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Review Article

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Prefrontal Cortex Dysfunction in Social Anxiety Disorder: A Critical Review

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ABSTRACT

Social anxiety disorder (SAD) is characterized by the fear of negative evaluation and impairment in social functioning. Research has identified altered prefrontal cortex (PFC) activation and connectivity as possible biological correlates of SAD. This paper critically reviews five recent studies that examined PFC functioning during emotion regulation, self-appraisal, social feedback, or rest. The studies identified differences involving medial and lateral prefrontal regions. Altered connectivity was also observed within prefrontal and default mode networks. The direction of the findings varied according to the experimental condition and participant characteristics. Early-life adversity moderated resting-state connectivity, while short-term escitalopram treatment was associated with a change in the left inferior frontal gyrus activation. Methodological concerns included limited sample sizes and cross-sectional designs. The available evidence supports an association between SAD and alterations in PFC functioning. Longitudinal research and independent replication are needed to determine whether these neural differences contribute to the development of SAD or change in response to treatment.

Keywords: Social Anxiety Disorder, Prefrontal Cortex, Functional Connectivity

Social anxiety disorder (SAD) is characterized by fear or anxiety concerning social situations in which an individual may be observed or evaluated by other people. Feared situations may involve social interaction or performing in front of others. Individuals with SAD may avoid these situations or endure them while experiencing anxiety. The fear must persist for at least six months and cause clinically significant distress or impairment to meet diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [1].

Fear of negative evaluation is central to SAD. Individuals may expect that others will notice signs of anxiety or judge their behavior negatively. These expectations can affect behavior before a social interaction and influence how the event is interpreted afterward. Avoidance may reduce anxiety in the immediate situation, but that can increase the likelihood of avoiding similar situations in the future. Continued avoidance also limits opportunities to evaluate whether expectations of rejection are accurate.

SAD affects between 5% and 13% of the general population across the lifetime [2]. Differences among prevalence estimates reflect variation in diagnostic criteria and sampling procedures. Okamura et al. reported that approximately half of individuals with SAD experience onset by age 13. Approximately 90% experience onset by age 23 [2]. Early onset can result in symptoms that continue during developmental stages.

SAD can interfere with social relationships and occupational functioning. Educational participation may also be affected when students avoid speaking or completing tasks that involve social interaction. Okamura et al. distinguished overall SAD from the performance-only presentation, in which fear is restricted to public speaking or performing [2]. The five studies included in this review examined SAD as a broader diagnostic condition.

Negative beliefs about the self-contribute to the cognitive features of social anxiety. Self-schemas are organized beliefs that influence how self-relevant information is interpreted. Individuals who hold negative self-schemas may assign greater importance to social experiences that reinforce these beliefs. Information that contradicts an established negative self-schema may have less influence on later self-evaluation.

Martin et al. examined associations among social anxiety symptoms, self-schemas, and appraisals of autobiographical memories in a community sample [3]. Participants recalled a social experience in which they felt valued or unvalued. Positive memories were generally rated as more meaningful and impactful than negative memories. This pattern was reversed among participants with greater social anxiety symptoms or stronger negative self-schemas. These participants rated negative social memories as more impactful. Stronger positive self-schemas were

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associated with lower ratings of the impact of negative memories [3].

The findings from Martin et al. indicate that social anxiety symptoms are associated with the appraisal of social memories [3]. The study used a community sample and did not establish that all participants met diagnostic criteria for SAD. Its findings provide evidence about processes associated with social anxiety symptoms. They do not establish a memory pattern that is specific to clinically diagnosed SAD.

Attentional allocation may also contribute to the maintenance of social anxiety. Liu et al. used a dot-probe task to examine attention to negative emotional information in college students [4]. Social anxiety severity was associated with attentional bias toward negative information. Participants with higher social anxiety responded more rapidly to negative stimuli. In a second study, participants with high social anxiety completed attentional bias modification or an attention-control condition. Participants who received attentional bias modification showed reductions in attentional bias and social anxiety scores after the intervention [4].

The Liu et al. findings support an association between social anxiety symptoms and attention to negative emotional information [4]. The dot-probe task also measures reaction-time differences. The study remains relevant because it demonstrates a behavioral process that may be associated with prefrontal cognitive control.

Prefrontal Cortex Functioning in Social Anxiety Disorder

Research concerning the biological basis of SAD has examined structural differences and functional connectivity. Functional magnetic resonance imaging (fMRI) studies have also measured activation during emotional or self-referential tasks. Findings across studies have varied. Differences in participant characteristics may contribute to this variation. Imaging methods can also influence the results.

Zhang et al. examined structural and resting-state functional abnormalities in adults with SAD who did not have psychiatric comorbidities [5]. The authors identified structural differences involving the putamen and thalamus. They also found altered functional connectivity involving regions within cortico-striato-thalamo-cerebellar circuitry. Connectivity differences partially mediated associations between regional volume and SAD diagnosis. These findings place prefrontal functioning within a distributed neural system associated with SAD.

Zhang et al. also identified limitations in the neuroimaging literature [5]. Many previous studies included small samples. Comorbid psychiatric conditions were handled inconsistently across studies. These factors may contribute to failures of replication and differences in reported neural abnormalities. The findings support examining PFC functioning through its connectivity with other regions.

The PFC contributes to cognitive control by maintaining information about current goals and influencing processing in other neural systems [6]. The dorsolateral PFC has been associated with adjustments in cognitive control when competing information must be resolved. Medial prefrontal regions contribute to the evaluation of self-relevant information and emotional value. These functions are relevant to SAD because social situations require evaluating social information and adjusting behavior.

The PFC does not perform one function. Its subregions differ in their connectivity and contributions to behavior [6]. A finding of reduced activation in one prefrontal region does not indicate reduced functioning throughout the PFC. A brain region may become more active when a task requires greater use of the function that region supports. Functional interpretation depends on the region and task used in the analysis.

Connectivity analyses provide information about relationships between neural signals. Functional connectivity measures associations between regions. Effective connectivity estimates the direction of influence within a specified model. Effective connectivity remains dependent on the regions included in that model. Neither method establishes that a difference in connectivity caused SAD.

The purpose of this review is to evaluate evidence that altered PFC functioning is associated with SAD. The review focuses on functional activation and connectivity in the five selected studies. The review also considers whether the reported findings are specific to SAD and whether the designs show conclusions about causation.

Critical Review

Effective Connectivity During Emotion Processing and Regulation

Schrammen et al. examined effective connectivity during emotion processing and emotion regulation in adults with SAD [7]. Effective connectivity refers to the estimated directional influence of one neural region on another. Previous studies of SAD frequently used functional connectivity, which measures statistical associations between regional signals without estimating the direction of influence. Schrammen et al. used dynamic causal modeling to examine connectivity among selected prefrontal regions and the amygdala [7]. The authors hypothesized that participants with SAD would demonstrate reduced prefrontal inhibition of the amygdala and altered connectivity among prefrontal regions.

The sample included 61 individuals with SAD and 41 healthy controls. SAD diagnoses were established through a structured clinical interview using DSM-IV criteria and confirmed according to DSM-5 criteria. Participants with SAD could have current or remitted major depressive disorder. Psychotropic medication was permitted, except for benzodiazepines. Eighteen participants with SAD reported taking psychotropic medication. Healthy controls could not have a current or lifetime psychiatric disorder.

During functional magnetic resonance imaging, participants viewed neutral faces and faces displaying anger or fear. In the observation condition, participants attended to the faces without receiving instructions to change their emotional responses. In the regulation condition, they attempted to reduce their emotional responses to the negative faces. Participants selected their own regulation strategies. Dynamic causal modeling assessed connectivity among the amygdala, ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and pre-supplementary motor area (preSMA). Group differences were evaluated using parametric empirical Bayes. Leave-one-out cross-validation assessed whether

the connectivity parameters predicted diagnostic group, social anxiety severity, or dysfunctional emotion-regulation scores.

Participants with SAD reported a greater increase in negative affect when viewing angry and fearful faces than healthy controls. Emotion regulation improved affective ratings in both groups. The groups did not differ significantly in self-reported regulation success. Participants reported using several regulation strategies, with variation occurring within both groups.

The effective connectivity findings did not support the predicted group difference in prefrontal-amygdala connectivity. Group differences occurred within prefrontal circuits. During the observation of negative faces, participants with SAD showed stronger inhibitory connectivity from the preSMA to the dlPFC. During deliberate regulation, participants with SAD demonstrated increased excitatory connectivity from the preSMA to the vmPFC and from the vmPFC to the preSMA [7].

The authors proposed that stronger preSMA inhibition of the dlPFC could reflect reduced cognitive control during emotional processing. Increased connectivity between the preSMA and vmPFC during regulation could reflect greater involvement of response monitoring during attempts to regulate emotion. These interpretations remain tentative because dynamic causal modeling estimates connectivity from a prespecified neural model. It does not directly manipulate activity in the selected regions.

Several aspects of the design support the validity of the findings. The sample size was larger than those used in most of the other studies included in this review. The research protocol and statistical plan were preregistered. Dynamic causal modeling allowed the researchers to estimate directional connectivity across the selected network. Cross-validation assessed whether the connectivity differences generalized to participants excluded from each analysis.

The clinical relevance of the cross-validation results was limited. Connectivity predicted the diagnostic group, although the association was weak. Prediction of social anxiety severity was limited and had wide confidence intervals. Connectivity did not predict dysfunctional emotion-regulation scores. These results do not support using the identified connectivity parameters as measures of symptom severity.

The study included several methodological limitations. The model excluded regions involved in emotion processing, including the insula and anterior cingulate cortex. The findings were therefore limited to the selected network. Self-selected regulation strategies increased variability in the processes used during the task. This variability may have reduced sensitivity to group differences in prefrontal-amygdala connectivity. Comorbid depression and psychotropic medication may also have affected neural connectivity. The groups differed in gender composition, although gender was included in the statistical model. The cross-sectional design could not establish whether intra-prefrontal connectivity differences came before the development of SAD.

Default Mode Network Connectivity During Self-Appraisal

Jamieson et al. examined effective connectivity within the default mode network during direct and reflected self-appraisal [8]. Direct self-appraisal required participants to determine whether an adjective described them. Reflected self-appraisal required them to determine whether other people would use the adjective to describe them. Reflected self-appraisal was expected to be relevant to SAD because the disorder includes fear of evaluation by others.

The sample size was 38 unmedicated participants with SAD. The researchers also recruited 122 healthy controls. After imaging, they selected 72 controls matched to the SAD group by age and gender. The final sample included 110 participants, 16 to 25-year-olds. Participants with SAD had a primary diagnosis established through a structured DSM-5 interview. Their symptoms were in the moderate-to-severe range on the Liebowitz Social Anxiety Scale.

Participants completed direct self-appraisal, reflected self-appraisal, external attention, and rest conditions during fMRI. Dynamic causal modeling assessed effective connectivity among the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and left inferior parietal lobule (liPL). These regions were selected because of their involvement in default mode network functioning and self-referential processing. Parametric empirical Bayes was used to estimate group differences in connectivity. Leave-one-out cross-validation evaluated whether connectivity parameters predicted anxiety symptoms.

The SAD and control groups displayed similar patterns of regional activation during direct and reflected self-appraisal. Between-group differences were not statistically significant after familywise error correction in the whole-brain analyses. Regional activation differences appeared when the researchers applied an uncorrected threshold. These findings should receive limited interpretive weight because they did not meet the corrected significance threshold.

The principal findings involved effective connectivity. Participants with SAD demonstrated reduced intrinsic excitatory connectivity from the PCC to the mPFC. They also demonstrated reduced intrinsic inhibitory connectivity from the LiPL to the mPFC. During reflected self-appraisal, participants with SAD showed greater excitatory connectivity from the PCC to the mPFC and greater inhibitory connectivity from the liPL to the mPFC. Group differences in connectivity modulation were not found during direct self-appraisal [8].

The PCC has been associated with an individual's understanding of their personal identity. The inferior parietal lobule (iPL) contributes to perspective-taking and autobiographical memory retrieval. Altered input from these regions to the mPFC during reflected appraisal may correspond with differences in processing beliefs about how others view them. The imaging data did not measure the content of participants' thoughts, so the findings cannot establish that the connectivity differences represented negative self-evaluation.

The design included an unmedicated clinical sample and controls matched on demographic variables. The comparison between direct and reflected appraisal provided a task condition related to fear of evaluation. Dynamic causal modeling allowed the authors to examine estimated directional influences within the selected default mode network. Cross-validation also evaluated the association between connectivity and anxiety measures outside

each participant's model estimation.

The cross-validation findings raise questions about diagnostic specificity. Intrinsic connectivity predicted trait anxiety measured by the State-Trait Anxiety Inventory. It did not predict social anxiety severity measured by the Liebowitz Social Anxiety Scale. The identified connectivity pattern may be associated with general anxiety. Additional studies comparing SAD with other anxiety disorders would be required to evaluate specificity.

The study also had limitations associated with sample size and participant age. The SAD group included 38 participants and was restricted to individuals between 16 and 25 years old. The findings may not generalize to older adults with SAD. The adjective task did not permit separate analysis of positive and negative reflected appraisals. The model included only three default mode network regions, so it did not evaluate interactions with the amygdala or insula. Task-based intrinsic connectivity was discussed in relation to resting-state research, although connectivity measured during an experimental task is affected by the task context. The cross-sectional design prevented conclusions about the temporal relationship between altered connectivity and SAD symptoms.

Early Life Adversity and Resting-State Functional Connectivity

Leypoldt et al. examined whether early life adversity moderated resting-state functional connectivity in individuals with SAD [9]. Previous studies reported increases and decreases in prefrontal connectivity. Differences in adversity exposure across samples could contribute to this variation. The study tested interactions between SAD diagnosis and early life adversity.

The sample included 120 German-speaking participants of European descent between 19 and 48 years old. Forty-nine participants met diagnostic criteria for SAD. Participants were divided into four groups. The groups consisted of 49 controls with low adversity, 22 controls with high adversity, 30 participants with SAD and low adversity, and 19 participants with SAD and high adversity. SAD was assessed using a structured DSM-IV interview. Social anxiety severity was measured with the Liebowitz Social Anxiety Scale.

Early adversity was assessed with the Childhood Trauma Questionnaire (CTQ). Participants were assigned to the high-adversity condition when they exceeded the threshold in at least one measured category. The categories included emotional forms of maltreatment and physical forms. Sexual abuse was also measured. The questionnaire did not establish the precise timing or duration of the reported experiences.

Resting-state fMRI data were evaluated using literature-derived regions of interest and seed-based correlation analysis. Multivoxel pattern analysis was used to identify distributed connectivity patterns. The researchers also conducted follow-up seed-based analyses using clusters identified through the multivoxel analysis. General anxiety and depressive symptoms were included in validation analyses.

The literature-derived region-to-region analysis did not identify a significant interaction between SAD and early adversity. The multivoxel analysis identified clusters in the subgenual anterior cingulate cortex (sACC), left middle frontal gyrus (lMFG), and left calcarine fissure or precuneus. Follow-up analyses identified connections between these clusters and an extended network of cortical and subcortical areas.

The direction of the connectivity differences associated with SAD depended on adversity status. Participants with SAD and high adversity demonstrated increased positive connectivity involving the sACC. They also displayed limited connectivity involving visual cortical regions. Participants with SAD and low adversity showed a different pattern. Controls with high adversity displayed some connectivity characteristics similar to those observed in participants with SAD and low adversity. Emotional abuse and emotional neglect showed the most consistent associations with the identified connectivity patterns [9].

The results remained significant after the researchers controlled for general anxiety and depressive symptoms. This reduced the likelihood that the findings reflected nonspecific distress. The results indicate that early adversity may moderate resting-state connectivity associated with SAD. The data does not establish whether adversity produced these differences.

The four-group design allowed the researchers to evaluate heterogeneity within SAD. The total sample was larger than comparative studies. The use of categorical adversity groups and continuous questionnaire scores provided two approaches to evaluating the interaction. The use of multiple connectivity methods allowed examination of predetermined regions and distributed patterns.

The nonsignificant region-to-region analysis is relevant to the interpretation of the findings. The principal results emerged from the multivoxel analysis and follow-up seed-based analyses. Clusters identified in the multivoxel analysis were examined further within the same sample. These follow-up analyses characterized the network identified in the data. They did not provide independent replication.

The adversity measure relied on retrospective self-report. Recall and current emotional state may affect responses. The questionnaire did not provide sufficient information about the developmental timing of adversity. Participants assigned to the high-adversity groups may have experienced different types of adversity, which could have different associations with neural development.

The subgroup sizes were unequal, and the SAD group with high adversity included 19 participants. All participants were German-speaking and of European descent. This limits generalization to populations with different cultural backgrounds. Physiological measures were not collected during the resting-state scan. Differences in heart rate variability or respiration could have influenced the blood-oxygen-level-dependent signal. The cross-sectional design could not establish a developmental pathway from adversity to altered connectivity.

Neural Responses to Social Feedback

Koban et al. investigated behavioral and neural responses to social feedback in adults with SAD [10]. The study examined whether participants with SAD updated their self-perceptions more strongly in response to negative feedback. It also evaluated neural responses associated with changes in self-evaluation and

state self-esteem.

The sample included 21 adults with SAD and 23 healthy controls. Diagnoses were assessed using structured DSM-5 interviews. Participants in the SAD group could not have a current mood disorder or psychotic disorder. Participants with a major depressive episode during the preceding five years were excluded. The control group could not meet the criteria for SAD or another current anxiety disorder. The groups were matched based on demographic characteristics.

Participants prepared and delivered a three-minute speech about their ideal job. They were told that judges would evaluate the speech. During the feedback task, participants rated specific aspects of their performance and then received feedback that was more positive or negative than their initial rating. After receiving the feedback, they rated how they felt about themselves. Participants completed another self-evaluation approximately 20 minutes later.

The feedback was generated experimentally and centered around each participant's initial evaluation. This procedure allowed the researchers to control the direction and size of the difference between the participant's evaluation and the judges' feedback. Computational models estimated the influence of positive and negative feedback on subsequent self-evaluation. A separate model estimated changes in state self-esteem across trials.

All 44 participants completed the behavioral procedure. Thirty-two participants completed the feedback task during fMRI. Twelve completed it outside the scanner because of scanning constraints. The imaging analyses included whole-brain mediation models and an established frontoparietal network mask.

Participants with SAD had lower initial state self-esteem than controls. They updated their self-evaluations more strongly in response to negative feedback. Healthy controls showed a positive affective-updating bias, with positive feedback producing greater changes in state self-esteem than negative feedback. This positive bias was not there in the SAD group. The bias in affective updating was associated with the bias in later self-evaluation across participants [10].

Healthy controls demonstrated greater frontoparietal network activation during social feedback. They also showed greater network activation to positive feedback compared to negative feedback. This valence-related response was reduced in the SAD group. Participants with SAD displayed reduced activity in the dlPFC and lateral parietal regions. Reduced precuneus activity was also observed. These areas were associated with more negative learning biases.

Activity in the anterior insula and frontal operculum was associated with feedback-related changes in self-evaluation. The involved cluster extended into the vlPFC. Activity in the dlPFC was also associated with individual differences in learning bias. The vmPFC showed a suppression effect in the mediation analysis, indicating that greater activity was associated with reduced influence of feedback on later self-evaluation.

The public-speaking task created a social-evaluative context related to SAD symptoms. The researchers measured changes in self-perception after feedback, which provided behavioral evidence of biased updating. Computational modeling separated responses to positive feedback from responses to negative feedback. The established frontoparietal network mask provided a defined network for the group comparison.

The imaging sample was small. Whole-brain group findings were reported using liberal thresholds, increasing the possibility of false-positive results. The analysis plan was not preregistered. Data was collected using two MRI scanners after an equipment upgrade. The groups were balanced across scanners, and controlling for scanner did not significantly change the findings. Scanner differences may still have increased measurement variability.

The feedback was experimentally generated and did not reflect the judges' assessment of the speech. Participants may have differed in their belief in the feedback. The public-speaking task also produced an acute social stressor before feedback was presented. Differences in distress after the speech may have contributed to group differences during the feedback task.

The mediation analyses identified neural activity statistically associated with feedback-related changes in self-evaluation. Statistical mediation in fMRI data does not establish that activity in a region caused the behavioral change. The predominantly White sample also limited generalizability. Excluding participants with recent major depression reduced the influence of depression but resulted in a sample that may not reflect the clinical population.

Self-Referential Processing and Early Escitalopram Effects

Rinne et al. examined neural responses during self-referential processing in adults with SAD [11]. The study also evaluated whether one week of escitalopram changed neural activation before participants reported symptom improvement. The authors focused on responses to positive and negative personality adjectives.

The researchers recruited 38 participants with SAD and 20 healthy controls. Following imaging exclusions, the baseline comparison included 35 participants with SAD and 16 controls. Participants with SAD were randomized to escitalopram or placebo. Thirty-one participants were included in the treatment analysis. Participants repeated the imaging task after one week.

During the task, participants viewed positive personality adjectives and negative adjectives. Neutral words were included as a comparison condition. Participants imagined hearing each personality adjective used to describe them and categorized the word as positive, negative, or neutral. The researchers conducted whole-brain analyses and analyses of predetermined regions associated with self-referential processing.

At baseline, participants with SAD showed lower activation than controls in the left inferior frontal gyrus (IFG) when negative adjectives were compared with positive adjectives. Participants with SAD also demonstrated lower left precentral gyrus activation when negative adjectives were compared with neutral words. A similar difference was found in the precentral gyrus when all adjectives were compared with neutral words. The predetermined region-of-interest analyses did not produce significant group differences [11].

The IFG has been associated with semantic processing and inner speech. It has also been implicated in response inhibition. Rinne et al. proposed that reduced IFG activation could correspond with less effective processing or regulation of negative self-referential information [11]. The task did not directly measure inhibitory control or cognitive reappraisal. The functional interpretation of reduced IFG activity remains inferential.

After one week, anxiety symptoms did not differ significantly between the escitalopram and placebo groups. The whole-brain analysis did not identify a significant group-by-time interaction. Within the left IFG region identified in the baseline SAD-versus-control comparison, the escitalopram group showed increased activation relative to placebo for negative compared with positive adjectives. The authors proposed that this change may precede clinical improvement.

The randomized, double-blind, placebo-controlled design reduced expectancy and allocation biases in the treatment comparison. The short treatment interval allowed the researchers to examine neural activation before symptom change. The self-referential task also examined a process associated with negative self-evaluation in SAD.

The final sample sizes were small because of attrition and imaging exclusions. The SAD group contained a higher proportion of women than the control group. Including sex as a covariate did not remove the baseline IFG finding. The imbalance may still have contributed to variability.

The researchers used a liberal statistical threshold and did not correct for the number of contrasts. This increased the probability of false-positive results. No group differences were found in the predetermined regions of interest. The treatment effect was absent from the whole-brain group-by-time analysis and appeared within the IFG region defined by the baseline group comparison. The same patient sample was used to identify the IFG region and evaluate treatment-related change. Independent replication with a predefined IFG region is needed.

Medication adherence was assessed through participant report without blood analysis. The study did not establish whether the IFG change persisted after the first week. It also did not determine whether early activation predicted subsequent symptom reduction. The term normalization should be used with caution because the study showed movement toward the control pattern without concurrent clinical improvement. The findings support a possible early effect of escitalopram on left IFG responses to negative self-referential information.

Future Research Directions

Longitudinal research is needed to determine the temporal relationship between altered PFC functioning and SAD. Four of the five reviewed studies used cross-sectional comparisons. These designs identify associations between diagnosis and neural functioning but cannot determine whether the observed differences preceded symptom development. Repeated neuroimaging beginning before the onset of SAD could examine whether altered PFC activation predicts later symptoms. Follow-up assessments could then determine whether neural changes correspond with the persistence or reduction of symptoms.

Developmental timing requires further attention because SAD often begins during adolescence [2]. The study by Jamieson et al. was restricted to participants between 16 and 25 years old, while Leypoldt et al. included primarily younger adults [8,9]. Studies that follow participants across developmental periods could examine whether PFC connectivity changes with age. This approach could also determine whether neural patterns associated with early life adversity remain stable over time.

Replication studies should include larger clinical samples. The imaging analysis in Koban et al. included 32 participants, and the treatment analysis in Rinne et al. included 31 [10,11]. Small samples reduce statistical power and can produce unstable estimates of brain-behavior relationships. Larger samples would allow narrower confidence intervals and provide more reliable tests of symptom associations.

Future samples should include participants from different cultural backgrounds. Leypoldt et al. included German-speaking participants of European descent [9]. Koban et al. reported a predominantly White sample [10]. These samples do not represent the range of populations affected by SAD. Recruitment across multiple research sites could increase representation and provide sufficient participants for subgroup analyses.

Comorbid diagnoses and medication exposure also require planned analysis. Schrammen et al. permitted current or remitted major depression, and some participants used psychotropic medication [7]. Koban et al. excluded participants with recent major depression [10]. These approaches address different research questions, but they reduce comparability across studies. Future research could include a clinically representative sample and conduct planned analyses according to comorbidity. Medication status should also be recorded and evaluated.

Greater consistency in experimental tasks would help comparison across studies. Schrammen et al. allowed participants to select their own emotion-regulation strategies [7]. This increased variation in the processes used during the task. Future studies could compare a standardized strategy with a self-selected condition. This design would allow researchers to evaluate whether neural differences depend on the regulation strategy.

Whether self-referential stimuli are positive or negative should be examined directly. Jamieson et al. could not separate positive and negative reflected self-appraisal because of the task design [8]. Koban et al. found group differences in responses to positive social feedback, while Rinne et al.) reported an IFG difference for negative compared with positive adjectives [10,11]. Tasks that vary the type of appraisal or whether its content is positive or negative could determine whether altered PFC functioning is associated with reflected appraisal or negative content.

Resting-state studies should measure physiological signals during scanning. Leypoldt et al. noted that heart rate variability may affect blood-oxygen-level-dependent signals [9]. Respiratory activity can also influence these measurements. Direct monitoring would allow physiological changes to be included in preprocessing and reduce uncertainty about group differences.

Multimodal imaging could examine the relationship between structural variation and functional connectivity. Zhang et al.

combined structural imaging with resting-state fMRI and found associations between regional volume and connectivity [5]. A similar approach applied to the processes examined in the five reviewed studies could test whether structural differences are related to task-dependent PFC functioning. Repeated multimodal assessment would provide information about changes during treatment.

Analytic findings should be tested in independent samples. Leypoldt et al. used clusters identified through multivoxel analysis to guide follow-up analyses in the same dataset [9]. Rinne et al. tested treatment effects within an IFG region identified through the baseline group comparison [11]. These procedures can identify potentially relevant brain regions, but confirmation requires either a separate dataset or a region defined prior to analysis. Preregistration would distinguish planned tests from exploratory findings.

Research on neural biomarkers should require prediction beyond the original sample. Schrammen et al. found that connectivity parameters predicted diagnostic group, although prediction of symptom severity was weak [7]. Jamieson et al. found that connectivity predicted trait anxiety but did not predict SAD severity [8]. Future studies should test whether neural measures predict symptom course or treatment response. Comparisons with other anxiety disorders would be needed to establish diagnostic specificity.

Treatment studies can examine whether changes in PFC functioning are associated with later clinical response. Rinne et al. found increased left IFG activation after one week of escitalopram without concurrent symptom improvement [11]. A longer follow-up is needed to determine whether this change in activation persists and predicts later symptom reduction. Neural changes should be assessed with regions defined before treatment analysis.

PFC-targeted interventions also require further evaluation. Jafari et al. examined electrical stimulation targeting lateral and medial prefrontal cortices in SAD [12]. Future trials could test whether changes in PFC functioning mediate symptom change following stimulation. These studies would require control conditions and adequate follow-up. Neural outcomes should be evaluated together with clinical measures to determine whether changes in activation have functional significance.

Conclusion

The five reviewed studies provide evidence that SAD is associated with altered PFC activation and connectivity. The findings occurred during emotion regulation and reflected self-appraisal. Differences were also observed during social feedback and self-referential processing. Leypoldt et al. further showed that early life adversity moderated resting-state connectivity associated with SAD [9].

The direction of the findings varied across studies. Jamieson et al. identified altered connectivity with the mPFC during reflected self-appraisal but found no corrected whole-brain activation differences [8]. Koban et al. reported reduced recruitment of the frontoparietal network during social feedback [10]. Schrammen et al. identified altered connectivity among prefrontal regions, but no predicted group difference in prefrontal-amygdala connectivity [7]. Rinne et al. found reduced left IFG activation during negative self-referential processing [11]. These findings do not support a single pattern of PFC underactivation across SAD.

Task conditions influenced the observed neural differences. Altered mPFC connectivity was specific to reflected appraisal in Jamieson et al. [8]. The frontoparietal findings reported by Koban et al. depended on the valence of social feedback [10]. Schrammen et al. found different intra-prefrontal connections during observation and deliberate regulation [7]. The results indicate that PFC functioning in SAD changes according to the process being measured.

Participant characteristics also affected the findings. Leypoldt et al. found that early-life adversity changed the direction of resting-state connectivity associated with SAD [9]. Medication exposure also differed across samples. These factors may account for some variation in reported PFC abnormalities.

The evidence does not establish that PFC dysfunction causes SAD. Most of the reviewed studies were cross-sectional. Effective connectivity estimates directional relationships within a selected model but does not demonstrate biological causation. The treatment findings from Rinne et al. provide preliminary evidence that PFC activation may change after escitalopram exposure [11]. The lack of concurrent symptom improvement limits conclusions about the clinical significance of that change.

The findings support altered PFC functioning as one component of the neural processes associated with SAD. The evidence is strongest for context-dependent differences in activation and connectivity during socially relevant processing. Current research does not support the use of a single PFC measure as a diagnostic marker. Longitudinal studies and independent replication are needed before these findings can inform clinical assessment or targeted intervention.

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