoms across multiple timepoints during the pandemic. Our results indicated that social but not monetary reward response predicted significantly more depressive symptoms during the

pandemic, adjusting for pre-pandemic levels. This association held after additionally controlling for gender, cohort effects, and objective pandemic-related stress exposure. However, neither the social nor monetary RewP moderated the strong positive association between episodic stress exposure and concurrent depressive symptoms at each timepoint.

These findings have implications for understanding depression risk and stress susceptibility. We had hypothesized, based on previous research (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Burani et al., 2019; Nelson et al., 2016; Pegg et al., 2019), that both the monetary and social RewP would predict increases in depression in the context of the chronic stress of the pandemic but that the social RewP would be a stronger predictor. Instead, only the social RewP was significantly associated with depressive symptoms during the pandemic. While the lack of an effect of the monetary RewP was unexpected, these results provide further evidence of the pertinence of social reward to depression risk (Ait Oumeziane et al., 2019; Forbes & Dahl, 2012; Freeman et al., under review).

Our findings also highlight the risk of assuming reward sensitivity is a monolithic construct in the study of depression vulnerability (Ethridge et al., 2017). Social and monetary reward sensitivity may show similar associations with depression or depression risk in some contexts (Ng, Alloy, & Smith, 2019; Zhang et al., 2020), but they also contain unique information (Ait Oumeziane et al., 2017; Banica et al., 2022; Ethridge et al., 2017; Pegg et al., 2021; Rademacher et al., 2010). Therefore, by treating monetary incentives as generic rewards or by pooling reward types together, we may overlook important information about pathways to depression. Furthermore, social reward itself is a multifaceted construct. We measured only one of its facets: social acceptance (though one that may be particularly relevant for young adults accustomed to giving and receiving similar feedback on social media). Future studies should

consider whether these findings generalize to other forms of social reward (e.g. verbal praise, naturalistic smiling, etc.; Dickey et al., 2021).

In this study, social reward sensitivity may have been more pertinent to depression risk due to the type of stress experienced by participants. Many of the most frequently reported stressors were social in nature (e.g. isolation, interpersonal conflict). It is therefore possible that, for our young adult university student participants, the most salient and stressful aspect of the pandemic was social (Elmer et al., 2020; Shanahan et al., 2020; Son, Hegde, Smith, Wang, & Sasangohar, 2020). During the time period captured by our data, students had to contend with lockdowns, school closures, remote learning, and the uncertainty of how long these measures might last. Many left their student housing to return home, away from their peers and sometimes in a different time zone. The nature of the challenges students faced varied across study waves as some students (i.e. Wave 4) had their first year of university cut short, while others (i.e. in Wave 1) lost their chance to finish their university experience and graduate in person with their friends and family present. Across waves, however, these changes constituted significant social stressors.

If impaired social reward sensitivity specifically confers vulnerability to social stress (Pegg et al., 2019), social reward sensitivity would be a more relevant predictor of pandemic-related depressive symptomatology for our participants. Perhaps those less sensitive to social reward are more prone to depression in times of social isolation and stress because they are more likely to withdraw from others (Auerbach et al., 2014; Barkus & Badcock, 2019; Kupferberg et al., 2016) rather than recruit social support, a strong protective factor against depression (Aneshensel & Stone, 1982) even during the COVID-19 pandemic (Grey et al., 2020). However,

the mechanisms by which social reward insensitivity might confer susceptibility to social stress warrant further study.

Our findings also point to a potential discrimination between vulnerability to chronic versus episodic stress. The significant association between the social RewP and depressive symptoms emerged during the pandemic, a time of heightened chronic stress (Arora et al., 2020; Jewell et al., 2020), and not at baseline. Considering this and the lack of a significant interaction between the RewP and episodic stressors, it is possible that blunted social reward response confers increased vulnerability to chronic stress but not to fluctuations in episodic stress. However, it is also possible that our dataset was not optimal to detect interactions between episodic stress exposure and the RewP. For one, 26% of our respondents completed only one survey and the median number of surveys completed was four. This may result in low power to detect level-one effects and cross-level interactions between stress exposure and the RewP. Further, the random slope of episodic stress was not significant in the interaction models, indicating relatively limited observed variance that could be explained by either RewP. Future experiments with more timepoints will be necessary to better evaluate whether the monetary or social RewP impacts vulnerability to episodic stressors.

Another limitation in this study is our measurement of stress. The PSQ has many advantages including covering a broad range of domains and assessing objective rather than subjective stress, which may be more vulnerable to bias and confounds with depression (Monroe, 2008). Nonetheless, there are inherent difficulties in measuring self-reported objective stress. For example, a life events checklist may overlook stressors not listed, disregard important contextual factors, and be susceptible to recall bias, perhaps especially in those with elevated depressive symptoms (Mathews & Bradle, 1983). Recall bias could partially explain the positive correlation

between baseline depressive symptoms and pandemic-related stressful events. Additionally, we assume that our participants were experiencing elevated levels of chronic stress across the early months of the pandemic as has been documented around the world (Arora et al., 2020; Kujawa, Green, et al., 2020; Shanahan et al., 2020; Zheng et al., 2021). However, because we do not have an equivalent pre-pandemic stress measure to which to compare, this is an assumption. These limitations should be taken into consideration when interpreting our findings.

Our results suggest that neural response to social reward may be a useful marker of vulnerability to depression under times of chronic stress, especially stress with an interpersonal dimension. However, this association is likely complex due to evidence of bidirectional associations between reward system functioning, stress, and depression. Although low levels of reward sensitivity predict increased stress susceptibility, acute and chronic stress can also blunt reward sensitivity (Admon et al., 2013; Ethridge et al., 2020; Ethridge, Sandre, Dirks, & Weinberg, 2018; Kujawa, Klein, Pegg, & Weinberg, 2020). Similarly, while stress often leads to depression (Keller, Neale, & Kendler, 2007; Kessler, 1997; Mazure, 1998; Monroe et al., 2019), depression also predicts increased stress (Hammen, 1991, 2005; Liu & Alloy, 2010), an effect that may be mediated by reward functioning (Mackin et al., 2019). To develop better predictions of which individuals are at greatest risk of depressive symptomatology, future research is needed to clarify how stress, depression, and reward sensitivity interact while acknowledging that sensitivity to different types of incentives may differentially impact depression risk.

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COVID-19 Stressor	T3 (n = 61) n (%)	T4 (n = 56) n (%)	T5 (n = 71) n (%)	T6 (n = 67) n (%)	T7 (n = 64) n (%)	T8 (n = 65) n (%)
Unable to be with close family, friends, partners	48 (78.7%)	43 (76.8%)	54 (76.1%)	43 (64.2%)	33 (51.6%)	31 (47.7%)
Unexpectedly separated from family, friends, or close others	43 (70.5%)	25 (44.6%)	33 (46.5%)	28 (41.8%)	21 (32.8%)	24 (36.9%)
Had to cancel/postpone important events	39 (63.9%)	32 (57.1%)	33 (46.5%)	30 (44.8%)	24 (37.5%)	25 (39.1%)
Unexpectedly moved due to COVID-19	30 (49.2%)	13 (23.2%)	16 (22.5%)	15 (22.4%)	13 (20.3%)	13 (20.0%)
Close other was quarantined for 2 weeks or longer	28 (46.7%)	27 (48.2%)	29 (40.8%)	23 (34.3%)	24 (38.1%)	25 (39.1%)
Had problems with online courses and/or remote work	27 (45.0%)	24 (42.9%)	25 (35.2%)	23 (34.3%)	10 (15.9%)	19 (29.7%)
Had to cancel travel or experienced disruptions in travel plans	24 (39.3%)	21 (37.5%)	31 (43.7%)	28 (41.8%)	23 (35.9%)	29 (44.6%)
Had conflicts/arguments with families due to COVID-19	23 (38.3%)	22 (39.3%)	36 (50.7%)	28 (41.8%)	23 (36.5%)	24 (37.5%)
Parents lost their job or had hours greatly reduced	17 (28.3%)	16 (28.6%)	16 (22.5%)	11 (16.4%)	7 (11.1%)	10 (15.6%)
Financial supporter lost their job or had hours greatly reduced	17 (28.3%)	9 (16.1%)	17 (23.9%)	11 (16.4%)	5 (7.9%)	11 (17.2%)
Was quarantined for ≥ 2 weeks due to possible exposure to COVID-19 or international travel	14 (23.3%)	12 (21.4%)	7 (9.9%)	15 (22.4%)	11 (17.5%)	13 (20.3%)
Had difficulty accessing/paying for physical or mental healthcare	12 (20.0%)	13 (23.2%)	13 (18.3%)	10 (14.9%)	12 (19.0%)	11 (17.2%)
Close other had symptoms of COVID-19	10 (16.7%)	8 (14.3%)	1 (1.4%)	1 (1.5%)	4 (6.3%)	1 (1.6%)
Experienced racism or discrimination due to COVID-19	10 (16.7%)	9 (16.1%)	8 (11.3%)	11 (16.4%)	3 (4.8%)	3 (4.7%)
Workload increased substantially	10 (16.4%)	9 (16.1%)	6 (8.5%)	8 (11.9%)	2 (3.2%)	5 (7.8%)
Had to take on additional responsibilities caring for others	9 (14.8%)	12 (21.4%)	12 (16.9%)	9 (13.4%)	9 (14.3%)	6 (9.4%)
Close other was tested for COVID-19	8 (13.3%)	12 (21.4%)	13 (18.3%)	15 (22.4%)	26 (41.3%)	25 (39.1%)
Unable to complete important requirements for education or professional goals	8 (13.3%)	9 (16.1%)	8 (11.3%)	8 (11.9%)	10 (15.9%)	6 (9.4%)
Close other was diagnosed with COVID-19	4 (6.7%)	3 (5.4%)	3 (4.2%)	4 (6.0%)	5 (7.9%)	4 (6.3%)
Had symptoms of COVID-19	3 (5.0%)	0	1 (1.4%)	1 (1.5%)	2 (3.2%)	0

Was tested for COVID-19	0	0	0	5 (7.5%)	5 (7.9%)	6 (9.4%)
Had problems with visa due to COVID-19	0	0	1 (1.4%)	0	1 (1.6%)	3 (4.6%)
Close other died of COVID-19	0	0	0	1 (1.5%)	1 (1.6%)	0
Mean total event count (sd)	**5.94 (2.84)**	**5.7 (2.85)**	**4.99 (2.93)**	**4.92 (3.02)**	**4.27 (3.37)**	**4.59 (3.40)**

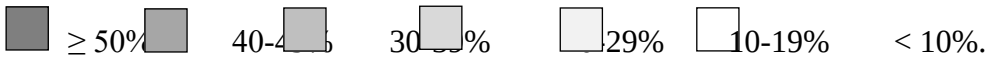

Table 1. Frequency of the items of the Pandemic Stress Questionnaire (PSQ) endorsed at each timepoint (T3-T8, spanning April 15, 2020 – August 15, 2020). More frequently endorsed items are highlighted in darker greyscale colors (see legend above). Mean total event count for each timepoint is reported in the bottom row of the table.

	M (SD)	1.	2.	3.	4.
1. Baseline depressive symptoms	44.92 (11.02)				
2. Average pandemic depressive symptoms[a]	46.33 (12.06)	.40***			
3. Social RewP	0 (1)	-.18	-.24*		
4. Monetary RewP	0 (1)	.13	-.01	.18	
5. Average pandemic stress[b]	5.63 (2.85)	.18*	.36***	-.01	-.06

Table 2. Descriptive statistics and Pearson correlations between all continuous variables included in the mixed-effects model analyses. [a]Average of the general depression scale of the IDAS-II across all completed COVID-19 surveys available for each participant. [b]Average number of stressful life events reported on the PSQ across all completed COVID-19 surveys for each participant.

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

	Model 1			Model 2			Model 3		
Predictors	*Estimate (SE)*	*β (95% CI)*	*p*	*Estimate (SE)*	*β (95% CI)*	*p*	*Estimate(SE)*	*β (95% CI)*	*p*
(Intercept)	45.59 (0.44)	0.04 (-0.45 – 0.52)	**<0.001**	46.49 (3.23)	0.09 (-0.39 – 0.57)	**<0.001**	45.44 (3.27)	0.02 (-0.47 – 0.51)	**<0.001**
Monetary RewP	-0.99 (1.03)	-0.08 (-0.24 – 0.08)	0.33				-0.48 (1.10)	-0.04 (-0.21 – 0.13)	0.66
Social RewP				-2.56 (1.11)	-0.19 (-0.35 – -0.03)	**0.02**	-2.44 (1.12)	-0.18 (-0.35 – -0.02)	**0.03**
Baseline depression[a]	0.45 (0.09)	0.36 (0.21 – 0.50)	**<0.001**	0.37 (0.10)	0.28 (0.13 – 0.44)	**0.001**	0.37 (0.10)	0.29 (0.13 – 0.45)	**0.001**
Wave 2[b]	-6.78 (3.34)	-0.53 (-1.03 – -0.02)	**0.05**	-4.16 (3.36)	-0.32 (-0.81 – 0.18)	0.22	-6.68 (3.40)	-0.51 (-1.02 – 0.00)	**0.05**
Wave 3[b]	-4.33 (3.12)	-0.34 (-0.81 – 0.14)	0.17	-4.07 (3.54)	-0.31 (-0.83 – 0.22)	0.25	-5.06 (3.69)	-0.39 (-0.94 – 0.17)	0.17
Wave 4[b]	-4.69 (2.84)	-0.36 (-0.80 – 0.07)	0.10	-4.69 (2.85)	-0.35 (-0.78 – 0.07)	0.10	-5.23 (2.87)	-0.40 (-0.83 – 0.03)	0.07
Female[c]	5.63 (2.60)	0.44 (0.04 – 0.83)	**0.03**	3.85 (2.68)	0.29 (-0.11 – 0.69)	0.15	5.95 (2.74)	0.45 (0.04 – 0.87)	**0.03**
Random Effects									
σ^2	**53.16**			**51.91**			**52.52**		
τ_{00}	**95.51** LabID			**101.48** LabID			**96.11** LabID		
ICC	0.64			0.66			0.65		

N	114 $_{LabID}$	107 $_{LabID}$	100 $_{LabID}$
Observations	470	431	408
Marginal R^2 / Conditional R^2	0.16 / 0.70	0.14 / 0.71	0.16 / 0.70

Table 3. Results from linear mixed-effects models 1, 2, and 3 all predicting depressive symptoms during the COVID-19 pandemic. Boldface text indicates a significant p-value <.05 for fixed effects or for random effects, significance based on a 95% confidence interval. σ^2 represents the within-individual residual variance. τ_{00} represents the variance in intercepts across individuals after accounting for the fixed-effect predictors. The subscript $_{LabID}$ represents each individual participant. ICC = Intraclass correlation, the proportion of variance accounted for by nesting after taking into account the fixed effect predictors. Marginal R^2 accounts for variance explained by fixed effects while conditional R^2 takes both fixed and random effects into account. [a]Mean-centered baseline depressive symptoms from the general depression scale of the IDAS-II. [b]Estimates relative to the reference group of Wave 1. [c] Estimate relative to male participants

	Model 4			Model 5		
Predictors	*Estimates (SE)*	*β (95% CI)*	*p*	*Estimates (SE)*	*β (95% CI)*	*p*
(Intercept)	45.76 (3.45)	0.08 (-0.45 – 0.61)	**<0.001**	46.52 (3.46)	0.11 (-0.41 – 0.63)	**<0.001**
Stress[a]	0.83 (0.21)	0.12 (0.06 – 0.18)	**<0.001**	0.80 (0.24)	0.11 (0.04 – 0.18)	**0.01**
Monetary RewP	-0.88 (1.08)	-0.07 (-0.25 – 0.10)	0.41			
Stress * Monetary RewP	0.24 (0.20)	0.04 (-0.02 – 0.10)	0.23			
Social RewP				-2.88 (1.18)	-0.21 (-0.38 – -0.04)	**0.01**
Stress * Social RewP				-0.00 (0.26)	-0.00 (-0.07 – 0.07)	0.99
Baseline depression	0.42 (0.10)	0.34 (0.18 – 0.50)	**<0.001**	0.37 (0.11)	0.29 (0.12 – 0.46)	**0.001**
Wave 2[b]	-6.61 (3.50)	-0.52 (-1.06 – 0.02)	0.06	-3.84 (3.43)	-0.29 (-0.81 – 0.22)	0.26
Wave 3[b]	-5.02 (3.32)	-0.39 (-0.90 – 0.12)	0.13	-4.54 (3.79)	-0.35 (-0.92 – 0.22)	0.23
Wave 4[b]	-5.30 (3.04)	-0.41 (-0.88 – 0.05)	0.08	-5.44 (3.00)	-0.42 (-0.87 – 0.03)	0.07
Female[c]	5.26 (2.77)	0.41 (-0.01 – 0.84)	0.06	3.69 (2.86)	0.28 (-0.15 – 0.71)	0.20
Random Effects						
σ^2	**47.93**			**46.91**		
τ_{00}	**100.57** $_{\text{LabID}}$			**103.56** $_{\text{LabID}}$		
τ_{11}	0.11 $_{\text{LabID.stress\_c}}$			0.49 $_{\text{LabID.stress\_c}}$		
ρ_{01}				0.44 $_{\text{LabID}}$		
ICC	0.68			0.69		
N	106 $_{\text{LabID}}$			97 $_{\text{LabID}}$		
Observations	361			331		

Marginal R^2 / Conditional R^2	0.164 / 0.730	0.160 / 0.742

Table 4. Results from linear mixed-effects models 4 and 5 predicting depressive symptoms during the COVID-19 pandemic. Boldface text indicates a significant p-value <.05 for fixed effects or for random effects, significance based on a 95% confidence interval. σ^2 represents the within-individual residual variance. τ_{00} represents the variance in intercepts across individuals after accounting for the fixed-effect predictors. τ_{11} represents the variance in the slope of stress across individuals. ρ_{01} represents the covariance between the random intercept and random slope – not estimated in model 4 due to singular fit. ICC = Intraclass correlation, the proportion of variance accounted for by nesting after taking into account the fixed effect predictors. Marginal R^2 accounts for variance explained by fixed effects while Conditional R^2 takes both fixed and random effects into account. [a] Count of stressful events from the PSQ at each timepoint, centered within-person. [b]Estimates relative to the reference group, Wave 1. [c]Estimate relative to male participants.

Figure 1.

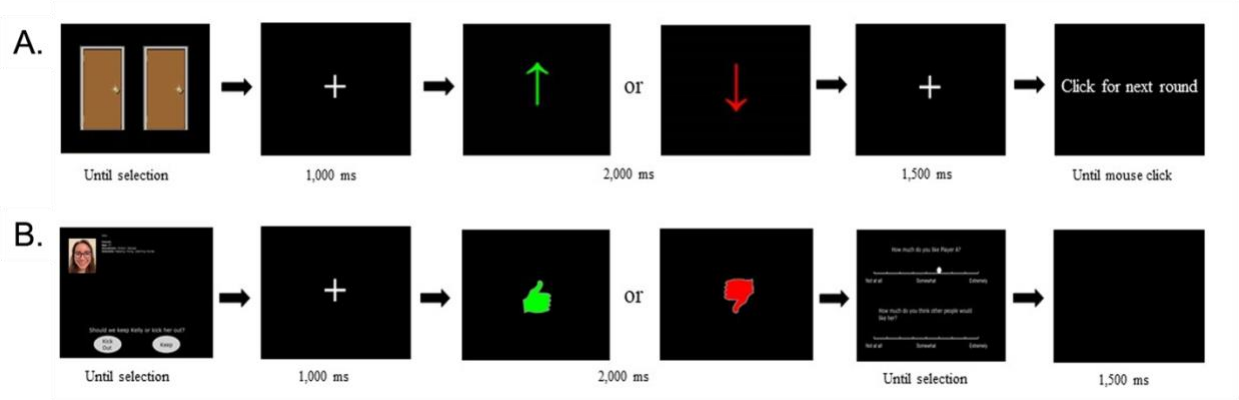

Figure 1. Task schematics with stimuli presentation lengths for the (A) Doors Task and (B) Island Getaway Task. Adapted from Banica et al. (under review) with permission.

Figure 2.

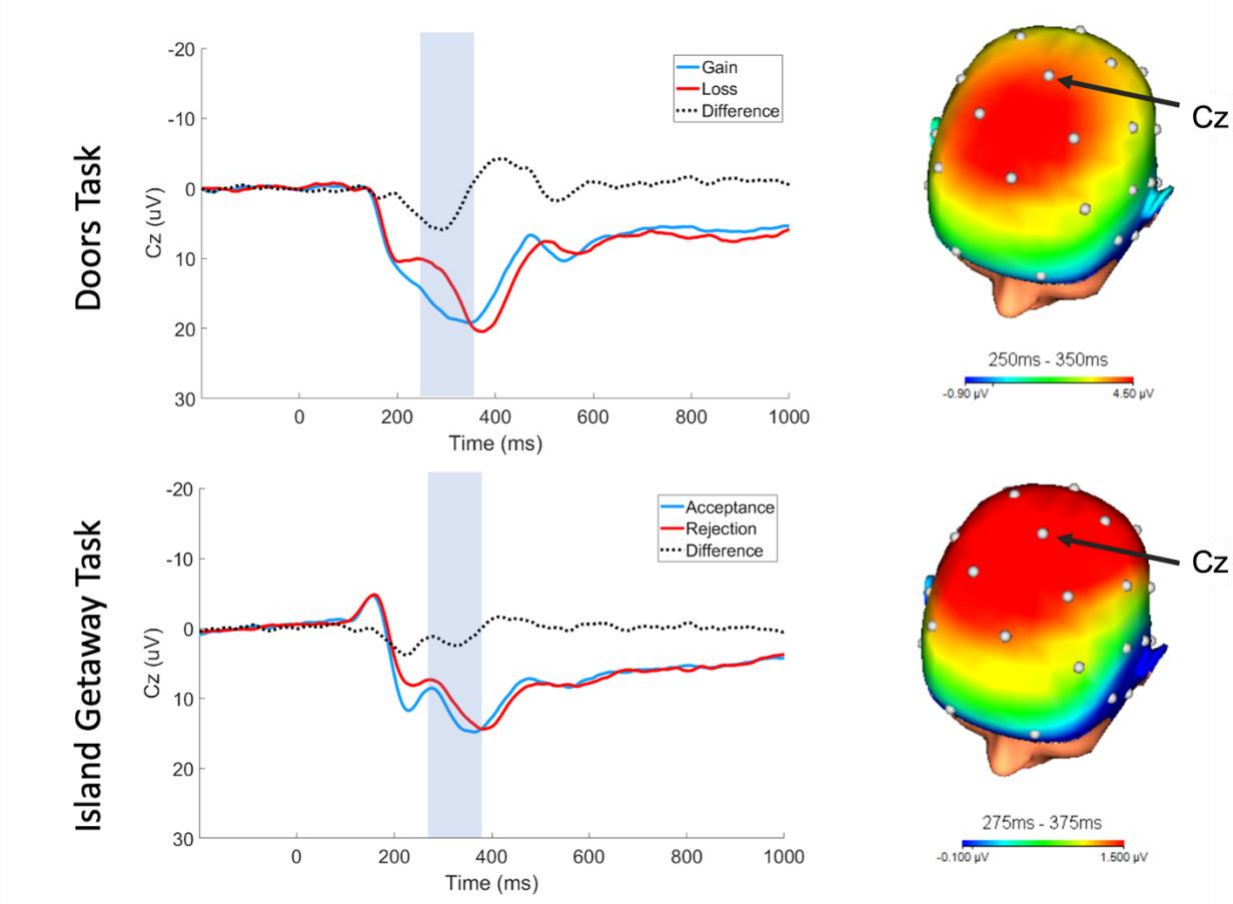

Figure 2. Event-related potential waveforms at Cz during the Doors Task (top) and Island Getaway Task (bottom) and associated scalp distributions representing the difference between reward outcome (gain, acceptance) and non-reward outcome (loss, rejection) in the highlighted time window. Time 0 on the x-axis is the time at which reward/nonreward feedback is presented.

Figure 3.

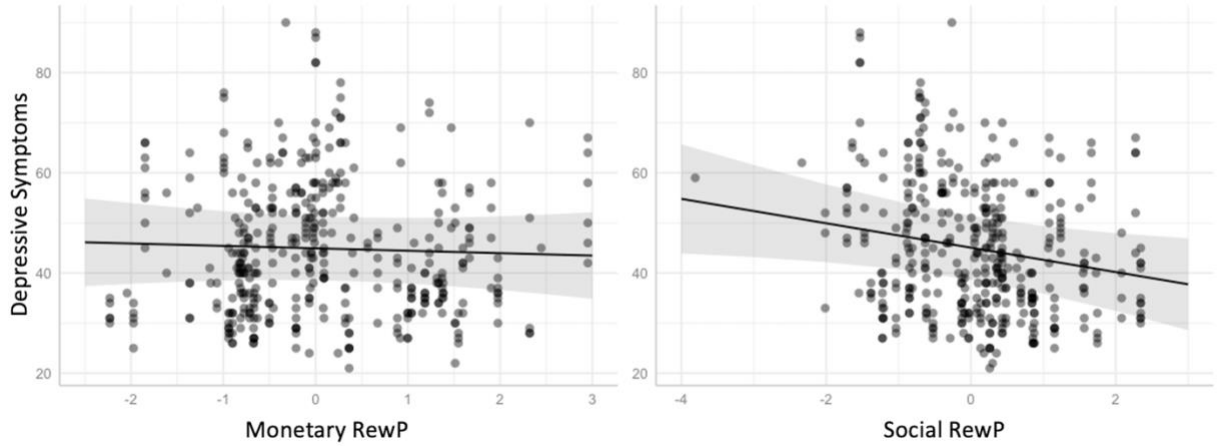

Figure 3. Partial regression plots depicting the fixed effects for each RewP predicting depressive symptoms reported during the COVID-19 pandemic. These slopes are taken from Model 3. Each slope is adjusted for wave, gender, baseline depression, and the other RewP.

Study 3: Supplemental Material

Multilevel Model Equations

Model 1:

Level 1: $Depression_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_monetary_j) + \gamma_{03}(Wave_j) + \gamma_{04}(gender_j) + u_{0j}$

Model 2:

Level 1: $Depression_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_social_j) + \gamma_{03}(Wave_j) + \gamma_{04}(gender_j) + u_{0j}$

Model 3:

Level 1: $Depression_{ij} = \beta_0 + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_monetary_j) + \gamma_{03}(RewP\_social_j) + \gamma_{04}(Wave_j) + \gamma_{05}(gender_j) + u_{0j}$

Model 4:

Level 1: $Depression_{ij} = \beta_0 + \beta_1(Stress_{ij}) + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_monetary_j) + \gamma_{03}(Wave_j) + \gamma_{04}(gender_j) + u_{0j}$

$\beta_1 = \gamma_{10} + \gamma_{11}(RewP\_monetary_j) + u_{1j}$

Model 5:

Level 1: $Depression_{ij} = \beta_0 + \beta_1(Stress_{ij}) + r_{ij}$

Level 2: $\beta_0 = \gamma_{00} + \gamma_{01}(depression\_baseline_j) + \gamma_{02}(RewP\_social_j) + \gamma_{03}(Wave_j) + \gamma_{04}(gender_j) + u_{0j}$

$\beta_1 = \gamma_{10} + \gamma_{11}(RewP\_social_j) + u_{1j}$

Legend:

- Dependent variable:
  - $Depression_{ij}$ refers to the general depression scale score from the IDAS-II at COVID-19 timepoint i for participant j
- Fixed effects:
  - γ_{00} represents the grand intercept across all surveys accounting for clustering within participants
  - γ_{01} - γ_{05} represent the coefficients for the level 2 fixed effects
  - γ_{10} represents the level-1 fixed effect for stress
  - γ_{11} represents the interaction term between the RewP and stress

    - depression_baseline represents the mean-centered general depression scale score from the IDAS-II measured at the time the RewPs were collected
    - Wave is a categorical variable indicating in which year the EEG data was collected
    - Gender is scored as a categorical variable differentiating between male and female participants
    - Stress represents the count of stressful pandemic-related life events reported on the PSQ at timepoint i for participant j, mean centered within-person
- Random effects:
    - r_{ij} represents the level 1 residual at timepoint i for participant j
    - u_{0j} represents the divergence in intercept from γ_{00} for each participant j
    - u_{1j} represents the divergence in slope from γ_{10} for participant j after accounting for γ_{11}

Using reward and nonreward as independent predictors of depressive symptoms

To supplement our models using the residualized RewP, the models below repeat Models 3-5 from the main text (here referred to as models 3a-5a), but enter neural response to reward (gain, acceptance) and neural response to non-reward (loss, rejection) as separate predictors. These models demonstrate that the effect of the social RewP on depressive symptoms is driven by the neural response to acceptance rather than the neural response to rejection (Table S1, S2). Consistent with the original model in the main text, neither response to monetary feedback significantly predicted depressive symptoms.

	Model 3a			
Predictors	*Estimates*	*β*	*95% CI*	*p*
(Intercept)	46.59	0.05	38.77 – 54.41	**<0.001**
Baseline depression[a]	0.35	0.28	0.14 – 0.55	**0.001**
Monetary gain	-0.04	-0.03	-0.47 – 0.38	0.84
Monetary loss	0.38	0.22	-0.11 – 0.87	0.13
Social acceptance	-0.68	-0.40	-1.19 – -0.18	**0.01**
Social rejection	0.33	0.19	-0.16 – 0.83	0.19
Wave 2[b]	-6.79	-0.52	-13.39 – -0.18	**0.04**
Wave 3[b]	-4.82	-0.37	-12.03 – 2.40	0.19
Wave 4[b]	-5.47	-0.42	-11.06 – 0.12	0.06
Female[c]	5.53	0.42	0.16 – 10.91	**0.04**
Random Effects				
σ^2	52.53			
$\tau_{00\ LabID}$	94.13			
ICC	0.64			
N_{LabID}	100			
Observations	408			
Marginal R^2 / Conditional R^2	0.193 / 0.711			

Table S1. Results from a linear mixed-effects model predicting depressive symptoms during the COVID-19 pandemic. σ^2 represents the within-individual residual variance. τ_{00} represents the variance in intercepts across individuals after accounting for the fixed-effect predictors. The subscript $_{LabID}$ represents each individual participant. ICC = Intraclass correlation, the proportion of variance accounted for by nesting after taking into account the fixed effect predictors. Marginal R^2 accounts for variance explained by fixed effects while conditional R^2 takes both

fixed and random effects into account. [a]Mean-centered baseline depressive symptoms from the general depression scale of the IDAS-II. [b]Estimates relative to the reference group of Wave 1. [c]Estimate relative to male participants

	Model 4a				Model 5a			
Predictors	*Estimates*	*std. Beta*	*CI*	*p*	*Estimates*	*std. Beta*	*CI*	*p*
(Intercept)	45.63	.08	36.98 – 54.29	**<0.001**	49.84	.12	41.75 – 57.92	**<0.001**
Baseline depression	0.41	.33	0.21 – 0.62	**<0.001**	0.38	.30	0.17 – 0.60	**<0.001**
Stress[a]	0.09	.12	-0.84 – 1.03	.84	0.48	.11	-0.38 – 1.35	.27
Monetary gain	-0.16	-.10	-0.58 – 0.26	.46				
Monetary loss	0.22	.12	-0.24 – 0.67	.35				
Wave 2[b]	-6.61	-.52	-13.49 – 0.28	.06	-3.81	-.29	-10.54 – 2.91	.27
Wave 3[b]	-4.83	-.38	-11.38 – 1.71	.15	-4.87	-.37	-12.37 – 2.63	.20
Wave 4[b]	-5.29	-.41	-11.28 – 0.70	.08	-5.58	-.43	-11.47 – 0.31	.06
Female[c]	5.18	.41	-0.27 – 10.63	.06	3.69	.28	-1.91 – 9.30	.20
Stress * monetary gain	0.04	.05	-0.01 – 0.09	.09				
Social acceptance					-0.63	-.35	-1.14 – -0.12	**.02**
Social rejection					0.45	.25	-0.07 – 0.97	.09
Stress * social acceptance					0.03	.03	-0.03 – 0.08	.39
Random Effects								
σ^2	47.93				46.59			
τ_{00}	101.13 $_{\text{LabID}}$				104.50 $_{\text{LabID}}$			
τ_{11}	0.06 $_{\text{LabID.stress\_c}}$				0.57 $_{\text{LabID.stress\_c}}$			
ρ_{01}					0.47 $_{\text{LabID}}$			
ICC	0.68				0.70			
N	106 $_{\text{LabID}}$				97 $_{\text{LabID}}$			
Observations	361				331			
Marginal R^2 / Conditional R^2	0.167 / 0.732				0.161 / 0.745			

Table S2. Results from linear mixed-effects models predicting depressive symptoms during the COVID-19 pandemic. σ^2 represents the within-individual residual variance. τ_{00} represents the variance in intercepts across individuals after accounting for the fixed-effect predictors. τ_{11} represents the variance in the slope of stress across individuals. ρ_{01} represents the covariance between the random intercept and random slope – not estimated in model S4 due to singular fit. ICC = Intraclass correlation, the proportion of variance accounted for by nesting after taking into account the fixed effect predictors. Marginal R^2 accounts for variance explained by fixed effects while Conditional R^2 takes both fixed and random effects into account. [a] Count of stressful events from the PSQ at each timepoint, centered within-person. [b]Estimates relative to the reference group, Wave 1. [c]Estimate relative to male participants.

Assessing the impact of survey completion on COVID-19 related stress, depressive symptoms, and study findings

We conducted a set of exploratory analyses in order to test whether there may have been systematic differences in pandemic-related stress or depressive symptom levels as a function of survey completion, and whether this may have influenced our results. First, we conducted bivariate associations between the number of follow-up surveys completed and average depressive symptoms during the pandemic and average stress count. Based on this, we found that those who completed more surveys tended to report fewer depressive symptoms ($r(119) = -.21$, $p = .02$) and fewer stressful events ($r(110) = -.37$, $p < .001$) during the pandemic.

Because survey completion was significantly associated with our outcome variable and one of the independent variables, we then modified the models from the main text by adding survey count as a fixed effect (Models 1b-5b, Tables S3, S4). This allowed us to determine whether differences in survey completion may have affected our study findings. We found that while survey count significantly predicted depressive symptoms during the pandemic in the modified models 1b, 4b, and 5b, the addition of this predictor did not meaningfully change the estimates for our other predictors of interest. For example, the social RewP was still a significant predictor in models 2b, 3b and 5b, as was stressful events in models 4b and 5b. Therefore, while survey count was in some cases a significant predictor of depressive symptoms during the pandemic, differences in survey completion did not change our interpretation of our main study findings.

	Model 1b			Model 2b			Model 3b		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	49.40	42.67 – 56.12	**<0.001**	49.37	42.39 – 56.35	**<0.001**	48.46	41.42 – 55.50	**<0.001**
Baseline depression[a]	0.41	0.23 – 0.59	**<0.001**	0.35	0.15 – 0.55	**0.001**	0.34	0.14 – 0.54	**0.001**
Monetary RewP	-0.85	-2.82 – 1.12	0.40				-0.26	-2.39 – 1.88	0.81
Social RewP				-2.47	-4.62 – -0.31	**0.03**	-2.41	-4.58 – -0.24	**0.03**
Wave 2[b]	-7.32	-13.74 – -0.91	**0.03**	-4.44	-10.96 – 2.07	0.18	-6.96	-13.53 – -0.39	**0.04**
Wave 3[b]	-3.41	-9.42 – 2.60	0.27	-3.64	-10.53 – 3.24	0.30	-3.95	-11.17 – 3.27	0.28
Wave 4[b]	-5.20	-10.65 – 0.26	0.06	-5.04	-10.58 – 0.50	0.08	-5.58	-11.15 – -0.01	**0.05**
Female[c]	6.93	1.84 – 12.02	**0.01**	4.70	-0.58 – 9.98	0.08	6.94	1.53 – 12.35	**0.01**
Survey count	-1.05	-1.85 – -0.26	**0.01**	-0.77	-1.60 – 0.06	0.07	-0.83	-1.69 – 0.03	0.06
Random Effects									
σ^2	53.03			51.87			52.49		
τ_{00}	90.40 $_{LabID}$			99.02 $_{LabID}$			93.07 $_{LabID}$		
ICC	0.63			0.66			0.64		
N	114 $_{LabID}$			107 $_{LabID}$			100 $_{LabID}$		
Observations	470			431			408		
Marginal R^2 / Conditional R^2	0.187 / 0.699			0.154 / 0.709			0.179 / 0.704		

Table S3. Results from linear mixed-effects models predicting depressive symptoms during the COVID-19 pandemic. [a]Mean-centered baseline depressive symptoms from the general depression scale of the IDAS-II. [b]Estimates relative to the reference group of Wave 1. [c]Estimate relative to male participants

	Model 4b			Model 5b		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	50.52	43.26 – 57.78	**<0.001**	50.53	43.03 – 58.04	**<0.001**
Baseline depression	0.39	0.19 – 0.58	**<0.001**	0.36	0.15 – 0.57	**0.001**
Stress[a]	0.82	0.41 – 1.23	**<0.001**	0.75	0.27 – 1.23	**0.002**
Monetary RewP	-0.81	-2.86 – 1.24	0.44			
Wave 2	-7.64	-14.32 – -0.97	**0.03**	-4.40	-10.99 – 2.19	0.19
Wave 3	-3.90	-10.23 – 2.42	0.27	-3.36	-10.70 – 3.98	0.37
Wave 4	-6.01	-11.80 – -0.23	**0.04**	-5.94	-11.70 – -0.17	**0.04**
Female	7.14	1.74 – 12.55	**0.01**	4.94	-0.65 – 10.54	0.08
Survey count	-1.30	-2.15 – -0.45	**0.003**	-1.04	-1.94 – -0.14	**0.02**
Stress * Monetary RewP	0.24	-0.15 – 0.63	0.23			
Social RewP				-2.85	-5.11 – -0.58	**0.01**
Stress * Social RewP				0.02	-0.49 – 0.53	0.93
Random Effects						
σ^2	47.67			46.85		
τ_{00}	92.92 $_{\text{LabID}}$			98.75 $_{\text{LabID}}$		
τ_{11}	0.12 $_{\text{LabID.stress\_c}}$			0.50 $_{\text{LabID.stress\_c}}$		
ρ_{01}				0.49 $_{\text{LabID}}$		
ICC	0.66			0.68		
N	106 $_{\text{LabID}}$			97 $_{\text{LabID}}$		
Observations	361			331		
Marginal R^2 / Conditional R^2	0.208 / 0.731			0.190 / 0.743		

Table S4. Results from linear mixed-effects models predicting depressive symptoms during the COVID-19 pandemic. [a] Count of stressful events from the PSQ at each timepoint, centered within-person.

Aggregated regression models testing the effect of mean stress on last reported depressive symptoms

We used regression models to assess whether individuals who experienced more pandemic-related stressors over the early months of the pandemic reported more depressive symptoms in the last survey they completed. We also tested whether the social or monetary RewP moderated the association between average COVID-19 stressors and the final report of depressive symptoms .

We found that mean stress had a significant effect on depressive symptoms such that participants who reported a greater number of stressors over the early months of the pandemic also reported more depressive symptoms in their last survey. However, we did not observe any moderation of this effect by either the social or monetary RewP.

DV: Last Reported Pandemic Depressive Symptoms						
	Social RewP Regression			**Monetary RewP Regression**		
Predictors	*Estimates (SE)*	*β*	*p*	*Estimates (SE)*	*β*	*p*
(Intercept)	35.35 (0.36)	0.36	**<.001**	30.43 (0.36)	0.36	**<.001**
Social RewP	-5.41 (-0.27)	-0.27	.122			
Mean stress	1.77 (0.39)	0.39	**<.001**	1.85 (0.42)	0.42	**<.001**
Wave 2	-6.97 (-0.56)	-0.56	**.044**	-9.24 (-0.74)	-0.74	**.009**
Wave 3	-6.43 (-0.51)	-0.51	.088	-4.73 (-0.38)	-0.38	.152
Wave 4	-4.97 (-0.40)	-0.40	.089	-4.54 (-0.36)	-0.36	.131
Female	1.88 (0.06)	0.06	.489	4.20 (0.13)	0.13	.115
Baseline depression	0.30 (0.25)	0.25	**.007**	0.28 (0.24)	0.24	**.008**
Social RewP * mean stress	0.33 (0.07)	0.07	.564			
Monetary RewP				0.29 (-0.11)	-0.11	.907
Monetary RewP * mean stress				-0.30 (-0.07)	-0.07	.495
Observations	96			105		
R^2 / R^2 adjusted	0.340 / 0.279			0.330 / 0.274		

General Discussion

Summary of Findings

The three studies presented here aimed to improve our understanding of how impaired neural reward response is implicated in risk for depression. The first two studies focused on predictors of blunted neural response to reward, helping to clarify associations between this phenotype and other known risk factors for depression. Study 1, capitalizing on the natural experiment of the COVID-19 pandemic, demonstrated that exposure to the stress of the pandemic was associated with a stark reduction in neural response to monetary reward. Study 2 identified additional predictors of blunted neural response to social reward. In this study, we found that adolescent girls with a maternal history of depression had a significantly blunted social RewP, despite having no personal history of depression. Mothers with a personal history of depression had a numerically smaller social RewP, though this was not statistically significant. We also found that chronic interpersonal stress was a significant and independent predictor of a smaller social RewP in the mother sample, but not in the adolescent daughter sample.

Study 3 turned from evaluating predictors of impaired reward response to using impaired reward response as a predictor of depressive symptoms. This study showed that the social RewP, but not the monetary RewP, was a significant prospective predictor of depressive symptoms measured multiple times during the first six months of the COVID-19 pandemic. However, in this study we did not observe a significant concurrent association between the social RewP and depressive symptoms measured at the pre-pandemic baseline. We also did not find that the RewP moderated concurrent associations between acute stressors and depressive symptoms at each

timepoint. These results seem to suggest that a smaller social RewP may specifically confer vulnerability to depression under conditions of chronic or prolonged stress.

Together, these studies provide incremental but important evidence of how different risk factors for depression come together with the potential to produce a depressive episode. At the same time, the results of these studies emphasize the fact that the links between neural reward responses and depression are not constant and universal. For example, in Study 3, only the social RewP predicted significantly increased depressive symptoms and only during the COVID-19 pandemic rather than at the time the RewP was measured. Moreover, associations between neural reward response and other risk factors for depression are also not constant and universal, consistent with the idea that this phenotype can emerge in different ways (Kujawa, Klein, et al., 2020). In Study 2, for example, interpersonal stress was associated with a smaller RewP in adult women but not in their adolescent daughters. These nuanced results highlight the need for tailored assessments of depression risk and a consideration of for whom blunted reward response is most important.

One striking pattern that emerged across studies was that neural response to social reward performed better as a marker of depression risk than neural responses to monetary reward. This was seen in Study 2, where adolescent girls at risk for first-onset depression had a markedly blunted social reward response. Although this study did not directly compare neural responses to social reward with responses to monetary reward, another study using data from the same adolescent sample found that maternal depression history was not significantly associated with a blunted monetary RewP (Allison et al., 2023). Allison and colleagues did find that the monetary RewP was numerically smaller in daughters of mothers with early-onset depression only, but this did not reach statistical significance (2023). By integrating the results of these two studies, we

see that, at least in this sample, impaired social reward response was more closely linked with depression risk than impaired monetary reward response.

The longitudinal design of Study 3 provided even more support for the assertion that impaired social reward response may be more closely linked with depression risk for some. In Study 3, pre-pandemic neural responses to social reward prospectively predicted increased reports of depressive symptoms during the COVID-19 pandemic whereas pre-pandemic monetary reward response did not. Surprisingly, not only was the social RewP a stronger of predictor of depression risk than the monetary RewP, but the monetary RewP was not a significant predictor of depressive symptoms at all, a finding that was echoed in Study 1. In that study, we did find a small negative association between the RewP and depressive symptoms at the follow-up visit but it did not meet statistical significance.

The lack of significant associations between monetary reward response and depression risk runs contrary to a number of studies that have found prospective associations between a blunted monetary RewP and depression (Bress et al., 2013; Mulligan et al., 2019; Nelson et al., 2016). This raises the question of why our findings might have diverged from prior studies. Other studies have found null main effects between a blunted RewP and depression but have still observed interactions with stress (Burani et al., 2021; Goldstein et al., 2020), including COVID-19-related stress (Feurer et al., 2021). Therefore, the lack of a significant prospective association between monetary reward response and depressive symptoms in Studies 1 and 3 is especially surprising given that depressive symptoms were measured during the stress of the COVID-19 pandemic. One possible reason for the discrepancy with prior results is the potentially lower severity of depression in our samples. This is difficult to directly compare because different studies used different measures of depression; however, the studies that found main effects of a

blunted monetary RewP on future depressive symptoms had samples in which a percentage of participants were either diagnosed with major depressive disorder by the follow-up visit (Bress et al., 2013; Nelson et al., 2016) or had a past history of depression (Mulligan et al., 2019). We did not have diagnostic assessments in Study 1 or 3 and therefore cannot quantify how many participants in these samples had a history of depression; however, these were unselected undergraduate samples and therefore relatively high functioning. It would be worthwhile to investigate whether greater depression severity or greater variance in depressive symptoms is needed to see significant associations with blunted monetary reward response.

Clinical Implications

The ultimate goal of this line of research is to use our findings to decrease the overall burden of depression. Knowing how neural reward responses are to be put to clinical use depends on whether impaired reward response is a risk factor or a risk mechanism of depression (Garber, 2006; Kraemer et al., 1997). These two terms can be distinguished by their causality. A risk factor precedes a diagnosis and is associated with increased prevalence of an outcome but does not necessarily cause or explain that outcome; in contrast, a risk mechanism plays a causal role such that altering the risk mechanism alters the outcome (Garber, 2006). Therefore, if blunted neural response to reward constitutes a risk factor for depression, its primary clinical use would be to help target those most at risk for developing depression to divert them toward a prevention intervention. Additionally, neural reward responses could be used to try to predict who would benefit most from specific depression treatments. If blunted neural response to reward is an actual mechanism of depression, then it can itself be a useful target of interventions. Interventions that upregulate neural responses to reward would then be expected to reduce depressive symptoms, at least for depressed individuals with impaired reward function.

Varying degrees of evidence exist for how well impaired reward response 1) improves the prospective prediction of clinical depression diagnoses, 2) can aid in treatment selection, and 3) can be a mechanism of depression symptom change or remission. I will review this evidence with a particular focus on the RewP when possible. This focus is warranted, first for the purpose of integration with the studies presented here, but also because the RewP is much more economical to measure, and EEG has fewer contraindications and risks than other methods of measuring neural reward response. This means that it could more readily be deployed as a clinical tool outside laboratory settings compared to a method like fMRI or PET.

Prospective prediction of depression

For the RewP to advance our ability to prospectively predict depression, not only must it meaningfully predict depression, but it must add predictive power beyond other well-established risk factors such as family history of depression or current depressive symptoms. This is especially important given that many of these other known risk factors are much more easily measured (e.g., with self-report). Previous studies have established that the monetary RewP can prospectively predict depression onset or depressive symptoms over and above risk factors such as baseline depressive symptoms, parental depression history, self-reported reward responsiveness, biological sex, and lifetime anxiety disorder in adolescents (Kujawa, Hajcak, et al., 2019; Nelson et al., 2016). One study took an especially comprehensive approach to compare 21 different clinical/family history, cognitive/dispositional, personality, interpersonal, and biological risk factors for depression in a sample of 479 never-depressed adolescent girls (Michelini et al., 2021). This study found that the RewP at baseline significantly and prospectively predicted a first onset of chronic/recurrent depression and, moreover, remained significant when all predictors were simultaneously added to the model (OR = .59). This

suggests that the RewP accounts for unique variance in depression liability that is not redundant with self-report measures. However, the RewP was a significant risk factor only for those who developed chronic/recurrent depression and not for those who experienced only a single MDD episode of <12 months during the 18-month follow-up. This discrepancy highlights the heterogeneity of depression and the premise that different risk factors may matter more for different presentations of depression. Overall, the studies reviewed here support the incremental validity of the RewP in predicting depressive symptoms and first-onset depression, at least depression with a chronic or recurrent presentation. Further work confirming that the RewP increases our ability to predict depression risk over and above self-report/clinical measures is warranted as are additional studies that help determine for which forms of depression is impaired reward response most relevant.

Another critical question is that even if we are able to improve our ability to catch those most likely to become depressed before the disorder develops, do we currently have the tools to effectively prevent depression? Many studies over the last 30 years have addressed this question by conducting randomized control trials of depression prevention interventions. A large number of these trials have targeted adolescents, though others have targeted young adults (Breedvelt et al., 2018), peripartum women, or adults with medical illness (Cuijpers et al., 2008; Pitceathly et al., 2009). Adolescence is an especially ideal time to intervene as rates of depression begin increasing steeply during this period (Kessler et al., 2001). Although the methods used to intervene in depression prevention trials have varied somewhat, most studies have delivered a group-therapy-style intervention based on a cognitive behavioral or an interpersonal model (Clarke et al., 1995; Feiss et al., 2019; Garber, 2006; Garber et al., 2009; Gladstone & Beardslee, 2009). While some experimental interventions were delivered universally (e.g. all seventh

graders), others targeted individuals considered to be at high risk for depression, typically due to a parental depression history, subsyndromal depressive symptoms, a past depressive episode, or some combination of these factors (Clarke et al., 1995; Cuijpers et al., 2008; Garber, 2006; Garber et al., 2009; Loechner et al., 2018; Stice et al., 2010). Other interventions have targeted children who recently experienced a significant stressor (e.g. children whose parents recently divorced; Garber, 2006).

Based on several reviews and meta-analyses of these studies, targeted interventions have generally proved to yield small but significant effects in preventing an increase in depressive symptoms or depression onset at post-intervention and for up to a year or more (Beekman et al., 2010; Gladstone & Beardslee, 2009; Werner-Seidler et al., 2021). Targeted interventions tend to outperform universal ones and some universal interventions only worked for those who were already experiencing elevated depressive or anxiety symptoms (Beekman et al., 2010; Garber, 2006; Pitceathly et al., 2009). However, one meta-analytic review found no significant difference between targeted and universal prevention interventions (Cuijpers et al., 2008) and another metanalysis found null findings across both intervention types after accounting for selection and publication bias (Caldwell et al., 2019). Taken together though, while effects of prevention interventions are small to moderate (Cuijpers et al., 2008; Werner-Seidler et al., 2021) and may not always have long-lasting effects (Loechner et al., 2018), prevention interventions do seem to have benefit, especially when targeting those most at risk (Beekman et al., 2010; Gladstone & Beardslee, 2009; Werner-Seidler et al., 2021).

These findings highlight the importance of accurately identifying the youth who are most at risk for depression so that prevention efforts can be more efficient and effective (Garber, 2006). This requires taking multiple risk factors into account to better calculate depression risk

as no one risk factor alone provides a sufficiently high degree of sensitivity and specificity (Beekman et al., 2010; Garber, 2006). Though to my knowledge no study to date has used biological variables to help target depression prevention interventions (Fusar-Poli et al., 2021), the RewP, and perhaps the social RewP in particular, could theoretically be a useful tool to help increase our accuracy in identifying those most at risk. Furthermore, it is conceivable that one of the reasons that prevention intervention effects are relatively modest is that different risk mechanisms matter for different populations. Therefore, beyond improving our ability to predict depression in general, the RewP and other risk markers might also help guide which interventions are likely to be most effective for which groups or individuals.

Treatment selection

Many studies have examined whether indices of reward responsiveness, including the RewP, can improve treatment selection for individuals with depressive disorders. This is a particularly important problem given that existing evidence-based treatments for depression, including antidepressant medication and therapy, are not effective for all people (Craske et al., 2016), with up to 50% of patients not responding to a first-line treatment (Hofmann et al., 2012; Warden et al., 2007). Therefore, the ability to pre-select a treatment that is more likely to be effective based on the presence of certain risk factors could have a significant impact on the overall burden of depression (Webb et al., 2019; Williams et al., 2014).

The majority of studies investigating the link between reward responsiveness and treatment response have found that a relatively intact reward response is associated with better treatment outcomes across modalities. To illustrate, a relatively larger RewP in depressed patients has been associated with a better response to an aerobic exercise intervention (Brush et al., 2020) and increased chance of remission at a 9-month follow-up, whether or not any form of

treatment was received (Klawohn, Brush, et al., 2021). A larger reward prediction error response in the ventral striatum predicted better response to Cognitive Behavior Therapy (CBT; Queirazza et al., 2019) and a dopamine agonist (Whitton et al., 2020). Increased VS-ACC resting state connectivity predicted treatment response to Bupropion, an antidepressant that acts on the dopamine system (Ang et al., 2020). Those with greater functional connectivity between the VTA, striatum, and ventromedial prefrontal cortex (vmPFC) responded better to repetitive transcranial magnetic stimulation to the dorsomedial prefrontal cortex (dmPFC; Downar et al., 2014). A behavioral index of reward learning has also been linked to better response to dopaminergic medications (Ang et al., 2020; Whitton et al., 2020) and an increased likelihood of depression remission after 8 weeks of unstandardized inpatient treatment (Vrieze et al., 2013). This pattern of improved treatment response in those with relatively intact reward function is theoretically consistent with evidence that patients with higher levels of self-reported anhedonia tend to have a worse longitudinal course of depression and poorer treatment response (Craske et al., 2016; Khazanov et al., 2020; Uher et al., 2012).

One exception to this pattern is that relatively intact markers of reward response, including the RewP, have been inversely (Burkhouse et al., 2018; Greenberg et al., 2020) or not significantly (Ang et al., 2020) associated with response to Selective Serotonin Reuptake Inhibitors (SSRIs), a class of medications that are common first-line pharmacological treatments for depression (Kennedy et al., 2016) and increase serotonin levels in the brain (Nutt et al., 1999). Furthermore, a recent study using a machine learning approach found that a behavioral measure of reward learning and self-reported anhedonia did not improve the model's ability to predict response to SSRI versus placebo (Webb et al., 2019). Interestingly, SSRIs have been found to have a dampening effect on neural reward responses, as well as responses to threat, and

may be associated with emotional blunting (Kranz et al., 2010; Macoveanu et al., 2014; McCabe et al., 2010). Therefore, the associations between treatment response and reward responsiveness appear to be somewhat counterintuitive. Treatments that more directly impact the dopaminergic reward system (e.g. dopaminergic medications) seem to be more effective for those whose reward functioning is more similar to healthy controls while those who have less reward responsivity may do better, or at least not worse, with a treatment that can potentially dampen reward responses. This pattern seems to be generally true at least for pharmacological treatments.

The pattern of how reward responses relate to psychotherapy outcomes is more mixed. Although one study found that a larger reward prediction error in the VS predicted a better response to CBT (Queirazza et al., 2019), two other studies found a relatively blunted RewP in CBT responders (Burkhouse et al., 2016; Kujawa, Burkhouse, et al., 2019). Yet another study found no association between the RewP and CBT response (Burkhouse et al., 2018). A null association was also found between the RewP and response to Parent-Child Interaction Therapy-Emotion Development, an intervention aimed at increasing positive emotions and regulating negative ones in depressed children (Barch et al., 2020). The discrepancy in findings may come from heterogeneity in the populations being treated and the method of eliciting a reward response across studies. For example, the studies that found that a blunted RewP predicted better CBT response measured the RewP with the Reward Guessing Task whereas the studies that found null effects used the Doors Task. Unlike the Doors Task, the Reward Guessing Task has both an anticipation phase and a consumption phase such that the RewP from this task is potentially capturing a more sustained reward response. It also has a more frontal scalp distribution than the Doors RewP (Burkhouse et al., 2018; Burkhouse et al., 2016), further indicating that the

components are not capturing the same exact process. Therefore, it is possible that these methodological differences contributed to the mixed results.

This area of research on how markers of reward function predict treatment response for depression is fairly new and few studies have been replicated as of yet. Although there is some consistency across studies suggesting that those with a relatively larger reward response do better, at least with non-SSRI treatments, the current state of the evidence does not yet support the use of reward markers in guiding treatment selection. More methodological consistency across studies and replication with larger samples may help determine whether this clinical use of reward markers might become possible. It is also noteworthy that all the studies on the RewP and treatment response measured the monetary RewP, which, again, based on the findings of this dissertation, may be less optimal for predicting depressive outcomes. Studies examining whether the social RewP predicts depression treatment outcomes are warranted.

Treatment mechanism

If impaired reward response is a cause of depression, then treatments that can upregulate reward responsiveness should ameliorate depressive symptoms. However, many standard treatments for depression do not explicitly or directly target reward functioning. As previously discussed, SSRI medications can decrease reward responses (Kranz et al., 2010; McCabe et al., 2010; though see Stoy et al., 2012 for an exception) and CBT often focuses more on alleviating negative affect than increasing positive affect and rewarding experiences (Craske et al., 2016). Nonetheless, researchers have studied whether change in reward responses might mediate the efficacy of these treatments while others have investigated novel treatments that target the reward system more directly.

A number of studies have examined whether change in reward functioning over the course of treatment is associated with the degree of improvement in depressive symptoms. For example, Burkhouse and colleagues found that even though patients exhibited no more change in the RewP than control participants, the increase in the RewP from pre- to post-treatment predicted the extent to which their depressive and anxiety symptoms decreased over a 12-week course of CBT or SSRI treatment (Burkhouse et al., 2018). Consistent with this finding, other studies have found that increase in VS activity predicted a decrease in depressive symptoms after treatment with an SSRI (Stoy et al., 2012) and a decrease in self-reported anhedonia after treatment with ketamine (Lally et al., 2014). Furthermore, Wichers and colleagues found that responders to a course of a tricyclic antidepressant (Imipramine) showed an increase in rewarding experience (enjoyment derived from positively appraised activities) whereas non-responders did not (Wichers, Barge-Schaapveld, Nicolson, Peeters, De Vries, et al., 2009). These studies support the premise that increasing reward function leads to a reduction in depressive symptoms. Other studies have found that a treatment for depression was effective at reducing symptoms but either didn't increase the measure of reward sensitivity (Brush et al., 2020; Whitton et al., 2020) or the increase wasn't correlated with change in depressive symptoms (Barch et al., 2020). Therefore, changing reward response may be one but not the only mechanism that matters for depression treatment.

Additional studies have provided evidence of whether reward system functioning is a mechanism of depression treatment by testing interventions that act directly on the reward system. For example, deep brain stimulation (DBS) of the bilateral ventral striatum was found to significantly alleviate depressive symptoms and increase enjoyable activities in five of ten severely depressed patients (Bewernick et al., 2010). This was quite remarkable considering that

the participants in this sample had not experienced relief through ECT and psychotherapy, had been through an average of 8.3 medication trials, and the mean length of their current episode at the time of the study was 10.8 years. However, this study was not controlled or blinded, and subsequent randomized control trials have found that DBS to the ventral striatum (Dougherty et al., 2015) or the subcallosal cingulate (Holtzheimer et al., 2017) was not more effective than sham stimulation. It is possible that these null findings resulted from insufficient duration of treatment or inadequate tuning of stimulation parameters (Schlaepfer, 2015). Nonetheless, more work is needed to assess whether directly manipulating the dopaminergic reward system in this way can reliably produce antidepressant and hedonic effects for a subset of patients.

Psychotherapies that directly target reward function are also effective for depression. Behavioral activation, which can be a component of CBT or a standalone treatment, works by increasing the number of positive and rewarding activities in which patients engage (Kanter et al., 2010). One study found that not only was behavioral activation therapy highly effective for depression in their sample, but it also led to changes in reward-related fMRI activation in regions including the caudate and the orbitofrontal gyrus (Dichter et al., 2009). Another research group developed a novel treatment called Positive Affect Therapy (PAT) designed to specifically target deficits in reward sensitivity (Craske et al., 2016). This therapy includes elements of behavioral activation as well as cognitive training to help patients attend to the positive and sessions focused on cultivating positivity through generosity, appreciation, gratitude, etc. (Craske et al., 2016). A recent empirical test of PAT found that it was more effective than a similar treatment focused on negative affect and improved composite indices of reward anticipation and consumption (Craske et al., 2023). These studies further the theory that targeting reward function can be an effective

way to treat depression and show that this can be done even without pharmacological or invasive methods.

To summarize, the literature on using indicators of reward sensitivity for clinical purposes is still somewhat new and not quite ready to be implemented widely (Nielson et al., 2021). However, there is evidence that reward responses may be both a risk factor and mechanism for depression, though not the only one. There is also promising evidence that neural markers like the RewP may improve our ability to prospectively predict depression diagnoses (Bress & Hajcak, 2013; Michelini et al., 2021; Nelson et al., 2016), which could help target prevention efforts (Garber, 2006). The evidence for using indicators of reward response as a guide for treatment selection is less consistent, perhaps especially so for the RewP (Barch et al., 2020; Brush et al., 2020; Burkhouse et al., 2018; Burkhouse et al., 2016; Kujawa, Burkhouse, et al., 2019), suggesting that more research in this area is needed. Studies evaluating whether social reward responses can improve the prediction of depression onset or treatment outcomes are especially warranted. While there is evidence that reward functioning is an important target or mediator of depression treatment (Dichter et al., 2009; Lally et al., 2014; Stoy et al., 2012; Wichers, Barge-Schaapveld, Nicolson, Peeters, de Vries, et al., 2009), only one study using the RewP has found direct evidence of this to date (Burkhouse et al., 2018). Therefore, more research is still needed on the extent to which the RewP might track depression treatment response. A particularly interesting question is whether change in the RewP might be a mechanism of treatment response for therapies that more explicitly target the reward system, like Positive Affect Therapy (Craske et al., 2016). One study did find that a brief intervention designed to increase motivation led to a same day increase in the monetary RewP (Pegg &

Kujawa, 2020). Although this was not a therapy study, it does suggest that the RewP can be upregulated, which is necessary for it to be a mechanism of treatment response.

Limitations and Future Directions

The three studies presented here help delineate associations between the RewP and other risk factors for depression (i.e. stress and family history) and highlight the parameters under which the RewP is more strongly relevant to depression risk (i.e. response to social reward, conditions of stress). Nonetheless, there are several limitations to these studies that require discussion and point to future directions. One such limitation is that although all three studies focused on risk for depression, none of the studies provided direct evidence that the RewP prospectively predicted clinically significant depression onset. Although in Study 3 we found evidence that a blunted social RewP predicted relatively increased depressive symptoms during the early phase of the COVID-19 pandemic, we did not assess whether it also predicted actual depressive episodes. In Study 2, we found that never-depressed adolescent girls at relatively high risk for depression had a very significantly blunted social RewP, but again did not follow up with these participants to determine whether this led to a depression diagnosis. Many of the reasons for not assessing future depression diagnoses in these samples were logistical. We did have a follow-up study visit that included diagnostic measures underway for Study 2, but it was interrupted by the COVID-19 pandemic and not completed. Furthermore, the samples for Studies 1 and 3 were unselected undergraduates, a relatively healthy and high-functioning group. Therefore, even if we had completed diagnostic interviews with these participants, we might have been underpowered for analyses predicting depressive episodes (Auerbach et al., 2018). Completing diagnostic interviews in these studies would also have most likely shrunk their sample sizes due to the time and personnel required, exacerbating this issue. To address this

limitation, future studies are needed to assess the extent to which the risk factors examined here including neural responses to monetary and social reward, family history of depression, and real-world stress, come together to predict clinically significant depressive episodes. This requires collecting larger samples or oversampling for those at relatively high risk for depression. Prospective studies using depressive episodes as outcomes are especially important for increasing the feasibility of targeting depression prevention interventions.

Another limitation of this dissertation was that the samples in all three studies were restricted in regards to demographic variables. One of the more striking examples of this is that the samples in all three studies either skewed heavily toward female-identifying participants, or in the case of Study 2, was exclusively made up of female participants. The advantage of this is that because depression is more prevalent in women (Kessler, 2000; Nolen-Hoeksema, 2002), this to some degree reflects the population of people at greater risk for depression; however, men still experience depression at high levels (Rehm & Shield, 2019). For that reason, it will be important to confirm whether or not the findings presented here replicate in male samples and to explore whether there are meaningful gender differences in how reward is implicated in depression. This is especially true for investigations of neural response to social reward as previous studies have found gender differences in social reward response (Soutschek et al., 2017; Spreckelmeyer et al., 2009) and how it relates to depression symptoms (Distefano et al., 2018). Additionally, the sample compositions in the present studies tended to be of relatively higher socioeconomic status and predominantly White. Diverse, representative samples are necessary to ensure that the findings presented here hold in other socioeconomic or cultural contexts (Henrich et al., 2010).

Beyond sample composition, an additional limitation in these studies has to do with the measurement of stress. Objective exposure to stress, as opposed to the subjective experience of stress, was a major element of all three studies. In Study 1, exposure to the stress of the COVID-19 pandemic was the main independent variable. In Study 2, chronic interpersonal stress was a simultaneous predictor of the social RewP, along with maternal or personal depression history. In Study 3, we measured depressive symptoms in the context of the stress of the COVID-19 pandemic, and also tested interactions between the RewP and stressor count in predicting depressive symptoms at each timepoint. However, the ways these stressors were quantified have drawbacks. For Studies 1 and 3, which had similar methods, the chronic/prolonged stress of the COVID-19 pandemic was inferred rather than directly measured. Although we know these participants were exposed to specific prolonged stressors (e.g. lockdowns, remote schooling, etc.), we had imperfect measures of individual experiences. We did have the Pandemic Stress Questionnaire (PSQ; Kujawa, Green, et al., 2020) in these samples, which measures discrete pandemic-related life events in multiple domains. This was useful to confirm that participants were experiencing stressful events related to the pandemic, but this measure, as with all life events checklists, does not account for context (Harkness & Monroe, 2016). To illustrate, two participants could endorse the item "I was unable to be with close family, friends, or partners because of the coronavirus pandemic" but have drastically different experiences (e.g. a participant living alone in a different city from family versus a participant who lived with friends and was able to see family only occasionally). This measure was also developed during the first few months of the pandemic and may not have remained as relevant or sensitive to stressors occurring later in the pandemic. Overall, the PSQ may have been an insufficiently sensitive and comprehensive way to accurately capture differences in stress exposure. The fact that we did not

observe significant correlations between neural responses and PSQ stressor count but did observe overall changes in the RewP or in the association of the RewP to depressive symptoms in the context of the COVID-19 pandemic seems to suggest this possibility.

A solution to the problem of missing important context in stress measurement is to conduct life stress interviews (Harkness & Monroe, 2016), such as we did in Study 2 with the UCLA Life Stress Interview (UCLA LSI; Hammen, 2004). This has the advantage of capturing objective yet contextualized stress exposure using a semi-structured interview, a simple rating system, and group scoring meetings to reduce bias. The use of the UCLA LSI was a strength of Study 2; however, the measure is time-consuming and resource-intensive such that it is not optimal or possible in all studies. Being able to replicate the findings of Studies 1 and 3 with contextualized COVID-19-related stress from the UCLA LSI or a similar measure would be a valuable addition to the literature.

Finally, the three studies presented here examined blunted neural response to reward as a marker of risk for depression. Depression, however, is far from the only disorder for which impaired reward response is a relevant construct. For example, abnormally heightened reward sensitivity has been linked to bipolar disorder and hypomania (Alloy et al., 2016; Johnson et al., 2005; Johnson et al., 2017; Whitton et al., 2015). On the other end of the spectrum, blunted or abnormally low levels of reward responsivity have been linked with a wide range of psychopathology besides depression (Gondre-Lewis et al., 2020), including schizophrenia (Olney et al., 2018; Whitton et al., 2015), posttraumatic stress disorder (Olson et al., 2018; Sailer et al., 2008), and substance use disorders (Baskin-Sommers & Foti, 2015; Nawijn et al., 2015; Vujanovic et al., 2017). Because depression has very high rates of comorbidity with these and other disorders (American Psychiatric, 2013; Steffen et al., 2020; Volkow, 2004), an important

future direction is to tease apart the extent to which impaired reward response creates shared risk for multiple or comorbid disorders (e.g., Crane et al., 2023) and the extent to which it might distinguish between disorders (e.g., Burkhouse et al., 2016; Kujawa, Burkhouse, et al., 2019; Weinberg, 2022).

Final Conclusions and Summary

The work presented here enhances our understanding of how impaired reward response is implicated in risk for depression. Specifically, these findings specify how neural responses to social and monetary rewards are concurrently or prospectively associated with other important risk factors for depression such as real-world stress, family history of depression, and depressive symptoms. Results demonstrated that prolonged naturalistic stress exposure predicts a blunted monetary RewP, and a maternal history of depression or chronic interpersonal stress predicts a blunted social RewP, at least for some individuals. Further, social reward responses, relative to monetary reward responses, may be more effective predictors of risk for depression, especially during times of stress. Together, these findings help specify how measures of neural reward response could be used, along with other risk factors, to improve our ability to prospectively predict who will become depressed and to guide preventative interventions. At the same time, the findings highlight the complexity of the associations between reward functioning and depression risk and point to future directions for research that will continue to untangle this complexity.

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