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Neuroimaging Predictors and Mechanisms of Treatment Response in Social Anxiety Disorder: an Overview of the Amygdala

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Abstract

Purpose of Review—Aberrant amygdala activity is implicated in the neurobiology of social anxiety disorder (SAD) and is, therefore, a treatment target. However, the extent to which amygdala predicts clinical improvement or is impacted by treatment has not been critically examined. This review highlights recent neuroimaging findings from clinical trials and research that test links between amygdala and mechanisms of action.

Recent Findings—Neuropredictor studies largely comprised psychotherapy where improvement was foretold by amygdala activity and regions beyond amygdala such as frontal structures (e.g., anterior cingulate cortex, medial prefrontal cortex) and areas involved in visual processes (e.g., occipital regions, superior temporal gyrus). Pre-treatment functional connectivity between amygdala and frontal areas was also shown to predict improvement signifying circuits that support emotion processing and regulation interact with treatment. Pre-to-post studies revealed decreases in amygdala response and altered functional connectivity in amygdala pathways regardless of treatment modality. In analogue studies of fear exposure, greater reduction in anxiety was predicted by less amygdala response to a speech challenge and amygdala activity decreased following exposures. Yet, studies have also failed to detect amygdala effects reporting instead treatment-related changes in regions and functional systems that support sensory, emotion, and regulation processes. An array of regions in the corticolimbic subcircuits and extrastriate cortex appear to be viable sites of action.

Summary—The amygdala and amygdala pathways predict treatment outcome and are altered following treatment. However, further study is needed to establish the role of the amygdala and other candidate regions and brain circuits as sites of action.

Keywords

Neuroimaging; Treatment; Predictors; Mechanisms; Anxiety; Amygdala; Prefrontal cortex

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Introduction

Social anxiety disorder (SAD) is a disabling illness [1, 2] characterized by excessive fear and avoidance in a range of social situations that involve potential scrutiny by others [3]. Once a largely neglected disorder by the medical community [4], it is now recognized as one of the most common mental health disorders [5, 6] and a public health problem across the world [7]. Efforts to elucidate the brain pathophysiology of SAD have largely focused on the amygdala (AMYG), a key structure in the "fear circuit" that directs defense mechanisms in response to threat [8–10]. Among functions, the AMYG mediates fear responses [9], rapidly detects motivationally relevant stimuli such as emotional faces, plays an important role in the selection and processing of threat-relevant cues and other operations critical for emotional processing [11, 12], and is involved in social cognition [13]. In light of its relevance to anxiety symptoms, the AMYG is a logical region of investigation. Functional magnetic resonance imaging (fMRI) studies consistently show the AMYG is a common locus of dysfunction in SAD; as a marker of the disease state, it is reasonable to expect that the AMYG is a target of treatment. However, the extent in which the amygdala predicts clinical improvement or is remediated by pharmacotherapy or psychotherapy has not been critically examined.

While first-line treatments are efficacious for many, response to treatment is unpredictably varied and patients who complete treatment frequently fail to achieve clinically meaningful improvement. As neuroimaging work suggests SAD is a "brain-based" disorder, delineating neural predictors and understanding mechanisms of change have the potential to optimize clinical outcome. Based on evidence for the role of the AMYG in the pathophysiology of SAD, treatment success may involve mechanisms that modulate AMYG reactivity and/or alter functional connectivity in circuits that intersect with the AMYG. Accordingly, in this review, we highlight recent studies of SAD that directly compare treatments that differ in mechanisms of action and discrete studies that link brain activity to theory for mechanisms of change. Due to gaps in the literature, we also review promising interventions that are not yet considered "gold standard." These interventions are acceptance and commitment therapy (ACT) which, like cognitive behavioral therapy (CBT), involves fear exposures but emphasizes "acceptance" of negative thoughts and feelings instead of modifying them directly [14]; attention bias modification, a behavioral intervention that aims to reduce social anxiety by decreasing biased attention to threat-relevant information [15]; and the neuropeptide, oxytocin. Though at a preclinical stage, oxytocin is associated with prosocial behaviors [16], has anxiolytic properties [17], and modulates AMYG activity in healthy and clinical samples (see [18] for review). Increased understanding of AMYG activity as a predictor and marker of change has inferences for precision medicine.

Amygdala and Neurobiology of SAD

Accumulating data from fMRI studies point to a hyperactive fear circuit in SAD. For example, Stein and colleagues [19] were among the first to demonstrate greater AMYG activation in SAD, relative to healthy controls (HC), to threat faces along with exaggerated activation in structures involved in emotion processing—bilateral medial prefrontal cortex (PFC), inferior frontal gyrus, superior frontal gyrus, parahippocampal gyrus, and uncus [20].

Since then, studies have largely replicated this finding (for reviews, see [21–23]) while also showing greater AMYG activation in SAD, relative to HC, to a variety of aversive cues such as loud angry voices [24], threat-relevant words [25, 26], and symptom provocation (e.g., speech anticipation) [27, 28]. In addition to exaggerated AMYG response, individuals with SAD display heightened activation in other subcortical regions (e.g., insula, hippocampus) and atypical (hyper- or hypo-) activity in the (pre)frontal areas (e.g., medial PFC, anterior cingulate cortex, orbitofrontal cortex) and sensory cortex (e.g., occipital regions, fusiform gyrus) [24, 29] (for reviews, see [21–23]). Regarding faces, a potent socioemotional cue, a meta-analytic study reported higher AMYG activity (among other regions) compared to HC to general facial expressions [30]. Thus, while a hyperactive AMYG response to threatening stimuli or situations relevant to SAD is widely documented, this response may extend to salient but not overtly threatening cues.

While the AMYG is usually examined as a unitary structure in SAD, it can be divided into basolateral, centromedial, and superficial regions based on connectivity patterns and functional specialization [31, 32]. Basolateral AMYG is connected to the visual cortex and thalamus and, therefore, mediates sensory input [31]; it is also involved in emotional learning [33] (e.g., positively linked with activity in the hippocampus [32]). By contrast, the centromedial AMYG is connected to diencephalic structures and responds only to stimuli that are aversive or signal threat [31]. Finally, the superficial nuclei of the AMYG processes olfactory information [34] and is associated with positive activity in the limbic lobe [32]. Thus, subregions serve complementary functions. In one of the few studies that reported on AMYG subregions, activation in the central portion was found to be greater to threat-relevant scenes in SAD compared to HC [35] signifying SAD is characterized by heighted activity to threat-relevant cues in a subsystem that engages preparatory responses [35]. There was also evidence of concurrent hyperengagement of the lateral AMYG in SAD [35]. Findings suggest disturbances in subregions that integrate fear-relevant information for optimal response to threat may contribute to SAD.

The AMYG has extensive connections in a distributed cortical–subcortical network [33, 36], therefore, aberrations in AMYG excitability in SAD may have “downstream” consequences on the engagement of other brain regions that are highly connected to the AMYG. For example, neural pathways relevant to emotion processing and emotion regulation include direct AMYG connections with ventral portions of the cortex, specifically the ventral anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), as well as indirect connections from dorsal and lateral portions of the prefrontal cortex [9, 33, 36]. Recent task-based and/or resting state studies show aberrant functional connectivity in SAD, relative to HC, between the AMYG and (1) (pre)frontal (e.g., ACC, OFC, lateral prefrontal cortices; [37–45]); (2) insula and subcortical/cingulate areas (e.g., parahippocampal gyrus, cingulate gyrus; [40, 46]); (3) temporal regions (middle, inferior, superior temporal gyrus; [40, 46, 47]); (4) visual regions (e.g., occipital cortex, fusiform gyrus; [40, 46–48]); and (5) cerebellum [40]. These findings expand on an early study that reported disturbances between the AMYG and cortical structures involved in sensory and emotion processing (e.g., medial PFC, inferior parietal lobule, superior temporal sulcus) to emotional faces in SAD, compared to HC [49]. Although the pattern of functional (dys)connectivity has been inconsistent and sometimes similar between SAD and controls (e.g., [50]), potentially

due to methodological differences across studies, overall findings suggest altered AMYG-related functional connectivity in SAD is relatively diffuse. In addition, AMYG functional connectivity differences are frequently associated with AMYG-(pre)frontal disturbances that may signal difficulty in regulating emotional states.

Treatment

SAD begins early in life and its course tends to be protracted unless appropriately treated [7]. Well-studied commonly accepted first-line treatments for SAD are individual CBT (Hedges' g = 0.56), group CBT (Hedges' g = 0.29) [51], and selective serotonin reuptake inhibitors (SSRIs) (Hedges' g = 0.44) [52]. Unfortunately, many patients do not attain clinically meaningful change after completing these treatments as indicated by the moderate effect sizes of these interventions. Identifying neural predictors of treatment outcome and neurobiological processes underlying treatment has the potential to match the right patient with the right treatment and inform novel treatments for those with an inadequate response.

CBT and SSRIs are thought to exert their therapeutic effects by targeting top-down and bottom-up brain regions, respectively. CBT emphasizes cognitive intervention to aid in the identification of negative thoughts associated with anxiety, which are subsequently challenged with the adoption of a rational, objective perspective (e.g., cognitive restructuring). Along with cognitive approaches, CBT encompasses exposure-based techniques aimed at reducing anxiety via fear extinction and/or habituation [53]. Thus, CBT is proposed to primarily interact with (pre)frontal areas, as opposed to bottom-up emotion generating/processing regions, as techniques practiced by patients tap into higher-order functions (e.g., inhibition, sustained attention, contingency learning) [54, 55]. In contrast, bottom-up limbic/paralimbic areas are considered primary targets for SSRIs. For example, the AMYG is densely innervated by fibers releasing 5-hydroxytryptamine (5-HT), and in healthy participants, 5-HT availability predicts AMYG reactivity [56]. Moreover, short-term administration of SSRIs (e.g., 7–10 days) appears to reduce AMYG responsivity to threat faces, among other regions (e.g., medial frontal gyrus), in healthy participants [57]. It remains to be established why SSRIs take several weeks to show their clinical effects despite evidence of early pharmacological manifestations. Mechanisms associated with placebo response are also unclear. For example, SAD patients who respond to either an SSRI or pill placebo exhibit comparable decreases in AMYG activity to emotional faces or symptom provocation [58–60] suggesting the AMYG is a common target for anxiolytic effects whether it be due to pharmacological or psychological factors [58–60].

As SAD is associated with both exaggerated AMYG reactivity and atypical AMYG-(pre)frontal cortex connectivity, the neural signatures of successful treatment may be treatment independent, rather than treatment dependent. For instance, if effectual CBT "normalizes" frontal activity, increased top-down control may downregulate limbic response to threat thereby reducing AMYG reactivity even though this region is not considered to be a principal site of action. Conversely, for SSRIs, the attenuation of AMYG activity to threat may in turn reduce the frequency and/or intensity of negative thoughts that contribute to social fears. This is supported by reports that SSRIs themselves modulate top-down regions and alter negative cognitions [61–63]. Thus, in the case of either CBT or SSRIs, reduced

AMYG activity may be a marker of clinical improvement in SAD. Indeed, an early positron emission tomography (PET) study by Furmark and colleagues [64] revealed the AMYG was a common site of action in responders ($n = 9$) to either 9 weeks of group CBT or an SSRI. In this study, responders exhibited equivalent post-treatment reductions in regional cerebral blood flow in the AMYG, along with decreases in the hippocampus, and temporal cortex during a speech challenge [64]. While these data point to a modality-independent mechanism of change involving the AMYG, it will be important to replicate findings. To date, we are not aware of another neuroimaging study that directly contrasted CBT with SSRIs in SAD, a reflection of the relatively nascent stage of this area of study.

Neurofunctional Predictors of Clinical Improvement

Intriguingly, far more psychotherapy than pharmacotherapy studies report neuroimaging predictors of treatment response in SAD. Regarding AMYG, we and others have observed greater pre-treatment AMYG activity to threat cues predicted better response to treatment. Specifically, more AMYG reactivity to video clips depicting social threat [65] and threatening face distractors [66] foretold better CBT outcome. However, this pattern of activation is not consistent. For example, we also found that less baseline AMYG engagement to emotional faces (vs. face distractors) corresponded with more symptom improvement following CBT [67]. With regard to functional connectivity as a predictor, Månsson and colleagues [68] demonstrated improvement a year after completing internet-delivered CBT (iCBT) was predicted by less pre-treatment AMYG-ACC coupling to threat (i.e., self-referential criticism). As a classifier, the investigators revealed AMYG activity together with ACC activity to threat significantly distinguished iCBT responders from non-responders (e.g., area under the curve (AUC) = 0.89); therefore, both regions were necessary to predict which patient was likely to benefit from iCBT. In a departure from regions as predictors, a resting-state connectomic study showed favorable improvement following group CBT was foretold by greater baseline AMYG connectivity with a ventral cluster (i.e., subgenual ACC/caudate/putamen) and less AMYG coupling with the central sulcus and temporal/occipital cortex [69•]. Importantly, brain-based activity was superior to baseline symptom severity in predicting which patient would improve [69•], which is consistent with prior CBT studies [66, 70–72]. Finally, greater resting-state AMYG connectivity involving subgenual ACC has also been shown to portend better CBT outcome [73].

Taken together, findings indicate baseline variance in AMYG activity and AMYG pathways interacts with CBT. The extent to which predictors relate to cognitive and/or behavioral components of CBT is unclear, however, as the neural correlates of CBT outcome are evaluated after patients complete all CBT modules. That said, one fear extinction study provides support for AMYG reactivity as a predictor of response to fear exposure, a core component of CBT [53]. The therapeutic effect of exposure comprises extinction learning, a form of inhibitory learning associated with biochemical changes in AMYG, which plays a role in memory consolidation [74]. In the context of extinction learning, the neural correlates of AMYG as a predictor were examined by Ball and colleagues [75]. As an analogue of fear exposures in clinical settings, SAD patients completed four sequential public-speaking challenges. Results revealed greater reduction in social anxiety following the public-speaking challenges corresponded to less baseline AMYG activity during fear

extinction (i.e., exposure to neutral stimulus previously paired with a scream). These investigators also observed symptom improvement corresponded with a ventral system that contributes to fear extinction [74] as patients with less insula and periaqueductal gray activity, yet more ventromedial PFC engagement, during extinction learning benefitted from the analogue fear exposure session [75]. Although replication is warranted given the relative lack of similar research, this study represents an important step in determining why certain patients with SAD may respond to an active ingredient in CBT.

In addition to AMYG, data suggest other brain regions "set the stage" for treatment outcome, particularly regions within the (pre)frontal cortex. For example, dorsal ACC to threat portends improvement a year after iCBT (AUC = 0.91) [68], and we and others have found CBT response is predicted by more activity in ventral portions of the ACC or OFC to threat stimuli [65, 66, 76, 77]. There are also reports that improvement corresponds with more activity in the insula and an array of cortical regions (e.g., superior frontal gyrus, supramarginal gyrus, precentral gyrus) to threat distractors [77] as well as less activity in the (pre)frontal regions (e.g., rostral ACC, dorsolateral prefrontal cortex) during explicit regulation of threat [66, 78]. Moreover, clinical improvement is predicted by enhanced activation to threat cues in areas involved in perceptual processing (e.g., occipital regions, superior temporal gyrus) [65, 70, 76] and parietal regions [65].

Evidence of treatment-dependent brain-based predictors is unclear as there has been little research in this area. However, in a study that examined two psychotherapy interventions for SAD, greater insula response to social threat foretold improvement after completing a trial of ACT but not CBT [65] suggesting baseline insula activity uniquely interacted with ACT. Illuminating potential candidate predictors, regions not strongly implicated in the neurobiology of SAD may nonetheless portend treatment response. For example, improvement after completing CBT corresponds with more baseline activation in the cerebellum to fearful faces [76] and greater resting-state functional connectivity between the cerebellum and dorsolateral prefrontal cortex and angular gyrus foretells improvement following group CBT [79]. Regarding pharmacotherapy, there seems to be only one study of SAD concerning neural predictors of response to medication and it examined the neural correlates of tiagabine, a selective gamma-aminobutyric acid reuptake inhibitor, with PET during resting state. Results revealed greater reduction in symptom severity after 6 weeks of treatment corresponded with lower pre-treatment activity (i.e., metabolic rate of glucose uptake) in the subcallosal cortex [80].

In summary, brain response and functional connectivity interact with treatment, although differences in subdivisions of structures and patterns of activation suggest that neuroimaging predictors are task dependent. Consequently, depending on the circuit probed by a paradigm (e.g., emotion processing, cognitive control, threat regulation, fear extinction), stimuli used (e.g., threat faces vs. emotional faces), and methodological factors (e.g., region-of-interest vs. whole-brain approach), neural predictors may or may not involve AMYG or AMYG pathways. Even so, the direction of activation has important implications for precision medicine. For example, in cases where more improvement is predicted by greater baseline activity in (pre)frontal structures during cognitive control, patients with intact or compensatory top-down control are expected to benefit more from treatment. Conversely,

when clinical improvement is predicted by greater baseline dysfunction during cognitive control, patients with more pre-treatment deficiency in top-down function are expected to benefit more from treatment. Although further study is necessary to disambiguate patterns of activation signifying a “play to strengths” or “play to weakness” model, results point to the use of neuroimaging as a promising predictor of treatment response for those with SAD. Importantly, accumulating data suggests neural activity may be more sensitive in predicting treatment outcome than non-imaging measures.

Neurofunctional Activity: Pre-to-Post Treatment

AMYG as a putative target of treatment is supported by discrete studies showing that reduced AMYG activation to threat stimuli or symptom provocation occurs after treatment with iCBT [81] or an SSRI [59, 82] along with pre-to-post changes in resting-state AMYG pathways after group CBT (e.g., reduced AMYG-ACC coupling [83]). Therefore, psychotherapy and pharmacotherapy appear to ameliorate exaggerated AMYG response or circuits that intersect with AMYG in SAD.

Highlighting mechanisms of fear exposure, a PET study examined the effects of sequential public speaking in SAD. Specifically, patients completed two back-to-back speech challenges followed by sequential exposure to faces [84]; findings revealed a decrease in AMYG activity after the second speech challenge ($\Delta_{1stSpeech\text{-}2ndSpeech}$) but no change in AMYG response to faces ($\Delta_{1stFaceTask\text{-}2ndFaceTask}$). Along with reduced AMYG activity, increased activation was observed in the dorsal ACC and cerebellum following repeated exposure to public speaking representing changes in self-focus during public speaking [84]. Taken together, neural changes were specific to a stress exposure and bottom-up processes appeared to account for anxiety reductions [84].

As to the anxiolytic mechanisms of pharmacotherapy, Frick and colleagues [59] examined the role serotonin synthesis plays in clinical improvement in light of animal and human data demonstrating SSRIs reduce serotonin synthesis [85–87]. In their study, SAD patients were randomly assigned to 6 weeks of an SSRI, 4 weeks of an NK1R antagonist, or placebo. All participants underwent a public-speaking task during PET and results showed reduced serotonin synthesis in the AMYG, regardless of condition, though the placebo group also exhibited an increase in synthesis in an AMYG subregion. Notably, greater decreases in symptom severity corresponded with greater reduction in serotonin synthesis rate suggesting improvement was associated with a decrease in serotonin turnover. Beyond AMYG, remediation of social fears was also linked with attenuated serotonin synthesis in the postcentral gyrus. Regions that interacted with the condition included the middle temporal gyrus in the SSRI group, ACC and superior parietal gyrus in the NK1R antagonist group, and middle frontal gyrus in the placebo group. Again, changes were in the direction of decreased serotonin synthesis [59]. Altogether, findings indicate that greater serotonergic tone in AMYG, sensory, and emotion processing regions may be a potential mechanism by which pharmacotherapy or placebo exerts its effects.

In contrast to standard psychotherapy and pharmacotherapy, several studies have also investigated the role of oxytocin (OXY), a neuropeptide produced in the hypothalamus,

as a therapeutic candidate for SAD due to its anxiolytic-like properties [88] and association with pro-social behaviors [16]. For example, in non-clinical samples, administration of intranasal OXYenhances trust behavior [89] and reduces stress response to a psychosocial stressor relative to placebo [90]. In SAD, intranasal OXY targets neural circuits implicated in emotion processing and emotion regulation as evinced by functional connectivity studies that demonstrate OXY remediates aberrant activity in AMYG pathways [91, 92]. Specifically, in a randomized double-blind placebo-controlled OXT challenge, Gorka and colleagues [92] showed OXY increased AMYG-middle cingulate/dorsal ACC coupling and AMYG-insula connectivity to threat faces in SAD such that connectivity patterns were comparable to HCs. Moreover, the SAD group who received OXY had greater AMYG-frontal and AMYG-insula coupling to threat faces than controls assigned to the placebo condition [92]. Findings are in line with an earlier resting-state study that found attenuated AMYG-medial PFC/ACC connectivity in SAD was enhanced following OXYadministration [91]. Together, these results build on previous data that point to OXY as a possible therapeutic agent [16], though the clinical value of OXY remains to be established as the intervention does not appear to have benefits beyond exposure therapy for SAD [93].

In clinical settings, an SSRI is frequently combined with CBT as patients may benefit from additive or synergistic therapeutic effects [94]. For example, socially anxious patients randomly assigned to 9 weeks of an SSRI together with iCBT (SSRI+iCBT) had a better clinical outcome than those assigned to iCBT+pill placebo [16]. The combined treatment group also tended to exhibit a greater pre- to post-treatment reduction in AMYG reactivity to threat faces though the effect was only observed at a liberal statistical threshold ($p_{\text{uncorrected}} < 0.05$). Regardless of condition, treatment responders had more preto post-treatment reduction in AMYG reactivity to threat and greater increase in connectivity between nodes in the fear network (i.e., enhanced AMYG–insula functional connectivity) relative to non-responders. Results indicate neural signatures of effectual treatment represent a common pathway for SAD treatment [95•]. Further support comes from a study that compared 12 weeks of CBT against 12 weeks of ACT. Results showed clinical improvement was comparable between psychotherapies [96], AMYG activity during implicit emotion regulation (affect labeling vs. gender labeling) decreased after psychotherapies, and there was increased functional connectivity between the AMYG and visual cortex, parietal regions, and primary motor cortex across SAD patients following treatments. Also, greater decrease in symptom severity corresponded with more negative change (i.e., reduced positive/greater inverse connectivity) in coupling between AMYG and ventral PFC pre- to post-treatment. Findings suggest mechanisms of CBT and ACT converge on a shared pathway that supports emotion regulation capability [96].

Evidence AMYG response may track the effectiveness of treatment involves a study that contrasted 9 weeks of iCBT against 4 weeks (twice weekly) of internet-delivered attention bias modification (ABM). Significantly more SAD patients benefitted from iCBT than ABM and AMYG response to threat (i.e., self-referential criticism) decreased more after iCBT than ABM [97]. However, with regard to long-term post-treatment amygdala activity, the same group found that the diminished AMYG response immediately after CBT was not maintained, nor did it correspond to differences in clinical outcome (i.e., 7 responders; 6 non-responders) [98]. Since gains with CBT are known to have enduring effects after

treatment is terminated [99], further study is needed to evaluate neural mechanisms that sustain improvement.

Collectively, findings verify the pivotal role AMYG plays in the disease state and as a target of treatment. Even so, some studies have failed to detect pre-to-post differences in AMYG response to threat [76, 100, 101] or alterations in AMYG-based functional connectivity [102] instead reporting treatment-related changes in regions and pathways implicated in emotion, emotion regulation, and sensory processes (e.g., insula, ACC, medial PFC, occipital gyrus, ACC-precuneus connectivity; [76, 100–102]). Broadly, these results suggest an array of regions beyond the AMYG may be viable treatment targets for those with SAD. In support, a recent meta-analysis of neuroimaging work comprising psychotherapy and pharmacotherapy in SAD did *not* find pre-to-post AMYG effects, possibly because the amygdala is too small to be significant when whole brain analysis is performed or that different treatments target different subregions of the AMYG and/or cortical activity patterns that modulate AMYG [103•].

In summary, few neuroimaging studies of SAD have directly compared treatments that differ in mechanisms of change. However, limited data suggests AMYG and its pathways may be common sites of action [64, 95•, 96] and a possible neural metric of effectual treatment [97]. Neuroimaging work focused on testing assumptions about elements of clinical improvement also verify AMYG as a putative target for interventions [59, 84, 91, 92]. Nevertheless, the neurobiology of SAD continues to evolve (e.g., [30]) and despite the relevance of AMYG in models of SAD and other illnesses associated with excessive fear, the AMYG may be one of multiple candidate treatment targets.

Conclusions and Future Directions

The AMYG is strongly implicated in the neurobiology of SAD and evidence AMYG and/or its functional pathways predict treatment outcome or change as a result of treatment further supports its putative role in SAD. However, data indicate neural predictors and sites of action go beyond AMYG and suggest regions in corticolimbic circuits and extrastriate cortex implicated in emotion, emotion regulation, and sensory functions may serve as predictors or treatment targets. Evidence of task-dependent effects—namely, improvement predicted by increased or decreased baseline activity—provides an opportunity to advance our understanding of factors that figure into successful treatment outcome and inform novel treatments. Reports of treatment-independent pre-to-post changes in neurofunctional activity and/or connectivity suggest effectual interventions converge on a final pathway.

While findings are promising, it is important to emphasize that considerable work remains due to substantive gaps in the literature and the tendency of studies to have small sample sizes. Also, more research is needed to explore time-dependency effects (e.g., SAD-related habituation in AMYG response to emotional faces [104]) and amygdala subregions as possible targets [103•]. Evidence of disruption in networks involved in social cognition, self-referential processing, and executive control in this population [38, 105] suggests it may be fruitful to shift from an AMYG-centric framework to a large-scale network model of SAD to delineate predictors and mechanisms of change. Moreover, it is important to consider

methods that would strengthen the reproducibility of findings. For example, reporting effect sizes of pre-to-post changes in brain response, sensitivity/specificity of predictors, and more standardization with regard to what constitutes a "successful" treatment response as various benchmarks have been used (e.g., 50% or more decrease in social anxiety symptoms; score based on a clinician-administered measure; standard deviation cut point; [64, 78, 81]). Challenges to generalization and replication need to be carefully considered if findings are to catalyze novel interventions and inform treatment planning in clinical settings.

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