The Stressed Brain: Neural Underpinnings of Social Stress Processing in Humans

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Abstract As humans, we face a variety of social stressors on a regular basis. Given the established role of social stress in influencing physical and psychological functioning, researchers have focused immense efforts on understanding the psychological and physiological changes induced by exposure to acute social stressors. With the advancement of functional magnetic resonance imaging (fMRI), more recent work has sought to identify the neural correlates of processing acute social stress. In this review, we provide an overview of research on the neural underpinnings of social stress processing to date. Specifically, we summarize research that has examined the neural underpinnings of three types of social stressors commonly studied in the literature: social rejection, social evaluation, and racism-related stress. Within our discussion of each type of social stressor, we describe the methods used to induce stress, the brain regions commonly activated among studies investigating that type of stress, and recommendations for future work. This review of the current literature identifies activity in midline regions in both prefrontal and parietal cortices, as well as lateral prefrontal regions, as being associated with processing social rejection. Activity in the insula, thalamus, and inferior frontal gyrus is often found in studies using social evaluation tasks. Finally, racism-related stress is associated with activity in the ventrolateral prefrontal cortex and rostral anterior cingulate

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cortex. We conclude by taking a “30,000-foot view” of this area of research to provide suggestions for the future of research on the neuroscience of social stress.

Keywords fMRI · Neuroimaging · Racism-related stress · Social rejection · Social stress

Think about the last time you had a really stressful day. What was the source of the stress? Perhaps you had an argument with a family member, had to give a presentation at work or school in front of an intimidating audience, got rejected by a date you really liked, or maybe someone treated you unfairly due to factors beyond your control, like your race, gender, or sexuality. For many humans, facing these *social stressors* is associated with both short- and longer-term changes in affect and physiology (Dickerson and Kemeny 2004; Sin et al. 2015). Over time, these psychological and physiological reactions to stressors can contribute to physical health and emotional well-being, including the development of chronic disease and psychopathology (Gianaros and Jennings 2018; Slavich 2020). Given the importance of social stressors in contributing to physical and psychological functioning, researchers in psychology and neuroscience across a variety of subdisciplines (e.g., social psychology, clinical psychology, psychoneuroimmunology, affective science, psychoneuroendocrinology) have focused their efforts on understanding the psychological and physiological changes induced by exposure to acute social stressors, both in the laboratory and “in the wild.” More recently, research in this area has begun to focus on how the brain responds to social stressors, which will be the focus of the present chapter.

Advancements in neuroimaging technology and the widespread use of functional magnetic resonance imaging (fMRI) over the past two decades have provided stress researchers with the exciting opportunity to understand the neural correlates of social stress processing in vivo in humans. Using fMRI to study the neural underpinnings of social stress provides a unique opportunity to answer a number of questions of interest in stress research. These include shedding light on how the brain initially orients to and ultimately regulates responses to social stressors, providing insight into the neurocognitive “ingredients” that comprise the experience of social stress. Further, fMRI research on stress facilitates our understanding of the neural signals that predict the extent to which individuals show physiological changes in response to a social stressor (Ginty et al. 2017; Muscatell and Eisenberger 2012; Thayer et al. 2012). Of course, utilizing brain imaging to understand the neural underpinnings of social stress in humans also presents some unique challenges. These include difficulties in inducing meaningful experiences of social stress within the confines of the MRI scanner environment, computational challenges related to adequately correcting for the multiple comparison issues inherent in fMRI research and the multivariate nature of neuroimaging data, and issues related to data interpretation, including making causal claims from correlational studies and utilizing reverse inference to infer psychological processes from neural data. Despite these challenges, dozens of studies investigating the neural underpinnings of social stress have been conducted in recent years, leading to exciting insights about the nature of social stress.

Given the ever-growing literature on the neural underpinnings of social stress, the present review is intended to provide an overarching summary of research in this area to date, while also looking to the future and offering suggestions for next steps in this area of research. Specifically, we provide an overview of research that has examined the neural underpinnings of three types of social stressors commonly investigated in the literature: social rejection, social evaluation, and racism-related stress. Within our discussion of each type of social stressor, we provide details regarding the methods used to induce stress (see also (Noack et al. 2019), the brain regions commonly activated among studies investigating that type of stress, and recommendations for future work (see Table 1 for an overarching summary of tasks used and commonly activated brain regions). We conclude by taking a "30,000-foot view" of this area of research to provide suggestions for next steps. This review is not intended to be comprehensive nor summative (see Dedovic et al. 2009a; Muscatell and Eisenberger 2012), but rather to provide an overview of the literature on the neural correlates of social stress to orient readers to the methods and results of past work, and new opportunities for moving the field forward.

1 Neural Correlates of Social Rejection

Overview Social rejection (sometimes called ostracism and/or social exclusion) is one of the most commonly studied social stressors in fMRI research. This is not by accident – indeed, social rejection experiences are commonly experienced in everyday life (Murphy et al. 2015) and are also among the most potent predictors of the development of psychopathology (Slavich 2020; Slavich et al. 2009), making them important to study empirically. Further, the relative ease with which social rejection experiences can be created despite the constraints of the MRI scanner makes this a popular social stressor to study. More details about specific methods for inducing social rejection in fMRI research are outlined below.

Methodological Approaches *Cyberball*. The most popular task used to study the neural correlates of social rejection is Cyberball (Eisenberger et al. 2003; Williams et al. 2000). In this task, participants are told they are playing a virtual game of catch with two other players, in which they will press a button to "throw" the (virtual) ball to each of the other players. Studies vary in the extent to which participants are actually introduced to two other players in-person; in these cases, the "other players" are typically members of the research team posing as study participants. In other studies, participants are just shown pictures or avatars representing the other players and are told they will be playing over the Internet. In the first round of Cyberball (the "inclusion" condition), players pass the (virtual) ball around equally, with each player, including the participant, receiving a roughly equal number of passes. In the next round of the game, the participant initially receives a few passes from the other players, but is subsequently completely excluded from the game (the "exclusion" condition) as the other players pass the ball back-and-forth to one another but

Table 1 Description of common social stressor fMRI tasks and their neural correlates

Type of social stress	Task	Task description	Targeted cognitive/affective processes	Associated regions of activation	Studies/papers for reference
Social evaluation	*Montreal imaging stress task* (MIST; Dedovic et al. 2005)	Participants complete difficult time-limited mental arithmetic while being evaluated on their performance. Feedback on performance is provided via computer screen	Social and time pressure to perform mental arithmetic; negative emotions associated with negative performance feedback	Insula, thalamus, claustrum, inferior frontal gyrus, precentral gyrus, inferior/middle temporal gyrus	Berretz et al. (2021)
Social evaluation	Scan*STRESS* (Streit et al. 2014)	Participants completed difficult visuospatial and mental arithmetic tasks while being evaluated on their performance. Feedback on performance is provided by a panel of evaluators, which participants can view and hear via live video streaming	Social and time pressure to perform mental rotation and arithmetic; negative emotions associated with negative performance feedback	Insula, thalamus, inferior frontal gyrus, precentral gyrus, inferior/middle temporal gyrus	Berretz et al. (2021)
Social rejection	*Cyberball* (Williams et al. 2000)	Participants play a computerized ball-tossing game with two confederates. After initially being included in the game, the confederates only pass the ball to each other, excluding the actual participant from the game	Negative emotions and cognitive processes associated with being socially excluded/rejected	Anterior cingulate cortex, posterior cingulate cortex, medial/lateral prefrontal cortex, ventrolateral prefrontal cortex, insula, thalamus, claustrum, inferior frontal gyrus	Berretz et al. (2021), Vijayakumar et al. (2017), Wang et al. (2017)

(continued)

Table 1 (continued)

Type of social stress	Task	Task description	Targeted cognitive/ affective processes	Associated regions of activation	Studies/ papers for reference
Racism-related stress	*Adaptation of Cyberball* (Masten et al. 2011)	Racial/ethnic minoritized participants play a computerized ball-tossing game with two white confederates. After initially being included in the game, the white confederates only pass the ball between each other, excluding the actual participant and leading some participants to believe their exclusion is due to race	Negative emotions associated with socially excluded/ rejected based on one's race (i.e., racial discrimination)	Ventrolateral prefrontal cortex, rostral anterior cingulate cortex	Masten et al. (2011)

never to the participant. This experience of being excluded from the game leads to negative emotions and self-reported feelings of being socially rejected (K. D. Williams et al. 2000; Zöller et al. 2010), as well as changes in neural activity, which are further detailed below.

Other Social Rejection Tasks. While Cyberball has certainly been the dominant task used to study the neural correlates of social rejection to date, a number of other MRI-compatible social rejection tasks exist and have also been utilized in research in this area. For example, an early task that attempted to disentangle the neural correlates of expectancy violation from social feedback (which are confounded in the Cyberball task) had college students submit a photograph of themselves prior to scanning, which they were told would be rated by individuals at other universities (Somerville et al. 2006). During the scan, participants received "feedback" about how others rated them, such that on each trial, they were told that either the rater thought they would like the participant (positive feedback) or that the rater thought they would *not* like the participant (negative, rejecting feedback). A similar task (sometimes called the "Chatroom task") wherein participants receive negative, rejecting feedback from peers based on their photograph has been primarily used in studies of the neural correlates of social rejection in adolescents (Guyer et al.

2008). Another, arguably more ecologically valid, social rejection task asked participants to view photographs of a person who had recently “dumped” them (i.e., an ex-romantic partner) and recall their feelings of rejection upon being dumped, and contrasted neural activity to these images/memories to viewing images of a friend while recalling a recent positive experience with that friend (Kross et al. 2011). Thus, while many studies of the neural correlates of social rejection utilize Cyberball to create a rejecting experience in the scanner, a number of other social rejection tasks also exist and have been used in the literature, albeit less frequently.

Summary of Findings What neural regions are commonly activated in response to social rejection tasks, as outlined above? Given widespread interest in this question in recent years, a number of quantitative and narrative reviews have already been published on this question. For example, a scoping review (Wang et al. 2017) identified 28 fMRI studies published prior to 2016 that had investigated the neural correlates of social rejection induced by the Cyberball task. Results of the scoping review showed that the anterior cingulate cortex (ACC), including ventral, dorsal, and subgenual sections, was significantly activated in 24 of the 28 published studies, with six studies also reporting significant activity in the posterior cingulate cortex (PCC). Other regions commonly activated in response to social exclusion during Cyberball identified in the scoping review included medial and lateral areas of the prefrontal cortex (PFC; observed in 18/28 studies) and the insula (observed in 17 of 28 studies), including both anterior and posterior subsections. Finally, in addition to examining activation of individual brain regions, a few studies in this area of work also examined functional connectivity, or assessments of interactions between regions. Among those studies, five of seven that examined connectivity also observed significant functional connectivity between the ACC and PFC in response to social exclusion in Cyberball; typically, this connectivity was negative, suggesting an inverse relationship between ACC and PFC during social exclusion. Taken together, this review highlights that the ACC (and, to a lesser extent, PCC), PFC, and insula are likely to engage in response to social rejection using the Cyberball task, demonstrating the critical role of regions of the salience network and default mode network in responding to social rejection.

In contrast to this qualitative approach to summarizing the Cyberball literature taken by Wang et al. (2017), a quantitative, coordinate-based meta-analysis of the same fMRI literature (Vijayakumar et al. 2017) suggested a different, largely non-overlapping, set of regions that activated in response to the Cyberball task. Specifically, the medial prefrontal cortex (MPFC; including VMPFC and medial orbitofrontal cortex and extending into perigenual and subgenual ACC), posterior cingulate cortex, and left ventrolateral prefrontal cortex (VLPFC) were observed to be reliably activated during social exclusion (vs. inclusion) in Cyberball in this meta-analysis. These results suggest that, rather than engaging neural regions thought to be involved in processing salience/pain (e.g., dACC, anterior insula), social exclusion is instead associated with greater activation in regions of the default mode network (i.e., MPFC, PCC), as well as regions of the fronto-parietal control network (i.e., VLPFC). While speculative, this pattern of results suggests that the brain responds to social rejection with greater activity in regions that are associated with social cognitive processing and mentalizing (i.e., MPFC, PCC), as well as negative affect regulation (i.e., VLPFC).

What are we to make of these seemingly opposing findings revealed in recent reviews regarding the neural underpinnings of processing social rejection? One likely contributor to the discrepancy in findings is the intentional omission of papers that solely utilized region-of-interest (ROI) analyses from the meta-analysis (Vijayakumar et al. 2017). Indeed, many papers in this literature report results from ROI analyses focused on the ACC (and, to a lesser extent, the anterior insula), which may be why ACC appears so prominently in a scoping review of the literature but not a quantitative meta-analysis focused on whole-brain activation patterns (Vijayakumar et al. 2017). While a-priori ROI analyses have the advantage of being hypothesis-driven rather than exploratory, such analyses are also often performed at a lower statistical threshold in which BOLD signal from many adjacent voxels is averaged together. As such, ROI analyses may be biased toward confirmatory findings (Buhle et al. 2013).

Opportunities for Future Research As outlined above, the neural correlates of social rejection are quite widely studied in the literature, particularly using the Cyberball task. While informative, such studies are plagued by a number of methodological concerns, which provide opportunities for future work in this area. First, whenever an area of research is over-reliant on a single task, this creates a situation in which we do not have a comprehensive understanding of the neural correlates of a broad social experience (i.e., social rejection) but rather a more limited knowledge of the neural correlates of a specific task (i.e., Cyberball) (Poldrack and Yarkoni 2016; Yarkoni et al. 2010). As such, we currently lack breadth in our understanding of how the brain responds to social rejection, including what neural activity might be common to many different social rejection experiences, and what neural activity might be specific to the particular task conditions of any individual social rejection task. While there is utility in using the same task in multiple studies and harmonizing data collection across projects (particularly when one is interested in moderators of neural activity previously established using that task), such an approach severely limits our knowledge of the "neural reference space" for social rejection writ large. Indeed, undersampling the psychological construct of interest is likely to bias the field to converge on oversimplified understanding of how these processes are represented in the brain (Jolly and Chang 2019). As such, it will be important for future research on the neural correlates of social rejection to move beyond Cyberball and utilize other approaches, making use of other social rejection tasks that already exist (including those mentioned previously) or developing new methods for studying social rejection in the MRI scanner.

Second, it is worth noting that some prior research suggests that laboratory-based social rejection paradigms such as Cyberball do not elicit strong physiological responses. For example, some work suggests that Cyberball does not lead to changes in the neuroendocrine hormone cortisol (Zöller et al. 2010) that is widely studied in social stress research (Dickerson and Kemeny 2004). This could be in part due to the fact that most MRI-compatible social rejection paradigms are not "motivated performance tasks" and thus do not require metabolic activation and physiological arousal to complete them (Blascovich and Tomaka 1996). As such, they are relatively passive compared to other types of social stressors studied in the literature (see *Social Evaluation* section below) and thus less likely to engender the physiological reactivity that is characteristic of other acute stress social paradigms that involve motivated performance. Future research efforts might thus focus on creating an MRI-compatible social rejection task that requires more metabolic and cognitive effort and is associated with physiological activation.

In sum, social rejection experiences are critical predictors of psychopathology and physiological functioning (Slavich 2020) and thus are important social stressors to study. Widespread use of the Cyberball paradigm to induce social rejection in neuroimaging research to date has led to a substantial literature on the neural correlates of Cyberball, which has reliably associated midline regions in both prefrontal and parietal cortices, as well as lateral prefrontal regions, with processing social rejection. Some work also suggests that dACC and anterior insula are commonly activated during social rejection, though such results are tenuous given overreliance on ROI analyses of these regions. Future research should explore new tasks beyond Cyberball to further our understanding of the broad neural reference space for processing social rejection.

2 Neural Correlates of Social Evaluation

Overview A second type of stressor commonly studied in research on the neural underpinnings of social stress is social evaluation. The focus on social evaluation is undoubtedly due to the ubiquity of the Trier Social Stress Test (TSST; (Kirschbaum et al. 1993), which is by far the most commonly used acute social stress paradigm used in stress research in humans. Though the specific parameters of the TSST vary somewhat from study to study, the overall approach is similar: A participant is asked to complete an impromptu performance-based task (e.g., giving a speech, performing mental arithmetic aloud, or both) in front of a panel of evaluators who are trained not to provide positive feedback to the participant about their performance and instead to remain neutral and stoic (or, in some cases, provide negative nonverbals, such as eye rolling and doodling). As such, the TSST encompasses features of uncontrollability and social evaluation, two characteristics of acute laboratory stressors that are associated with the largest cortisol responses (Dickerson and Kemeny 2004).

Given that the TSST reliably elicits psychological and physiological reactions and is widely used in the literature, it makes sense that neuroimaging researchers thought to adapt features of this paradigm for use in the MRI scanner to study the neural correlates of social stress. Of course, the constraints of the MRI environment make certain features of the TSST more amendable for use than others, and researchers made additional methodological decisions that deviate from the standard

TSST approach. More details regarding the specific social evaluation tasks used in the neuroimaging literature to date are outlined below.

Methodological Approaches *Montreal Imaging Stress Test (MIST).* The most widely used social evaluative stressor task used in fMRI research to date is the MIST (Dedovic et al. 2005, 2009b). At the core of the MIST is a mental arithmetic task, in which participants complete mental math while undergoing MRI scanning. Critically, during stressor trials (or blocks), there is time pressure for completing the math problems, which is calibrated to each individual's average reaction time such that participants fail to answer correctly within the given time limit 55–80% of the time. Further, to create a feeling of social evaluation, the participant's overall task performance is displayed on the screen, as well as the supposed average performance of other participants, though in reality the average performance listed is rigged such that participants are always performing worse than others, with the intention of creating feelings of failure/inferiority. Finally, in between runs of the task the experimenter reminds the participant of their poor performance relative to others, and states that the participant must reach a minimum performance level in order for their data to be used. This feedback from the experimenter is intended to further enhance the social evaluation present in the MIST procedures. To contrast with neural responses to these stressful trials (or blocks), the MIST also includes control trials in which participants complete mental arithmetic at a similar difficulty level and rate to the stressful trials, but with no performance feedback or time pressure. Performance on control trials is much higher, with participants failing to provide a correct answer only 10% of the time (on average). Thus, contrasts comparing neural responses to the stressful vs. control trials control for neural activity involved in solving mental arithmetic problems, and what (theoretically) remains is neural activity associated with the stress of time pressure, social evaluation, negative performance feedback, and lower task performance.

ScanSTRESS. A second social evaluation task that has been developed for use in the MRI scanner is the Scan*STRESS* paradigm (Lederbogen et al. 2011; Streit et al. 2014). Scan*STRESS* is similar to the MIST in many ways, incorporating elements of time pressure, performance pressure, forced failure, social evaluative threat, uncontrollability, and unpredictability. During scanning, participants complete two challenging cognitive tasks: a mental rotation task and a mental arithmetic task. Task speed and difficulty are adapted to the participant's performance to ensure frequent failure. Further, participants are also shown a live video transmission of a panel of evaluators seated in the scanner control room, who are monitoring the participant's behavior and task performance and providing negative visual and auditory feedback when the participant makes a mistake. Activity during these stress blocks is contrasted to activity in control blocks, during which no time pressure is provided, performance is much higher, and no social evaluation is present.

Other Social Evaluation Tasks. It is worth mentioning two other social evaluation tasks that have been used in the literature and are distinct from the MIST and Scan*STRESS* in that they attempt to isolate distinct components of these social stressors. First is a task that largely mimics the "speech preparation" phase of the

TSST (Wager et al. 2009a, b). In this task, participants are told they are going to have to give a speech to a panel of experts, and that they have 2 min to prepare for the speech in their heads, while they are being scanned. This creates a feeling of anticipatory stress in participants as they must quickly prepare, without the use of writing or research material, to give a challenging, evaluative speech.

The second task (Eisenberger et al. 2011; Muscatell et al. 2015) removes cognitive performance pressure entirely and isolates the social evaluative feedback component of the other stressor tasks mentioned above. In this task, prior to being scanned, participants complete an interview that is either video or audio recorded. During the scan, they are given feedback from a "fellow participant" (actually a member of the research team) about how they come across during their interview. Critically, participants receive positive, neutral, and negative evaluative feedback (in the form of different adjectives being selected from a grid) over the course of the scan. This task thus isolates the evaluative feedback component of social stress, as the cognitive effort from the interview is completed prior to scanning.

Summary of Findings A recent meta-analysis of research on the neural correlates of social stress processing attempted to identify BOLD signal changes that were common to many social stressor tasks (e.g., Cyberball, MIST, Scan*STRESS*; Berretz et al. 2021). Analyses identified convergent activity in the bilateral insula, bilateral claustrum, thalamus, and the inferior frontal gyrus across all social stress induction paradigms. Meanwhile, there was convergent deactivation in the parahippocampal gyrus, extending into right amygdala, across all stressor tasks. When coordinates derived from papers that used Cyberball as a stressor were omitted from analyses, two additional clusters of activation were identified; one in precentral gyrus extending into the insula, and a second in the inferior/middle temporal gyrus extending into the middle occipital gyrus. Two additional clusters of reliable deactivation were also identified in the analysis that omitted Cyberball; one in precuneus/posterior cingulate cortex, and a second in superior temporal gyrus.

The reliable activation of the insula, thalamus, and inferior frontal gyrus during social evaluative stress processing suggests that regions that play a critical role in coordinating information transfer across different regions of the brain (e.g., insula, thalamus) and in regulating psychological and physiological responses (i.e., inferior frontal gryus) are especially likely to activate in response to a stressor. This makes sense because during stress, the brain must be especially nimble at integrating visual input from the environment, sending signals to subcortical and brainstem regions that start cascades of physiological responding, and also to receiving afferent signals from the body about its metabolic state. These integrated processes occur in an effort to coordinate adaptive behavioral responses to a stressor. As such, activation in coordination/relay centers like the thalamus and insula, as well as regions that facilitate attention and cognitive control like the inferior frontal gyrus, are critical to orchestrating this complex stress response.

It is interesting to note that, contrary to what some may have predicted, this meta-analysis actually found consistent *deactivation* in the parahippocampus/amygdala in response to social stressors. It should be noted that deactivation results from fMRI meta-analyses should be interpreted with caution, as there is inconsistent reporting of deactivation across studies in the literature and thus meta-analytic estimates of deactivation patterns may be less reliable than those for activation. Nevertheless, Berretz et al. (2021) suggest that, as a region critical for processing salience, the amygdala *is* active during the first few moments of a stressor task, facilitating the identification of relevant salient information in the environment. Over time, however, the amygdala may habituate to the repeated task demands (given that many social evaluation tasks used repeated stimuli/cognitive processes) and thus appear as deactivation when averaged over the course of a long scan. Alternatively, it may be the case that the amygdala is particularly involved in signaling salience/uncertainty of visual and auditory stimuli, but is not responsive to all forms of threat, especially not those that are more abstract or self-generated, such as the social stress tasks outlined here. Consistent with this idea, other meta-analytic work finds that amygdala responses are associated with affectively evocative visual stimuli (as in the perception of fearful facial behaviors or disgusting images) but not experiences of fear or affective states induced by imagery or recall (Lindquist et al. 2012). Thus, while it may seem surprising that studies associated with threat such as social evaluative stressors report consistent deactivation of the amygdala, it is likely a misconception that the amygdala consistently underlies all instances of threat responding. Rather, amygdala-prefrontal functional connectivity – as well as the broader swath of areas involved in visceromotor control and representation of affective states such as the insula, thalamus, and inferior frontal gyrus – may be what is critical during social stress processing.

Opportunities for Future Research What are critical next steps for research addressing the neural correlates of social evaluation? There are a number of interesting opportunities for future work in this area. First, work exploring the neural correlates of physiological responses to social evaluation is needed. While some work has been done in this area (for a review, see Ginty et al. 2017; Kraynak et al. 2018; Muscatell and Eisenberger 2012; Thayer et al. 2012), more research that examines the neural activity patterns that are common to many physiological responses vs. unique to a specific physiological channel (e.g., autonomic responses; immune responses) is needed (Eisenbarth et al. 2016). Unlike Cyberball, which, as mentioned above, does not elicit reliable physiological reactions in participants, many of the social evaluation tasks described above do lead to changes in physiological parameters of interest to stress researchers, including heart rate and skin conductance (Wager et al. 2009a, b), cortisol (Dedovic et al. 2009b), and inflammation (Muscatell et al. 2015). As such, future work that continues to explore the neural predictors of physiological responses to social evaluative stressors is needed.

A second future direction for this area of work is to “break down” the complex social evaluation tasks that include elements of performance stress, uncertainty, time pressure, cognitive effort, and social feedback into their component parts to isolate the neural underpinnings of each individual process. Currently, many tasks include all of these various elements which combine together to create a stressor, but it is also important for translational efforts to determine *which* brain activity is specific to each component part. As mentioned above, one recent task isolated the social evaluative feedback component that is a feature of the other tasks in this area to examine the neural correlates of that component specifically (Eisenberger et al. 2011; Muscatell et al. 2015). Future work could examine how the brain responds to time pressure, performance evaluation, and/or cognitive effort, independently of the other factors. This would facilitate our understanding of the neural "ingredients" that combine to construct an overall experience of stress. As we discuss next, another avenue of future work is to build on work of racism-related stress to identify the specific aspects of social stress that are particularly pernicious for members of individuals from marginalized communities.

To conclude, a number of different tasks exist that can be used to elucidate the neural underpinnings of social evaluative stress. A recent meta-analysis of this area of work identified that the insula, thalamus, and inferior frontal gyrus are reliably active across these different tasks (Berretz et al. 2021), highlighting the important role that coordination/integration regions as well as cognitive control regions play in responding to social evaluative stress. Future research that builds on a small but critical literature investigating the neural correlates of physiological responses to social evaluative stress, as well as work that isolates the specific neural correlates of the various components of these stressor tasks, will move the field forward.

3 Neural Correlates of Racism-Related Stress

Overview Within the social stress literature, a small but emerging body of work has begun to examine how racism-related stress (e.g., racial discrimination) is represented in the brain. Like general social stress, racism-related stress has been clearly associated with negative physical and mental health outcomes, particularly among Black Americans (D. R. Williams and Mohammed 2013). Moreover, research suggests that exposure to racism-related stress can alter reactivity to other general social stressors (Akdeniz et al. 2014; Brondolo et al. 2009; Wright et al. 2020), thus creating compounding effects of stress among individuals from marginalized racial/ethnic backgrounds.

Despite these well-documented associations between racism-related stress and negative outcomes, much is still unknown about the mechanisms through which this type of stress impacts the brain and body. As such, it is important to investigate the neural correlates of racism-related stress processing. Currently, there are a limited number of studies in this area and very little work to date has examined how the brain responds to a racism-related stressor. However, one existing study by Masten et al. (2011) offers promising insights for future work investigating the neural correlates of racism-related social stress. Here we review the methods in this study, summarize results, and discuss future directions for this line of research.

Methodological Approaches Masten et al. (2011) utilized an adapted version of Cyberball in order to examine neural responses during an experimentally-manipulated experience of racial discrimination among Black Americans (Masten et al. 2011). In this paradigm, a real, interactive experience of interpersonal discrimination is simulated, as Black participants engaged in a game of Cyberball with two White individuals (confederates). Similar to the Cyberball protocol described earlier, participants were excluded by the White "players," allowing the possibility that Black participants would attribute the exclusion to being about their race, thus inducing the stress of racial discrimination. To increase the likelihood that discrimination attributions would be made by the Black participants, race was made salient by having participants meet the White confederates prior to the scanning procedure. While in the scanner, participants were also able to see images representing the other players. Besides the visual cueing of race, race was not brought up at any point during the experimental procedures.

Following scanning, participants completed self-report measures of distress and discriminatory attributions. Participants also completed a videotaped interview, describing their thoughts and feelings about being excluded during the game. These interviews were then rated by trained observers to index participants' nonverbal negative affect. Taken together, these post-scan measures provided a way to assess whether participants attributed their social exclusion during the Cyberball task as being due to their race and measure the immediate behavioral and affective consequences of such racism-related stress. Moreover, the inclusion of the questions about discrimination allowed the researchers to investigate differences in neural activity based on whether the participants experienced the exclusion episode as an instance of racial discrimination, thus, creating a paradigm to examine the direct effects of racism-related stress on neural activity.

Summary of Findings Results from the Masten et al. (2011) study offer novel findings about the neural correlates of perceiving racial discrimination in a social context. Specifically, findings demonstrated that Black individuals who attributed the experience of social rejection to racial discrimination displayed *decreased* activity in the dACC, which has been established as a key region in the salience network (Menon and Uddin 2010; Perini et al. 2018; Uddin 2015). Furthermore, findings of Perini et al. (2018) demonstrate that the dACC is involved in monitoring salient, self-relevant social information, and thus *deactivation* in this region may indicate disengagement or a lack of monitoring/attention. Though speculative, this suggests the possibility that individuals who experienced their rejection as racial discrimination may have been reducing attention to or disengaging from such rejection, perhaps in effort to cope with the negative experience of racism-related stress. This pattern of neural activity aligns with behavioral findings that show adopting a self-distanced (vs. self-immersed) approach to processing stressful experiences can result in reduced feelings of distress and negative affect, thus reflecting an effective coping strategy (Kross et al. 2014; Kross and Ayduk 2011; Mischkowski et al. 2012). This possibility could be addressed in future research on the neural underpinnings of coping processes engaged in response to racism-related social stress. Finally, discrimination attributions were also linked to increased activity in VLPFC and rostral ACC, which have been implicated in emotion regulation processes (Buhle et al. 2013; Eisenberger et al. 2003; Masten et al. 2011), further suggesting that individuals who attributed rejection to racial discrimination may have engaged to a greater degree in emotion regulating coping strategies.

Overall, results of this study provide seemingly counterintuitive findings regarding the neural underpinnings of racism-related stress. Indeed, given the well-established literature on the adverse effects of experiencing racial discrimination for health and well-being among minority individuals, it would seem that such experiences would trigger neural activity consistent with experiencing adversity. Yet, Masten et al. (2011) found neural activity associated with potentially "buffering" effects of perceiving negative treatment as being due to racial discrimination. Given these findings and the general lack of similar studies, further research is certainly needed to disentangle the nuances of neural activity associated with experiencing racism-related stress.

Opportunities for Future Research Given that there is just this one known study investigating the neural underpinnings of race-related social stress, more research is needed in this area, and opportunities for future studies abound. Research exploring how the brain responds to racism-related stress would offer important insights into the ways in which the brain may give rise to downstream physiological changes in response to such stress, and subsequently contribute to racial inequities in health and well-being. However, before successful research in this area can progress, a few challenges must be addressed.

First, studies investigating the neural correlates of racism-related stress have remained difficult due in part to the challenges of simulating "real-world" experiences of racism-related stress within the scanner. As reviewed previously, there currently exist a number of "standard" tasks used to elucidate the neural mechanisms of experiencing general social stress (e.g., Cyberball, Scan*STRESS,* MIST). However, no such "standard" tasks exist for inducing racism-related stress in the scanner. One potential solution to this methodological issue may lie in the development of a standardized, scanner-based racism-related stress task that would allow for the replicable and generalizable study of the neural correlates of racism-related stress. One approach to this task development may be to adapt elements of existing general social stress tasks, such as what was done in Masten et al. (2011) for the Cyberball task. Similarly, such a task could capitalize on the stressful nature of social evaluation and involve monitoring neural activity of historically oppressed racial/ethnic groups while they are being evaluated by oppressors (i.e., in the U.S., White confederates).

Second, racism is increasingly appreciated as a systemic and structural problem in addition to an interpersonal issue (Bailey et al. 2017; Jones 2000; Neblett 2019). As such, it will be important for future research to examine if and how exposure to structural racism shapes neural functioning. Along these lines, the recent "bias of crowds" model (Payne et al. 2017) suggests that, rather than racial bias being something that occupies the minds of specific individuals, it is rather reflective of the history and current day practices of particular contexts and places (Payne and Hannay 2021). As such, Black individuals (and likely those from other oppressed groups) may experience greater racism-related stress as a function of where they live (Payne et al. 2019). Given this, it would be interesting for future work to utilize a multi-cite collaborative model wherein researchers in different areas of the country that vary in their history of racial oppression and current levels of systemic racism could each scan a set of participants, and examine if there are regional differences in neural responses as a function of both historical (e.g., history of slavery) and present day (e.g., prevalence of red-lining) structural racism.

Finally, it will be important to conduct future research in large samples such that additional risk and resilience factors that influence neural reactivity to racism-related stress can be examined as moderators. For example, past experiences of perceived discrimination and high identification with one's race (i.e., racial centrality) have been found to increase physiological reactivity to experimentally manipulated experiences of racism-related stress (Neblett 2019). As such, future work may seek to investigate how race-related individual differences may moderate neural activity while experiencing racism-related stress. The inclusion of such relevant moderators may then further highlight the nuances of racial/ethnic minorities experiences with racism-related stress. fMRI research investigating individual differences as predictor of neural responses to tasks is notoriously challenging, given that it requires large sample sizes to produce reliable, replicable effects. Thus, such work will need to be conducted in larger-than-typical samples and will require significant funding; we encourage funding agencies to take note of this and to allocate funds for well-powered fMRI studies to investigate predictors of neural responses to racism-related stress.

In sum, despite a few challenges, many opportunities exist for social neuroscientists to uniquely contribute to existing knowledge about the neural pathways through which racism can impact health and well-being.

4 Overall Next Steps for Research Investigating the Neural Underpinnings of Social Stress

The past 20 years of neuroimaging research on stress and the brain have shed significant light on the neural correlates of social stress processing. As outlined above, we now have robust literatures on the neural correlates of social rejection and social evaluation, and we also have the foundation for a new literature on the neural correlates of racism-related stress. While a number of future research directions are included in the separate sections above, we end by "zooming out" and recommending two critical, overall next steps for the literature on the neuroscience of social stress moving forward.

A first overall next step is to move beyond merely studying the neural correlates of social stress and to instead work to build a literature that examines how neural responses to social stress are predictive of subsequent cognitions, emotions, behaviors, physiology, and ultimately, downstream consequences on health. For example, behavioral research shows that exposure to a stressor is associated with subsequent changes in reward processing (Boyle et al. 2020), emotion regulation success (Raio et al. 2013), and cognitive control strategies (Steinhauser et al. 2007). However, only a few known neuroimaging studies have investigated the neural contributors to these effects, and particularly, how neural activity *during* a stressor might be predictive of neural activity and behavioral performance during a subsequent cognitive task, or at rest (Shermohammed et al. 2017; Zhang et al. 2020). Thus, we currently have only a cursory knowledge of the neural predictors of alterations to behavior following stress, as well as how stress impacts neural responses during subsequent tasks. This is an important next step for research in this area, as it is likely that many of the negative health effects of social stress are driven not solely by responses *during* a stressor, but also how one behaves (and how one's brain functions) after encountering a stressor. Similarly, as we note above, little research examines how neural responses to *social* stress are associated with physiological shifts in the periphery of the body (e.g., autonomic nervous system responding, HPA-axis responding, inflammatory responding), responses themselves that likely have long-term consequences for health and well-being.

A second overall next step for work in this area is to utilize advanced quantitative techniques to create more reliable, replicable "neural signatures" of social stress reactivity. For example, machine learning techniques characterizing multivariate patterns of neural activity to distinguish between different psychological and/or physiological states have become more widely utilized in neuroimaging research over the past few years, but are only starting to be used in stress research. One seminal recent paper, for example, used this technique to identify both common and unique neural patterns that distinguish heart rate from skin conductance reactivity to a social evaluative threat task (Eisenbarth et al. 2016). We encourage future research in this area to test whether similar (or different) neural patterns in response to social evaluation predict other types of physiological and psychological reactivity. Another example of a quantitative technique that should be applied to future neuroimaging research on social stress is network analysis (Bassett and Sporns 2017; Bassett et al. 2018). Network analytic tools can facilitate the quantification of the degree to which different brain networks are relatively more integrated or segregated in response to changing task demands (i.e., dynamic functional connectivity). The relative level of network segregation/integration has emerged as an important predictor of behavioral task performance in recent work (Cohen 2018; Cohen and D'Esposito 2016; Kucyi et al. 2018), and yet, this approach is only just beginning to apply to understand how brain networks reconfigure in the face of a social stressor (Wheelock et al. 2018). Thus, future research should also use graph theoretic techniques to further our understanding of how brain networks connect (or disconnect) in response to social stress. We look forward to these future approaches that will further weigh in on how social stressors impact the brain, body, and ultimately, human health and wellness.

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