FULL TEXT ARTICLE

Medial Prefrontal Cortex Activity to Reward Outcome Moderates the Association Between

Kristen L. Eckstrand, Jennifer S. Silk, Melissa Nance, Meredith L. Wallace, Nicole Buckley, Morgan Lindenmuth, Luis Flores, Gabriela Alarcón, Karina Quevedo, Mary L. Phillips, Ca

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Abstract

Background

Sexual minority youth (SMY) are 3 times more likely to experience depression than heterosexual peers. Minority stress theory posits that this association is ex may worsen depression by altering activity in neural reward systems. This study examines whether neural reward systems moderate the influence of sexual ori

Methods

A total of 81 participants ages 15 to 22 years (41% SMY, 52% marginalized race) reported sexual orientation victimization, depression severity, and anhedonia $_{\text{familywise error}} < .05$) was determined within a meta-analytically derived Neurosynth reward mask. A univariate linear model examined the impact of reward act

Results

SMY reported higher depression ($p < .001$), anhedonia ($p = .03$), and orientation victimization ($p < .001$) than heterosexual youth. The bilateral ventral stria moderated associations between sexual orientation victimization and depression ($p = .03$), with higher depression severity observed in those with a combinat

Conclusions

Sexual orientation victimization was related to depression but only in the context of higher mPFC activation, a pattern observed in depressed youth. These nov are a first step toward a clinical neuroscience understanding of minority stress in SMY.

There are crisis-level inequities in depression among sexual minority youth (SMY), adolescents, and young adults with romantic identities/attractions to the s higher than their straight peers (2 , 3). Recent research has examined social factors contributing to depression in SMY, such as victimization (4 , 5). The pe factors for depression in SMY can impact neural systems and the extent to which neural systems themselves can contribute to depression in SMY (7).

Minority stress theory posits that the health inequities experienced by populations who are marginalized [i.e., populations that experience unequal power and Distal stressors, which are external to an individual and can include discrimination, victimization, prejudice, and rejection, are often based on that individual's are internal processes, often occurring in reaction to distal stressors, such as negative thoughts about the marginalized group that one is a part of, expectations depression severity. This relationship has been consistently demonstrated for many marginalized communities including people who are marginalized due to s orientation (i.e., sexual orientation victimization) (15), including harmful words or behaviors, commonly from peers or parents (3). Such victimization prec this evidence lends support for the validity of the minority stress model in SMY (17), additional research is necessary to understand whether neurobiological

Neural reward systems are implicated in the associations between stressors and adolescent depression and anhedonia, a cardinal symptom of depression (18 cortex, and dorsal anterior cingulate cortex (dACC). The VS encodes the difference between expected and received rewards (22), while the amygdala encodes PFC influences decision making to obtain immediate rewards (28 , 29), and the orbitofrontal cortex encodes the incentive salience of expected rewards (26 , consistently associated with adolescent depression. Because reward system dysfunction precedes the onset of depression in youth (36) and may thus represe emerge in those with altered reward system function depends on exposure to stress (39). VS activation to reward moderates relationships between exposure 41), and poorer reward responsiveness in those with histories of trauma is associated with the development of depression (42). Identifying patterns of susce understanding risk for, detection of, and interventions targeting depression in communities with depression inequities (43).

Prior research has examined differences in neural and neuropsychological function on the basis of sexual orientation identity, hypothesizing that observed diff psychiatric disorders impacting sexual minority persons (48 49 50). This approach differs from minority stress theory by focusing on sexual orientation ident to confer risk for psychopathology (51 , 52). Consistent with prior research on stress and neural reward systems, conceptual models posit that neural reward the respective impacts of sexual orientation identity, sexual orientation victimization, and neural reward systems on adolescent depression. Understanding tha environmental factors disproportionately experienced by SMY, not intrinsic differences in neural structure/function based on sexual orientation identity, are neural reward system function, this research is also critical to understand who is at risk for depression in the setting of victimization.

In this cross-sectional study, a diverse sample of youths and young adults (ages 15–22 years) was recruited to examine how neural reward systems interact wi evidence suggesting that neural reward systems moderate the association between stress and depression severity (19 , 40 , 43), we hypothesized that neural r hypothesized that higher sexual orientation victimization, particularly in those exhibiting a pattern of higher mPFC and lower VS activation to reward, would l

sexual orientation identity and depression. Given that exposure to victimization based on identity impacts multiple marginalized groups (11 12 13 14), explor

Methods and Materials

Participants/Study Design

This cross-sectional study included a subset of 81 youths and young adults enrolled in a larger, prospective, longitudinal study (ages 13–22; $N = 132$) examini associated psychiatric illnesses during an age range when such illnesses typically emerge, to observe the course and neural correlates of anhedonia developme clinics with higher proportions of SMY. Participants were eligible to participate in the study if they were between the ages of 13 and 22 and able to undergo ma

All parents and affected adult siblings completed the Structured Clinical Interview for DSM-5 to assess participant eligibility and, if possible, completed a seco Board, and adolescents (and their parents, if under age 18 years) provided written informed consent.

Identity data regarding sexual orientation [6 response options (54)], race (7 response options), and sex (open-ended text) was collected. Sexual orientation w responses: “100% heterosexual (straight),” “mostly heterosexual (straight but somewhat attracted to people of your own sex),” “bisexual (attracted to men and know,” or “not listed.” Race and sex demographic details are discussed in the Supplement (appsec1) along with rationale for demographic measurement selectio

While the parent longitudinal study recruited individuals ages 13 to 22 to study the development of anhedonia and neural reward systems across adolescents, they may be SMY and/or are in the process of disclosing their orientation to others (55 56 57). No participants under age 15 identified as SMY. Data for this s Supplemental Methods (appsec1)), past-6-month victimization exposure, and current depression and anhedonia. Participants were excluded from the final sampl <50% ($n = 2$). The final sample comprised 81 youths and young adults ages 15 to 22 (41% SMY, 52% marginalized race, 59% female sex) (Table 1 (tbl1)).

Table 1
Baseline Participant Demographics

Demographics	*n*	Mean ± SD
Age, Years	–	17.42 ± 2.16
Sex		
Female	48	–
Male	33	–
Race		
Asian	7	–
Black	27	–
More than one race	8	–
White	38	–
Other race not listed	1	–
Sexual Orientation		
Heterosexual (straight)	48	–
Mostly heterosexual	5	–
Bisexual	13	–
Mostly gay or lesbian	5	–
Gay or lesbian	9	–
Orientation not listed	1	–
Victimization (Range, 0–6) [a] (tbl1fna)		
Gender	–	0.64 ± 1.25
Sexual orientation	–	1.01 ± 1.44
Race	–	1.02 ± 1.28
Depression		
Depression severity (CESD; range, 0–54) [b] (tbl1fnb)	–	13.68 ± 10.08
Anhedonia severity (SHAPS; range, 14–56) [c] (tbl1fnc)	–	25.74 ± 5.26

CESD, Center for Epidemiologic Studies Depression Scale; SHAPS, Snaith-Hamilton Pleasure Scale.

a Scale obtained from (59).

b Scale obtained from (61).

c Scale obtained from (62).

Victimization and Depression Measures

Identity victimization was measured with a previously validated 24-item self-reported questionnaire (58) assessing the frequency of being bullied, being hit/k called hurtful or insulting names based on race, sexual orientation, gender (not sex), and/or weight (6 items each; 24 items total) during the past 6 months. Re measures of adversity that assess presence or absence of exposures (60), victimization exposure was operationalized as the number of exposure types endorse Epidemiologic Studies Depression Scale (61) and the 14-item Snaith-Hamilton Pleasure Scale (62), respectively, in which greater sum scores indicated grea

Monetary Reward fMRI Task

Neural reward systems were examined using an adapted, pseudorandomized, event-related card-guessing task (63 , 64) that included 3 outcome contexts (wi monetary value associated with trial outcome ($1 per win; $0.75 deduction per loss; $0 for neutral). Trials were fixed in a pseudorandomized fashion in which MRI acquisition parameters, and preprocessing.

Data Analyses

For first level neuroimaging analyses, completed in SPM12, a fixed-effect general linear model (GLM) was performed for each participant. The GLM included outcome of the trial. The first-level GLM included 5 contrasts: win > neutral outcome and anticipation, win > loss outcome and anticipation, and win > nonwi artifacts were identified using Artifact Detection Tools (image intensity deviated > 3 SD from the mean intensity or in which there was movement 0.5 mm in t noise. Last, the 6 motion realignment parameters were entered as covariates to control for head movement. A 128-second high-pass filter and autoregressive r

First-level contrast images for the win > neutral outcome condition, reflecting neural reward activity, were entered into second-level SPM analyses. Age was e within a Neurosynth mask (67) defined by the term “reward” (Supplemental Methods (appsec1)), with significance determined using a cluster extent threshold representing blood oxygen level–dependent (BOLD) activity for regions with significant activation in second-level voxelwise analyses.

Statistical analyses were completed in SPSS version 26 (IBM Corp). We used univariate linear models to test hypotheses of whether neural reward systems mo neural regions significantly activated to reward (see Results (sec2)) with 2 outcomes, depression severity (Center for Epidemiologic Studies Depression Scale) victimization, neural activation to reward, the interaction between sexual orientation victimization and neural activation to reward, and the interaction betwee

$$Y = \beta_0 + \beta_1 Age + \beta_2 SO + \beta_3 SOVictimization + \beta_4 BOLD +$$

where Y refers to either depression or anhedonia severity, SO refers to sexual orientation identity, SOVictimization refers to sexual orientation victimization, a within each model using sequential goodness-of-fit metatests (68). Sequential goodness of fit is an effective tool for adjustment with high-dimensional biolog neuroimaging analyses (22 , 40 , 69 , 70). Supplemental analyses examined differences in victimization exposure by identity using 2 sample *t* tests, differenc multivariate linear analyses (Supplemental Results (appsec1)).

Results

Sample Characteristics

A total of 16% ($n = 13$) of the sample reported all majority identities (White, self-identified male, heterosexual), 30.9% ($n = 25$) reported 1 marginalized iden differences, SMY experienced greater victimization based on sexual orientation ($t_{1,79} = -6.39$, $p < .001$) (Table S2 (appsec1)), gender ($t_{1,79} = -3.66$, $p < .00$ victimization ($t_{1,79} = -2.30$, $p = .020$) (Table S3 (appsec1)) compared with White individuals. Individuals who reported a female sex experienced more victimi

Neural Activity to Reward Outcome

Five functional clusters were significantly activated in the main effects fMRI analysis examining neural activity to reward outcome (Table 2 (tbl2) , Figure 1A (fig1 orbitofrontal cortex, with extension to the inferior frontal gyrus and anterior insula (58 voxels). No regions met cluster-level significance ($p_{\text{familywise error}} < .05$

Table 2

Neural Activation During Reward > Neutral Outcome

Region	Hemisphere	Voxels	T Score	MNI Coordinates		
				x	y	z
Ventral Striatum	R	84	6.89	10	12	−4
	L	35	5.25	−6	8	−2
Medial Prefrontal Cortex	L/R	155	5.62	0	38	8
Anterior Cingulate Cortex	R	58	4.95	30	26	−10
Orbitofrontal Cortex	R	37	4.71	4	32	18

Thresholded at $p_{\text{familywise error}} < .05$.

L, left; MNI, Montreal Neurological Institute; R, right.

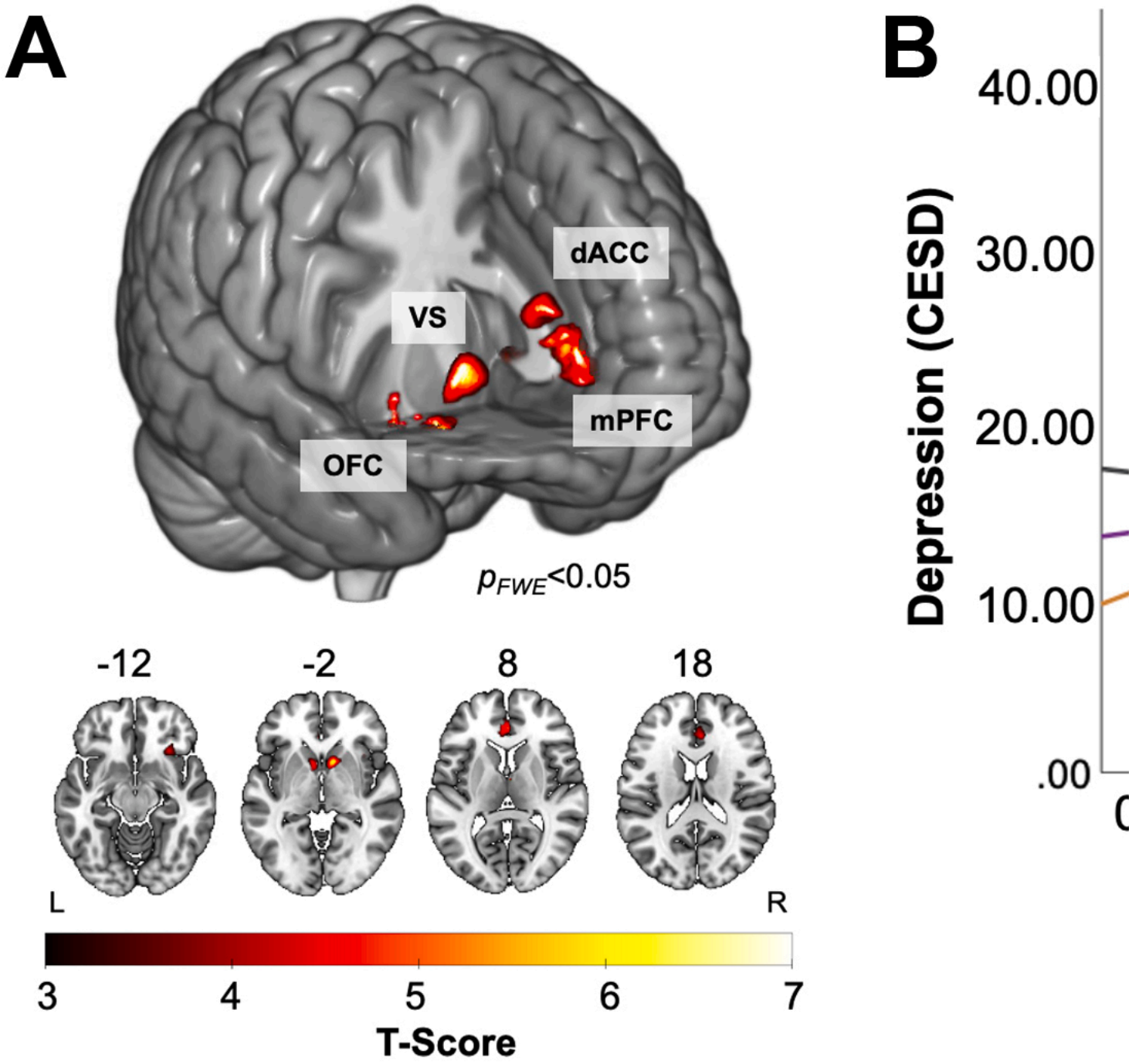

Figure 1

(A) Neural activation to reward outcome compared with neutral outcome ($p_{FWE} < .05$) within the Neurosynth reward mask in the bilateral ventral striatum (VS), medial prefrontal co combination of higher mPFC activation to reward outcome (displayed as mean ± 1 SD) and greater victimization based on sexual orientation was associated with higher depression

Identity victimization was not associated with neural activation to reward (Table S6 (appsec1)). Significant differences in neural activation by identity are prese

mPFC Activity Moderates the Relationship Between Orientation Victimization and Depression Severity

The overall univariate linear models examining the moderating effect of neural reward activation between sexual orientation victimization and sexual orientat multiple comparisons, neural activation to reward outcome in the mPFC moderated the effect of sexual orientation victimization on depression severity ($F_{1,7}$ experienced higher depression (Table 3 (tbl3) , Figure 1B (fig1)). In the univariate model, sexual orientation identity was associated with depression ($F_{1,79} = 19.$ reward outcome. No other regions of significant activation to reward outcome moderated the impact of sexual orientation victimization and sexual orientation on racial identity and racial identity victimization, and sex and gender victimization, were not significant.

Table 3

Univariate Linear Model Examining the Moderating Effect of Neural Activation to Reward Outcome in the mPFC on the Associations Between Sexual Orientation Identity and Sexual

	R	R^2	$F_{6,79}$	p Value
Model Summary	0.619	0.383	7.541	<.001 [a] (tbl3fna)

Model	β	SE	t	p Value	95% CI	
					Lower Limit	Upper Limit
Intercept	37.327	11.297	3.304	.001	14.813	59.841
Age	−1.725	0.688	−2.507	.014 [a] (tbl3fna), [b] (tbl3fnb)	−3.096	−0.354
Orientation Victimization	−2.263	1.558	−1.452	.151	−5.367	0.842
mPFC	−0.122	0.819	−0.149	.882	−1.755	1.511
Sexual Orientation Identity	21.339	4.806	4.44	<.001 [a] (tbl3fna), [b] (tbl3fnb)	11.76	30.918
mPFC × Orientation Identity	−3.629	1.972	−1.841	.070	−7.559	0.300
mPFC × Orientation Victimization	1.686	0.783	2.154	.035 [a] (tbl3fna), [b] (tbl3fnb)	0.126	3.246

CESD, Center for Epidemiologic Studies Depression Scale; mPFC, medial prefrontal cortex.

a $p < .05$.

b Significant after sequential goodness-of-fit multiple comparisons correction.

Discussion

There is a dire need for rigorous research, including in biological psychiatry, that addresses the crisis-level inequities in depression among SMY (7). To the be victimization, but also more strongly associated for those who exhibit a pattern of higher mPFC activation to reward. Specifically, in a diverse adolescent and y response to reward was associated with higher depression severity. This suggests that neural reward systems may play a critical role in depression in SMY, par

While mPFC reward activation was not a direct marker of depression in this sample, mPFC reward activation moderated the relationship between sexual orien victimization. This is consistent with prior diathesis-stress studies demonstrating that activity in neural reward systems moderates relationships between stres lower VS activation to reward was associated with higher anhedonia (19), while another longitudinal study in young adults found that higher lifetime trauma measure of neural activity inversely correlated with activation in medial prefrontal regions (71), moderates the relationship between life stress and developm orientation victimization functions similarly to general stress exposures, as opposed to an independent mechanism, when considering the relationships betwe intervention to reduce depression severity and may offset the development of depression in those who may have a preexisting vulnerability. Alternatively, for t may benefit from targeted prevention strategies. Combined, these data suggest that for individuals at risk for depression because of sexual orientation victimiz

SMY identity remained strongly associated with depression independent of differences in reward activation, likely reflecting the importance of other neural sy status with sexual orientation victimization by mPFC activation in impacting depression. This supports the central tenet of the minority stress model: Social ar risk for psychopathology (51). Clarifying this distinction is necessary given that prior research has suggested that neural differences based on sexual orientati understanding of emotions and psychiatric disorders impacting sexual minority persons (48 49 50). Neuroscience research aiming to support the mental heal sexual orientation identity alone. For example, longitudinal prospective studies exploring temporal relationships between victimization, neural reward system victimization. Such research should include additional components of minority stress, such as the proximal stressors of internalized negativity or identity conc and, potentially, their impact on depression inequities in SMY.

Models describing victimization as chronic stress, trauma, and/or threat posit that such exposures impact multiple neural systems (43 , 73 74 75). For examp research, we did not find a relationship between any type of identity victimization and neural reward systems. This may be because our measure of victimizatic function in neural reward systems (19 , 40 , 77 , 78). Alternatively, the impact of identity victimization may be more evident in threat and social systems in c can mediate relationships between stress and future depression, we were unable to test this relationship in the current cross-sectional sample, limiting our abi adolescents, to examine relationships between victimization—as it is experienced by marginalized communities—and neural function across neural systems th

There were several limitations to this study. Sex and gender terminology were used inconsistently in the demographics and victimization measures. Sex was ar diversity in an adolescent and young adult sample. This limits the extension of this research to transgender and gender-diverse communities, other population it likely does not capture the range of sexual orientation diversity in adolescents (1). Future research should measure sex, sexual orientation, and gender iden Medicine (80). We also dichotomized participants based on reported demographics as marginalized or not in order to examine victimization based on margir 52). A larger proportion SMY experienced sexual orientation victimization and more sexual orientation events than heterosexual youths. While heterosexual y research aiming to examine how environmental influences and neural systems can impact inequities in depression should utilize well-powered, longitudinal d impact depression. Altered activation in neural reward systems is often, but not always [see (81)], observed in individuals with depression diagnoses compar because a diagnosis of depression was not a criterion for study inclusion. Alternatively, while altered neural reward activation between depressed and nondepr is a less consistent finding (82). The present study defines victimization exposures broadly across witnessing, emotional, and physical categories. This is cons

73); however, we acknowledge that the present approach prohibits examining specificity in type of victimization. In the present sample, SMY reported an ave particularly if combined with general stressors or other trauma events, is associated with depression (83 84 85). While this victimization scale did not examin victimization based on sexual orientation is likely to impact depression symptoms given the cumulative psychopathology risk with increasing adversity exposu

In conclusion, this cross-sectional study in a diverse youth and young adult sample aimed to examine relationships between sexual orientation victimization, r orientation victimization and higher mPFC activation to reward. This suggests that certain patterns of neural reward function may impact depression severity in SMY in the setting of victimization to prevent the negative effects of victimization.

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Supplementary Material

Supplementary Data (/ui/service/content/url?section=static%2fimage&eid=1-s2.0-S2451902222002105&path=24519022%2FS2451902221X00134%2FS2451902222002105%2Fr

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