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Brain responses to social feedback in internalizing disorders: A comprehensive review

Brent I. Rappaport, Deanna M. Barch



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5 Tables, 0 Figures

Title: Brain responses to social feedback in internalizing disorders: A comprehensive review

Authors: *Brent I. Rappaport, M.A.^a and Deanna M. Barch, Ph.D.^{a,b,c}

Affiliations: ^aDepartment of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO, USA

^bDepartment of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

^cDepartment of Radiology, Washington University School of Medicine in St Louis, St. Louis, MO, USA

*-corresponding author

Location of work: Department of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO, USA

Address for reprints:

Brent Rappaport
Department of Psychological & Brain Sciences
Washington University in St. Louis
One Brookings Drive Box 1125
St. Louis, MO 63130
Email: brappaport@wustl.edu

Highlights

- Depression associated with cingulo-opercular hyperreactivity to negative feedback
- BPD associated with default model network hyperactivity to negative feedback
- Methodological considerations are required for future studies

Abstract

Problems with interpersonal relationships are often a chief complaint among those seeking psychiatric treatment; yet heterogeneity and homogeneity across disorders suggests both

common and unique mechanisms of impaired interpersonal relationships. Basic science research has begun yielding insights into how the brain responds to social feedback. Understanding how these processes differ as a function of psychopathology can begin to inform the mechanisms that give rise to such interpersonal dysfunction, potentially helping to identify differential treatment targets. We reviewed 46 studies that measured the relationship between brain responses to social feedback and internalizing psychopathology. We found that socially relevant anxiety was associated with amygdala hyperactivity to the anticipation of social feedback. Depression was related to hyperreactivity of regions in the cingulo-opercular network to negative social feedback. Borderline personality disorder (BPD) was associated with hyperactivity of regions in the default mode network to negative social feedback. The review also identified key insights into methodological limitations and potential future directions for the field.

Keywords: social feedback, internalizing, psychopathology, fMRI, neuroimaging

1. Introduction

Problems forming and maintaining interpersonal relationships are associated with worse physical health and increased mortality risk (House et al., 1988), equaling the effect of cigarette smoking, obesity, and lack of exercise (Holt-Lunstad et al., 2010). Such interpersonal challenges are also a chief complaint of individuals seeking psychiatric treatment and arise in numerous psychiatric disorders (American Psychiatric Association, 2013; Kennedy & Adolphs, 2012). However, heterogeneity and homogeneity across disorders suggests both common and unique mechanisms of impaired interpersonal relationships. For example, clinically, major depressive disorder (MDD) is often associated with disinterest in social interactions, possibly due to anhedonia, or a reduction in pleasure experienced in social interactions. Social anxiety disorder (SAD) on the other hand, is associated with avoidance of social situations out of fear. Finally, borderline personality disorder is related to more negativistic views (Barnow et al., 2009) and

inappropriate affective appraisal of relationships. For internalizing and related disorders, then, the problem appears to lie in how individuals respond to social feedback—information received from one or multiple con-specific(s) about one's own social standing. This review will summarize studies of the relationship between brain response to social feedback and specific forms of psychopathology. This will inform the mechanisms of interpersonal dysfunction found across internalizing and related disorders.

1.1 Social feedback processing in the brain

In the basic science literature, recent reviews have yielded findings about how social rejection feedback is processed in humans, both adolescents and adults. These studies have implicated the ventrolateral prefrontal, subgenual anterior cingulate cortex (ACC), and striatum—among other regions—in developmental samples. However, the meta-analyses generating these insights about brain mechanisms have typically focused exclusively on tasks of social *exclusion* (S. Cacioppo et al., 2013; Vijayakumar et al., 2017), relying heavily on findings using the Cyberball paradigm — a game of virtual catch with other individuals during which the participant is either included in the game of catch or excluded (i.e. the other players do not throw the ball to them; see below for more details). Although it is certainly important to understand how humans respond to social exclusion, this represents just one piece of a growing literature that uses different paradigms to examine the response to social feedback. The current review seeks to incorporate findings from different types of tasks beyond Cyberball to begin to make sense of how the findings can inform the neural and psychological mechanisms contributing to interpersonal dysfunction in psychiatric disorders.

1.2 Types of social feedback

Social feedback takes many forms, and in order to maintain ecological validity, we need to study how the brain responds to different kinds of feedback. Prior meta-analyses and reviews have typically focused on “social rejection” and “social exclusion” as elicited by the Cyberball task (S. Cacioppo et al., 2013; Reinhard et al., 2020; Vijayakumar et al., 2017). This is a sensible

approach for meta-analysis, where differences between studies and paradigms can obscure effects. However, it also limits the generalizability of these findings to other types of social feedback. A critical review of the literature thus can strike a balance between aggregating findings from similar paradigms to draw meaningful conclusions and using similarities and differences between studies and paradigms to better inform the generality of conclusions. As such, the current review will examine findings from studies that used different social feedback paradigms that measure different types of social feedback.

For the sake of clarity, we will first define social exclusion, rejection, insults, inclusion, acceptance, compliments, and anticipation of feedback. Rejection is defined as negative social feedback by one individual (e.g., being told by another person that they do not like you). Exclusion is defined as negative social feedback (e.g., rejection) by more than one other individual that contains information about the participant's membership in a group (e.g., being either removed or barred from joining a social group). Insults are defined as negative feedback that does not clearly indicate rejection or exclusion, or feedback from a reputationally hostile other (e.g., being called a mean name, teasing, taunting). Likewise, acceptance is positive social feedback by one individual, inclusion is positive social feedback by more than one other individual that contains information about the participant's membership in a group, and compliments are positive feedback that does not clearly indicate acceptance or inclusion, or feedback from a reputationally kind other. Finally, anticipation is defined as the period prior to the receipt of social feedback, when feedback is expected. Where participants were anticipating negative, positive, or ambiguous feedback, that is specified (e.g., anticipated exclusion/rejection/insult).

These definitions and distinctions are important for delineating the mechanisms underlying psychopathology. For example, both the number and type of feedback may have unique processes and thus unique relationships with specific symptom dimensions. In terms of number, it is possible that rejection by more than one individual is interpreted differently than rejection by a single individual. In terms of type, receiving a compliment may elicit a more graded positive

reaction than full social acceptance or even inclusion by a group. Likewise, insult or social rejection, as defined here, may elicit an angry response towards the specific person, whereas social exclusion may elicit sadness. These represent just some examples but emphasize the importance of clearly characterizing the type of social feedback used in each study.

1.3 Social feedback tasks

Different tasks have been used to measure the above types of social feedback. Many of these tasks measure response to the receipt of social feedback. As noted above, the most common is the Cyberball task (K. D. Williams & Jarvis, 2006), which measures response to inclusion and exclusion. In this task, participants play a game of virtual catch with other individuals which they are led to believe are other people interacting with them live. This task is typically administered in blocks, with separate inclusion and exclusion blocks, during which the participant is included in the game of catch, or excluded—the other players do not throw the ball to them. Although typically labeled as “inclusion,” the creator of the Cyberball task even notes that the inclusion condition should be considered a neutral condition rather than a positive or rewarding condition (K. D. Williams & Jarvis, 2006). Another task is the Chatroom task (Guyer et al., 2008), which measures response to acceptance and rejection by peers that the subject has previously identified as either being interested in (“selected”), or not interested in (“non-selected”), based on their picture. In this task, participants receive feedback, typically in an event-related design, about whether each individual peer indicated they were interested in speaking with the subject, or not interested. An extension of this task is the Chatroom Interact task (Silk et al., 2012), which asks participants instead to identify whether they would be interested in chatting online with another person about a specific topic. Like Chatroom, participants receive feedback about whether each player wanted to chat with them. The Island Getaway task (Kujawa et al., 2014) measures response to acceptance and rejection feedback. In the task, participants are told that they are playing a game with other participants and will vote on whether to keep each co-player in the game, or kick them out of the game. The participant then receives feedback about how each co-

player voted for them.

Other tasks additionally measure responses to the anticipation of social feedback. For example, the Virtual School task (Jarcho et al., 2013) measures the brain's response to the receipt of and anticipation of compliments and insults from reputationally nice (those that exclusively give compliments), mean (those that exclusively give insults), and ambiguous peers (those that give compliments half the time, and insults half the time). Similarly, the Social Judgement paradigm (Gunther Moor et al., 2010; Somerville et al., 2006) measures the response to the anticipation of and receipt of acceptance and rejection from peers that the subject has previously identified as liking or disliking. This design results in "mutual liking" conditions where the participant received feedback that a co-player they rated as "liking" also "liked" them, as well as a more general "received liking" condition where participants received feedback that any co-player "liked" them. Together, these tasks share similar characteristics that allow us to pool their results to better understand the neural deficits in diverse psychiatric disorders. At the same time, their differences allow for a more comprehensive understanding of different types of social feedback.

1.4 Neuroimaging and psychophysiological methodologies

Different neuroimaging methodologies carry specific advantages and disadvantages. By integrating findings, we can use each method's strengths to account for the weaknesses in other methodologies. For reference, spatial resolution is the ability to detect the location of brain activity. Temporal resolution is the ability to detect the onset and duration of brain activity. Functional magnetic resonance imaging (fMRI) has high spatial resolution, but low temporal resolution and relies on blood-oxygen-level-dependent (BOLD) signal, a reliable but indirect measure of brain activity. Functional near-infrared spectroscopy (fNIRS), like fMRI, measures hemodynamic responses in the brain but offers improvements in temporal resolution (up to 0.1 seconds) and is less invasive than fMRI. However, where fMRI uses magnetic field changes to detect deoxygenation, fNIRS uses near-infrared light waves to detect light absorption of hemoglobin and deoxygenated-hemoglobin. It therefore is limited in the depth of brain tissues it can measure (only

about 1 cm deep) and with worse spatial resolution than fMRI. Electroencephalography (EEG) and event-related potentials (ERP) offer the highest temporal resolution and directly measure neuronal potentials; however they have the most limited spatial resolution. Finally, positron emission tomography (PET) detects metabolic activity and specific neurotransmitter release and uptake throughout the brain, but uses radioactive material resulting in reduced sample sizes (due to monetary cost and participant interest) and has limited spatial resolution. PET is useful for examining the more specific molecular mechanisms. Comparing findings across methodologies can better inform which areas are well-studied and where there are gaps in our understanding.

1.5 Classification of brain regions

Because studies occasionally use different terms to refer to anatomically similar brain regions (e.g., the pregenual ACC may also be referred to as the rostral ACC), we defined the terms to be used across neuroimaging studies in this review in Table 1. Regions referred to only in one study (e.g., superior temporal gyrus) are not included in the table. Likewise, ERP components are defined as follows. The N1 is an early fronto-central negative component that peaks around 140 to 200ms after a stimulus, and reflects visual processing and orienting of attention (Hillyard & Anllo-Vento, 1998). The reward positivity (RewP) is a positive fronto-central component that peaks around 200 to 400ms, reflecting response to rewards or positive feedback, minus or residualized for neutral or negative feedback (Proudfit, 2015). The counterpart to the RewP is the feedback related negativity (FRN). This component reflects response to negative feedback. This is calculated by measuring the ERP response to negative feedback, accounting for activity to neutral or positive feedback. **Some reviewed studies used non-difference waves to measure ERP components; however, this is considered to be less accurate for measuring the components of interest, since the activity may be confounded by other, idiosyncratic factors that influence the overall magnitude, shape, or latency of the waveform (Kappenman & Luck, 2016; S. J. Luck & Kappenman, 2012). Furthermore, interpreting raw waveforms can lead to misinterpretation of individual differences. For**

example, one study showed that while there was a difference between a schizophrenia and control group in the P3 to both rare and frequent stimuli, there was not a group difference in the difference in the P3 to rare compared to frequent stimuli (Steven J. Luck et al., 2009; Potts et al., 2002). If one only examined the P3 to rare stimuli, one might conclude that there was an impairment in novelty detection. However, the fact that the difference waveform was not different between the groups suggests that the impairment is likely in some other process common to both types of stimuli. Such examples emphasize the importance of using difference waves to isolate and measure ERP components of interest. The P3 or P300 component is a centro-parietal positive component that peaks around 300 to 600ms following a stimulus. The P3 can be subdivided into the P3a (an early frontal component) and later P3b (a later parietal component). The P2 component is less clearly defined, reflecting the second positive peak in an ERP waveform. For a more detailed review of the relevant components, see Luck & Kappenman (2012), as well as Glazer, Kelley, Pornpattananangkul, Mittal, & Nusslock (2018).

[TABLE ONE HERE]

1.6 Classification of psychopathology

With the introduction of the Research Domain Criteria (RDoC), there has been growing emphasis on transdiagnostic research that investigates the underlying neurobiological and behavioral mechanism of psychiatric symptoms, in order to “carve nature at its joints.” Dysfunctional interpersonal relationships and interactions are a very common complaint of patients seeking mental health treatment and affect large proportions of the population. **The traditional diagnostic method categorizes symptoms (e.g., low mood, lack of energy, rejection sensitivity, etc.) that can affect interpersonal relationships. However, examining the causes of interpersonal relationship dysfunction across disorders allows us to identify transdiagnostic deficits. While such deficits could and should be evaluated in a clinical interview, self and informant report measures, however, have a variety of limitations,**

including self-presentation biases, method bias, and issues related to insight (e.g., Campbell & Fiske, 1959; Podsakoff et al., 2003). Furthermore neural deficits may appear before behavioral deficits and symptoms (Kujawa & Burkhouse, 2017) making them ideal targets for prevention and intervention efforts. As such, neural measures could be used as a complement to behavioral or self-report measures of symptoms, and detect risk for anhedonic responses to reward (such as social acceptance), enhanced sensitivity to rejection, reduced emotion regulation abilities, or some combination of these and other factors. This differentiation could result in earlier treatments more specifically targeted at, for example, pairing rewarding reinforcements with social interactions, exposure and habituation to rejection feedback, or practicing emotion regulation techniques. Thus, identifying the specific deficit responsible for a person's dysfunctional interpersonal relationships can lead to more individualized care and more efficacious and responsive treatment.

Further, deficits in interpersonal relationships arise in mood, anxiety, personality, schizophrenia spectrum/psychotic, and neurodevelopmental disorders (American Psychiatric Association, 2013; Kennedy & Adolphs, 2012; Reinhard et al., 2020). Understanding shared mechanisms of interpersonal deficits across psychiatric disorders could inform the common etiology of comorbidities, though heterogeneity across disorders (as well as within disorders) makes it important to understand how the unique aspects of each disorder might contribute to deficits in interpersonal relationships. **Within the context of the NIMH RDoC project (Cuthbert, 2014; Insel et al., 2010), responses to social feedback cut across many RDoC constructs in the social processes, positive valence, and negative valence systems. For example, response to social acceptance informs the construct of reward responsiveness, while rejection informs the construct of loss. That being said, the brain's processing of social feedback is no doubt complex, and thus an argument can be made for such findings informing numerous constructs within the RDoC framework. Therefore, some constructs such as dysfunction in negative valence systems, may be common across internalizing**

disorders, while dysfunction in others (e.g., positive valence systems) may be more localized to specific symptoms such as social anhedonia. Thus, studying responses to social feedback can yield both transdiagnostic and diagnostic-specific risk factors.

Moreover, though prior work has mostly focused on reactions to negative feedback, dysfunctional responses to positive feedback are similarly likely to give rise to psychopathology, with potential variability in mechanisms both within and across disorders (David T. Hsu & Jarcho, 2020). For example, blunted responses to monetary gains has already been shown to be as informative to the etiology of depression as response to losses (Keren et al., 2018; W.-N. Zhang et al., 2013). Thus, understanding the mechanisms that contribute to these deficits has far reaching consequences for reducing the humanitarian and economic burden of mental illness. Although problems with responding to social feedback arise in a myriad of different disorders, reviewing the entirety of this literature is beyond the scope of the current review. This review focuses on internalizing disorders and their associated symptoms so as to draw more focused conclusions about the mechanisms of these types of disorders. Borderline personality disorder (BPD) is also included since it shares symptoms with internalizing disorders (e.g., suicidal ideation [SI], non-suicidal self-injury [NSSI], suicide attempt [SA]), and is often compared against patient control groups with internalizing symptoms or diagnoses (e.g., low self-esteem, NSSI, MDD). We include disorders typically considered to fall within the categories of internalizing (e.g., depression, anxiety) disorders, symptoms, or behaviors characteristic of or thought to precede these disorders (e.g., BPD, SI, NSSI, SA, anxious attachment, fear of negative/positive evaluation, behavioral inhibition). We do not include schizophrenia, autism spectrum disorders, eating disorders, substance use disorders, obsessive compulsive disorder, post-traumatic stress disorder, and other personality disorders beyond BPD. **Of note, although we initially sought to also include externalizing disorders, only one study of externalizing symptoms met inclusion criteria for this review (Babinski et al., 2019). Though not included in this review, this presents an important future direction.**

2. Methods

For the current review the following criteria were used in selection of studies. Studies were required to have been: peer reviewed, written in English, include human subjects exclusively, be empirical investigations/original reports, have used at least one of the following neuroimaging techniques: fMRI, EEG, ERP, PET, fNIRS, magnetoencephalography (MEG), diffuse optical tomography (DOT), included sample sizes greater than or equal to 20 total participants, excluded participants with brain injuries or lesions, used a task to measure response to a form of social feedback directed at the participant, and reported a measure of psychiatric symptoms or diagnosis of an internalizing disorder. **These criteria therefore exclude studies that exclusively used tasks: where participants witnessed other players being excluded, rejected, included, or accepted; where performance is socially evaluated (e.g., Flanker task with an observer); where participants are given pos/neg social feedback depending on behavioral performance; that induce anxiety (e.g., Trier Social Stress task or public speaking); of emotional labeling or that only involve viewing faces without explicit feedback; and who's primary measure was of physical pain.** These tasks were excluded to assure that comparisons between studies were not confounded by differences in the psychological processes being manipulated in different feedback conditions. For example, watching another player receive acceptance feedback was considered to implicate different systems than receiving acceptance feedback themselves. Likewise, without explicit feedback, participants may interpret positive or negative faces many different ways.

Studies were included regardless of whether they measured current or past diagnoses or symptoms, and regardless of whether they used diagnostic interviews or self/informant report instruments. Finally, studies were included regardless of the sample age or developmental period. Selecting studies of adults or adolescents exclusively would have too severely limited the scope of the review. However, the age of samples are noted throughout the review. All studies included samples of participants that were 11 years-old or older.

The following search terms were used to search the abstracts of articles in the PsycInfo and Medline databases. The initial search term was “((((social OR peer) n2 (rejection OR acceptance OR feedback OR reward OR interact* OR evaluation) OR ostracism OR exclusion OR cyberball)) AND (psychopathology OR depress* OR anx* OR "personality disorder" OR adhd OR temperament)) AND (brain OR neural OR imaging OR neuroimaging OR mri OR fmri OR eeg OR erp OR meg OR pet OR fnirs OR dot).” Articles from this search were compiled and used to generate further keywords using the R package litsearchr (Grames et al., 2019). This led to a final search term of “((((social OR peer) n2 (rejection OR acceptance OR feedback OR reward OR interact* OR evaluation OR behavior OR isolation) OR ostracism OR exclusion OR cyberball)) AND (psychopathology OR depress* OR anx* OR "personality disorder" OR adhd OR temperament)) AND (brain OR neural OR imaging OR neuroimaging OR mri OR fmri OR eeg OR erp OR meg OR pet OR fnirs OR dot OR "anterior cingulate" OR prefrontal OR striatum OR cortex OR "magnetic resonance").” This search yielded 1785 results from PsycInfo, and 2075 results from the Medline database. Out of 3860 total results, 1183 were duplicates, yielding 2677 unique items. Of those, 47 were selected based on inclusion criteria.

Because this initial search did not include search terms allowing for papers that included terms such as “internalizing” or “externalizing” in the abstract, a search was rerun with the following search term: “((((social OR peer) n2 (rejection OR acceptance OR feedback OR reward OR interact* OR evaluation OR behavior OR isolation) OR ostracism OR exclusion OR cyberball)) AND (internal* OR external*)) AND (brain OR neural OR imaging OR neuroimaging OR mri OR fmri OR eeg OR erp OR meg OR pet OR fnirs OR dot OR "anterior cingulate" OR prefrontal OR striatum OR cortex OR "magnetic resonance”).” This yielded one more unique item that fit the inclusion criteria. Upon review of each article, three were excluded upon verification that they did not specifically examine the relationship between neural activity and psychopathology, but rather included an interaction with a moderator that makes the main effect uninterpretable, one because it measured associations between maternal negative affect and response to social feedback and

overlapped with the sample of another study (Silk et al., 2014), one because it measured avoidant attachment, two because they reported null results but were underpowered (N 's ≤ 65) to detect correlational or group differences of a medium effect size or smaller (i.e. $d \leq 0.5$, $r \leq 0.3$), and two were excluded due to questionable analytic practices. Finally, the initial review was conducted in May 2019. The literature review was conducted again in June 2020, yielding eight additional studies included in this review. Only one study investigated externalizing disorders (Babinski et al., 2019); therefore findings related to externalizing disorders, though much needed in future research, are not discussed. Thus, the current review includes 46 total articles.

2.1 Network identification

Spherical ROIs were used to identify the cortical networks within which each region falls. Specifically, for each region, bilateral 10mm spherical ROIs were drawn at the center coordinates for that region using Analysis of Functional Neuroimages (AFNI) (Cox, 1996). For example, for the pregenual ACC, the center of the bilateral spheres were set to MNI coordinates 5.5, 36, 18 and -5.5, 36, 18. Likewise, for each network, because resting-state functional connectivity networks are based on brain surfaces and the studies in this review reported on brain volumes, 10mm spheres were drawn at each coordinate of each network. Network coordinates were from Power et al. (2011) and included: cingulo-opercular, default mode, fronto-parietal, salience, ventral attention, dorsal attention, subcortical, sensory/somatomotor, auditory, and visual networks. Each regional ROI was combined with all network ROIs, and the number of overlapping voxels is reported in Table 1. Of note, no regions in the current review overlapped with the dorsal attention or visual networks. Relatedly, only the dACC overlapped with the sensory/somatomotor network, and only the TPJ and MTG overlapped with the auditory network. The subgenual ACC did not overlap with any of the a priori defined networks. Regions were categorized into specific brain networks that had the majority ($\geq 50\%$) of overlapping voxels (see Table 1).

For example, the insula ROI had voxels that overlapped with the subcortical, cingulo-opercular, and salience networks; however 95% of the total overlapping voxels were in the cingulo-opercular network (CON) and therefore it was categorized as belonging to the CON.

3. Results

The evidence is first organized by class of disorders/symptoms, then by the valence of the feedback (e.g., negative, positive), and then by brain network (e.g., default mode, cingulo-opercular). When a form of psychopathology did not have any research papers testing responses to a specific type of feedback, that type of feedback is omitted. Throughout the results, “signal” is used to refer to BOLD signal from fMRI studies, to distinguish it from neuronal activity measured by EEG and ERP.

3.1 *Socially relevant anxiety*

3.1.1 Behavioral Findings

Socially relevant anxiety refers to studies of social anxiety disorder, fear of negative or positive evaluation, behavioral inhibition, social reticence, and anxious attachment. Behaviorally, findings overall support hypotheses of increased sensitivity to rejection and a negativity bias. Specifically, individuals with SAD reported greater distress to rejection and higher ratings of feeling excluded (Burklund et al., 2017; Heeren et al., 2017). Finally, there also appeared to be biases in their memory. That is, socially anxious individuals reported having experienced more rejection following a task compared to those without social anxiety (Harrewijn et al., 2017), and were even more conservative in endorsing whether a co-player had previously accepted them compared to controls (Qi et al., 2017).

[TABLE TWO HERE]

3.1.2 Negative feedback

3.1.2.1 Default mode network

One experimental study administered “anxious sweat” (i.e., sweat collected from donors during anticipation of an important oral examination) in an attempt to experimentally manipulate anxiety. This led to deactivation in the hippocampus and middle temporal gyrus (MTG) to exclusion (Wudarczyk et al., 2015). However, this study did not show any behavioral differences between the anxious sweat and control sweat groups, calling into question the success of the experimental manipulation. Likewise, among adults with SAD, reduced signal in the middle temporal gyrus (MTG) in response to rejection predicted worse response to cognitive behavioral therapy (Burklund et al., 2017), and reduced signal in the preACC in response to rejection predicted worse response to cognitive behavioral therapy, as did signal in the left vmPFC (Burklund et al., 2017). However, in the same study, the Liebowitz Social Anxiety Scale pre-therapy was positively associated with signal in the right precuneus and precentral gyrus to rejection (Burklund et al., 2017).

Studies have also added additional levels of nuance. For example, one study found that when participants selected the peers they wished to interact with, adolescents with childhood behavioral inhibition showed *greater* left superior temporal gyrus (STG) signal to rejection by *selected* peers (i.e. peers they were interested in talking to), compared to controls, but *reduced* signal in the same region when rejected by *non-selected* peers (i.e. peers who they previously endorsed not being interested in talking to) (Guyer et al., 2014). Another found that, among preadolescents, social anxiety severity was found to be positively associated with MTG and TPJ signal to *unpredictable insults*, as well as MTG signal to *predictable compliments* (A. R. Smith et al., 2020).

One finding suggests that this pattern of hyperactivation may be due to a lack of reduction in signal from anticipation. Among early adolescents with SAD, signal in the hippocampus (as well as the precentral gyrus, left cuneus, right lingual gyrus, and claustrum) persisted from the anticipation of rejection to feedback phases of each trial, whereas it decreased in controls (Lau et al., 2012).

In terms of connectivity, a study of anxious adolescents found positive connectivity between a seed in the right fusiform face area and left pregenual ACC signal to rejection (relative to acceptance), while control adolescents, adults, and even anxious adults showed negative connectivity (Beer et al., 2016).

3.2.2.2 Subcortical network

Studies of social anxiety and rejection point to dysfunction in the amygdala as well. Adults with SAD showed reduced signal in amygdala to rejection (compared with neutral feedback), a pattern not present in controls, with greater signal in the left amygdala predicting better response to cognitive behavioral therapy (Burklund et al., 2017). Previously highly socially reticent 11 year-olds also had reduced left amygdala signal to unpredictable negative feedback (relative to predictable negative feedback), compared to controls (Jarcho et al., 2016). Similarly, among older adolescents, social anxiety severity was negatively associated with caudate signal to unpredictable (relative to predictable) insults (A. R. Smith et al., 2020). However, in contrast to this pattern, among preadolescents in the same sample, social anxiety severity was positively associated with caudate signal to unpredictable insults and predictable compliments (A. R. Smith et al., 2020). However, responses to feedback may be confounded by signal that occurs in anticipation of the feedback. Early adolescents with SAD showed persistent amygdala signal from the anticipation to feedback phases of each trial, whereas it decreased among controls (Lau et al., 2012).

3.1.2.3 Cingulo-opercular network

In response to rejection, among adults with SAD, greater posterior insula signal predicted better response to acceptance and commitment therapy (Burklund et al., 2017). However, in young adults responding to exclusion (relative to an inclusion condition), anxious attachment was positively associated with dACC, anterior insula, and vIPFC BOLD signal (DeWall et al., 2012). As above, early adolescents with SAD showed persistent right insula signal from the anticipation to rejection feedback phases of each trial, whereas it decreased in controls (Lau et al., 2012).

Therefore, although BOLD signal was similar between the SAD and control groups during the anticipation phase, the difference in signal was detected only during the feedback.

3.1.2.4 ERP

Among ERP studies, findings are mixed. The feedback related negativity (FRN) has been shown to be positively associated with the Interaction Anxiousness Scale (IAS), and SAD individuals (children through adults) had an increased FRN to unexpected rejection compared to all other conditions (i.e., unexpected acceptance, and expected rejection and acceptance) (Harrewijn et al., 2017). Interestingly, there was one case in which findings from two studies contradicted one another. These studies used the same paradigm (Social Judgement task) but differed in their samples and specific nuances of their findings. The study by Harrewijn et al. (2017) used a large sample of participants from nine families (using those without SAD as the control group) and found that SAD individuals had an increased theta power to unexpected rejection compared to other conditions. The van der Molen et al. (2018) study used a smaller sample of females (using healthy controls as the control group) and found SAD individual showed reduced theta power to rejection in general.

3.1.3 Positive feedback

There is a more limited body of work examining associations between anxiety and response to positive social feedback (i.e. inclusion, acceptance, or compliments).

3.1.3.1 Default mode network

Adults with SAD show greater left IFG BOLD signal during re-inclusion, with left IFG signal showing positive associations with perceived social exclusion and LSAS in the SAD group (Heeren et al., 2017). Adolescents with childhood behavioral inhibition (BI) showed no difference between selected and non-selected peers in a Chatroom study, whereas previously behaviorally non-inhibited (BN) adolescents showed greater left superior temporal gyrus signal to acceptance from selected compared to non-selected peers (Guyer et al., 2014).

3.1.3.2 Cingulo-opercular network

One study found that previously socially reticent 11 year-olds had negative functional connectivity between an insula seed and vmPFC/rIPFC/preACC signal to unpredictable feedback, relative to predictably positive feedback, while participants low on social reticence showed positive connectivity (Jarcho et al., 2016).

3.1.3.3 Subcortical network

Adolescents with behavioral inhibition (BI) showed a relatively reduced signal in the caudate to acceptance relative to rejection, demonstrating a lack of differentiation between acceptance and rejection feedback; whereas BN adolescents showed greater signal in the right caudate to acceptance relative to rejection (Guyer et al., 2014). However, in the context of unexpected acceptance, SAD adolescents showed greater striatum signal to unexpected acceptance (relative to expected acceptance) from selected peers in the Chatroom task, with all other groups (i.e. anxious adults and non-anxious adolescents and adults) showing no difference (Jarcho et al., 2015).

3.1.2.4 ERP

Findings from ERP studies have been mixed. Young adults with SAD showed increased P3 to acceptance (Harrewijn et al., 2017), and in a separate study, highly socially anxious young adults showed greater FRN activity to unexpected acceptance than unexpected rejection, a pattern not present in low socially anxious young adults (Gu et al., 2020). However, young adults low on social anxiety showed greater P3a activity to expected acceptance than expected rejection and greater LPP activity to acceptance than rejection, patterns not present in highly socially anxious young adults (Gu et al., 2020). Finally, two well powered studies found no association between SAD symptoms and RewP to acceptance (Kujawa et al., 2017; Pegg et al., 2019).

3.1.4 Feedback in general

Social anxiety severity among young adults was positively associated with delta activity to feedback in general (Jin et al., 2019), and young adults with SAD showed reduced P2 to feedback in general (Cao et al., 2015). In response to feedback in general, BI youth showed greater signal

in the fusiform gyrus than controls (Guyer et al., 2014). One study presented an intriguing future direction—examining prediction errors. They found that SAD adolescents showed more negative functional connectivity between a striatum seed and preACC signal to prediction errors (i.e. unexpected relative to expected feedback). Moreover, this functional connectivity was positively associated with later recall of which co-players gave unexpected feedback (Jarcho et al., 2015).

3.1.4 Anticipation of feedback

Social anxiety, though, is characterized by a fear of social situations, and thus avoidance of them. Therefore, we might expect socially anxious individuals to show differences during their *anticipation* of social feedback. The limited behavioral evidence supports this, as socially anxious individuals predict fewer instances of future acceptance (van der Molen et al., 2018), more frequent rejection (Harrewijn et al., 2017), and expect to be rated as less desirable by peers (Guyer et al., 2008).

3.1.4.1 Default mode network

Anxious youth show increased signal in the preACC and subACC to the anticipation of feedback from non-selected peers (relative to selected peers) (Guyer et al., 2008). Two studies tested whether the predictability of the feedback was more uniquely associated with social anxiety, since anticipating feedback from an unpredictable peer (i.e. a peer that is sometimes mean and sometimes nice) may be the most anxiety provoking. Indeed, they found somewhat conflicting results. Namely, while anticipating unpredictable (relative to predictable) feedback, children high in early life social reticence showed greater signal in the precuneus (Jarcho et al., 2016). Another study using the same task (Virtual School) found that social anxiety severity was negatively related to precuneus signal while anticipating all feedback (A. R. Smith et al., 2020).

In functional connectivity analyses, Spielberg et al. (2015) subdivided their sample into younger and older adolescents, and found that anxious early adolescents showed similar patterns of connectivity to older anxious and control adolescents. That is, all three groups showed positive connectivity of a preACC seed and left amygdala signal to anticipation of feedback from selected

peers, but negative connectivity for non-selected peers. Early adolescent controls were the only group that differed—showing the opposite pattern (Spielberg et al., 2015).

3.1.4.2 Subcortical network

There is mixed evidence that anxious individuals have increased BOLD signal in areas typically associated with threat response (e.g., the amygdala). (Table 2). Anxious adolescents show greater signal in the amygdala to the anticipation of feedback from non-selected compared to selected peers (Guyer et al., 2008). There was even a positive association between anxiety severity (as measured by the SCARED) and BOLD signal of the right amygdala (Guyer et al., 2008). The diagnostic group difference (i.e. comparing controls and anxious youth) finding was replicated in another sample from the same research group (Spielberg et al., 2015). Guyer et al. (2008) also found a positive association between anxiety severity and connectivity between an amygdala seed and vIPFC signal to anticipation of feedback from non-selected peers.

There is also evidence of differences in striatal BOLD signal, though findings are limited there as well. One study found, during anticipation of feedback from non-selected peers (relative to selected peers), increased signal in the putamen among adolescents with prior behavioral inhibition (Guyer et al., 2014)—a temperamental precursor of social anxiety, while another found reduced nucleus accumbens activity among anxious adolescents (Spielberg et al., 2015).

3.1.4.3 Cingulo-opercular network

Anxious youth show increased signal in the dIPFC and even cerebellum to the anticipation of feedback from non-selected peers (relative to selected peers) (Guyer et al., 2008). Similarly, Jarcho et al. (2016) found that while anticipating unpredictable (relative to predictable) feedback, children high in early life social reticence showed greater signal in the dACC and insula (Jarcho et al., 2016). Moreover, for the same contrast, connectivity analyses showed that socially reticent youth had negative functional connectivity of a right insula seed and vmPFC signal, as well as a right insula seed and right premotor cortex signal—whereas youth low in early life social reticence

showed positive connectivity (Jarcho et al., 2016).

3.1.4.4 ERP

Highly socially anxious young adults showed greater P1 activity to anticipation of feedback compared to young adults low on social anxiety (Gu et al., 2020).

3.1.5 Summary

The literature examining socially relevant anxiety shows mixed findings for response to and anticipation of different forms of social feedback and few general conclusions can be drawn. Many of the studies used nuanced designs such as contrasting rejection from peers that the participant had selected with rejection from peers that the participant had not selected such as in the Chatroom task, or altering the predictability of the feedback as in the Virtual School task.

Findings suggested some, albeit nascent, support for theories of social anxiety and brain development in childhood and adolescence. Spielberg et al.'s (2015) general finding that anxious youth showed similar patterns of brain activity to anxious and non-anxious adults is reminiscent of Gee et al.'s (2013) finding that institutionalized youth exhibit a “mature” pattern of mPFC–amygdala connectivity. **That is, in both cases the findings point towards anxious youth as showing developmentally more advanced patterns of brain activity compared to their non-anxious peers.** However, as noted above, the findings on social anxiety and anticipation of social feedback have been confined to one research group. Therefore, research with other samples would assess the generalizability of these results.

3.2 Depression

3.2.1 Behavioral Findings

Depression in this review refers to studies of current, lifetime, or risk for major depressive disorder, social anhedonia, or subthreshold symptoms of major depressive disorder. Behaviorally, findings overall support hypotheses of reduced anticipated enjoyment of positive feedback, greater negative affect during negative feedback, and sustained negative affect even after the social feedback tasks. Similar to social anxiety, depressed patients showed greater sensitivity to

rejection and exclusion (Groschwitz et al., 2016; Malejko et al., 2018). Depressed individuals indicated reduced expectations to like peers in the game if they met, and rated feedback as less rewarding compared to controls (Davey et al., 2011). Depressed individuals also showed more persistent negative affect (feeling “sad and rejected”) following rejection (D. T. Hsu et al., 2015). They also endorse greater feelings of sadness, nervousness, exclusion, and less happiness (Silk et al., 2014) as well as reduced happiness and satisfaction and greater fear and inner tension immediately following the task (Malejko et al., 2018). However, there was no increase in self-reported self-esteem or desire for social interaction following acceptance (D. T. Hsu et al., 2015; Q. Zhang et al., 2017). Furthermore, though depressed individuals showed greater positive affect (feeling “happy and accepted”) while being accepted, this positive affect was not sustained, reaching similar levels to controls. Therefore, depressed individuals show evidence of maladaptive patterns of over-sustained negative affect but under-sustained positive affect to social feedback.

[TABLE THREE HERE]

3.2.2 Negative feedback

3.2.2.1 Default mode network

Studies found a positive association between signal in the dmPFC to exclusion (relative to inclusion) and an increase in MDD symptoms over the following year (Masten et al., 2011) and concurrent MDD severity (Rudolph et al., 2016). Depressed adolescents show greater left dmPFC, right TPJ, and lingual gyrus signal to exclusion (relative to inclusion) than controls (Harms et al., 2019). Thirteen year-olds showed a positive relationship between posterior cingulate cortex signal to exclusion (relative to inclusion) and concurrent depression severity (Masten et al., 2011).

However, BOLD signal in even more posterior regions, such as the precuneus, cuneus, and inferior parietal lobule to exclusion (relative to inclusion) was negatively associated with concurrent depression severity (Masten et al., 2011). Jankowski et al. (2018) also found that MDD

adolescents showed *reduced* precuneus and medial PFC signal to exclusion (relative to inclusion). Further, signal in the middle temporal gyrus to exclusion (relative to inclusion) was reduced in a large sample of depressed adolescents—an effect that, when decomposed, more specifically reflected controls having greater signal in the MTG to exclusion than inclusion, while depressed adolescents did not show this difference (Jankowski et al., 2018).

3.2.2.2 Subcortical network

Adults with MDD showed greater amygdala signal to exclusion (Kumar et al., 2017), and adolescents less deactivation to rejection (Silk et al., 2014). Amygdala signal to exclusion (relative to inclusion) was also positively associated with depression severity (Rudolph et al., 2016). Contrary to these findings, a study using PET imaging found μ -opioid receptor (MOR) *deactivation* in the amygdala to rejection (relative to baseline) among depressed adults, whereas controls showed *activation* (D. T. Hsu et al., 2015). This same study found that whereas control adult subjects showed an increase in MOR activity in the right nucleus accumbens, midline thalamus, and periaqueductal gray to rejection (relative to baseline), the depressed adults did not show increased activity (D. T. Hsu et al., 2015). In contrast, [Silk et al. \(2014\)](#) found enhanced signal in the nucleus accumbens to rejection among depressed adolescents.

3.2.2.3 Cingulo-opercular network.

Hyperactivity of the cingulo-opercular network seems to be a shared finding across five studies. Signal in the dACC to exclusion (relative to inclusion) was positively associated with concurrent depression in one study (Rudolph et al., 2016) and increase in depression symptoms over 1 year in another (Masten et al., 2011). Studies have found that individuals with MDD show greater left insula signal to exclusion (relative to inclusion feedback) (Jankowski et al., 2018) and to rejection feedback (Silk et al., 2014), and greater right insula signal to exclusion feedback (Kumar et al., 2017). Moreover, right insula signal to exclusion (relative to inclusion) was positively associated with depression severity in adolescent females (Rudolph et al., 2016) and increase in depressed mood in adult females over 2 hours following exposure to an endotoxin (Eisenberger

et al., 2009), while posterior insula signal was positively associated with concurrent depression severity (Eisenberger et al., 2009). Finally, depressed individuals showed greater insula signal to exclusion than inclusion, while controls showed greater signal in these regions to inclusion than exclusion (Jankowski et al., 2018).

3.2.2.4 Salience network.

Two studies found elevated left vIPFC signal to increasing exclusion and exclusion (relative to inclusion) among depressed individuals (Harms et al., 2019; Kumar et al., 2017); though another found reduced signal in the lateral PFC to exclusion (relative to inclusion) among depressed adolescents, while controls showed greater signal in these regions to inclusion than exclusion (Jankowski et al., 2018).

3.2.2.5 Subgenual ACC

The subgenual ACC did not overlap with any of the a priori defined networks; however, given that numerous studies find alteration in the subACC in depression, those results are described separately here. Studies showed alterations in the subgenual ACC related to depression severity and amongst individuals with depression in response to negative social feedback, though at times conflicting in the direction of the effect. For example, signal in the subACC to exclusion (relative to inclusion) was positively associated with concurrent depression severity (Rudolph et al., 2016), and an increase in depression symptoms over 1 year (Masten et al., 2011). Another study found that depressed adolescents showed greater subACC signal to rejection (Silk et al., 2014). A study with a larger sample size than those three studies combined, however, found that depressed adolescents showed reduced subACC signal to exclusion (relative to inclusion) (Jankowski et al., 2018).

3.2.3 Positive feedback

3.2.3.1 Default mode network

One study of young adults found that dmPFC (and precuneus) signal to mutual liking (relative to received liking) was positively associated with depression severity, and more

specifically social anhedonia severity (Healey et al., 2014), and that social anhedonia severity was also positively associated with preACC and precuneus signal to mutual liking (relative to received liking) (Healey et al., 2014). On the other hand, a study of the offspring of depressed mothers found reduced left preACC/dACC signal but greater precuneus, right fusiform, and right S1 to acceptance (relative to a control condition) (Olinio et al., 2015). Considering that both samples were small ($N < 30$), further research is needed to test the reliability of these findings.

Only one study looked at connectivity, and found a positive association between connectivity of a nucleus accumbens seed and mPFC signal to mutual liking (relative to received liking) and social anhedonia (Healey et al., 2014).

3.2.3.2 Subcortical network

Many other regions showed positive associations with social anhedonia, though not depression, including the ventral striatum, thalamus, and caudate tail (Healey et al., 2014). MDD adolescents and young adults showing greater left amygdala signal to acceptance (relative to control condition) (Davey et al., 2011).

In contrast, offspring of depressed mothers showed reduced signal in the ventral striatum to acceptance (relative to a control task) (Olinio et al., 2015). In a PET study, control adults showed MOR activation in the left amygdala and MOR deactivation in the midline thalamus to acceptance (relative to baseline). In contrast, the depressed adults showed no MOR activation or deactivation to acceptance in the left amygdala, and showed MOR *activation* in the midline thalamus (D. T. Hsu et al., 2015).

3.2.3.3 Cingulo-opercular network

One study of young adults found a positive association between dACC and insula (along with orbitofrontal cortex and superior parietal cortex) signal to mutual liking (relative to received liking) and current social anhedonia (Healey et al., 2014). Superior anterior insula signal to inclusion (relative to rest) was positively associated with depression severity (Cáceda et al., 2019).

On the other hand, a study of the offspring of depressed mothers found reduced left dACC and left insula signal to acceptance (relative to a control condition) in these offspring (Olino et al., 2015). A PET study also found that MDD adults showed a lack of MOR activation in the right insula to acceptance (relative to baseline), while controls showed an increase in MOR activation (D. T. Hsu et al., 2015).

3.2.3.4 Fronto-parietal network

DIPFC signal to mutual liking (relative to received liking) was positively associated with depression severity, and more specifically social anhedonia severity (Healey et al., 2014).

3.2.2.5 Subgenual ACC

A PET study found relative greater MOR activation in the subACC among depressed adults than controls, likely due to MOR deactivation in controls to acceptance (relative to baseline) (D. T. Hsu et al., 2015).

3.2.2.6 ERP

MDD adults showed a reduced P3 component to inclusion (Q. Zhang et al., 2017) and the reward positivity to acceptance was negatively associated with depression severity in a large sample of 12 year-olds (Kujawa et al., 2017). However, in an independent sample, depression severity was not associated with RewP to acceptance (Pegg et al., 2019).

3.2.4 Feedback in general

Those studies that investigated group differences to feedback in general found that depressed adolescents and young adults showed greater salience network (vIPFC), right inferior parietal cortex, default mode network (preACC), and cingulo-opercular network (right anterior insula) signal than controls (Davey et al., 2011). One other study examined change in signal across blocks of alternating positive and negative feedback. They found that those young adult females with a history of MDD showed increased cingulo-opercular network (dACC) signal, while control participants showed decreased signal (Dedovic et al., 2016). Finally, in the ERP literature, dysphoria severity in young adults was negatively associated with delta activity to feedback in

general (Jin et al., 2019).

3.2.5 Summary

Depression appears to be somewhat consistently related to heightened BOLD signal in the cingulo-opercular network—particularly the insula—in response to negative feedback. A large body of research has already suggested that the CON and insula are associated with depression. Depression is associated with lower gray matter volume in the insula and dACC (Goodkind et al., 2015; Wise et al., 2017) and differences in the function connectivity of regions within the CON and with other networks (e.g., the default mode network) (Goya-Maldonado et al., 2016; Wu et al., 2016). Furthermore, antidepressant treatment reduces insula activity to emotional stimuli (Delaveau et al., 2011), and greater baseline insula activation predicts worse treatment response (Fu et al., 2013). Hyperactivity of the insula to negative social feedback may be a marker of increased affective pain to negative social feedback in depression, since insula activity has been associated with affective pain (Peyron et al., 2000) and social-emotional tasks elicit anterior insula activity (Kurth et al., 2010).

3.3 Borderline personality disorder

3.3.1 Behavioral finding

Borderline personality disorder (BPD) refers to the symptoms and diagnosis of BPD. Similar to those in the study with social anxiety, young adults with BPD reported greater expectancy of being excluded (Gutz et al., 2015). Similar to both social anxiety and depression, adults with BPD reported greater sensitivity to exclusion, even compared to female adults with current NSSI as well as controls (Malejko et al., 2019). Adults with BPD also reported greater negative self-views and a lower mood following both negative and intermediate feedback (neither distinctly negative nor positive feedback) compared to controls (van Schie et al., 2019), and rated a lower sense of belongingness across inclusion and exclusion conditions (Wrege et al., 2019).. Moreover, adults with BPD rated negative feedback as more applicable to them and positive feedback as less applicable, compared to adults with low self-esteem (van Schie et al., 2019).

Unique to BPD, one study found that adults with both BPD and MDD reported greater anger following the task than those with MDD without BPD (Malejko et al., 2018). Finally, behavioral findings present evidence for an intriguing theory of BPD: namely, that individuals with BPD have greater difficulty discriminating between exclusion and inclusion. Adults with BPD reported feeling more excluded during inclusion and control trials (Domsalla et al., 2014a; Gutz et al., 2015).

[TABLE FOUR HERE]

3.3.2 Negative feedback

3.3.2.1 Default mode network

In the brain, there appears to be a general pattern of hyperactivity in different regions of the DMN in BPD in response to negative feedback. Specifically, BPD adolescents and young adults showed greater dmPFC signal to exclusion (relative to passive watching, and relative to inclusion) using fMRI and fNIRS, respectively (Brown et al., 2017; Ruocco et al., 2010). Left mPFC signal (from fNIRS) was positively associated with rejection and abandonment fears, a characteristic of BPD (Ruocco et al., 2010). Adults with BPD also showed greater preACC and right rIPFC signal to exclusion (relative to inclusion) compared to controls (Wrege et al., 2019). A conjunction analysis of adolescents and young adults with BPD and those with NSSI showed greater preACC signal to exclusion (relative to inclusion) (Brown et al., 2017). Finally, adults with BPD showed greater left precuneus signal to insults (relative to compliments) compared to subjects with low self-esteem (van Schie et al., 2019).

3.3.3 Positive feedback

3.3.3.1 Default mode network

Adolescents, young adults, and adults with BPD showed greater dmPFC signal to inclusion (relative to passive watching), compared to those with current NSSI and those with only MDD (Brown et al., 2017; Malejko et al., 2018, 2019). Young adults and adults with BPD and MDD showed greater precuneus and right preACC signal to inclusion (relative to passive watching) compared to those with only MDD and controls, as well as greater right TPJ compared

to controls (Malejko et al., 2018, 2019).

In another study, however, adults with BPD showed reduced right TPJ signal to compliments (relative to insults), a finding which might be due to the BPD subjects showing less deactivation to insults (van Schie et al., 2019). Signal in the precuneus and dmPFC was modulated by condition among controls, but not among adults with BPD (Domsalla et al., 2014a). Over these regions, controls showed the greatest signal to inclusion, less to exclusion, and the least to the control condition (Domsalla et al., 2014a). One concern however is that peak-voxel activity was measured, rather than mean voxel activity across the cluster—a more reliable measure of BOLD signal.

3.3.3.2 Cingulo-opercular network

Young adults with BPD also showed increased left anterior insula signal to inclusion (relative to passive watching) compared to controls (Malejko et al., 2019), adolescents with NSSI, and control young adults (Brown et al., 2017). Finally, signal in the insula was modulated by condition among controls, but not among adults with BPD (Domsalla et al., 2014a).

3.3.3.3 Fronto-parietal network

Adolescents and young adults with BPD showed increased dlPFC signal to inclusion (relative to passive watching), compared to those with NSSI as well as controls (Brown et al., 2017). Signal in the dlPFC was modulated by condition among controls, but not among adults with BPD (Domsalla et al., 2014a).

3.3.3.4 ERP

The ERP literature shows that young adults with BPD have an increased P3b to inclusion, with the P3b being negatively associated with exclusion expectancy during inclusion (relative to exclusion) (Gutz et al., 2015). That is, greater rejection expectancy was associated with a smaller difference in the P3b between the inclusion and exclusion conditions. This is in line with the findings from Domsalla (2014a) that individuals with BPD show a lack of modulation between conditions.

3.3.4 Summary

Together, findings suggest that borderline personality disorder involves hyperactivity in the default mode network to negative feedback. Hyperactivation of the DMN in individuals with BPD has been found both at rest and during emotional processing (Visintin et al., 2016). BPD may also be associated with structural abnormalities within the DMN (Yang et al., 2016); however there is also evidence to contrary (Baranger et al., 2020).

There is also converging evidence between one fMRI and ERP study suggesting that BPD is characterized by a deficit in distinguishing positive and negative social feedback. Domsalla et al. (2014) note in their discussion of their findings that this supports the hypothesis that individuals with BPD “feel rejected by others even in situations in which they are actually being included (Staebler et al., 2011) or in which social actions cannot be attributed to voluntary decisions of others” (p. 1793). Indeed, BPD is characterized by a fear of rejection or abandonment and unstable identity (American Psychiatric Association, 2013). BPD patients show a negative bias towards themselves and others (Arntz et al., 2004; Baer et al., 2012; Butler et al., 2002), and thus may treat inclusion as if it were excluding in an effort to reduce cognitive dissonance (Festinger, 1957). At the same time, this lack of flexibility between social feedback conditions could represent a cognitive deficit. BPD patients show deficits in a broad range of neuropsychological domains, including cognitive flexibility and learning (Ruocco, 2005). Therefore, tasks like Cyberball in which the co-players remain the same, but the participant receives different feedback from them, may require these neuropsychological abilities. Further research using different tasks and examining more specific hypotheses are need to clarify the nature of this deficit in BPD. Of note, all studies of BPD used either mostly or exclusively female samples.

3.4 Self-injurious and suicidal behaviors

3.4.1 Behavioral findings

This section includes studies of suicidal ideation (SI), attempts (SA), or non-suicidal self-injury (NSSI). There are limited behavioral findings, however one study showed that individuals

with MDD and NSSI endorsed increased sensitivity to exclusion compared to controls and individuals with MDD but without NSSI (Groschwitz et al., 2016).

[TABLE FIVE HERE]

3.4.2 Negative and positive feedback

Because studies of self-injurious and suicidal behaviors distinct from depression are sparse, the findings regarding both negative and positive feedback are discussed together.

3.4.2.1 Default mode network

Those with a history of NSSI in the past year showed increased preACC (along with left fusiform) signal to exclusion (relative to inclusion), compared to MDD adolescents without NSSI and healthy controls (Groschwitz et al., 2016). Studies that conducted conjunction analyses of adolescents and young adults with NSSI and those with BPD found increased signal in the preACC to exclusion (relative to inclusion) (Brown et al., 2017), and greater right preACC signal to inclusion (relative to passive watching) (Malejko et al., 2019).

3.4.2.2 Subcortical network

The only subcortical findings showed that adolescents and young adults with NSSI in the past year had greater putamen signal to exclusion (relative to inclusion), compared to BPD and control adolescents and young adults (Brown et al., 2017).

3.4.2.3 Cingulo-opercular network

For NSSI, a conjunction analyses of adolescents and young adults with NSSI and borderline personality disorder found greater left anterior insula signal to inclusion (relative to passive watching) (Malejko et al., 2019).

In light of the above findings showing heightened CON signal among depressed participants, two findings are especially interesting: for suicidality, female adults with a prior suicide attempt showed reduced signal in the left supramarginal gyrus and left posterior insula to exclusion (relative to inclusion), compared to both patient and healthy controls (Olié et al., 2017). Second, right superior insula signal showed a positive relationship with suicide risk spectrum to

inclusion (relative to rest) (Cáceda et al., 2019). That is, adults with suicidal ideation showed greater insula signal than those with non-suicidal depression, who in turn showed greater insula signal than controls (Cáceda et al., 2019). It should be noted, however, that adults with a history of a suicide attempt showed similar insula signal to the controls (Cáceda et al., 2019). This finding has been partially replicated, with another study finding that SI severity (controlling for depression severity) is positively associated with right anterior insula signal to rejection (relative to acceptance) (Oppenheimer et al., 2020). It should be noted however, that Cáceda (2019) measured BOLD signal to inclusion, while Oppenheimer (2020) measured BOLD signal to rejection.

3.4.2.4 Salience network

Those with a history of NSSI in the past year showed increased vIPFC (along with left fusiform) signal to exclusion (relative to inclusion), compared to MDD adolescents without NSSI and healthy controls (Groschwitz et al., 2016). Also, SI severity (controlling for depression severity) was positively associated with left vIPFC to rejection (relative to acceptance) (Oppenheimer et al., 2020).

3.4.3 Feedback in general

In response to feedback in general (inclusion and exclusion feedback relative to a non-social condition), adolescents high on suicidal ideation showed greater right inferior parietal lobule signal and reduced signal in the cingulo-opercular (right insula) and subcortical networks (right putamen and left globus pallidus) compared to controls (Harms et al., 2019). Adolescents high on suicidal ideation also showed reduced signal in the left pre/postcentral gyrus and cingulo-opercular (right insula) and subcortical networks (right putamen) to feedback in general compared to adolescents that reported lower severity of suicidal ideation (Harms et al., 2019). Finally, adolescents that had reported a recent suicidal attempt showed greater default mode network (dmPFC and preACC) signal compared to adolescents with high suicidal ideation but without a recent attempt, and greater left rIPFC signal than adolescents low on suicidal ideation and without

a recent attempt (Harms et al., 2019).

3.4.4 Summary

Findings are mixed. For example, even the finding that insula signal is positively associated with suicide severity is complicated by the fact that one study found this in response to inclusion (Cáceda et al., 2019), and the other in response to rejection (Oppenheimer et al., 2020). Both studies were published recently though, so this may suggest a potentially fruitful future direction.

[TABLE SIX HERE]

4. Discussion

4.1 Summary of Review

The studies described in this review point to interesting patterns of both mixed and complementary findings. **Most of the findings from the literature thus far are mixed, due in large part to a lack of consistency in tasks used, types of psychopathology measured, and limited sample sizes. Even when examining studies that used similar tasks and measures, clear and consistent findings do not appear to be present. Large-scale future studies are needed to assess the extent to which these findings replicate.**

That being said, some commonalities appear across studies. Depression appeared to be related to cingulo-opercular network hyperreactivity to negative social feedback. The cingulo-opercular is thought to play a role in cognitive control, including conflict and error detection and adjustment of behavior in response to feedback (Dosenbach et al., 2006, 2008). However, in some studies the cingulo-opercular network also overlaps with the salience network (Power et al., 2011)—which plays a role in integrating information to identify the most relevant (or salient) stimuli (Seeley et al., 2007), though the two are dissociable. In terms of the role these networks might play in psychopathology, one proposed taxonomy suggests that the insula, dACC, and related regions (i.e., regions of the cingulo-opercular and salience network, which the insula is also commonly

categorized into) are involved in negative bias and anxious avoidance (L. M. Williams, 2016). Relevant to the current review, functional connectivity of cingulo-opercular regions was positively associated with perceived social isolation (Layden et al., 2017), suggesting CON hyperactivity as a potential correlate of negative views of social relationships. Thus, this network may be a key target for treatments aimed at reducing psychiatric impairment (Downar et al., 2016).

The findings for the cingulo-opercular network were in large part due to findings of insula hyperactivity to negative feedback. The insula appears to show somewhat reliable BOLD signal to social exclusion, with one meta-analysis using multi-kernel density analysis finding support for group-level activation of the insula to social exclusion (S. Cacioppo et al., 2013), though another meta-analysis using activation likelihood estimation did not (Vijayakumar et al., 2017). The dorsal anterior insula plays a role in cognitive control and task set maintenance (Dosenbach et al., 2006), and the ventral anterior insula plays a role in emotion processing (Kurth et al., 2010). Thus, it is possible that heightened insula and CON network BOLD signal is the result of a greater negative emotional response to being excluded, rejected, or insulted (Hamilton et al., 2011; Palaniyappan, 2012). It is also possible that this hyperactivity represents emotion regulation in response to said negative affect (Beauregard et al., 2006; Giuliani et al., 2011; Johnstone et al., 2007).

A second finding from this review was that borderline personality disorder appears to be associated with default mode network hyperactivity to negative social feedback. Though a more unexpected finding, there is some support for hyperactivation of the DMN in BPD (Visintin et al., 2016). BPD is often characterized by more negativistic views (Barnow et al., 2009) and inappropriate affective appraisal of relationships. The default mode network is thought to reflect a number of different psychological processes, including emotion processing and self-referential cognitions (Andrews-Hanna et al., 2010; Raichle, 2015). Hyperactivity of the DMN has also been found in depressed individuals

(Sheline et al., 2009), with difficulty properly down-regulating DMN activity during tasks thought to reflect greater self-reflection (Gusnard et al., 2001), and possibly—together with the subgenual ACC—rumination (Hamilton et al., 2015; Zhou et al., 2020). Importantly, since studies of BPD often included depressed (Malejko et al., 2018) or non-suicidal self-injurious control groups (Brown et al., 2017; Malejko et al., 2019), such findings suggest that BPD might be characterized by even more severe self-referential negative cognitions following the receipt of negative feedback than depression.

There was also overlap in networks and regions that showed disruption related to social feedback across dimensions of psychopathology. Similar prefrontal regions and areas of the anterior cingulate cortex were identified. For example, alterations in the medial PFC, pregenual ACC, and subgenual ACC were found in anticipation of feedback in social anxiety, and in response to positive and negative feedback in depression and BPD. This supports prior research suggesting that the subgenual ACC, pregenual ACC, and mPFC play a role in both mood and anxiety disorders (Drevets et al., 2008; Marusak et al., 2016; Shin & Liberzon, 2010), and that associated networks such as the default mode network show disturbance in mood disorders (Sheline et al., 2009). **More specifically, there appears to be an association between altered BOLD signal in the subgenual ACC to social feedback and depression. This is in line with a great deal of evidence of the subACC's role in negative emotions and depression (Drevets et al., 1997; Keedwell et al., 2010; Mayberg, 2003; Mayberg et al., 1999). Though some studies find hyperactivity of this region (D. T. Hsu et al., 2015; Masten et al., 2011; Rudolph et al., 2016; Silk et al., 2014) while another finds hypoactivity (Jankowski et al., 2018), this is no doubt an important future direction in better understanding depression in the context of social behavior.**

Hyperreactivity of the dlPFC and vlPFC was found while anticipating feedback in both social anxiety and in response to positive and negative feedback in depression. The lateral PFC is hypothesized to be involved in emotion regulation, and reactivity of this region is often

implicated in emotion regulation (Delgado et al., 2008). As such, these findings may suggest either that depressed and anxious individuals experience more severe emotions that require greater emotion regulation, or that they may have greater difficulty regulating emotions and thus need to put in more effort to successfully regulate their emotions. Furthermore, studies also support the involvement of limbic regions across disorders. Amygdala hyperreactivity was found in the anticipation of feedback in social anxiety, and in response to positive and negative feedback in depression. Alterations in the striatum (i.e., ventral striatum, caudate, putamen) were also found in both social anxiety and depression to positive and negative feedback.

These findings begin to point to a picture of both shared and unique disruptions in neural systems associated with internalizing disorders. Nonetheless, many areas of research remain relatively unexplored. As noted in the results, only one study examined how externalizing symptoms are related to response to social feedback (Babinski et al., 2019), despite a long line of research showing that deficits in social relationships exist among individuals with clinically significant levels of ADHD (Hoza, 2007; Wiener & Mak, 2009), oppositional defiant disorder, and conduct disorder (Greene et al., 2002). One of the most apparent gaps in the literature reviewed is studies of males with BPD. All of the BPD studies reviewed used either exclusively or mostly female participants. Although the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that 75% of those diagnosed with BPD are female (American Psychiatric Association, 2013), other epidemiological studies suggest no difference in the prevalence rates among women and men (Grant, 2009). Therefore further studies are needed to test whether these results replicate in men with BPD.

4.2 The reverse inference problem

The most notable issue in this line of research is the challenge of reverse inference, which plagues much of behavioral neuroscience, but particularly clinical research where types and severity of symptoms cannot be manipulated experimentally. Reverse inference refers to “the inference of a psychological process from an observed pattern of brain activity” (Amodio, 2010,

p. 702). Poldrack (2006) explains it in the context of cognitive neuroscience:

- (1) *In the present study, when task comparison A was presented, brain area Z was active.*
- (2) *In other studies, when cognitive process X was putatively engaged, then brain area Z was active.*
- (3) *Thus, the activity of area Z in the present study demonstrates engagement of cognitive process X by task comparison A.*

Although tempting, such inferences are problematic, since the same pattern of brain activity could be associated with many psychological processes (J. T. Cacioppo et al., 2003; Poldrack, 2006). This is especially true of social and affective neuroscience, where it can be challenging to manipulate social interactions or affective states without also changing a cognitive or perceptual variable. It is also unlikely that the processing of social information is localized to a set of discrete regions (Amodio, 2010). One example of reverse inference is the basic science research on social exclusion that concluded that because exclusion and physical pain both led to activity in the dACC, humans co-opt their physical pain system in experiencing social pain (Eisenberger, 2012). However, this conclusion has been called into question, with one study demonstrating that the ventral ACC is more involved in response to social feedback, and the dACC more so to expectancy violations (Somerville et al., 2006). Two meta-analyses also failed to find consistent dACC BOLD signal to social exclusion (S. Cacioppo et al., 2013; Vijayakumar et al., 2017), and one study using multivariate pattern analysis also found distinct representations of physiological and social pain (Woo et al., 2014). This shows how even in carefully controlled studies, reverse inference can be misleading. For example, differences in the use of the dlPFC may indicate emotion regulation deficits (Delgado et al., 2008). However, the dlPFC is also involved in a broad range of executive functions (E. E. Smith & Jonides, 1999). Therefore, both possibilities must be considered as equally likely. Alternatively, studies may experimentally separate the two functions. An excellent example of this approach was taken by Somerville et al. (2006) when they experimentally tested whether the ACC's response to social exclusion is merely

a product of its role in expectancy violation.

Even though experimental manipulation of clinical variables is unethical, there are other steps researchers can take to reduce the risk of spurious conclusions based on reverse inference. Perhaps the most important step is to test whether individual or group differences in brain activity are also related to a behavioral measure (Poldrack, 2006). Relating brain differences to specific behavioral differences constrains the interpretation of the brain activation. For example Jarcho et al. (2015) showed that SAD adolescents showed more negative functional connectivity between the striatum and preACC to prediction errors (i.e. unexpected relative to expected feedback), while also showing that this functional connectivity was positively associated with later recall of which co-players gave unexpected feedback. This presents supporting evidence, then, for the theory that social anxiety is associated with a deficit in learning from unexpected positive feedback.

Some of the reviewed studies take this relatively simple, albeit important step. Such behavioral differences could, however, create “performance confounds” (Carter et al., 2008; Church et al., 2010). That is, if a certain diagnosis (or a dimension of psychopathology) is related to worse performance on a task (for example, judging another person’s emotional expression) it is difficult to know whether associated disruptions in brain activity are a cause or a consequence of that behavioral difference. Therefore it will be necessary to conduct studies with and without behavioral measures to address issues of reverse inference and performance confounds. The strongest evidence will be from forward inference studies. That is, studies that may be able to manipulate rejection sensitivity within-subjects or between randomly assigned groups and measure intraindividual or interindividual differences in brain activity in a priori regions of interest. Such studies could test more specific hypotheses about the function of regions that covary with psychopathology, such as the amygdala and insula.

4.3 Statistical and methodological challenges and future directions

In light of the recent replication crisis (Open Science Collaboration, 2015), it is important

to evaluate the extent to which the studies reviewed in this article are likely to be replicated. First, no studies appeared to attempt to be direct replications of one another, and no studies mentioned being preregistered. Preregistering studies of this kind is relatively new, and therefore is something for future studies to strive to implement. Second, many studies were underpowered. It can be difficult to measure the statistical power afforded in neuroimaging studies post hoc, particularly with whole brain analyses. However, in order to identify a moderate effect size ($d=0.5$) between two groups with 80% power, one would need at least 128 total participants, or 82 participants if a dimensional measure of psychopathology was used. **Few of the studies reviewed here had this many participants, and thus we were careful not to discuss null results from studies with less than 128 (if a categorical diagnoses used) or 82 participants (if a dimensional measures of symptom severity was used).** It is not novel to suggest that neuroimaging research requires larger samples to detect reliable individual and group differences. That being said, steps to improve the rigor of methodologies and statistical analyses can lead to demonstrable improvements in power. For example, many studies relied on categorical measures of psychopathology (i.e. diagnoses). Measuring psychopathology dimensionally greatly improves power (Markon et al., 2011), and is in line with the Research Domain Criteria (RdoC) (Cuthbert, 2014; Insel et al., 2010) and the recently proposed Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017). In these studies, using dimensional measures of psychopathology with greater variability in symptoms severity can increase the measured effect size. **That being said, just as a categorical approach requires a substantial number of participants in each diagnostic group, a dimensional approach requires variability in the measured symptom. Therefore, community recruited samples may require greater sample sizes to achieve the same variability as a clinically recruited sample.** Another option would be to increase the number of conditions or trials in the task to improve its reliability.

One aim of this review was to examine different social feedback tasks, and examine how these might contribute to differences in their results. One interesting difference between tasks is

their design. The Cyberball paradigm is typically analyzed in a block design (with inclusion and exclusion blocks) while other tasks use event-related designs (e.g., Island Getaway, Social Judgement, Virtual School). Block designs may differ from event-related designs in psychological ways. For example, an “exclusion” block may be different from a “rejection” trial. The former may lead to hopelessness or defeat through repeated exclusion, while the latter may lead to more surprise and anger if rejection does not occur on every trial. Future studies should seek to compare block and event-related versions of the same task to determine whether effects are due to design differences.

A second aspect of the design that warrants further attention is the player’s attribution of intention to the co-players. Studies often use the same co-players across conditions. Being accepted and then rejected by the same co-player may differ in important ways from being rejected and then accepted by different co-players. This shift with the same co-player may actually lead to inadvertently measuring deficits in cognitive flexibility or reversal learning, rather than just responses to social feedback. Therefore, designing studies that limit the amount of social cognition needed to infer social feedback is necessary to separate dysfunction in social cognitive skills from dysfunction in affective responses to feedback. Alternatively, tasks such as the Virtual School paradigm leverage the ambiguity of responses to measure anticipation of positive, negative, and ambiguous feedback. That is, measuring how participants anticipate and respond to feedback from co-players that are typically nice, mean, or equally nice and mean.

There also remain questions of how differences in the qualities of virtual peers affect processing of social feedback. For example, how does rejection from a non-familiar peer compare to rejection from a likeable or similar peer? Studies that are able to separate and compare different aspects of the qualities of virtual peers are needed to address such questions. Unfortunately, there were not enough studies using each paradigm (other than Cyberball) to be able to evaluate how different task designs contribute to different patterns of brain activity and BOLD signal. Future studies should carefully select the task that will best answer their

research question, and not default to tasks that are “well-known.” **As more and more studies are conducted using these tasks, it will become possible to conduct group-level meta-analysis to identify differences in the brain’s response to different types of social feedback (e.g., exclusion, inclusion, rejection, acceptance, insults, compliments). Furthermore, studies using within-subjects designs to directly compare BOLD signal or ERPs between different tasks will be integral to such meta-analyses.**

As has been tradition in neuroimaging research, most fMRI studies reviewed used contrasts (i.e. BOLD signal that was greater in one condition than in another condition). Although a useful way to isolate brain activity unique to a given condition, there remain questions about whether exclusion vs. inclusion contrasts are valid ways to describe brain activity to exclusion feedback, for example. That is, if the brain response to inclusion differs from the response to exclusion only in the magnitude of brain activity, then this contrast would be valid. One example of this is in the Cyberball task, where the inclusion condition is considered a neutral condition rather than a positive condition, since the subject expects to be equitably included in the game of catch (K. D. Williams & Jarvis, 2006). On the other hand, an acceptance condition may be considered more rewarding, since the subject does not necessarily expect to be accepted by every co-player.

Future research should seek to verify the extent to which these are valid contrasts. It will be important to test questions such as do inclusion and exclusion vary upon a continuum, leading to activation and deactivation of the same brain regions? Or are they processed differently in the brain? For example, studies could test whether portions of the ACC are exclusively activated to negative feedback, while the striatum is only active to positive feedback. On the other hand, regions such as the insula may respond to both negative and positive feedback. One way to answer these questions would be by decomposing these contrasts. For example, one study found reduced MTG signal among depressed adolescents in an exclusion>inclusion contrast. When this finding was broken down, it revealed that depressed participants were not showing a

differentiation between the two conditions in the MTG, while the controls showed greater BOLD signal to exclusion than inclusion in this region (Jankowski et al., 2018). **Yet another option would be to include a neutral or control condition, as a number of studies in the current review did (Burklund et al., 2017; Davey et al., 2011; Domsalla et al., 2014b; Harms et al., 2019; Olino et al., 2015). This has the benefit of removing within-subject BOLD signal to an aspect of the stimuli that is not of interest. However, in some paradigms there is not a clear neutral version of the task. That being said, these studies offer potential neutral conditions for the Cyberball and Chatroom Interact, as well as other tasks, making them a jumping off point for other studies.**

Yet another important future direction will be characterizing normative development of the brain's response to social feedback. Meta-analyses have begun to inform such questions, finding that "developmental" samples tended to show BOLD signal to exclusion in the left vIPFC, lateral OFC, and ventral striatum, with "emerging adults" showing signal in the preACC, subACC, vmPFC, mOFC, and left PCC (Vijayakumar et al., 2017). The ventral striatum in particular showed hyperactivity to exclusion in these developmental samples compared to the emerging adult samples (Vijayakumar et al., 2017). In line with these findings, many studies of adolescent samples showed differences in striatal BOLD signal (Brown et al., 2017; Guyer et al., 2014; Harms et al., 2019; Jarcho et al., 2015; Olino et al., 2015; A. R. Smith et al., 2020), along with one study of young adults (Healey et al., 2014). Cross-sectional studies have proposed an intriguing theoretical reason for such developmental differences, specifically that adolescents internalize negative feedback (i.e. exhibit greater "rejection reactivity") to a greater extent than adults who have developed a "self-protection bias" (Rodman et al., 2017; Yoon et al., 2018). Longitudinal studies that administer social feedback tasks from childhood to adolescence and into adulthood will be integral to further testing such theories and understanding the normative development of the brain's response to social feedback. Furthermore, meta-analyses thus far have

focused on aggregating studies of social exclusion; therefore as the field grows, future meta-analyses of the development of the brain's response to positive social feedback will be needed.

This research would also be strengthened by more within-subjects comparisons of different forms of psychopathology. For example, studies like Kujawa et al. (2017) and Babinski et al. (2019) used the same sample to test different hypotheses. One was about how the RewP relates to social anxiety and depression severity, and the other about how the N1 and RewP related to ADHD severity (while covarying for depression and anxiety). This is one way to help account for comorbidity. Future studies should also seek to flesh out the literature further, by testing areas not yet covered by extant studies, such as including dimensional measures of BPD and externalizing disorders along with measures of depression and anxiety and recruiting even more diverse samples. Such samples are more likely to vary along these dimensions in ways that allow researchers to assess what behavioral and neural aspects of social feedback processing are uniquely associated with specific dimensions versus shared across dimensions. Furthermore, studies should also test whether reported effects replicate. Together, these efforts should further clarify the extent and limits of deficits in responding to social feedback.

It is noteworthy that most of the reviewed studies relied on fMRI, with only eleven of the studies using ERP, one study using PET, and one study using fNIRS. This has resulted in a body of research aimed mostly at identifying deficient *regions*. The neural mechanisms of interpreting, processing, and responding to social feedback is likely complex, involving a broad set of regions and networks (Amodio, 2010). This is supported by the different emotional reactions individuals show to the same social stimulus. That is, in response to being socially rejected, some may exhibit sadness, some anger, and others perhaps neither. This amount of variability suggests that there are numerous processes that determine the way someone reacts to social feedback. Therefore, more spatially coarse but temporally precise measures like EEG or ERP may have benefits for identifying certain aspects of neural mechanisms that are associated with psychiatric phenotypes.

If we adopt the idea that the brain mechanisms underlying the response to social feedback are complex, then integrating gross signals across the brain using ERP may be a complementary approach to detecting individual differences in the overall activity of complex brain networks.

4.4 Assessment of psychopathology

Many of the studies reviewed here used categorical diagnoses based on clinical interviews. Others used self or informant-report measures of psychopathology. There are some critical issues to take into account when self-report measures are used. Namely, that the relationship found between self-reported psychopathology and brain function may be the result of individual differences in *reporting style* rather than psychiatric symptoms. That is, relying on the same person to report on their symptoms and participate in the task increases the number of possible confounding third variables. This is noted in Eisenberger et al. (2009). They found distinct sex differences which the authors note could be due to greater stigma of depression in males that led to underreporting of symptoms. Use of multiple informants (e.g., partner/spouse, peer, friend, parent, clinician) could help mitigate or reduce some of these effects. Indeed, frameworks such as the Operations Triad Model exist to address issues with using multiple informants (De Los Reyes et al., 2013). On the other hand, as noted above, dimensional measures of psychopathology provide more powerful and reliable measures of psychiatric symptom severity. Therefore, the ideal measure may be a dimensional measure of symptom severity from a combination of different reports.

4.5 Limitations

The current review has a number of strengths, most importantly the assessment and integration of results from different types of social feedback and different forms of psychopathology. That being said, it must be considered in light of its limitations. First, we did not review or examine moderators such as age, race, or gender. We felt that there were too few studies to draw meaningful conclusions. The studies presented in the current review are drawn from different age populations. Although their respective developmental stages (e.g., adolescent,

young adult, adult) have been noted throughout, the relative variability between studies varies to such a degree that it requires its own review specifically devoted to comparing the similarities and differences in developmental periods across studies once there are a sufficient number of studies at different developmental stages to do so. Further, a growing literature emphasizes the use of *pubertal hormones* to measure development instead of or in addition to chronological age. This is because pubertal status appears to moderate associations between psychopathology and response to peer feedback (e.g., Silk et al., 2014). Therefore, future studies should seek to use pubertal status whenever possible in lieu of age when testing developmental changes to social feedback.

Second, this review was focused on internalizing disorders, excluding studies of other forms of psychopathology also known to have social deficits (e.g., schizophrenia spectrum/psychotic and neurodevelopmental disorders). Though studying social deficits in these disorders remains crucial, we believe that, given limited space, the current review could not do an adequate job of reviewing this additional literature. We hope that this review and other recent reviews (Reinhard et al., 2020) serve as a jumping off point for similar future reviews. Third, we used a somewhat broad conceptualization of socially relevant anxiety. This was meant to increase the ability to compare and contrast between studies, but may have sacrificed important distinctions between social anxiety disorder, for example, and behavioral inhibition, a hypothetical precursor of SAD. Fourth, the role of comorbidities in each of the studies was not explored. Although all comorbidities could not be fully accounted for in all studies, many studies accounted for some aspects of comorbidity by, for example, recruiting patient groups of MDD without NSSI, and groups of MDD with NSSI. However, for studies focused on only one or two disorders comorbidities unquestionably influenced results. Future studies should better account for the role of comorbidities both by collecting dimensional measures of different forms of psychopathology (to include as covariates in analyses), and recruiting samples with similar symptoms (e.g., anhedonia) but not necessarily similar diagnoses (e.g., major depressive disorder).

Fifth, we did not include null findings from the reviewed studies that had below 80% power to detect a moderate effect size (i.e. 128 participants if between groups, and 82 if correlational). This resulted in the exclusion of two papers. Although null findings are important in well-powered and replicated studies, the absence of an effect in a study can at most provide exploratory evidence that an association or group difference does not exist. Recent meta-analyses (S. Cacioppo et al., 2013; Vijayakumar et al., 2017) are helpful prototypes of studies that draw meaningful conclusions from null results. These meta-analyses suggested support for, among other things, the lack of dACC activity to social exclusion.

Sixth, we were not able to explore the degree to which each type of social feedback elicited similar or different emotions, since often this was not measured in the reviewed studies. Studies often were limited to using the Rejection Sensitivity Questionnaire or Need-Thread Scale to assess reactivity to feedback. However, as noted above, there are a variety of emotional responses that individuals use to respond to feedback. Current literature suggests that rejection might elicit a neutral emotional state, while acceptance a more positive one (Blackhart et al., 2009). Future studies measuring participants' emotional response to different forms of feedback would inform neural and behavioral deficits found in psychopathology.

Seventh, as with all reviews, we do not know whether unpublished null results might have altered our conclusions. We support the continued effort to publish well-powered null results. Such studies would inform the conclusions in such reviews. Eighth, one may take issue with the organization of this review. Because some studies focused on comparing two or more groups using only one social feedback task, the review was organized by type of psychopathology (e.g., depression) rather than by type of social feedback (e.g., exclusion). This allows for one study to contribute to multiple sections of the review, and we felt it was more integrative and straightforward to compare studies using this approach. It also allowed us to compare the relationships between a form of psychopathology and responses to different kinds of feedback (e.g., exclusion and rejection). **Ninth, regions were categorized to specific brain networks,**

despite often overlapping with more than one network. This was done for the sake of clarity in organizing results across studies. Finally, a quantitative meta-analysis would mitigate some of the limitations raised. An important future direction will be to conduct a meta-analysis once there are sufficient studies published on each type of social feedback.

4.6 Future directions

There are a number of directions that both future studies and reviews could take. Most of the studies identified in this review used samples of adolescents, young adults, or middle-aged adults, but few examined childhood. Understanding deficits in response to social feedback in early childhood is likely integral to understanding the development of internalizing and externalizing disorders. Additionally, studies of older adults would lead to a more comprehensive understanding of the lifetime trajectory of the response to social feedback. This would also assess the stability of the neural correlates identified in this review. That is, does insula activity to negative feedback remit with the remission of a depressive episode, or remain as a trait-like risk factor? Longitudinal studies are needed to test these hypotheses and provide crucial clinical information.

There are a number of additional intriguing future directions. First, dysfunction in these tasks is more likely to be related to transdiagnostic symptom dimensions (e.g., anhedonia, suicidal ideation, emotion dysregulation, etc.) than exclusive to specific disorders (e.g., SAD, MDD, BPD). Categorical diagnoses often lead to comorbidity and can obscure the true mechanistic relationship between brain and behavior. For example, a study that compares a diagnostic group like those with major depressive disorder and a group of control subjects, tells us how the groups differ, but not which aspect or symptom of depression is responsible for this difference (e.g., anhedonia, low mood, irritability, suicidal ideation, fatigue, worthlessness, or excessive guilt). A number of studies in the current review have begun to address this, for example by comparing BPD, SAD, MDD, and/or SI and NSSI groups (Brown et al., 2017; Cáceda et al., 2019; Groschwitz et al., 2016; Gutz et al., 2015; Harms et al., 2019; Kujawa et al., 2017; Malejko et al., 2018, 2019; Olié et al., 2017; van Schie et al., 2019), to identify the correlates of the unique dimensions of each

diagnosis/behavior. Future studies though are needed that test how each of these transdiagnostic dimensions relates to deficits in behavioral and brain responses to social feedback.

Second, multi-task studies would be able to compare response to different types of social feedback within-subjects. That is, studies using both the Cyberball and Chatroom tasks could compare and contrast brain responses to social exclusion and rejection. Third, experimental manipulations of subjects' mood or rejection sensitivity would allow for forward inference. Participants may be randomly assigned to conditions that induce greater, less, or no change in rejection sensitivity (e.g., with the Trier Social Stress task). Such studies would clarify the extant literature by testing conclusions that have relied on reverse inference assumptions.

4.7 Conclusions

The current article represents the first review of relationships between brain responses to different types of social feedback and psychopathology. The review aimed to identify common and distinct patterns and candidate neural mechanisms. In doing so, there were two primary findings. First, cingulo-opercular network hyperreactivity (particularly the insula) to negative social feedback may be linked with depression. Second, borderline personality disorder may be associated with hyperactivity of the default mode network. These findings present possible avenues for further study, though other more preliminary findings may also prove fruitful.

The studies reviewed have been largely beneficial towards advancing our understanding of psychiatric disorders. Moreover, by addressing the common and impairing aspect of mental illness that is interpersonal dysfunction, the potential clinical ramifications for such findings are substantial. They would allow us to better identify more targeted individualized interventions based on the mechanisms associated with each person's interpersonal deficits. More tailored treatments and interventions aimed at alleviating different causes of impairments in social relationships promise to reduce the burden of mental illness.

Disclosures

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Table 1. Brodmann's areas and approximate MNI coordinate of primary reviewed brain regions

Region	BA	Approximate coordinates (MNI) x ^b ,y,z	Number of voxels that overlap with each network																	
			DMN	SUB	CON	SAL	FPN	AUD	VAN	SEN	DAN	VIS								
Subgenual ACC (subACC)	25	5:7, 17, -13:-14																		
Pregenual ACC (preACC)	32 ^c	5:6, 33:39, 16:20	13012				5321													
Dorsal ACC (dACC)	24	5, 1:5, 31:32			3165	291						1140								
Insula (anterior/posterior [AI/PI])	13	44, 4, 0		578	19903	412														
Ventrolateral PFC (vlPFC)	44, 45, 47	38:49, 12:30, -13:17	60		3848	13828					6431									
Ventromedial PFC (vmPFC)	11 ^d	12, 37:38, -19	4696				1372													
Dorsomedial PFC (dmPFC)	8, 9	22:39, 24:39, 31:45	4772				2958	1224												
Dorsolateral PFC (dlPFC)	46, 8 ^e	43:46, 38, 8:12					2317	8653			2074									
Rostrolateral prefrontal (rlPFC)	10	23, 55, 4:7	3077				2822	2958												
Amygdala	53	26, 3, -23		20																
Hippocampus	36, 54	26:29, -19:-22, -14:-25	182																	
Ventral striatum (VS)	52	10, 10, -12		7760																
Caudate	48	11:14, 13, 10:11		7755			81													
Putamen	49	25:26, 3, -1		16976	6995		492													
Posterior cingulate cortex (PCC)	23	9:10, -45, 24	12496																	
Precuneus	23,7,31	8, -48:49, 38:39	12496																	
Middle temporal gyrus (MTG)	21	59:60, -25:27, -9:13	15460							30	2136									
Temporoparietal junction (TPJ)	22	54:57, -19:20, 1	5154							9954	3520									

- a- Bolded voxel values indicate networks that most overlapped with the region of interest ($\geq 50\%$ of the total voxels that overlapped with networks)
- b- x coordinate is positive or negative depending on laterality
- c- At genu of the corpus collosum
- d- Excluding the orbitofrontal cortex
- e- Specifically the lateral portions of BA8
- f- ACC: anterior cingulate cortex
- g- PFC: prefrontal cortex
- h- BA: Brodmann area, approximate MNI coordinates for each Brodmann area from Lacadie et al., (2008)
- i- MNI: Montreal Neurological Institute
- j- CON: cingulo-opercular networks, DMN: default mode network, FPN: fronto-parietal network, SAL: salience network, VAN: ventral attention network, SUB: subcortical network, SEN: sensory/somatomotor network, AUD: auditory network, VIS: visual network, DAN: dorsal attention network

k- The subgenual ACC did not overlap with any of the a priori defined networks

Table 2. Reviewed studies of socially relevant anxiety

Author	Psycho-pathology	Measures	Method	Task	Sample size (% female)	Population (age range in years)	Reviewed findings
<i>Negative feedback</i>							
DeWall et al., 2012	Anxious attachment	Attachment Style Questionnaire	fMRI	Cyberball	25 (64.0)	Young adults †	• Anxious attachment pos associated w/ dACC , AI , & vIPFC to exclusion
Heeren et al., 2017	SAD	BDI-2, STAI-Trait, STAI-State, LSAS	fMRI	Cyberball	46 (100.0)	Adults (25.13 ± 6.05, NR)	• SAD → greater distress to rejection & higher ratings of feeling excluded • SAD → greater L IFG during re-inclusion; L IFG pos associated w/ perceived social exclusion & LSAS in SAD group
Wudarczyk et al., 2015	Chemo-sensory anxiety cues	SCID, BDI	fMRI	Cyberball	24 (41.7)	Adults (24.33 ± 2.91, 18-29)	• Administered “anxious sweat” → deactivation in hippocampus & MTG to exclusion
Gutz et al., 2015	BPD, SAD	SCID	EEG	Cyberball	75 (88.0)	Adults (26.33 ± 5.35, NR)	• SAD → greater self-reported expectancy of being excluded
Beer et al., 2016	Anxiety	FNE, LSAS	fMRI	Chatroom	90 (46.2 & 62.7)	Young adolescents (20.97 ± 5.09, 8-17.4) & adults (26.82 ± 6.31, 18.3-49.6)	• Anxious adolescents → pos R FFA-L preACC connectivity to rejection; control adolescents, adults, & anxious adults → neg connectivity
Guyer et al., 2014	Behavioral inhibition	SCARED, Social Anxiety Scale-Adolescents, KSADS, Behavioral Inhibition Composite	fMRI	Chatroom	39 (56.4)	Adolescents (17.89 ± 1.62, NR)	• BI → greater L STG to rejection by selected peers, compared to controls, but reduced when rejected by non-selected peers
Harrewijn et al., 2017	SAD	Mini-Plus International Neuropsychiatric Interview, MINI Kid Interview,	EEG/ERP	Social Judgment Paradigm	115 (51.3)	Children & adults from nine families (30.29 ± 15.57, 8-61)	• SAD → experienced more rejection following task • SAD → predict more frequent rejection • SAD severity pos associated w/ FRN

		Interaction Anxiousness Scale					
van der Molen et al., 2018	SAD	LSAS, Rosenberg Self-Esteem Scale, Fear of Positive Evaluation Scale, BDI-2	EEG/ERP	Social Judgment Paradigm	39 (100.0)	Young adults (19.75 ± 1.54)	<ul style="list-style-type: none"> • SAD → greater FRN to unexpected rejection compared to all other conditions • SAD → greater theta power to unexpected rejection • SAD → reduced theta power to rejection
Jarcho et al., 2016	Social reticence	KSADS, SCARED, Pubertal Development Scale, Early Adolescent Temperament Questionnaire	fMRI	Virtual School	53 (45.3)	Preadolescents (11.08 ± 0.19, NR)	<ul style="list-style-type: none"> • High SR → reduced L amygdala to unpredictable neg feedback
Smith et al., 2020	SAD	SCARED, FNE, Social Anxiety Scale	fMRI	Virtual School	112 (67.0)	Preadolescents & adolescents (12.81 ± 2.80, 8-18)	<ul style="list-style-type: none"> • SAD severity pos associated w/ caudate, MTG, & TPJ signal to unpredictable insults among preadolescents • SAD severity neg associated w/ caudate signal to unpredictable insults among adolescents
Burklund et al., 2017	SAD	LSAS, Social Interaction Anxiety Scale, Mood & Anxiety Symptom Questionnaire	fMRI	Disapproving, rejecting, negative, & neutral feedback video clips	87 (50.6)	Adults (27.80 ± 7.71, NR)	<ul style="list-style-type: none"> • SAD → greater distress to rejection & feelings of exclusion • SAD → greater preACC, L vmPFC, L amygdala, & MTG to rejection predicted better response to CBT; greater PI predicted better response to ACT • SAD severity pos associated w/ R precuneus & precentral gyrus to rejection
Lau et al., 2012	SAD	KSADS, Pediatric Anxiety Rating Scale, Child Global Assessment Schedule	fMRI	Not interested or interested used to simulate rejection or acceptance	24 (66.7)	Young adolescents (12.06 ± 2.46, NR)	<ul style="list-style-type: none"> • SAD → persistent R insula, hippocampus, precentral gyrus, L cuneus, R lingual gyrus, & claustrum from anticipation to rejection feedback phases of each trial; reduced in controls

Positive feedback

Guyer et al., 2014	Behavioral inhibition	SCARED, Social Anxiety Scale-Adolescents, KSADS, Behavioral Inhibition Composite	fMRI	Chatroom	39 (56.4)	Adolescents (17.89 ± 1.62, NR)	<ul style="list-style-type: none"> • BI → reduced caudate to acceptance; BN → greater R caudate • BI → no difference b/w selected & non-selected peers; BN → greater L STG to acceptance from selected vs. non-selected peers
Jarcho et al., 2015	SAD	KSADS, SCID, FNE	fMRI	Variation of Chatroom that includes: valuation, prediction of, receipt of, and recall of feedback	90 (55.6)	Adolescents & adults (20.97 ± 5.08, NR)	<ul style="list-style-type: none"> • SAD → greater striatum to unexpected acceptance from selected peers • SAD → greater neg striatum-preACC connectivity to predictions errors; connectivity pos associated w/ later recall of co-players that gave unexpected feedback
Kujawa et al., 2017	MDD, SAD	Children's Depression Inventory, SCARED	ERP	Island Getaway	412 (46.8)	Young adolescents (12.64 ± 0.47, NR)	<ul style="list-style-type: none"> • SAD severity not associated w/ RewP to acceptance
Pegg et al., 2019	MDD, SAD	STRAIN, IDAS	ERP	Island Getaway	231 (71.9)	Young adults (18.16 ± 0.41, NR)	<ul style="list-style-type: none"> • Depression and social anxiety severity not associated with RewP to acceptance feedback
Gu et al., 2020	SAD	LSAS, BDI-II, STAI-Trait, Revised Social Anhedonia Scale	ERP	Social Judgment Paradigm	60 (50.0)	Young adults (20.42 ± 1.73, NR)	<ul style="list-style-type: none"> • High social anxiety → greater FRN to unexpected acceptance than unexpected rejection, pattern not present in low social anxiety • Low social anxiety → greater P3a to expected acceptance than expected rejection, pattern not present in high social anxiety • Low social anxiety → greater LPP to acceptance than rejection, pattern not present in high social anxiety
Harrewijn et al., 2017	SAD	Mini-Plus International Neuropsychiatric Interview, MINI Kid Interview, Interaction Anxiousness Scale	EEG/ERP	Social Judgment Paradigm	115 (51.3)	Children & adults from nine families (30.29 ± 15.57, 8-61)	<ul style="list-style-type: none"> • SAD → greater P3 to acceptance

van der Molen et al., 2018	SAD	LSAS, Rosenberg Self-Esteem Scale, Fear of Positive Evaluation Scale, BDI-2	EEG/ERP	Social Judgment Paradigm	39 (100.0)	Young adults (19.75 ± 1.54)	• SAD → predict fewer instances of future acceptance
Jarcho et al., 2016	Social reticence	KSADS, SCARED, Pubertal Development Scale, Early Adolescent Temperament Questionnaire	fMRI	Virtual School	53 (45.3)	Preadolescents (11.08 ± 0.19, NR)	• High SR → neg insula-vmPFC connectivity to unpredictable pos feedback
Smith et al., 2020	SAD	SCARED, FNE, Social Anxiety Scale	fMRI	Virtual School	112 (67.0)	Preadolescents & adolescents (12.81 ± 2.80, 8-18)	• SAD severity pos associated w/ caudate & MTG signal to predictable compliments among preadolescents
Qi et al., 2017	SAD	SCID, STAI, Interaction Anxiousness Scale	ERP	Rejection & Acceptance feedback followed by recall	44 (66.0)	Young adults (20.14 ± 1.00, NR)	• SAD → more conservative in endorsing whether a co-player had previously accepted them compared to controls
<i>Feedback in general</i>							
Guyer et al., 2014	Behavioral inhibition	SCARED, Social Anxiety Scale-Adolescents, KSADS, Behavioral Inhibition Composite	fMRI	Chatroom	39 (56.4)	Adolescents (17.89 ± 1.62, NR)	• BI → greater fusiform gyrus to feedback in general
Gu et al., 2020	SAD	LSAS, BDI-II, STAI-Trait, Revised Social Anhedonia Scale	ERP	Social Judgment Paradigm	60 (50.0)	Young adults (20.42 ± 1.73, NR)	<ul style="list-style-type: none"> • High social anxiety → greater P1 to anticipation of feedback in general than low social anxiety • High social anxiety → greater FRN to unexpected acceptance than unexpected rejection, pattern not present in low social anxiety • Low social anxiety → greater P3a to expected acceptance than expected rejection, pattern not present in high social anxiety

							<ul style="list-style-type: none"> • Low social anxiety → greater LPP to acceptance than rejection, pattern not present in high social anxiety
Cao et al., 2015	SAD	SCID	ERP	Acceptance & Rejection feedback	40 (62.8)	Young adults (20.21 ± 0.89, NR)	<ul style="list-style-type: none"> • SAD → reduced P2 to feedback in general
Jin et al., 2019	Dysphoria, SAD	IDAS-II	EEG	Participants guess which of two co-players likes or dislikes them and receive feedback that they were correct or incorrect	204 (63.7)	Young adults (19.92 ± 2.50, NR)	<ul style="list-style-type: none"> • SAD severity pos associated w/ delta activity to feedback in general • Dysphoria severity neg associated w/ delta activity to feedback in general
Lau et al., 2012	SAD	KSADS, Pediatric Anxiety Rating Scale, Child Global Assessment Schedule	fMRI	Not interested or interested used to simulate rejection or acceptance	24 (66.7)	Young adolescents (12.06 ± 2.46, NR)	<ul style="list-style-type: none"> • SAD → persistent amygdala from anticipation to feedback phases of each trial; reduced in controls
Qi et al., 2017	SAD	SCID, STAI, Interaction Anxiousness Scale	ERP	Rejection & Acceptance feedback followed by recall	44 (66.0)	Young adults (20.14 ± 1.00, NR)	<ul style="list-style-type: none"> • SAD → more conservative in endorsing whether a co-player had previously accepted them compared to controls
<i>Anticipation of feedback</i>							
Guyer et al., 2008	Anxiety	KSADS, Pediatric Anxiety Rating Scale, SCARED	fMRI	Chatroom	28 (71.4)	Young adolescents (12.44 ± 2.65, NR)	<ul style="list-style-type: none"> • SAD → expect to be rated as less desirable by peers • SAD → greater amygdala to anticipation of feedback from non-selected peers compared to selected peers; SAD severity pos associated w/ R amygdala • SAD severity pos associated w/ amygdala–vIPFC connectivity to anticipation of feedback from non-selected peers • SAD → greater preACC, subACC, dIPFC, &

Author	Condition	Measures	Method	Task	N	Participants	Findings
Spielberg et al., 2015	Anxiety	KSADS, FNE	fMRI	Chatroom	42 (52)	Preadolescents & adolescents (13.3 ± 2.8, 8-17)	<ul style="list-style-type: none"> • cerebellum to anticipation of feedback from non-selected peers • Anxious adolescents → greater L amygdala to anticipation of feedback from non-selected peers • Anxious adolescents, anxious adults, & adults controls → pos preACC-L amygdala connectivity to anticipation of feedback from selected peers & neg connectivity for non-selected peers; early adolescent controls → opposite pattern • Anxious adolescents → reduced NAcc to anticipation of feedback from selected peers
Jarcho et al., 2015	SAD	KSADS, SCID, FNE	fMRI	Variation of Chatroom that includes: valuation, prediction of, receipt of, and recall of feedback	90 (55.6)	Adolescents & adults (20.97 ± 5.08, NR)	<ul style="list-style-type: none"> • SAD → greater neg striatum-preACC connectivity to predictions errors; connectivity pos associated w/ later recall of co-players that gave unexpected feedback
Gu et al., 2020	SAD	LSAS, BDI-II, STAI-Trait, Revised Social Anhedonia Scale	ERP	Social Judgment Paradigm	60 (50.0)	Young adults (20.42 ± 1.73, NR)	<ul style="list-style-type: none"> • High social anxiety → greater P1 to anticipation of feedback in general than low social anxiety
Jarcho et al., 2016	Social reticence	KSADS, SCARED, Pubertal Development Scale, Early Adolescent Temperament Questionnaire	fMRI	Virtual School	53 (45.3)	Preadolescents (11.08 ± 0.19, NR)	<ul style="list-style-type: none"> • High SR → greater dACC, insula, & PCC to anticipation of unpredictable feedback • High SR → neg connectivity of R insula-vmPFC & R insula-R premotor cortex; low SR → pos connectivity
Smith et al., 2020	SAD	SCARED, FNE, Social Anxiety Scale	fMRI	Virtual School	112 (67.0)	Preadolescents & adolescents (12.81 ± 2.80, 8-18)	<ul style="list-style-type: none"> • SAD severity neg associated w/ precuneus signal to anticipation of feedback

L=left, R=right; pos=positive, neg=negative; SCID- Structured Clinical Interview for DSM-IV; KSADS- Kiddie Schedule for Affective Disorders and Schizophrenia; FNE- Fear of neg Evaluation; BDI- Beck Depression Inventory; SCARED- Screen for Child Anxiety and Related Emotional Disorders; LSAS- Liebowitz Social Anxiety Scale; STAI- State-Trait Anxiety Inventory; BI- behavioral inhibition; BN-behaviorally non-inhibited; SR- socially reticent; FFA- fusiform face area; CBT- cognitive behavioral therapy; ACT- acceptance & commitment therapy; STG- superior temporal gyrus; CC- cingulate cortex; NR- no age range provided; † no age information provided

Table 3. Reviewed studies of depression

Author	Psycho-pathology	Measures	Method	Task	Sample size (% female)	Population (age range in years)	Reviewed findings
<i>Negative feedback</i>							
Eisenberger et al., 2009	Cytokine-induced depressed mood	SCID, Profile of Mood States	fMRI	Cyberball	36 (~51)	Young adults (21.8 ± 3.4, 18–36)	<ul style="list-style-type: none"> • Exposure to endotoxin → greater depressed mood after 2 hours • Concurrent depression severity pos associated w/ PI to exclusion
Groschwitz et al., 2016	MDD w/ & wo/ NSSI	KSADS, Self-injurious thoughts and behaviors interview, BDI-2, Children's Depression Rating Scale	fMRI	Cyberball	43 (79.1)	Adolescents (15.25 ± 1.74)	<ul style="list-style-type: none"> • MDD → greater sensitivity to exclusion • MDD w/ NSSI → greater sensitivity to exclusion compared to MDD wo/ NSSI & controls • History of NSSI in past year → greater preACC, vIPFC, & L fusiform to exclusion compared to MDD wo/ NSSI & controls
Harms et al., 2019	SI, SA, MDD	KSADS, CDRS	fMRI	Cyberball	126 (61.1)	Adolescents (14.74 ± 1.56, NR)	<ul style="list-style-type: none"> • MDD → greater L vIPFC, L dmPFC, R TPJ, & lingual gyrus to exclusion than HC
Jankowski et al., 2018	MDD	KSADS	fMRI	Cyberball	126 (50.6)	Adolescents (14.75 ± 1.62, 11.3-17.8)	<ul style="list-style-type: none"> • MDD → reduced subACC, PCC, mPFC, & IPFC to exclusion • MDD → reduced MTG to exclusion: controls → greater MTG to exclusion than inclusion, while MDD → no difference b/w exclusion & inclusion • MDD → greater L insula signal to exclusion • MDD → greater insula & vIPFC to exclusion than inclusion; controls → greater to inclusion than exclusion
Kumar et al., 2017	MDD	BDI, Hamilton Depression Rating Scale, Snaith-Hamilton Pleasure Scale, Spielberger Trait Anxiety, Rosenberg	fMRI	Cyberball: modified for increasing exclusion over time	32 (59.4)	Adults (43.10 ± 11.93, NR)	<ul style="list-style-type: none"> • MDD → greater L vIPFC to exclusion • MDD → greater amygdala to exclusion • MDD → greater R insula to exclusion

		Self-Esteem scale					
Malejko et al., 2018	BPD, MDD	SCID, Borderline Symptom List, BDI,	fMRI	Cyberball: Inclusion & Passive viewing conditions	48 (100.0)	Young adults & adults (25.03 ± 4.33, NR)	<ul style="list-style-type: none"> • MDD → greater sensitivity to rejection • MDD → reduced happiness & satisfaction, greater fear & inner tension after task
Masten et al., 2011	MDD	Childhood Behavior Checklist	fMRI	Cyberball	20 (65.0)	Young adolescents (12.94†, 12.4–13.6)	<ul style="list-style-type: none"> • MDD symptoms over 1 year pos associated w/ subACC to exclusion • Increase in depression symptoms over 1 year pos associated w/ dACC to exclusion • Concurrent depression severity pos associated w/ PCC • Concurrent depression severity neg associated w/ precuneus, cuneus, & inferior parietal lobule to exclusion • Increase in MDD symptoms over the following year pos associated w/ dmPFC to exclusion
Rudolph et al., 2016	MDD	Short Mood & Feelings Questionnaire, Social Anxiety Scale for Adolescents	fMRI	Cyberball	47 (100.0)	Adolescents (15.41 ± 0.36, NR)	<ul style="list-style-type: none"> • Concurrent depression severity pos associated w/ subACC, dACC, dmPFC, amygdala, & R insula to exclusion
Silk et al., 2014	MDD	KSADS	fMRI	Chatroom Interact	48 (70.8)	Adolescents (15.48 ± 1.68, 11-17)	<ul style="list-style-type: none"> • MDD → greater feelings of sadness, nervousness, exclusion, & less happiness • MDD → greater subACC, L insula, & NAcc to rejection due to reduced deactivation to rejection
Hsu et al., 2015	MDD	SCID, Hamilton Depression Rating Scale	PET	Task similar to Chatroom	35 (74.3)	Adults (30.68 ± 10.84, NR)	<ul style="list-style-type: none"> • MDD → more persistent neg affect following rejection compared to controls • MDD → MOR deactivation in amygdala to rejection among depressed adults; controls → amygdala activation • Controls → greater MOR activity in R NAcc, midline thalamus, & periaqueductal gray to rejection; MDD → no greater activity

Positive feedback

Cáceda et al., 2019	SA, SI, MDD wo/ SI	SCID, Columbia Suicide Severity Rating Scale, BDI-2	fMRI	Cyberball	52 (42.3)	Adults (35.53 ± 12.05, NR)	• Depression pos associated w/ superior AI to inclusion
Zhang et al., 2017	MDD	Positive and Negative Affect Schedule, BDI	ERP	Cyberball	50 (68.0)	Adults (32.54 ± 7.41, NR)	• MDD → reduced P3 to inclusion
Davey et al., 2011	MDD	SCID	fMRI	Accepted & Neutral feedback task similar to Chatroom, no language, symbol to represent feedback	39 (64.9)	Adolescents & young adults (18.97 ± 2.59, NR)	• MDD → reduced expectations to like peers in the game if they met; MDD → rated feedback as less rewarding • MDD adolescents & young adults → greater L amygdala to acceptance
Healey et al., 2014	Social anhedonia	KSADS, Revised Chapman Social Anhedonia Scale, Center for Epidemiologic Studies Depression Scale	fMRI	Task similar to Chatroom	27 (51.9)	Young adults (20.4 ± 0.80, 18-21)	• Current social anhedonia pos associated w/ preACC, dACC, & PCC to mutual liking • Depression severity & social anhedonia severity pos associated w/ dIPFC, dmPFC, & precuneus to mutual liking • Social anhedonia pos associated w/ orbitofrontal cortex, ventral striatum, thalamus, caudate tail, superior parietal cortex, & insula to mutual liking • Social anhedonia pos associated w/ NAcc-mPFC connectivity to mutual liking
Hsu et al., 2015	MDD	SCID, Hamilton Depression Rating Scale	PET	Task similar to Chatroom	35 (74.3)	Adults (30.68 ± 10.84, NR)	• MDD → greater pos affect during inclusion compared to controls • MDD → greater MOR activation in subACC to acceptance; likely due to MOR deactivation in controls to acceptance • Controls → greater MOR activation in R insula to acceptance; MDD → no MOR activation • Controls → MOR activation in L amygdala &

Author(s)	Sample	Measures	Method	Task	N	Age	Findings
Olino et al., 2015	Depressed parent	KSADS, SCID (for parental history), Patient Reported Outcomes Measurement Information Systems Depression scale	fMRI	Chatroom Interact	33 (57.4)	Young adolescents (12.98 ± 2.14, 10.10-16.89)	<p>MOR deactivation in midline thalamus to acceptance; MDD → no MOR activation/deactivation in L amygdala to acceptance & MDD → MOR activation in midline thalamus</p> <ul style="list-style-type: none"> • Children of depressed mothers → reduced L preACC/dACC, L insula, & ventral striatum to acceptance • Children of depressed mothers → greater precuneus, R fusiform, & R S1 to acceptance
Kujawa et al., 2017	MDD, SAD	Children's Depression Inventory, SCARED	ERP	Island Getaway	412 (46.8)	Young adolescents (12.64 ± 0.47, NR)	<ul style="list-style-type: none"> • Depression severity neg associated w/ RewP to acceptance
Pegg et al., 2019	MDD, SAD	STRAIN, IDAS	ERP	Island Getaway	231 (71.9)	Young adults (18.16 ± 0.41, NR)	<ul style="list-style-type: none"> • Depression and social anxiety severity not associated with RewP to acceptance feedback
<i>Feedback in general</i>							
Harms et al., 2019	SI, SA, MDD	KSADS, CDRS	fMRI	Cyberball	126 (61.1)	Adolescents (14.74 ± 1.56, NR)	<ul style="list-style-type: none"> • High SI → greater R inferior parietal lobule to feedback in general (inclusion & exclusion > non-social condition) than HC • High SI → reduced R insula, R putamen, & L pre/postcentral gyrus to feedback in general than low SI • High SI → reduced R insula, R putamen, & L globus pallidus to feedback in general than HC • SA → greater dmPFC & preACC to feedback in general than high SI • SA → greater L rIPFC to feedback in general than low SI

Davey et al., 2011	MDD	SCID	fMRI	Accepted & Neutral feedback task similar to Chatroom, no language, symbol to represent feedback	39 (64.9)	Adolescents & young adults (18.97 ± 2.59, NR)	• MDD adolescents & young adults → greater vIPFC , R IPC , preACC , & R AI to feedback in general
Dedovic et al., 2016	MDD history	SCID	fMRI	Exclusively verbal evaluative positive & negative feedback by a live confederate	46 (100.0)	Young adults (19.33 ± 1.35, NR)	• History of MDD → greater dACC ; controls → reduced dACC to feedback in general
Jin et al., 2019	Dysphoria, SAD	IDAS-II	EEG	Participants guess which of two co-players likes or dislikes them and receive feedback that they were correct or incorrect	204 (63.7)	Young adults (19.92 ± 2.50, NR)	• SAD severity pos associated w/ delta activity to feedback in general • Dysphoria severity neg associated w/ delta activity to feedback in general

L=left, R=right; pos=positive, neg=negative; SCID- Structured Clinical Interview for DSM-IV; KSADS- Kiddie Schedule for Affective Disorders and Schizophrenia; BDI- Beck Depression Inventory; SCARED- Screen for Child Anxiety and Related Emotional Disorders; IPC- inferior parietal cortex; PCC- posterior cingulate cortex; MOR- μ -opioid receptor; NR- no age range provided; † no age standard deviation provided

Table 4. Reviewed studies of borderline personality disorder

Author	Psycho-pathology	Measures	Method	Task	Sample size (% female)	Population (age range in years)	Reviewed findings
<i>Negative feedback</i>							
Brown et al., 2017	BPD, NSSI	KSADS, SCID	fMRI	Cyberball	60 (89.8)	Adolescents & young adults (19.39 ± 3.35, NR)	<ul style="list-style-type: none"> • BPD → greater dmPFC to exclusion • BPD & NSSI → greater preACC to exclusion
Malejko et al., 2019	BPD, NSSI	SCID, Self-injurious Thoughts & Behaviors Interview, Borderline Symptom List, BDI-2	fMRI	Cyberball: Inclusion & Passive viewing conditions	48 (100.0)	Young adults (22.43 ± 3.75, NR)	<ul style="list-style-type: none"> • BPD → greater sensitivity to exclusion
Ruocco et al., 2010	BPD	BPD module of the Diagnostic Interview for DSM-IV Personality Disorders	fNIRS	In person card game similar to Cyberball	20 (100.0)	Young adults (20.55 ± 5.22, NR)	<ul style="list-style-type: none"> • BPD → greater dmPFC signal to exclusion • Rejection & abandonment fears positively associated w/ L mPFC
Wrege et al., 2019	BPD	PANAS	fMRI	Cyberball	68 (76.9)	Adults (26.73 ± 7.35)	<ul style="list-style-type: none"> • BPD → lower sense of belonging across conditions • BPD → greater preACC & R rIPFC to exclusion
van Schie et al., 2019	BPD, low self-esteem	Mini International Neuropsychiatric Interview; IPDE Borderline Personality Disorder-Severity Interview, Rosenberg Self-Esteem Scale	fMRI	Exclusively verbal evaluative positive & negative feedback	80 (100.0)	Adults (29.92 ± 9.37, 18–54)	<ul style="list-style-type: none"> • BPD → greater neg self-views & lower mood following both neg & intermediate feedback • BPD rated neg feedback as more applicable to them & pos feedback as less applicable • BPD → greater L precuneus to insults

<i>Positive feedback</i>							
Brown et al., 2017	BPD, NSSI	KSADS, SCID	fMRI	Cyberball	60 (89.8)	Adolescents & young adults (19.39 ± 3.35, NR)	<ul style="list-style-type: none"> • BPD → greater dmPFC to inclusion • BPD → greater L AI signal to inclusion • BPD → greater dIPFC signal to inclusion
Domsalla et al., 2014	BPD	IPDE, SCID, Borderline Symptom List, Brief Symptom Inventory, BDI	fMRI	Cyberball	40 (100.0)	Adults (28.95 ± 58.55, NR)	<ul style="list-style-type: none"> • BPD → felt more excluded during inclusion & control trials
Gutz et al., 2015	BPD, SAD	SCID	EEG	Cyberball	75 (88.0)	Young adults (26.33 ± 5.35, NR)	<ul style="list-style-type: none"> • BPD → greater self-reported expectancy of being excluded • BPD → felt more excluded during inclusion & control trials • BPD → greater P3b to inclusion: P3b neg associated w/ exclusion expectancy during inclusion
Malejko et al., 2018	BPD, MDD	SCID, Borderline Symptom List, BDI	fMRI	Cyberball: Inclusion & Passive viewing conditions	48 (100.0)	Young adults & adults (25.03 ± 4.33, NR)	<ul style="list-style-type: none"> • Comorbid BPD & MDD → greater anger following task • BPD → greater dmPFC to inclusion • Comorbid BPD & MDD → greater precuneus & PCC to inclusion compared to MDD & controls, greater TPJ to inclusion compared to controls
Malejko et al., 2019	BPD, NSSI	SCID, Self-injurious Thoughts & Behaviors Interview, Borderline Symptom List, BDI-2	fMRI	Cyberball: Inclusion & Passive viewing conditions	48 (100.0)	Young adults (22.43 ± 3.75, NR)	<ul style="list-style-type: none"> • BPD → greater dmPFC to inclusion • BPD & NSSI → greater L AI & R preACC to inclusion in conjunction analysis compared to controls
van Schie et al., 2019	BPD, low self-esteem	Mini International Neuropsychiatric Interview; IPDE Borderline Personality Disorder-Severity	fMRI	Exclusively verbal evaluative positive & negative feedback	80 (100.0)	Adults (29.92 ± 9.37, 18–54)	<ul style="list-style-type: none"> • BPD → reduced R TPJ to compliments

		Interview, Rosenberg Self- Esteem Scale					
<i>Feedback in general</i>							
Domsalla et al., 2014	BPD	IPDE, SCID, Borderline Symptom List, Brief Symptom Inventory, BDI	fMRI	Cyberball	40 (100.0)	Adults (28.95 ± 58.55, NR)	<ul style="list-style-type: none"> • Controls → insula, dIPFC, precuneus, & dmPFC modulated by condition; BPD → not modulated • Over these regions, controls showed the greatest signal to inclusion, less to exclusion, & least to the control condition

L=left, R=right; pos=positive, neg=negative; SCID- Structured Clinical Interview for DSM-IV; IPDE- International Personality Disorder Examination; KSADS- Kiddie Schedule for Affective Disorders and Schizophrenia; BDI- Beck Depression Inventory

Table 5. Reviewed studies of non-suicidal self-injury, suicidal ideation, suicide attempt

Author	Psycho-pathology	Measures	Method	Task	Sample size (% female)	Population (age range in years)	Reviewed findings
<i>Negative feedback</i>							
Brown et al., 2017	NSSI, BPD	KSADS/SCID	fMRI	Cyberball	60 (89.8)	Adolescents & young adults (19.39 ± 3.35, NR)	• NSSI in past year → greater putamen to exclusion compared to BPD & controls
Groschwitz et al., 2016	MDD w/ & wo/ NSSI	KSADS, Self-injurious thoughts & behaviors interview, BDI-2, Children's Depression Rating Scale	fMRI	Cyberball	43 (79.1)	Adolescents (15.25 ± 1.74)	• Comorbid MDD & NSSI → greater sensitivity to exclusion • History of NSSI in past year → greater preACC, vIPFC, & L fusiform to exclusion
Harms et al., 2019	SI, SA, MDD	KSADS, CDRS	fMRI	Cyberball	126 (61.1)	Adolescents (14.74 ± 1.56, NR)	• MDD → greater L vIPFC, L dmPFC, R TPJ, & lingual gyrus to exclusion than HC
Olié et al., 2017	History of depression w/ & wo/ SI	BDI, Risk Rescue Rating Scale, Suicide Intent Scale	fMRI	Cyberball	105 (100.0)	Adults (37.34 ± 2.93, 19.4-54.2)	• Prior suicide attemptors → reduced L supramarginal gyrus & L PI to exclusion
Openheimer et al., 2020	SI	KSADS, SCARED, MFQ-SI, CDRS-R	fMRI	Chatroom Interact	36 (53.0)	Preadolescents & adolescents (13.56 ± 1.50, 11-16)	• SI severity (controlling for depression severity) pos associated w/ R AI & L vIPFC to rejection
<i>Positive feedback</i>							
Cáceda et al., 2019	SA, SI, MDD wo/ SI	SCID, Columbia Suicide Severity Rating Scale, BDI-2	fMRI	Cyberball	52 (42.3)	Adults (35.53 ± 12.05, NR)	• Suicide risk spectrum (controls, non-suicidal depression, suicide ideators) pos relationship w/ R superior insula to inclusion; though history of a suicide attempt → similar insula to controls

Malejko et al., 2019	NSSI, BPD	SCID, Self-injurious Thoughts & Behaviors Interview, Borderline Symptom List, BDI-2	fMRI	Cyberball: Inclusion & Passive viewing conditions	48 (100.0)	Young adults (22.43 ± 3.75, NR)	<ul style="list-style-type: none"> • NSSI → greater R preACC & L AI to inclusion (in conjunction analysis)
<i>Feedback in general</i>							
Harms et al., 2019	SI, SA, MDD	KSADS, CDRS	fMRI	Cyberball	126 (61.1)	Adolescents (14.74 ± 1.56, NR)	<ul style="list-style-type: none"> • High SI → greater R inferior parietal lobule to social feedback in general than HC • High SI → reduced R insula, R putamen, & L pre/postcentral gyrus to social feedback in general than low SI • High SI → reduced R insula, R putamen, & L globus pallidus to social feedback in general than HC • SA → greater dmPFC & preACC to social feedback in general than high SI • SA → greater L rIPFC to social feedback in general than low SI

L=left, R=right; pos=positive, neg=negative; SCID- Structured Clinical Interview for DSM-IV; KSADS- Kiddie Schedule for Affective Disorders and Schizophrenia; BDI- Beck Depression Inventory