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FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES
DOCTORAL SCHOOL “EVIDENCE-BASED PSYCHOLOGICAL
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Ph.D. THESIS SUMMARY
**ANXIETY IN ADOLESCENTS AND ADULTS:
INVESTIGATING NEURAL VARIABILITY AND
COGNITIVE PROCESSES**

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Notes. _____

(1) This is to certify by MUNTEANU-FORIJ OANA-GEORGIANA that:

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The results of the present work are in the process of publishing as follow:

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1.THEORETICAL BACKGROUND

1.1. Introduction and Research Problem

1.1.1. Anxiety Disorders

Anxiety is a fundamental emotional response to perceived threat, present from early life and expressed along a continuum of intensity. While it is typically adaptive by promoting avoidance of potential danger, it becomes maladaptive when it is excessive, persistent, and interferes with daily functioning (Pine et al., 2009). In such cases, anxiety disorders may develop and are characterized by heightened anxiety, physiological arousal, avoidance behaviors, and associated distress or functional impairment (*American Psychiatric Association. Diagnostic Statistical Manual Mental Disorders: DSM-5 5th edn*, n.d.). The differentiation between anxiety disorders largely depends on the situational context and the specific triggers that precipitate these symptoms (Kowalchuk et al., 2022). Evidence from a large meta-analysis suggests that approximately 6.5% of children and adolescents worldwide meet diagnostic criteria for an anxiety disorder (Polanczyk et al., 2015). Lifetime prevalence rates are substantially higher, with estimates from the United States suggesting that between 20% and 30% of individuals will experience an anxiety disorder at some point during their lifetime (CDC, 2026).

1.1.2. Social Anxiety Disorder

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), social anxiety disorder (SAD) is characterized by persistent fear and anxiety in social situations, often leading to avoidance and significant impairment in social or academic/professional areas. The fear is typically disproportionate to the actual threat and must persist for at least six months. In addition, the symptoms cannot be better explained by substance use, another mental disorder, or a medical condition (*American Psychiatric Association. Diagnostic Statistical Manual Mental Disorders: DSM-5 5th edn*, n.d.).

1.1.3. Cognitive Mechanisms in Social Anxiety Disorder

Several theoretical models have been proposed to explain the maintenance of SAD in adults (Clark, 1995; Heimberg et al., 2014; Hofmann, 2007; Rapee & Heimberg, 1997), with substantial empirical support for their key mechanisms. Although adapted models have been developed for younger populations (Leigh & Clark, 2018; Spence & Rapee, 2016; Wong & Rapee, 2016), empirical evidence in children and adolescents remains more limited and less consistent (Halldorsson & Creswell, 2017). Existing findings (Rapee et al., 2024) suggest that pediatric social anxiety is associated with heightened expectations of negative evaluation (Erath et al., 2007; Kley et al., 2011), negative self-perceptions of performance (Alfano et al., 2006; Lau et al., 2023), and increased self-focused attention (Blöte et al., 2014), although some studies report mixed results (Halldorsson et al., 2019; Leigh et al., 2023).

Cognitive-behavioural models of social anxiety disorder emphasize the role of biased information processing in the development and maintenance of symptoms (Clark & McManus, 2002; Heimberg et al., 2014). One key bias is interpretation bias, whereby individuals tend to assign negative or catastrophic meanings to ambiguous or mildly negative social situations (Chen et al., 2020). Another key bias is attentional bias, commonly defined as either rapid orienting toward threatening stimuli (Bantin et al., 2016) or difficulty disengaging from them, relative to neutral cues (Fox et al., 2002).

Anticipatory anxiety represents the affective component of a broader maladaptive cognitive process referred to as anticipatory or pre-event processing (Wong, 2016). The anticipatory processing involves reviewing potential outcomes, focusing on predicted anxiety, recalling past social failures, generating negative self-images, and forecasting poor performance or social rejection (Vassilopoulos et al., 2017; Wong, 2016).

1.1.4. Neuroimaging in Psychiatry

Advances in neuroimaging are transforming psychiatric research by enabling more precise mapping of brain structure and function across multiple levels, from molecules to large-scale networks. Noninvasive neuroimaging measures may serve as valuable indicators of individual differences, as psychiatric disorders can be understood in terms of brain dysfunction (Doehrmann et al., 2013).

Since its introduction in 1990, fMRI has become a widely used, non-invasive technique for investigating brain function, offering high spatial resolution and broad applicability across research domains (Glover, 2011). It measures the blood oxygen level-dependent (BOLD) signal, reflecting changes in neural activity during both task-related and resting-state processes (Nosari et al., 2024).

1.1.5. Neural Variability in Psychiatry

Despite progress toward precision medicine, psychiatry still lacks robust biomarkers. A major limitation lies in the low reliability and limited validity of commonly used neuroimaging measures (Elliott et al., 2020; Noble et al., 2019), which undermines their predictive value. These challenges cannot be addressed by increasing sample sizes alone, emphasizing the need for neural metrics with greater reliability, validity, and clinical utility (Tsikonofilos et al., 2025). In fMRI research, brain function is typically inferred from mean activation, calculated by averaging signals over time within individuals. This approach assumes that mean activation captures the most meaningful neural signal, treating variability as noise rather than informative activity (Garrett, et al., 2013a). Moment-to-moment brain signal fluctuations, once considered noise, are now recognized as meaningful indices of neural function, providing complementary insights into cognition, development, and clinical conditions (Garrett et al., 2013b).

1.1.6. Evidence Based Psychological Interventions in Anxiety Disorders

Extensive empirical research for treating childhood anxiety disorders supports cognitive behavioural therapy (CBT) (Cartwright-Hatton et al., 2011; Dickson et al., 2022; James et al., 2020), which is widely recognized as the gold-standard psychological intervention (Stiede et al., 2023). In adults, a recent meta-analysis (Öst et al., 2023) found that CBT for anxiety disorders in routine clinical settings leads to large reductions in anxiety and depression symptoms at both post-treatment and follow-up. Nevertheless, treatment outcomes remain variable. Meta-analytic findings from randomized controlled trials indicate recovery rates ranging from 47-66% in children and adolescents (Warwick et al., 2017), highlighting the need to identify reliable predictors of therapeutic response. Moreover, although CBT is well established as an effective treatment for various mental disorders (Cuijpers et al., 2013), its face-to-face format can be hindered by factors such as cost, limited access, and stigma (Gunter & Whittal, 2010; Mohr et al., 2010). Internet-delivered CBT (iCBT) has emerged as a promising alternative that may help overcome these barriers (Andersson, 2016).

1.2. Relevance of the Research Problem

Anxiety disorders are among the most common mental health conditions worldwide and typically emerge in childhood, adolescence, or early adulthood. This pathology has wide-ranging impacts on mental and physical health (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018), leading to social difficulties, reduced quality of life, increased economic burden, and an increased risk of suicide (Chen et al., 2025). Because of the wide variability in clinical presentation, frequent comorbid psychiatric conditions, and the disorder's chronic course, identifying individuals at risk and differentiating between anxiety disorder subtypes remains challenging, limiting the ability to tailor optimal interventions. The development of reliable biomarkers remains a critical objective, given their potential to improve early risk identification and diagnostic precision. Beyond detection, such markers could offer insight into the marked heterogeneity of anxiety disorders

symptomatology, enable more objective staging of severity, and support the stratification of patients into clinically meaningful subgroups for targeted interventions (Lisboa et al., 2023).

1.3. Current State of the Art

Experts from the National Institutes of Health and the U.S. Food and Drug Administration introduced a framework defining biomarkers as “a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathological process, or a biological response to a therapeutic intervention” (FDA-NIH Biomarker Working Group, 2016). Efforts to identify objective biomarkers in psychiatry originated from early links between brain pathology and dementia (*Context of use*, 2026; Kalia & Costa E Silva, 2015) and have expanded to include neuroimaging, EEG, cognitive and behavioral measures, genetic and omics approaches (Abi-Dargham et al., 2023), physiological (Mens et al., 2025), blood (Niculescu et al., 2015; Niculescu & Le-Niculescu, 2022) and digital biomarkers (Mulinari, 2024). Despite this progress, psychiatric classification in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association. *Diagnostic Statistical Manual Mental Disorders: DSM-5 5th edn*, n.d.) remains symptom-based, as most biomarkers lack sufficient validity and clinical applicability (Cuthbert et al., 2026).

2. RESEARCH OBJECTIVES AND OVERVIEW OF THE METHODOLOGY

2.1 General Aim

This thesis aimed to investigate neural correlates of anxiety across the lifespan, with a focus on their potential as biomarkers. This perspective is in line with dimensional models of psychopathology, such as the Research Domain Criteria (RDoC) framework (Insel, 2014), which prioritizes the integration of neurobiological and behavioral data over traditional diagnostic categories. By focusing on underlying mechanisms, this approach aims to delineate more homogeneous subgroups, thereby improving diagnostic precision and enabling the development of more targeted and effective interventions. In line with this goal, precision approaches in psychiatry and clinical psychology seek to move beyond the traditional one-size-fits-all model by using objective markers to guide individualized treatment selection, optimize therapeutic outcomes, and enhance clinical decision-making (Williams & Whitfield Gabrieli, 2024). Moreover, beyond the primary objective, a secondary aim was to examine cognitive processes, such as interpretation bias in adolescents and anticipatory processing in adults, in relation to social anxiety, highlighting the importance of capturing a comprehensive picture of psychopathology.

2.2. Specific Objectives

The first objective of this thesis was to systematically and critically evaluate the existing MRI-based evidence on neural correlates associated with CBT in children and adolescents with anxiety disorders (Study 1). More specifically, (1) we integrated findings on brain changes following CBT across studies, and (2) we explored pre-treatment neural indicators that may predict clinical improvement in this population (Study 1).

The second objective focused on mapping the relationships between interpretation biases and social anxiety in adolescents using a network analysis approach. Specifically, (1) we examined how different forms of interpretation bias (hostile, threatening, and neutral) are associated with various subclinical expressions of social anxiety, and (2) we tested whether these network structures remain consistent across age and sex (Study 2).

The third specific objective was to characterize moment-to-moment neural variability during an anticipatory public speaking task using a whole-brain PLS framework. Specifically, we (1) examined whether neural variability differed between speech anticipation and the baseline conditions, both within and between groups (SAD vs. healthy controls), and (2) examined the association between neural variability and the severity of social anxiety symptoms (e.g., LSAS-SR) (Study 3).

The last specific objective was to investigate moment-to-moment neural variability in SAD in relation to treatment-related symptom severity change (Δ LSAS-SR). Specifically, (1) we examined whether pre-intervention neural variability predicts symptom improvement, (2) whether neural variability is modulated by iCBT and ABM, and (3) if changes in neural variability are associated with symptom-severity change. Additionally, (4) differences in treatment-symptom severity change between interventions were explored (Study 4).

3. ORIGINAL RESEARCH

3.1. Study 1. Neuroimaging Anxious Children and Adolescents Before and After Cognitive Behavioral Therapy: A Systematic Review

3.1.1. Introduction

Anxiety disorders are the most prevalent mental health condition in children and adolescents with worldwide point prevalence estimated at 6.5% (Polanczyk et al., 2015). If left untreated, anxiety disorders can lead to a wide range of severe and long-lasting consequences, including an increased risk of substance abuse, suicidal behaviors, and the development of additional mental and physical health issues (Asselmann et al., 2018; Strawn et al., 2021). Clinical guidelines, systematic reviews and meta-analyses suggest cognitive behavioral treatment (CBT) as first-line treatment for anxiety disorders (Higa-McMillan et al., 2016), with a post-treatment recovery rate of approximately 60% in youth (Warwick et al., 2017). Although research supports CBT as an effective approach to reducing anxiety symptoms, a significant proportion of individuals do not reach remission within a 12-week treatment period (Bertie & Hudson, 2021; Ginsburg et al., 2011). These findings highlight the need for treatment development and refinement efforts to prioritize enhancing response and remission rates in this population.

Compared to behavioral or clinical indicators, neuroimaging markers may be stronger predictors of treatment response (Gabrieli et al., 2015), and the development of these indicators has the potential to identify specific neurobiological mechanisms to improve personalized treatment approaches in the future (Sequeira et al., 2021). However, there is no current systematic review of the literature including a critical assessment of the validity or limitations of CBT related studies including neuroimaging investigations. Given these gaps, a comprehensive evaluation of the field is necessary to clarify the clinical relevance of neuroimaging in pediatric anxiety.

The aim of the present study is twofold: (1) to systematically review the existing literature on brain changes associated with CBT in youths diagnosed with an anxiety disorder, and (2) to synthesize the literature on pre-treatment brain predictors of clinical improvement in children and adolescents with anxiety disorders.

3.1.2. Methods

We conducted this systematic review in accordance with PRISMA guidelines. The protocol was registered a priori in February 2019 (PROSPERO CRD42019126340).

3.1.2.1. Literature search

Systematic searches were conducted in the electronic databases PubMed, Web of Science, ProQuest on 27 October 2025. No date restriction was used. Titles and abstracts were screened. We used a combination of the following keywords: CBT, MRI, anxiety disorder, child OR adolescent.

3.1.2.2. Study selection

3.1.2.2.1. Inclusion criteria

We included studies that met the following criteria: published in a peer-reviewed journal; utilized neuroimaging techniques (e.g., magnetic resonance imaging - MRI) to identify specific brain regions (functional: task-based and/or resting state, or structural); examined neural changes associated with CBT treatment (either pre- and post-intervention or as predictors of response); evaluated CBT as a stand-alone intervention or combined with other forms of psychotherapy; focused on children or adolescents (up to 18 years old) with a primary clinical diagnosis of an anxiety disorder (including social anxiety, separation anxiety, specific phobia, agoraphobia, panic disorder, or generalized anxiety disorder) as defined by international diagnostic criteria (e.g., DSM-IV, DSM-5); and were published in English.

3.1.2.2.2. Exclusion criteria

Studies not evaluating children and adolescents were excluded (N=2). If the anxiety disorder was not the primary disorder, the study was not included, and all studies employing neuroimaging methods other than MRI (e.g., electroencephalography) were excluded. Also, dissertations, conference abstracts, single case studies, reviews of the literature or non peer-reviewed articles were not included in the current review.

3.1.2.3. Data extraction

Data regarding participants' demographics (mean age, percentage of female participants), sample size of the CBT group, the primary diagnosis, duration of the CBT intervention, the comparison group, the measure used for clinical improvement, the effect size can be found in Table 1 and Table 2.

3.1.2.4. Quality assessment

Two independent reviewers verified all the studies according to the Risk of Bias in Non-randomised studies of Interventions tool (ROBINS-I) (Sterne et al., 2016), and Risk of Bias 2 (RoB) (Higgins et al., 2016). In those cases where disagreements arose, the two independent reviewers discussed with a third author.

3.1.3. Results

3.1.3.1. Characteristics of the included studies

After conducting systematic searches in the electronic databases, 532 articles that fulfilled the criteria were identified. After removing duplicates (69 duplicates), 463 abstracts were screened, 446 of them were excluded because they were not related to the subject. Finally, full texts of the remaining 17 studies were evaluated which resulted in further two exclusions (articles did not focus on children or adolescents). The remaining 15 studies were included in the review. See Figure 1 for the Prisma flow diagram.

The age range of the children and adolescents included in these studies was between 6 and 18 years, with a generally higher proportion of females than males (see Table 1 and 2 for details). Several studies (n=10) also included healthy control participants, matched for age and other demographic characteristics.

Table 1*Characteristics of the included studies on neural changes from before to after CBT (primary aspect)*

Study	Total patients N (% Females)*	Mean age (SD)*	Primary diagnosis	Treatment(s)	Comparator	Clinical outcome(s)	Pre-post Cohen's <i>d</i>
Maslowsky et al., 2010	7 (57.1%)	13.4 (1.7)	GAD	8 w. CBT	8 w. SSRI (fluoxetine), and HC	PARS	1.56
Strawn et al., 2016**	9 (77.8%)	12.9 (2.0)	GAD, SP, SP at risk for BD	12 w. MBCT-C	No	PARS	Not reported
Burkhouse et al., 2018	9 (77.8%)	14.6 (2.7)	GAD, SP, SAD	12 w. CBT	12 w. SSRI (sertraline), and HC	PARS, MASC, LSAS	2.66
Haller et al., 2024**	69 (77.8%)	12.8 (3.0)	GAD, SP, SAD	12 w. CBT + ABMT***	HC	PARS, CGI-I	0.90

Abbreviations: SD=standard deviation, CBT=Cognitive Behavioral therapy, ABMT=Attention Bias Modification Treatment, HC=healthy control, GAD=generalized anxiety disorder, SP=social phobia, SAD=separation anxiety disorder, BD=bipolar disorder, PARS=Pediatric Anxiety Rating Scale, CGI-I= Clinical Global Impression - Improvement scale, MASC=Multidimensional Anxiety Scale for Children, LSAS=Liebowitz Social Anxiety Scale for Children and Adolescents. *Only for CBT; **Also included a part of prediction; ***Active/sham computerized.

Table 2*Characteristics of the included studies about neural predictors of CBT outcomes (primary aspect)*

Study	Total CBT patients N (% Females)*	Mean age (SD)*	Primary diagnosis	Treatment	Comparator	Outcome	Pre-post Cohen's d
McClure et al., 2010	7 (NR)	11.8 (1.8)	GAD, SP	8 w. CBT	8 w. SSRI (fluoxetine)	CGI-S, CGI-I	2.34
Kujawa et al., 2016	17 (64.7%)	13.1 (3.4)	GAD, SP, SAD	Up to 18 s. CBT	12 w. SSRI (sertraline)	PARS	2.19
Burkhouse et al., 2017	16 (68.8%)	14.5 (3.0)	GAD, SP	Up to 18 s. CBT	12 w. SSRI (sertraline)	PARS	2.58
White et al., 2017	54 (59.3%)	12.1 (2.8)	GAD, SP, SAD	Up to 12 w. CBT+ placebo/active ABMT**	HC	PARS	1.33 (active ABMT); 1.00 (placebo ABMT)
							1.16
Gold et al., 2017	75 (58.7%)	12.1 (3.0)	GAD, SP, SAD	Minimum 3 s. CBT + active/placebo ABMT***	HC	PARS	1.19
Burkhouse et al., 2020	28 (53.5%)	12.7 (3.7)	GAD, SP	Up to 18 s. CBT	12 w. SSRI (sertraline)	PARS	2.36
Sequeira et al., 2021	50 (NR)	11.0 (1.5)	GAD, SP, SAD	16 w. CBT	16 w. CCT, and HC	PARS	2.75 treatment responders/ 0.24 non-responders §
							1.49

Byrne et al., 2025	121 (60.3%)	12.8 (2.6)	GAD, SP, SAD	12 w. CBT + 9 w. active/sham gamified ABMT	HC	PARS, CGI-I	0.88 (active ABMT); 1.23 (sham ABMT)
							1.05
Linke et al., 2025	80 (≈62.1%)	12.5 (2.9)	GAD, SP, SAD	8–12 w. CBT + active/sham ABMT	HC	PARS	NR
Westbrook et al., 2025	67 (62.7%)	11.13 (1.37)	GAD, SP, SAD	16 s. CBT	16 s. CCT, and HC	PARS	NR
Zugman et al., 2025	54 (61%, dataset A); 15 (67%, dataset B)	13.1 (2.7; dataset A); 13.2 (3.4; dataset B)	any DSM-5 AD	12 w. CBT + active/ sham ABMT (dataset A); 8 w. CBT (dataset B)	HC	PARS	1.52 (dataset A); 0.95 (dataset B)
							1.23
							Total: 1.73

Abbreviations: NR=Not reported; SD=Standard deviation; GAD=Generalized anxiety disorder; SP=Social phobia; SAD=Separation anxiety disorder; AD=Anxiety disorder; PARS=Pediatric anxiety rating scale, CGI-S=Clinical Global Impression Severity scale; CGI-I=Clinical Global Impression - Improvement scale, CCT=Child Centered Therapy, CBT=Cognitive Behavioral therapy, ABMT=Attention Bias Modification Treatment; s.=session.

*Only for CBT; **From 5-12th CBT session; ***Only 40 participants, beginning 5th week; §Cohen's d not reported across all participants receiving CBT.

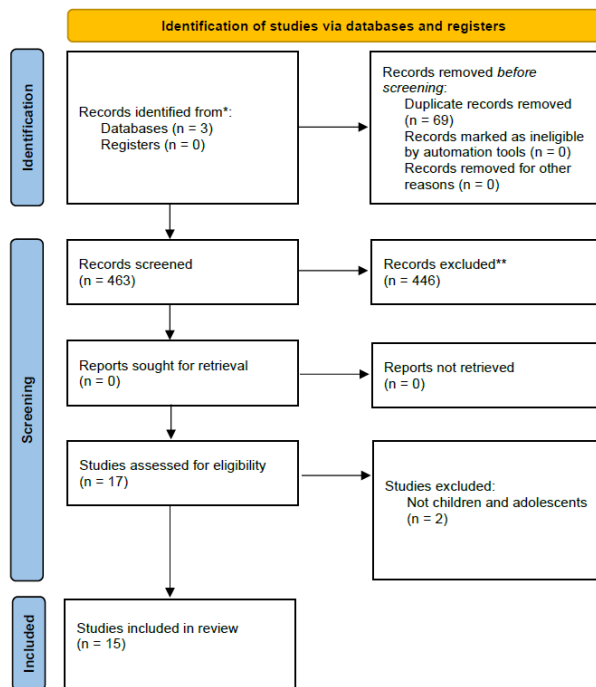


Figure 1. Prisma flow diagram

3.1.3.2. Quality of assessment

While many studies show a low risk of bias, there are instances where biases are unclear, particularly in terms of attrition and reporting, which may require further attention. Medication reporting was largely sufficient throughout the studies, though inconsistencies remain in a few cases. The documentation of inclusion and exclusion criteria was mostly robust, although not universally consistent. Moreover, four studies (Burkhouse et al., 2020; Maslowsky et al., 2010; McClure et al., 2007; Strawn et al., 2016) relied solely on ROI-based analyses, resulting in a relatively narrow analytical perspective and limiting comparability with studies using whole-brain approaches.

3.1.3.3. Neural changes from before to after cognitive behavioral therapy

Eight studies examined neural changes from pre- to post CBT, and six of these (Byrne et al., 2025; Haller et al., 2024; Linke et al., 2025; Strawn et al., 2016; Westbrook et al., 2025; White et al., 2017) also investigated pre-treatment predictors of treatment outcome.

Neural response in the ACC (Burkhouse et al., 2018; Strawn et al., 2016) and insula (Strawn et al., 2016) increased from pre to post CBT (2/8, 25%; 1/8, 12.5%, respectively) and these changes were further correlated with clinical symptom improvements (see Figure 2A, 2C).

3.1.3.4. Neural predictors of CBT outcomes

Neural response in the ACC (K. L. Burkhouse et al., 2017; Sequeira et al., 2021; Strawn et al., 2016) and amygdala-related activity or connectivity (Byrne et al., 2025; Maslowsky et al., 2010; White et al., 2017) was found to predict CBT outcomes in 3 studies (3/13, 23%). A small portion of studies (2/13, 15%) found insula (Strawn et al., 2016; White et al., 2017) and precuneus/cuneus (Byrne et al., 2025; Westbrook et al., 2025) activity or connectivity, postcentral gyrus (Kujawa et al., 2016; White et al., 2017) activity and nucleus accumbens activity or structure (Burkhouse et al., 2020; Sequeira et al., 2021) to predict treatment outcome (see Figure 2B, 2D).

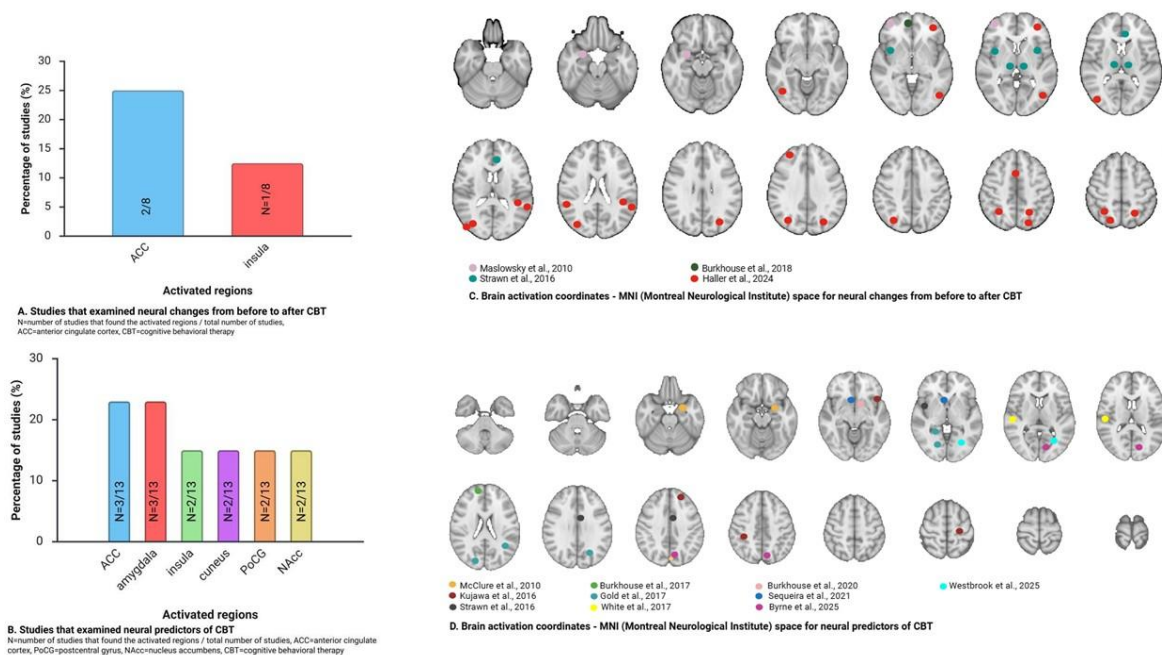


Figure 2. Study findings and activation patterns

3.1.4. Discussion

The aim of the present study was to systematically review studies on 1) neural changes before and after CBT in youths with anxiety disorders, and 2) neural predictors of clinical improvement after CBT. Some convergence across the reviewed literature suggests the involvement of the ACC, insula, amygdala. ACC and insula showed increased activity from pre- to post-CBT (2/8, 25%, and 1/8, 12.5% of studies, respectively), which was correlated with symptom changes. In addition, activity or connectivity in these regions was identified as a pre-treatment predictor of CBT outcomes (3/13, 23%, and 2/13, 15% of studies, respectively). Furthermore, amygdala activity or connectivity was also reported as a predictor of treatment outcome (3/13, 23%). While the current number of studies investigating neural markers of CBT in youth is relatively small, these results highlight the feasibility of identifying potential neural markers and predictors of CBT outcomes, which could enhance personalized interventions and improve clinical outcomes. However, there are several key limitations in the current literature that need to be addressed in future studies.

A minority of studies included in this review emphasized network-level analyses rather than focusing solely on individual brain regions. Specifically, only three studies (Haller et al., 2024; Linke et al., 2025; Sequeira et al., 2021) broadened their focus to include networks like the reward circuitry, the salience and attentional pathways, moving away from an emphasis on singular and isolated regions (e.g., amygdala).

The clinical profile of participants can influence therapeutic outcomes, with factors such as age, primary disorder, comorbidities, symptom severity, and social support shaping the course of psychopathology. In the present review, most participants were between 10 and 16 years old, and GAD was the most common primary diagnosis across all studies. This likely reflects the higher prevalence of GAD in adolescents compared to younger children (Rapee et al., 2023), but this also limits the generalizability of current findings to other common psychiatric disorders.

Another critical consideration is the variability in treatment modalities. Several studies combined cognitive behavioral therapy (CBT) with adjunctive interventions, such as active or sham attention bias modification training (ABMT) or mindfulness-based cognitive therapy. This methodological diversity complicates direct comparisons between standalone CBT and CBT integrated with other therapeutic approaches.

The variability in CBT protocols across studies, such as Social Effectiveness Therapy for Children, Coping CAT, or the CAT Project (Kendall & Hedtke, 2006), poses challenges for synthesizing results. Most studies employed the CAT protocol (Coping CAT or CAT Project) for CBT (Burkhouse et al., 2020; Burkhouse et al., 2018, 2017; Byrne et al., 2025; Gold et al., 2017; Kujawa et al., 2016; Linke et al., 2025; Westbrook et al., 2025; Zugman et al., 2025), which has been shown to effectively reduce anxiety symptoms in children and adolescents (Lenz, 2015). Moreover, this protocol is diagnosis-specific, targeting generalized anxiety, separation anxiety, and social anxiety. As a result, the current findings cannot be readily generalized to other CBT protocols tailored for panic disorder, specific phobias, or selective mutism, or to conditions.

The success of therapy is influenced not only by the chosen treatment approach but also by therapists' expertise, patient engagement, and individual differences such as comorbidities. Notably, only one study (Strawn et al., 2016) assessed children's involvement in therapy during the midpoint of treatment, utilizing the Therapeutic Alliance Scale for Children, and one study (Maslowky et al., 2010) accounted for patients' comorbidities. Regarding methodological quality and our risk of bias estimation, all studies raised concerns in at least one domain (e.g., attrition, concurrent medication, or inclusion/exclusion bias).

Reliability, the consistency of a measure under similar conditions, is fundamental to its utility in both research and clinical settings (Elliott et al., 2020). Recent meta-analyses (Elliott et al., 2020; Noble et al., 2019) have highlighted the strikingly low test-retest reliability of traditional fMRI measures such as functional connectivity and task-based fMRI. Measures with low reliability inherently limit their predictive power, hindering their use as biomarkers or forecasting clinical outcomes. Byrne et al. (2025) documented poor test-retest reliability for amygdala connectivity and no evidence of treatment-specific neural change, further reinforcing concerns that dot-probe-based connectivity measures lack the stability required for clinical translation. By contrast, Linke et al. (2025) showed that neural efficiency demonstrated moderate test-retest reliability across an 11–18-week interval, an uncommon level of stability for youth fMRI metrics, supporting its potential viability as a reproducible biomarker.

3.1.5. Limitations and future directions

This systematic review highlights several limitations that should be considered when interpreting the findings. The literature on our topic contains a limited number of studies, with significant heterogeneity in the methods employed. As a result, conducting a meta-analysis of the available research is currently not feasible. Additionally, the small or limited sample sizes in the studies may lead to findings that are less generalizable, statistically weaker, and potentially influenced by sample bias. An additional limitation in the current body of research is the notable variation in methodological approaches, including differences in imaging paradigms and data analysis techniques. The study samples were heterogeneous in terms of clinical presentations, with many participants exhibiting comorbid conditions. An important consideration is the feasibility of fMRI-based prediction in clinical settings. While MRI is a less accessible technology globally, the number of hospitals with an MRI is on the rise. Importantly, if MRI is demonstrated to be effective for clinical prediction, this could justify increased funding and drive efforts to enhance its accessibility and availability in healthcare systems.

We propose future research to address limitations highlighted in this review. Nearly half of the studies (7/15) are currently relatively small ($N < 30$), and larger studies are necessary to increase

statistical power to test the generalizability of results to new unseen individuals. While our review included a wide range of ages (6-18 years), adolescents are overrepresented in the literature, and future studies should also target younger individuals (i.e., 6-9 years) and incorporate developmental perspectives on anxiety disorders. Furthermore, in most of the reviewed studies, there are more female participants, which also limit the generalizability of the current findings in the literature.

Regarding practical applicability, while neuroimaging biomarkers such as ACC, insular, or amygdala activity show promise for predicting differential treatment responses, their clinical utility remains limited. Comparative studies evaluating multiple treatment approaches based on distinct biotypes are scarce, leaving clinicians to default to standard first-line options. Nonetheless, pediatric neuroimaging has made important strides toward closing this gap.

3.1.6. Conclusions

This systematic review highlights the potential of neuroimaging to enhance our understanding of CBT-related changes in youths with anxiety disorders. While promising, the field faces challenges due to methodological inconsistencies, small sample sizes, and limited replication. Future research should prioritize larger studies, standardized protocols, and rigorous validation techniques to improve reliability and clinical applicability.

3.2. Study 2. Mapping Associations Between Interpretation Bias and Adolescent Social Anxiety: A Network Analysis

3.2.1. Introduction

Adolescence constitutes a critical developmental window during which profound transformations occur in neural architecture, cognitive abilities, and socio-emotional adaptation (Andrews et al., 2021; Dahl et al., 2018; *Global Accelerated Action for the Health of Adolescents (AA-HA!) - Second edition*, n.d.). During this transition, peer relationships become increasingly central, and adolescents display heightened neural responsivity, attentional bias, and emotional sensitivity to social signals and evaluative feedback (Blakemore & Mills, 2014; Cheng et al., 2024; Sequeira et al., 2025). Within this developmental context, social fears serve an adaptive function by fostering attunement to group norms and safeguarding social acceptance (Gilbert, 2001). Yet, when apprehension regarding potential negative evaluation is amplified beyond normative levels, these fears can crystallize into persistent avoidance and distress (Sequeira et al., 2025). This maladaptive trajectory may culminate in social anxiety disorder (SAD), a condition that most frequently has its onset during adolescence and is often a chronic and deeply impairing condition (Alves et al., 2022).

Social anxiety exists on a continuum of severity, with many adolescents reporting substantial symptoms without meeting diagnostic thresholds (Knappe et al., 2015; Spence & Rapee, 2016). However, even at subclinical levels, social anxiety is linked to significant functional impairment and heightened risk for additional mental health problems (Knappe et al., 2009a; Tillfors & Van Zalk, 2015). The global prevalence of social anxiety disorder among adolescents has been estimated at 8.3% (Salari et al., 2024), with up to half of them reporting subclinical symptoms of social anxiety (Aune et al., 2022; Jefferies & Ungar, 2020; Mörtberg et al., 2022; Ranta et al., 2024; Walder et al., 2025). Therefore, progress in the field should outline the developmental course of social anxiety symptoms within the broader population and elucidate the mechanisms underlying the onset of anxiety disorders.

3.2.1.1. Relationship between interpretation biases and social anxiety symptoms

One promising cognitive mechanism is interpretation bias, which has been reliably linked to anxiety in both pediatric and adult population (Chen et al., 2020; Rozenman et al., 2024) and suggested as a potential pathway through which anxiety is transmitted from parents to their offspring (Subar & Rozenman, 2021). This bias appears to represent a dimensional feature of adolescent social anxiety (Loscalzo et al., 2018), evident not only in clinical SAD but also in manifestations of social anxiety within the general population (Haller et al., 2016; Miers et al., 2008; Rodgers et al., 2022; Yu et al., 2019).

Interpretation biases can manifest as hostile, where ambiguous social situations are perceived as intentionally harmful, or as threatening, where such situations are perceived as signaling potential danger (Dapprich et al., 2024). Usually, anxiety disorders are associated with threatening interpretation bias (Barrett et al., 1996; Waite et al., 2015), whereas disruptive behavior disorders are linked to hostile interpretation bias (Martinelli et al., 2018; Verhoef et al., 2019). Yet, evidence shows overlap (Barrett et al., 1996; Bell-Dolan, 1995; Reid et al., 2006), with anxious children also showing hostile bias and aggressive children displaying threatening bias, likely due to their shared roots in the fight-or-flight system (Andrews et al., 2021; Granic, 2014).

3.2.1.2. Network theory

To better understand how cognitive variables interact with symptoms of SAD, the network theory of psychopathology offers a valuable framework (Borsboom, 2017; Borsboom & Cramer, 2013; Fried & Cramer, 2017). This perspective conceptualizes mental disorders not as the result of a single hidden cause but as systems of interrelated elements, symptoms and other relevant variables, that mutually influence one another (Borsboom, 2017). Therefore, network analysis provides a

methodological approach for modeling these dynamics, treating symptoms and cognitive factors as nodes and their statistical associations as edges. Unlike classical latent variable models, which assume that a disorder reflects an underlying factor and rely on factor structures specified a-priori, network models capture the entire pattern of relations among variables (Borsboom, 2017). This enables researchers to examine which nodes are most central, which clusters of symptoms or cognitions form ‘communities’, and which connections may represent potential leverage points for intervention (Borsboom & Cramer, 2013; Epskamp, Borsboom, et al., 2018; Epskamp & Fried, 2018).

3.2.1.4. Objective

The present study had two primary aims. The first was to investigate the dynamic associations among distinct types of interpretation biases (hostile, threatening, and neutral) and various manifestations of sub-clinical levels of social anxiety in adolescents. The second aim was to examine the invariance of these network structures across adolescent sex and age.

3.2.2. Methods

3.2.2.1. Sample

Participants were 1,431 adolescents (714 females; 693 males; $M_{\text{age}}=12.87$, $SD_{\text{age}}=1.06$; range = 10–16 years). Data were collected from students in grades 5–8 across nine schools from 5 counties (Alba, Braşov, Cluj, Satu Mare and Suceava), $N=178$ in the fifth grade, $N=392$ in the sixth grade, $N=429$ in the seventh grade, and 362 in the eighth grade. The sample was ethnically diverse, comprising Romanian ($n=1384$), Hungarian ($n=9$), Roma ($n=6$), German ($n=2$), and adolescents from other ethnic backgrounds ($n=27$).

3.2.2.2. Measures

Interpretation bias was evaluated with Ambiguous Social Scenario Task-Youth Version (ASST) (Dapprich et al., 2022). This measure presents 10 brief social situations, each followed by three alternative interpretations reflecting hostile, threatening, or neutral appraisals. An example would be: “Some people you know are looking at you and start talking to each other. Would you think ...” and the possible answers could be: neutral - “They are looking into my direction randomly.”, threatening - “They are probably gossiping about me” and hostile - “They look really stupid.”; all the items can be found in (Dapprich et al., 2024). Participants estimate, on a 0–100% visual analogue scale, how likely each interpretation would come to mind, which allows simultaneous endorsement of multiple interpretations for the same scenario.

Social Anxiety Symptoms were measured with the Social Anxiety Scale for Adolescents-Short Form (SAS-A-SF) (Nelemans et al., 2019) and assesses three core dimensions of adolescent social anxiety - fear of negative evaluation (FNE), social avoidance and distress in novel situations (SAD_New), and generalized social avoidance and distress (SAD_General), each represented by four items (Alam et al., 2021).

Socio-economic status (SES) was measured via the Family Affluence Scale (Currie et al., 2024), which provides information about family car and laptop ownership, number of holidays and child room ownership.

3.2.2.3. Procedure

After obtaining informed parental consent and adolescent assent, participants completed a standardized battery of self-report questionnaires designed to ensure procedural consistency. The instruments were administered in schools, either via a printed QR code or an online link accessible on both mobile and desktop devices. Data collection occurred in a confidential and distraction-free environment under the supervision of a trained researcher and the class teacher.

3.2.2.4. Data analysis plan

All data analyses were carried out in R via the RStudio interface (Posit, n.d.). First, we screened the data to ensure values were within acceptable ranges, and we computed the percentage of missing

data for each item. We also computed Little's test to check whether data were missing completely at random (Little, 1988). If Little's test is statistically significant ($p < .05$), the null hypothesis (MCAR) must be rejected and the analyses are conducted under the alternative hypothesis, stating that missingness depends on the available scores from the model.

The network models were estimated as Graphical Gaussian Models (GGMs), in which relationships between variables (edges) represent partial correlation coefficients. (Epskamp, Waldorp, et al., 2018). All models were estimated with the 'ggmModSelect' algorithm (Isvoranu et al., 2022). Stability of the edges was tested via a 25% case-drop, 1,000-bootstrap procedure. Regarding centrality, we computed bridge expected influence (Jones et al., 2021). This centrality index is computed by adding up the values of each edge a node has outside its community. To test the stability of the centrality values, we computed the correlation-stability (CS) coefficient. CS represents the percentage of data that can be dropped while maintaining the confidence interval of the correlation between the order of the centrality indices computed on the full data and on the subsample above .80. CS values higher than .50 are regarded as acceptable, and centrality indices are deemed interpretable (Epskamp et al., 2018a).

We tested the invariance of all networks across adolescents' biological sex and age (preadolescents (≤ 12) vs. adolescents (≥ 13)). Invariance was assessed using the Network Comparison Test with 1,000 permutations (van Borkulo et al., 2019).

For the first network, estimated using the total scores of ASST and SAS, missing data were handled via univariate item-level imputation. Finally, for the networks estimated at the ASST item level together with the SAS total scores, missing data were handled via Full Information Maximum Likelihood. Note that the SAS total scores were computed from data after the univariate item-level imputation. The data and R scripts used in this study are publicly available online (https://osf.io/gst4n/overview?view_only=80f41c731cb34ad9bcd94512e3e01ab2).

3.2.3. Results

3.2.3.1. Descriptive statistics

Missing data at the item level ranged from 0.07% for information on the adolescent's sex to 31.52% for item ASST_8B. For the SAS items, the average percentage of missing data was 0.54% (median = 0.56, range: 0.35 - 0.70), whereas for the ASST items it was 20.48% (median = 20.68, range: 10.13 (ASST_5B) - 31.52 (ASST_8B)). Regarding missingness patterns, Little's test was not statistically significant ($\chi^2 = 14716$, $df = 24499$, $p = .999$), indicating that the missing completely at random (MCAR) hypothesis cannot be rejected. The assumption of univariate normality was supported: skewness ranged from -0.18 to 1.5, and kurtosis ranged from -1.41 to 0.83. However, multivariate normality was not supported (Henze-Zirkler test = 5724, $p < .001$).

3.2.3.2. Network for the total score

For the first network, with total scores, including ASST (threatening, hostile, and neutral interpretations) and SAS (Fear of Negative Evaluation, Social Avoidance and Distress-New, Social Avoidance and Distress-General), we obtained excellent fit indices (RMSEA = 0.035, CFI = 1.00, TLI = 0.99). Threatening interpretation had positive connections with all three SAS subscales, the strongest being with Fear of Negative Evaluation (see Figure 3). This connection was replicated in 100% of 1,000 bootstrap samples using 75% subsamples of the total data, indicating a stable connection. Stable connections (present in more than 80% of bootstrap estimates) were also found between threatening interpretation and Social Avoidance and Distress-General (positive; present in 96% of subsample estimates), as well as between hostile interpretation and Social Avoidance and Distress-General (negative; present in 86% of the estimates).

Regarding centrality, the correlation-stability (CS) coefficient for bridge expected influence was excellent ($CS = .75$), supporting the interpretation of the centrality indices. The highest bridge expected influence level was observed for threatening interpretation (see Figure 4), followed by fear of negative evaluation. The lowest centrality (negative bridge expected influence) was observed for hostile interpretation.

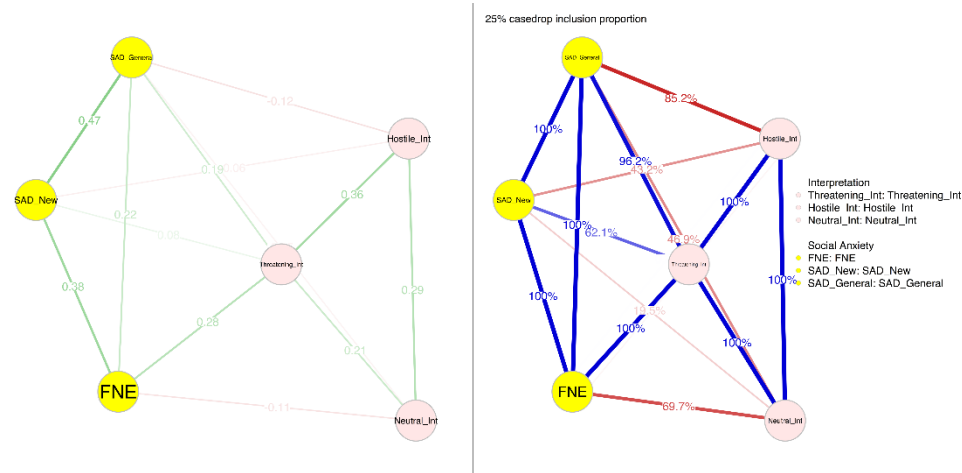


Figure 3. Network Associations Between Social Anxiety Dimensions and Interpretation Biases

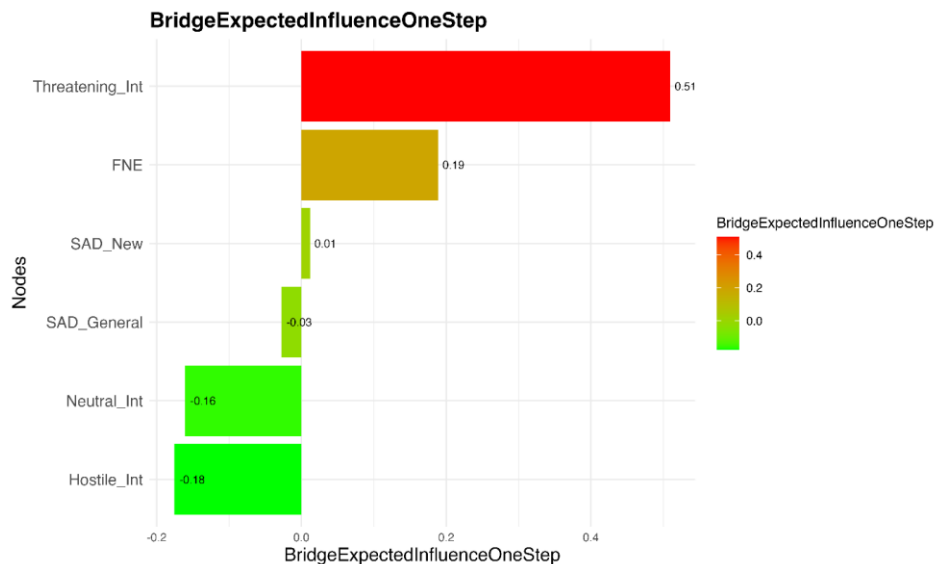


Figure 4. Bridge Expected Influence Across Social Anxiety Dimensions and Interpretation Bias Nodes

3.2.3.3. Network between threatening interpretation scenario and SAS total scores

For this network we obtained excellent fit indices ($RMSEA = 0.029$, $CFI = 0.99$, $TLI = 0.99$). The strongest connection was between ASST-10A ('Now that all of them know, they are definitely going to gossip about me.') and fear of negative evaluation (see Figure 5). This connection was

replicated in 97% of 1,000 bootstrap samples using 75% subsamples of the total data, indicating a stable connection. Another stable connection between communities (present in more than 85% estimates) was between ASST-9C ('Why doesn't he like me? I hope nobody saw that I just got the push.') and fear of negative evaluation.

Regarding centrality, the correlation-stability (CS) coefficient for bridge expected influence was excellent ($CS = .75$), supporting the interpretation of the centrality indices. The highest centrality level was observed for fear of negative evaluation (see Figure 6), followed by ASST-9C, Social Avoidance and Distress-General, and ASST-10A.

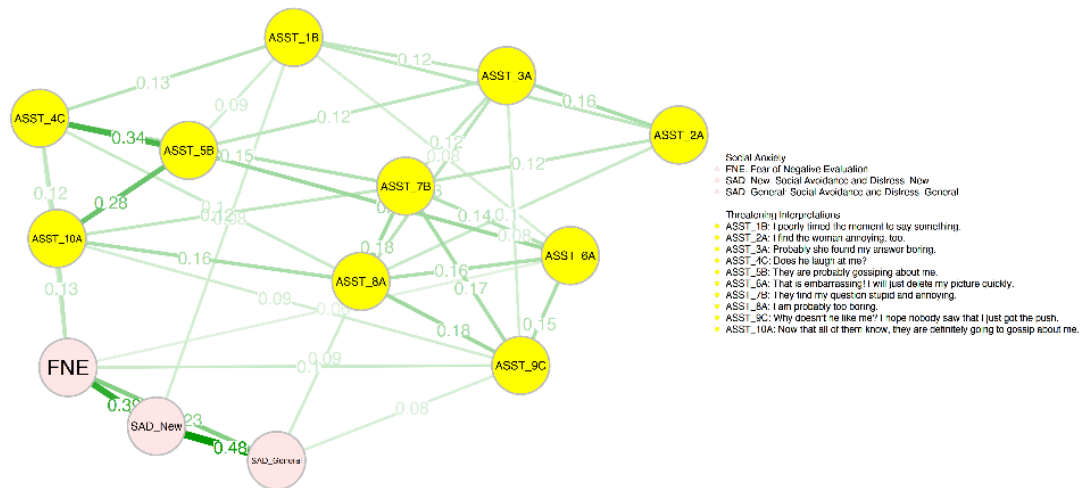


Figure 5. Network Structure of Threatening Interpretations and Social Anxiety

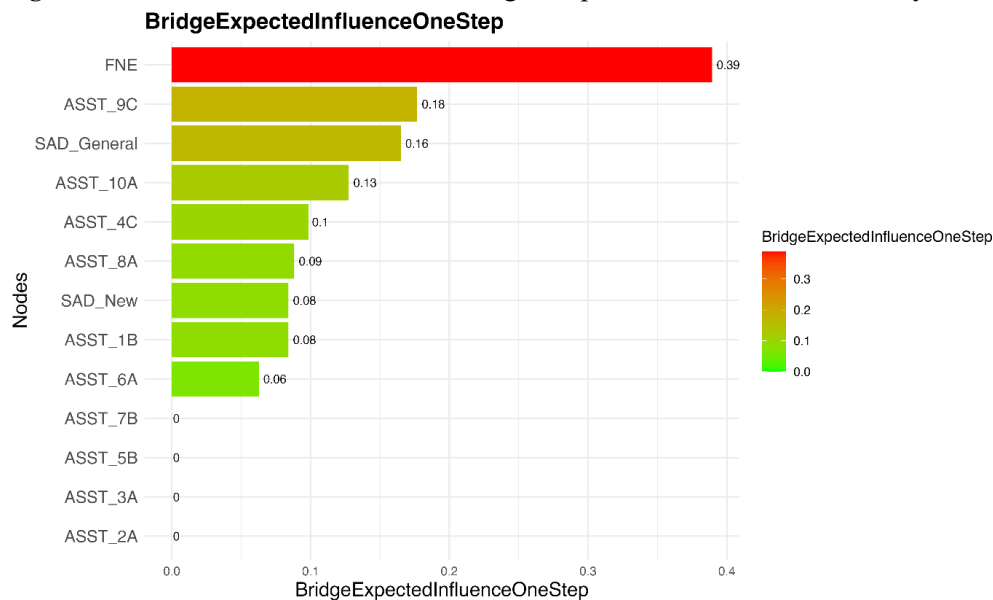


Figure 6. Bridge Expected Influence of Threatening Interpretation Items and Social Anxiety Dimensions

3.2.3.4. Network between hostile interpretation scenario and SAS total scores

For this network we obtained good fit indices ($RMSEA = 0.025$, $CFI = 0.99$, and $TLI = 0.99$). The strongest connection was between ASST-2B ('I find the woman annoying, too') and fear of negative evaluation (see Figure 7). This connection was replicated in 73% of 1,000 bootstrap samples using 75% subsamples of the total data, indicating a relatively stable connection. A worth mentioning edge

(negative valence) was between ASST-1C ('They just don't look at me by chance but they are certainly interested in what I say.') and fear of negative evaluation (replicated in 57% of the subsamples). The rest of the connections between communities were not worth mentioning as they were not replicated in at least 50% of the bootstraps.

Regarding centrality, the correlation-stability (CS) coefficient for bridge expected influence was excellent ($CS = .67$), supporting the interpretation of the centrality indices. The highest centrality level was observed for fear of negative evaluation, followed by ASST-2B, while the lowest (negative valence) was for ASST-1C.

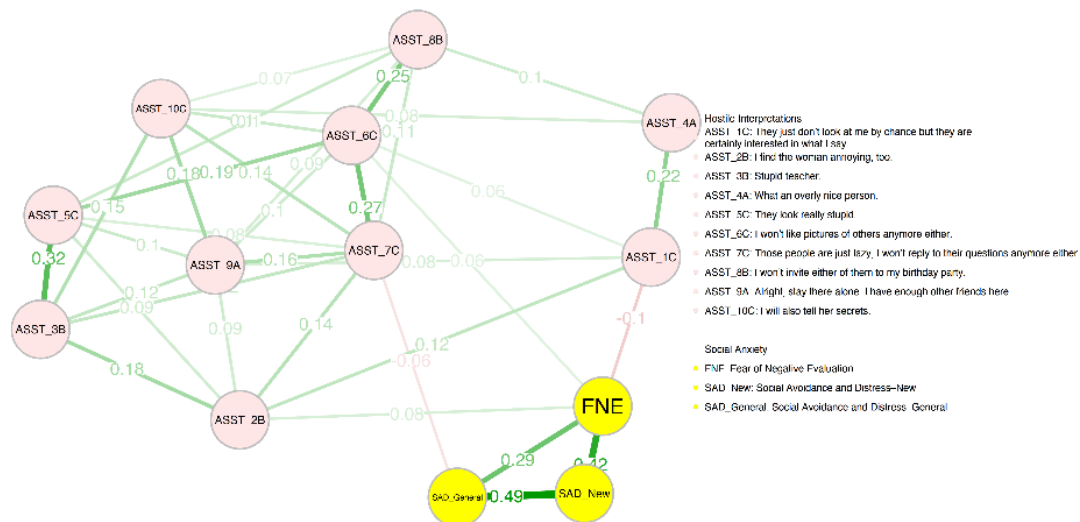


Figure 7. Network Structure of Hostile Interpretations and Social Anxiety Dimensions

3.2.3.5. Network between neutral interpretation scenario and SAS total scores

For this network we obtained excellent fit indices ($RMSEA = 0.025$, $CFI = 0.99$, $TLI = 0.99$). The strongest connection was between ASST-1A ('They did not expect me to start talking.') and Social Avoidance and Distress-General (see Figure 8). This connection was replicated in 99% of 1,000 bootstrap samples using 75% subsamples of the total data, indicating a stable connection.

Regarding centrality, the correlation-stability (CS) coefficient for bridge expected influence was excellent ($CS = .75$), supporting the interpretation of the centrality indices. The highest centrality level was ASST-1A and the lowest (negative) was for ASST-4B ('He greets everyone like this.').

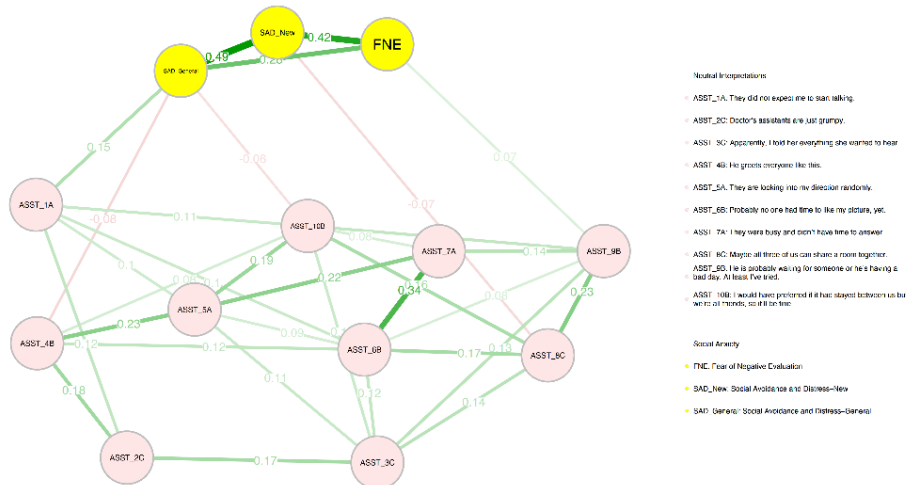


Figure 8. Network Structure of Neutral Interpretations and Social Anxiety Dimensions

3.2.3.6. Network invariance across the sex and age

Regarding the network estimated at the level of total scores, we found no significant differences with respect to adolescents' sex in the total connectivity strength of the network ($p = .665$), or in the connection patterns (network structure) ($p = .075$). However, for the connection between threatening and hostile interpretation we found a sex significant difference ($p = .029$): the edge was weaker in males (edge weight = 0.29) than in females (edge weight = 0.43). We found no significant differences with respect to adolescents' age in the total connectivity strength of the network ($p = .847$), or in the connection patterns (network structure) ($p = .083$). However, for the connection between fear of negative evaluation and neutral interpretation, we found a significant age difference ($p = .029$): the edge was weaker in preadolescents (edge weight = 0.00) than in adolescents (edge weight = -0.14).

3.2.4. Discussion

The main objective of the present study was to explore how different types of interpretations (hostile, threatening, neutral) are associated with social anxiety symptoms within the general adolescent population. We further examined whether these associations vary as a function of sex and age. In addition, group differences were investigated both at the level of edge weights and at the centrality level of the nodes.

The present study provides robust evidence that interpretation biases are closely linked to social anxiety symptoms in adolescents. Consistent with the current literature (Chen et al., 2020; Stuijzand et al., 2018; Subar et al., 2022), threatening interpretations showed the strongest association with fear of negative evaluation. At the total-score level, threatening interpretations exhibited the highest bridge expected influence, highlighting their role as a key link between cognitive biases and anxiety symptoms. Given the cross-sectional nature of the data, no causal conclusions can be drawn. However, the observed link between social anxiety and threatening interpretations is in line with theoretical frameworks that conceptualize emotional disorders as systems of interconnected cognitive, affective, physiological, and behavioral components (Chorpita et al., 1998; Dapprich et al., 2024; Schniering & Rapee, 2004).

Compared to threatening interpretations, the hostile interpretation network showed a more limited and less consistently replicated pattern of associations with social anxiety symptoms. These results indicate that threatening interpretations occupy a central role within the network of social anxiety, whereas hostile attributions may reflect related but less specific processes.

The network analysis of neutral interpretations revealed that the strongest and most stable connection was between the neutral interpretation “They did not expect me to start talking” (ASST-1A) and Social Avoidance and Distress-General. This finding suggests that even ostensibly neutral or ambiguous interpretations may be closely linked to avoidance-related aspects of social anxiety. While this pattern is consistent with cognitive models emphasizing biased processing of social information (Clark & Wells, 1995), the cross-sectional nature of the data precludes conclusions regarding the directionality of this association.

Overall, the network connectivity and structure of social anxiety and interpretation biases were consistent across sex and age in adolescents, with only a few specific differences. The observed age-related difference may suggest developmental increases in sensitivity to social evaluation (Waite et al., 2015). This interpretation is consistent with research indicating that fear of negative evaluation plays a central role in linking social comparison processes to maladaptive outcomes, particularly in socially evaluative contexts (Feng et al., 2025; Henricks et al., 2023; Li et al., 2023). However, given the cross-sectional nature of the data, these findings should be interpreted cautiously and warrant further investigation using longitudinal designs.

3.2.5. Limitations and Future Directions

This study has several limitations. Its cross-sectional, self-report design precludes causal inference and may be influenced by social desirability. Future work should replicate these findings using longitudinal designs, as well as behavioral measures, to clarify the temporal direction of associations and test whether interpretation bias prospectively predicts changes in social anxiety.

Despite these limitations, the network approach revealed robust, interpretable patterns. Future research should investigate whether these networks generalize to clinical populations and across cultures. Another important direction for future research would be to incorporate measures of functional impairment within network models to better understand how interpretation biases relate to clinically meaningful outcomes. Additionally, future studies should consider the use of more objective and multi-indicator assessments of key constructs, such as social anxiety and interpretation bias. Recent evidence suggests that network models based on single indicators may be substantially affected by measurement error, which can impair the reliability and stability of estimated associations (de Ron et al., 2022).

3.2.6. Conclusions

This study examined the network linking hostile, threatening, and neutral interpretation biases with social anxiety symptoms in adolescents. Threatening interpretations showed the strongest and most consistent associations, particularly with fear of negative evaluation, highlighting their important role in adolescent social anxiety. In contrast, hostile interpretations showed fewer and less consistently replicated associations, suggesting a more limited and less specific relationship with social anxiety symptoms. Network structures were largely similar across sex and age with minor edge-level differences.

3.3. Study 3. Moment-to-Moment Neural Variability During Anticipation of Public Speaking in Social Anxiety Disorder

3.3.1. Introduction

As the lifetime burden of mental disorders continues to rise, there is still a lack of reliable brain-based markers to support precise diagnosis and treatment of prevalent conditions such as social anxiety disorder (SAD) (Williams & Whitfield Gabrieli, 2024). Cognitive-behavioural frameworks of SAD (Clark, 1995; Rapee & Heimberg, 1997) suggest that negative self-imagery and anticipation of adverse outcomes heighten anxiety, promoting avoidance and safety behaviours that hinder learning and maintain maladaptive outcomes (Morrison et al., 2016). Despite its clinical relevance, the anticipatory processes underlying pre-event anxiety remain relatively underexplored in the literature (Vassilopoulos et al., 2017).

Neuroimaging, particularly functional magnetic resonance imaging (fMRI), aims to parse the heterogeneity of processes underlying SAD by identifying distinct patterns of circuit-level dysfunction (Williams & Whitfield Gabrieli, 2024). However, resting-state fMRI primarily captures intrinsic brain activity in the absence of externally driven cognitive processes (Mizzi et al., 2024), and task-based experiments, largely centered on emotional face processing (Yu et al., 2021), remain limited in ecological validity. These limitations highlight the need for experimental approaches that better approximate real-world social-evaluative contexts. Paradigms that simulate the anticipation of, or exposure to, socially threatening situations, such as public speaking, could offer a valuable framework for investigating the dynamic psychophysiological processes underlying anxiety as it unfolds in real time (Miskovic & Schmidt, 2012).

Advances in fMRI have improved the understanding of SAD neurobiology (Bas-Hoogendam & Westenberg, 2020). However, recent meta-analytic findings highlight the limited reliability of both task-based and resting-state fMRI when evaluated using conventional metrics such as functional connectivity and mean brain activation (Elliott et al., 2020; Noble et al., 2019).

Against this backdrop, moment-to-moment fluctuations in brain activity, commonly indexed as signal variability (e.g., the standard deviation of the blood oxygen level-dependent [BOLD] signal over time), are increasingly recognized as meaningful aspects of neural function rather than mere noise (Garrett et al., 2010b), given their enhanced predictive power and promising reliability (Garrett et al., 2011; Garrett et al., 2013a). Although brain signal variability has gained increasing attention in recent years (Garrett et al., 2013b; Tsikonofilos et al., 2025), its investigation in anxiety disorders is still scarce, with only a few studies addressing its relevance for diagnosis (Li et al., 2019) and treatment prediction (Månsson et al., 2022).

Therefore, current research is constrained by limited ecological validity and measurement reliability, alongside a predominant reliance on region-of-interest (ROI)-based approaches. To address these limitations, we used a whole-brain, voxel-wise Partial Least Squares (PLS) (McIntosh & Lobaugh, 2004) approach to examine moment-to-moment neural variability during an ecologically valid anticipatory public speaking task. We tested whether variability differs between social-evaluative threat and a baseline condition, within and between groups (SAD vs. healthy controls). A second objective is to investigate the relationship between neural variability (speech anticipation vs baseline) and the severity of social anxiety symptoms.

3.3.2. Methods

3.3.2.1. General procedure

In the current study, participants were drawn from a previously conducted randomized controlled trial (ClinicalTrials.gov identifier: NCT01312571), described in detail in prior publications (Månsson et al., 2015, 2016; Månsson et al., 2013). Although the present study was not

preregistered but relies on data collected under this preregistered protocol. All participants provided written informed consent, and the study was approved by the local ethics committee. Briefly, participants with SAD and healthy controls completed an anticipatory speech anxiety task during a single fMRI session.

3.3.2.2. Participants

Recruitment was conducted primarily through online and media advertisements. Individuals completed web-based self-report measures assessing social anxiety, depression, and MRI safety eligibility. Those meeting preliminary criteria underwent a structured diagnostic telephone interview. Diagnoses of SAD were established using structured clinical interviews based on DSM-IV criteria (SCID-I; First & Gibbon, 2004). Healthy participants were screened using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to confirm the absence of psychiatric disorders. Eligibility criteria required participants to be at least 18 years old, without neurological disorders or suicidal ideation, and not engaged in concurrent psychological treatment. Individuals receiving pharmacological treatment were included only if their dosage had remained stable for a minimum of three months prior to participation.

The final sample included a total of 50 participants: 26 individuals with SAD (mean age: 32.27 ± 9.63 , 84.6% females, mean Liebowitz Social Anxiety Scale - Self Report (LSAS-SR): 76.31 ± 18.72) and 24 healthy controls (mean age: 31.58 ± 9.38 , females 70.8%, mean LSAS-SR: 21.29 ± 11.55).

3.3.2.3. Clinical assessment

We assessed symptom severity of SAD using the self-report version of the LSAS-SR, a well-established measure with high internal consistency ($\alpha \geq 0.79$) and strong agreement with the clinician-administered version ($r = 0.78-0.85$, $p < 0.01$) (Baker et al., 2002).

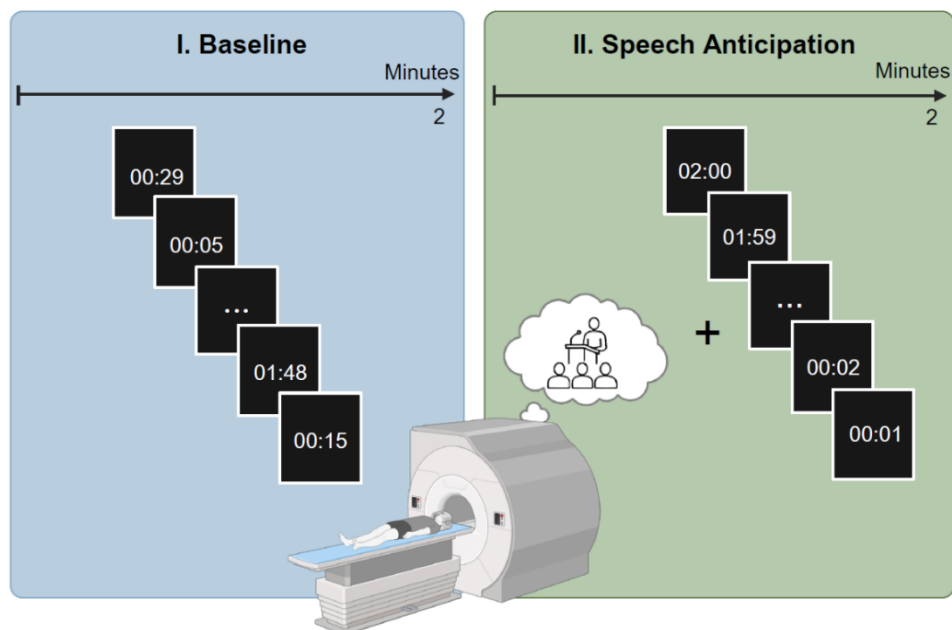


Figure 9. Experimental design during fMRI. *Panel A I.* Baseline: Participants passively observed a 2-minute sequence of randomly presented numbers. *Panel B II.* Speech anticipation: Participants watched a 2-minute countdown while getting ready to speak in front of an audience, designed to elicit anticipatory social anxiety.

3.3.2.4. Image acquisition, preprocessing and neural variability estimation

Functional MRI data were collected using a 3T. Neural variability was quantified as the standard deviation of the BOLD signal (SD_{BOLD}) across time within each condition, computed voxelwise for each participant. This measure captures the amplitude of moment-to-moment fluctuations in neural activity over the duration of each run and provides an index of temporal variability independent of mean activation (see also (Garrett et al., 2010b; Månsson et al., 2022)).

3.3.2.5. fMRI experimental task

In this experiment, participants were instructed to prepare for a public speech following the scanning session. The task comprised two conditions (baseline and speech anticipation), both performed during MRI scanning (Figure 9).

3.3.2.6. Data analysis

In MATLAB (version R2024a; The MathWorks, Inc.), we applied partial least squares (PLS) analysis, a multivariate technique, was used to identify latent variables (LVs) capturing the maximal covariance between whole-brain neural variability and external variables (e.g., task conditions or behavior) (McIntosh & Lobaugh, 2004). This approach is well-suited for neuroimaging data, as it captures spatially distributed conditions (e.g., anticipation and baseline), groups (e.g., SAD and HC), and interaction effects across the whole brain rather than testing each voxel independently (Mihalik et al., 2022).

The reliability of voxel saliences was evaluated via bootstrap resampling (1000 iterations), and bootstrap ratios (BSRs; salience divided by bootstrap standard error) exceeding ± 3.5 threshold were considered robust. The statistical significance of each latent variable was assessed using permutation testing (1000 permutations).

To complement the multivariate analyses, brain scores derived from the significant latent variable were subsequently analyzed using Linear Mixed-Effects Model (LMM). These models were implemented in Python (Version 3.12; Python Software Foundation) using the statsmodels (Version 0.14.6) to examine the effects of condition (baseline vs. speech anticipation) and group (SAD vs. HC) on neural variability while controlling for age and sex.

3.3.3. Results

Question 1: Does task-based neural variability differ between the speech anticipation and a baseline condition in SAD patients, relative to healthy controls?

PLS identified one statistically significant latent variable explaining 70.82% of cross-block covariance (permuted $p < 0.001$). LMM confirmed effects of group ($\beta = 4.691$, $p = 0.032$) and condition ($\beta = -6.410$, $p < 0.001$), with no group $\times$ condition interaction ($p = 0.871$). After adjusting for age ($\beta = -0.214$, $p = 0.026$) and sex ($\beta = 2.949$, $p = 0.177$), the group effect was attenuated and marginal ($\beta = -4.137$, $p = 0.051$), while the condition effect remained robust ($\beta = -6.410$, $p < 0.001$). Higher neural variability was observed during the speech anticipation condition (relative to baseline), and lower neural variability in SAD patients compared to HC, across regions reported in Figure 10A, 10B and Table 3. Highlighted activations in Figure 10C demonstrate effects on both condition and group: left amygdala/hippocampus (Figure 10C), right occipital gyrus (Figure 10D) and right insular cortex (Figure 10E).

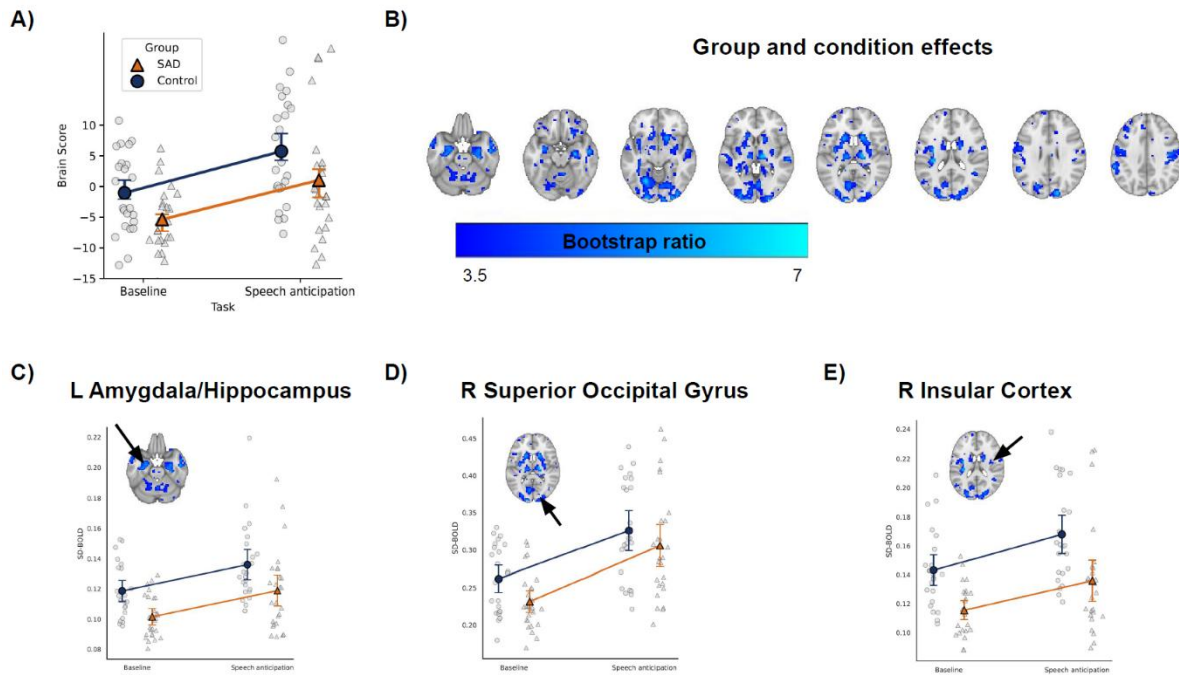


Figure 10. *A)* Individual data points (light gray, jittered) represent subject-level brain scores reflecting multivariate pattern expression across brain regions. *B)* Brain regions showing significant clusters for LV1 reflecting the interaction between condition (baseline vs. speech anticipation) and group (SAD vs. HC). *C)* Mean SD_{BOLD} reflecting LV1 expression in one cluster (left hippocampus). *D)* LV1 mean SD_{BOLD} expression in the right occipital gyrus. *E)* LV1 mean SD_{BOLD} expression in the right insular cortex. **Abbreviations:** HC, healthy controls; SAD, social anxiety disorder; LV1, latent variable 1; PLS, partial least squares; MC, mean-centering; BSRs, bootstrap ratios; SEM, standard error of the mean.

Table 3

Significant activations for both the between-condition contrast (baseline vs. speech anticipation) and the between-group contrast (SAD vs. HC)

	MNI				
Cluster Region	X	Y	Z	Size	BSR
R Insular Cortex	33.0	-6.0	15.0	2738	7.207
R Superior Occipital Gyrus	18.0	-99.0	6.0	2492	6.878
L Ventral Posterolateral Nucleus, Thalamus	-18.0	-18.0	6.0	150	6.775
R Supramarginal Gyrus	60.0	-33.0	42.0	122	6.316
L Middle Temporal Gyrus	-54.0	3.0	-27.0	265	6.292
L Amygdala/Hippocampus	-27.0	-15.0	-18.0	702	6.207
L Postcentral Gyrus	-39.0	-15.0	36.0	253	6.024
R Middle Temporal Gyrus	57.0	6.0	-27.0	48	5.350
R Superior Frontal Gyrus (dorsolateral part)	15.0	24.0	60.0	97	5.058
R Superior Temporal Gyrus	54.0	-15.0	-3.0	91	4.955
R Mid Frontal Gyrus (dorsolateral part)	39.0	9.0	54.0	28	4.801
L Inferior Temporal Gyrus	-48.0	-45.0	-21.0	23	4.788
R Inferior Frontal Gyrus (opercular part)	45.0	18.0	6.0	21	4.762
R Medial Superior Frontal Gyrus	9.0	39.0	42.0	44	4.729
R Mid Frontal Gyrus (dorsolateral part)	36.0	51.0	3.0	23	4.571
L Rolandic Operculum	-60.0	-3.0	12.0	41	4.525
R Mid Frontal Gyrus (dorsolateral part)	33.0	30.0	36.0	50	4.500
L Supplementary Motor Area	-6.0	6.0	63.0	22	4.365

R Medial Superior Frontal Gyrus	9.0	63.0	27.0	26	4.300
R Posterior Orbitofrontal Cortex	36.0	30.0	-21.0	23	4.185

Note. Only clusters with size > 20 voxels are reported. Coordinates are in MNI space.
Abbreviations: BSR - bootstrap ratio, MNI - Montreal Neurological Institute, R - right, L - left, SAD - social anxiety disorder, HC - healthy control, Mid - middle.

Question 2: Does task-based neural variability differ between the speech anticipation and the baseline condition in patients with SAD?

In SAD patients, PLS identified a significant condition effect (LV1; 100% covariance, permuted $p < 0.001$), showing higher neural variability during speech anticipation in occipital, cerebellar, frontal, and temporal regions, as well as subcortical structures including the striatum (putamen, nucleus accumbens), hippocampus, and parahippocampal gyrus (see Table 3, Figure 11).

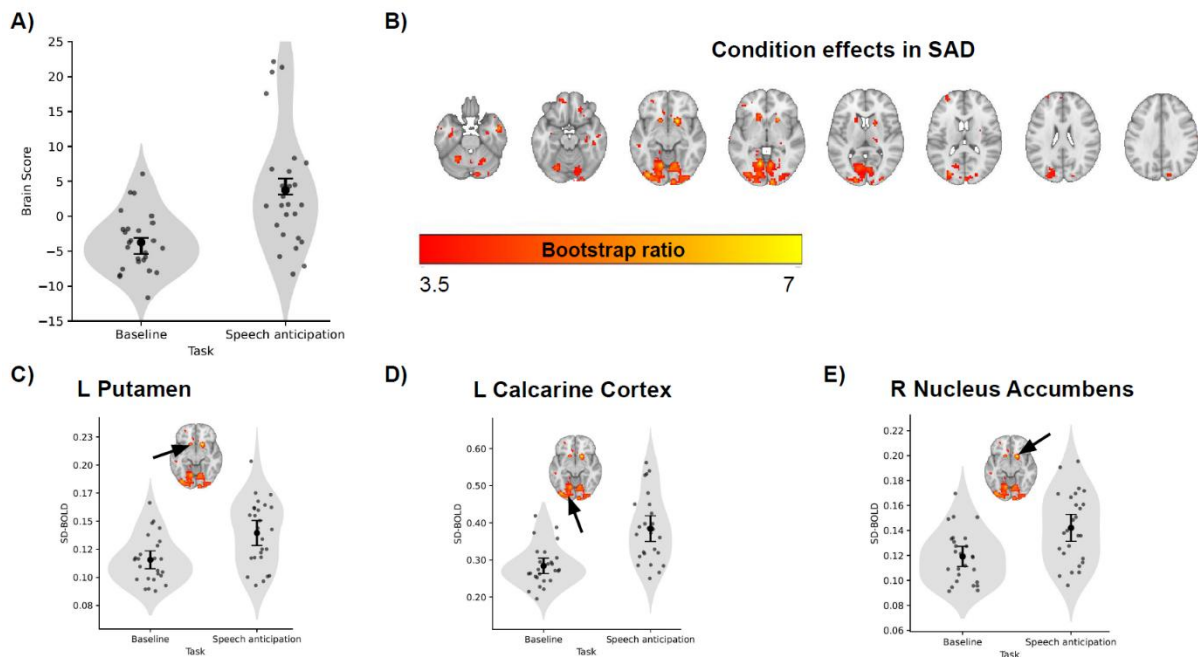


Figure 11. *A)* Individual data points (light gray, jittered) represent subject-level brain scores reflecting multivariate pattern expression across brain regions. *B)* Brain regions showing significant clusters for LV1 reflecting the interaction between baseline vs. speech anticipation conditions. *C)* Mean SD_{BOLD} reflecting LV1 expression in one cluster (left putamen). *D)* Mean SD_{BOLD} of LV1 in the left calcarine cortex. *E)* Mean SD_{BOLD} of LV1 in the right nucleus accumbens. **Abbreviations:** SAD, social anxiety disorder; LV1, latent variable 1; PLS, partial least squares; MC, mean-centering; BSRs, bootstrap ratios; SEM, standard error of the mean.

Question 3: Does task-based neural variability differ between the speech anticipation and the baseline condition in healthy controls?

In HC, PLS identified a significant condition effect (LV1; 100% covariance, permuted $p < 0.001$), indicating higher neural variability during speech anticipation in occipital, cerebellar, frontal, temporal, and parietal regions, as well as the insula, amygdala, and caudate nucleus (see Table 4).

Table 4

Clusters for within-group analysis (healthy control) - anticipation vs baseline condition
MNI

Cluster Region	X	Y	Z	Size	BSR
R Supramarginal Gyrus	60	-45	30	128	-6.918
L Inferior Occipital Gyrus	-12	-99	-9	891	-6.462
R Insula	36	-9	15	105	-6.322
R Lingual Gyrus	24	-69	-3	893	-6.207
L Supplementary Motor Area (SMA)	-9	9	69	78	-6.067
R Cerebellar Crus I	24	-69	-39	118	-5.656
Subcallosal Cortex	-15	24	-12	102	-5.552
L Mid Temporal Gyrus	-57	3	-30	81	-5.522
White Matter	0	0	-3	37	-5.411
R Mid Temporal Gyrus	57	-60	12	57	-5.344
R Precuneus	9	-48	75	36	-5.212
R Mid Temporal Gyrus	57	-24	-9	91	-5.200
R Mid Frontal Gyrus (posterior part)	39	36	39	26	-5.152
L Amygdala	-27	0	-24	44	-5.062
R Middle Temporal Pole	36	3	-33	50	-4.996
L Precentral Gyrus	-21	-24	75	54	-4.965
R Mid Front. Gyrus (posterior/dorsal part)	39	48	27	37	-4.923
L Mid Temporal Gyrus	-63	-6	-15	94	-4.882
R Cerebellar Lobule VIII	24	-48	-57	39	-4.876
R Caudate Nucleus	12	12	12	29	-4.804
Brain-Stem	9	-36	-27	39	-4.795
R Mid Temporal Pole	45	12	-39	42	-4.660
R Sup Front. Gyrus (posterior/dorsal part)	30	63	12	22	-4.512

Note. Only clusters with size > 20 voxels are reported. Coordinates are in MNI space. **Abbreviations:** BSR - bootstrap ratio, MNI - Montreal Neurological Institute, R - right, L - left, HC - healthy control, Mid - Middle.

Question 4: Does anticipatory anxiety related neural variability correlate with symptom severity in adults with social anxiety disorder?

Behavioral PLS revealed no statistically significant association between neural variability and social anxiety symptom severity in SAD patients (permuted $p = 0.431$); see figure 12.

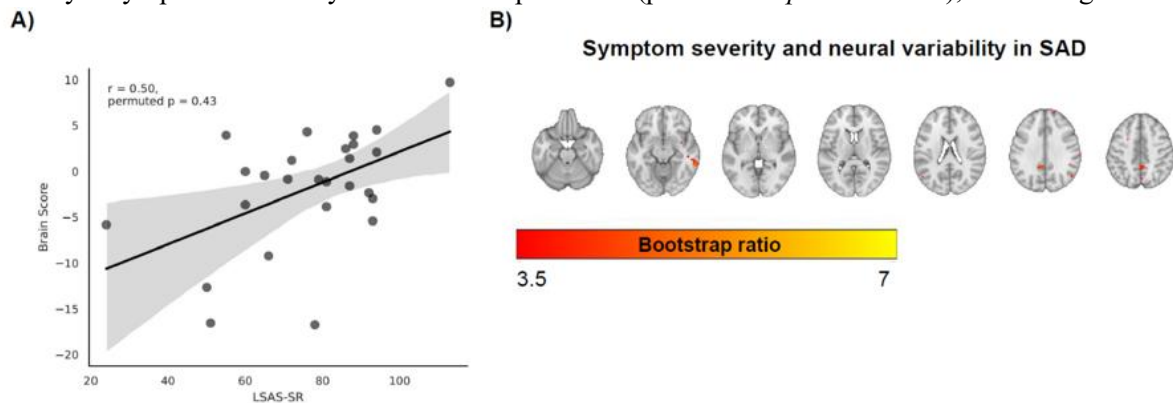


Figure 12. *A)* Association between social anxiety symptom severity (as defined by the LSAS-SR) and neural variability during speech anticipation. *B)* Brain regions showing significant clusters for LV1 reflecting the association. **Abbreviations:** SAD, social anxiety disorder; LSAS-SR, the Liebowitz Social Anxiety Scale - self-report version; LV1, latent variable 1; BSRs, bootstrap ratios; SEM, standard error of the mean.

3.3.4. Discussion

Our findings showed that brain signal variability increased during speech anticipation in both patients with social anxiety disorder and matched healthy controls. SAD patients displayed overall lower neural variability compared to healthy controls during both conditions (i.e., baseline and speech anticipation) across cortical (e.g., frontal, temporal, parietal, occipital), subcortical (e.g., insula, amygdala/hippocampus), and sensorimotor regions. We report no statistically significant association between speech anticipation-related neural variability and social anxiety symptom severity.

The main effect of the group, lower neural variability in SAD within the amygdala/hippocampus, insula, and right superior occipital gyrus, may point to a more stable, trait-like characteristic in neural dynamics that is not dependent on task context. Consistent with emerging evidence that aberrant neural variability (Tsikonofilos et al., 2025), SAD is characterized by reduced brain signal variability. A recent resting-state study examining GAD (Li et al., 2019) reported reduced neural variability in some regions similar to those identified in our study. While overlap with GAD is evident in frontal, occipital, and thalamic regions, greater involvement of the insula and amygdala–hippocampal complex in SAD may reflect disorder-specific socio-emotional and interoceptive alterations.

The lack of a task $\times$ group interaction indicates that anticipatory speech anxiety elicited comparable increases in neural variability across individuals with SAD and healthy controls, suggesting that this response may reflect a general neural mechanism engaged during socio-evaluative threat. Neural variability is increasingly understood as a fundamental feature of brain function that supports flexible, context-dependent processing rather than reflecting noise (Garrett et al., 2013b; Waschke et al., 2021). Within this framework, increased neural variability during speech anticipation may reflect an expanded dynamic range that supports adaptive responses to socially evaluative contexts, consistent with accounts linking variability to efficient behavior in complex environments (Findling et al., 2025), such as social exposures. This interpretation is further supported by prior work showing that SAD during speech anticipation is associated with more sustained and less temporally variable amygdala responses, with lower variability linked to greater symptom severity (Davies et al., 2017). Together, these findings support reduced baseline flexibility in SAD, while suggesting that task-related increases in variability during social threat anticipation may reflect adaptive or compensatory neural engagement.

3.3.5. Limitations and future directions

This study has several limitations. The modest sample size may have limited sensitivity to detect robust group and brain-behavior effects. The cross-sectional design precludes inferences about causal mechanisms, particularly given age-related attenuation of group differences. Neural variability was indexed using SD_{BOLD} , capturing only one aspect of brain dynamics, and the inclusion of medicated participants may have further reduced group differences.

Future studies should use larger longitudinal designs, incorporate complementary measures of neural dynamics, and examine associations with behavior, physiology (Renart & Machens, 2014; Waschke et al., 2021), and treatment outcomes (Månsson et al., 2022).

3.3.6. Conclusions

These findings suggest that SAD is characterized by reduced neural variability across distributed corticolimbic systems. In contrast, the preserved increase in variability during anticipatory social threat across groups indicates that context-dependent modulation of neural dynamics remains largely intact, potentially reflecting a conserved mechanism supporting adaptive responses to socio-evaluative demands.

3.4. Study 4. Neural variability changes during cognitive-behavioral therapy in social anxiety disorder

3.4.1. Introduction

CBT response rates in anxiety disorders remain moderate, with only about half of patients achieving sustained benefit (Loerinc et al., 2015), underscoring the need for biologically informed markers to guide treatment. Efforts to bridge psychiatry and neuroscience have therefore focused on integrating biomarkers into clinical practice, with neuroimaging approaches such as MRI playing a central role (Cuthbert et al., 2026). However, task-based fMRI measures relying on mean activity show poor test-retest reliability, limiting their clinical utility (Elliott et al., 2020). This has shifted focus toward neural variability (Garrett et al., 2010b; Garrett et al., 2013b; Tsikonofilos et al., 2025), which may better capture dynamic processes underlying adaptive behavior (Waschke et al., 2021). The present study investigated moment-to-moment neural variability during anticipatory anxiety in SAD and its relevance for treatment outcomes. Specifically, we examined whether pre-treatment neural variability predicts post-treatment symptom change, whether it is modulated by psychological interventions (i.e., iCBT and ABM), and whether these changes relate to clinical improvement. Additionally, differences in treatment-related symptom change between interventions were explored. Together, these aims assess whether neural variability during anticipatory public speech may serve as a biomarker of treatment-related symptom change in SAD.

3.4.2. Methods

3.4.2.1. General procedure

During fMRI scanning, participants performed an anticipatory public speaking task described in our previous manuscript. Participants completed self-report measures (e.g., LSAS-SR) before and after treatment. Group assignment to iCBT or ABM was determined by an independent researcher blinded to the study, using an external randomization tool, with allocation revealed only after the first imaging session.

3.4.2.2. Participants

The present study is based on the data from a previously preregistered randomized controlled trial (ClinicalTrials.gov identifier: NCT01312571). Ethical approval for the study was obtained from the local review board. The recruitment and screening procedures followed protocols used in earlier randomized controlled trials investigating iCBT and ABM (Månsson et al., 2015; Månsson et al., 2013). Participants were mainly recruited through online platforms and media advertisements. They first completed web-based self-report questionnaires assessing social anxiety, depressive symptoms, and MRI eligibility. Individuals who met initial screening criteria then participated in a structured diagnostic interview conducted by telephone. Diagnoses of social anxiety disorder were determined using structured clinical interviews based on DSM-IV criteria (SCID-I; First & Gibbon, 2004). Inclusion criteria specified that participants had to be at least 18 years of age, had a primary diagnosis of SAD, be free from neurological conditions and suicidal ideation, and not be currently undergoing psychological treatment. A total of 26 participants met the criteria for primary SAD and absence of current MDD and were enrolled (mean age = 32.27 ± 9.63 , 85% females). Baseline symptom severity was high (mean LSAS-SR_{PRE-TREATMENT} = 76.30, SD = ± 18.72) with a mean reduction of 22.48 points (SD = ± 17.94) following treatment. Of the initial sample, neuroimaging data from 20 participants were included in the pre-post treatment change analyses, with five participants excluded due to withdrawal or unusable fMRI data. An additional participant was removed following identification as a multivariate outlier based on Mahalanobis distance (7.47), as this case exerted disproportionate influence on the results. For the prediction analyses, neuroimaging data were available for 26 participants; however, one participant was excluded due to missing LSAS-SR scores, resulting in a final sample of 25 participants.

During the study, nine participants (five in the iCBT group and four in the ABM group) were receiving stable SSRI treatment.

3.4.2.3. Clinical assessment

Structured clinical interviews based on DSM-IV criteria were used to diagnose social anxiety disorder (SCID-I; First & Gibbon, 2004). Treatment-related changes in social anxiety symptoms were evaluated using the self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR).

3.4.2.4. Image acquisition and preprocessing

Functional MRI data were collected on a 3T GE. Neural variability was quantified as the standard deviation of the BOLD signal (SD_{BOLD}) across time within each condition, computed voxelwise for each participant.

3.4.2.5. fMRI experimental task

During the experiment, participants were informed that they should deliver a public speech after the MRI session, creating an anticipatory context. While undergoing scanning, they completed two conditions: a baseline condition and a speech anticipation condition. In the baseline condition, participants passively observed a 2-minute stream of randomly generated numbers. In the speech anticipation condition, participants viewed a 2-minute countdown and were asked to mentally prepare a speech they would later present to an audience.

3.4.2.6. Treatment

In this study, CBT was delivered over 9 weeks with weekly therapist feedback provided in written form. An evidence-based CBT program for SAD was delivered online, based on previously validated protocols (Andersson et al., 2012, 2006), and has also been published as a self-help manual in Swedish (Furmark, 2006). As a comparison condition, ABM, a computer-based intervention targeting threat-related cognitive biases in SAD, was administered twice weekly over 4 weeks. For more details regarding both interventions, see (Månsson et al., 2013).

Participants were randomly assigned to iCBT ($n=13$) or ABM ($n=13$) by an independent blinded researcher, with treatment allocation revealed after the pre-treatment neuroimaging session.

3.4.2.7. Data analysis

Partial least squares (PLS) was used to examine the relationship between whole-brain activity and behavioral measures.

Task PLS (mean-centering type 0) was used to isolate condition effects, and behavioral PLS to assess the relationship between brain activity patterns and behavioral measures. Neural variability was operationalized as the difference between anticipatory and baseline SD_{BOLD} (Speech Anticipation SD_{BOLD} - Baseline SD_{BOLD}). Also, for behavioral PLS, we used $\Delta LSAS$ ($LSAS-SR_{POST-TREATMENT} - LSAS-SR_{PRE-TREATMENT}$). Statistical analyses were conducted in Python (Version 3.12; Python Software Foundation) using the *statsmodels* module (Version 0.14.6).

3.4.3. Results

Question 1: Does pre-treatment neural variability during anticipatory speech anxiety relative to baseline predict treatment-related changes in LSAS-SR scores?

Behavioral PLS analysis did not show an overall effect, as indicated by permutation testing (permuted $p = 0.854$), see Figure 13.

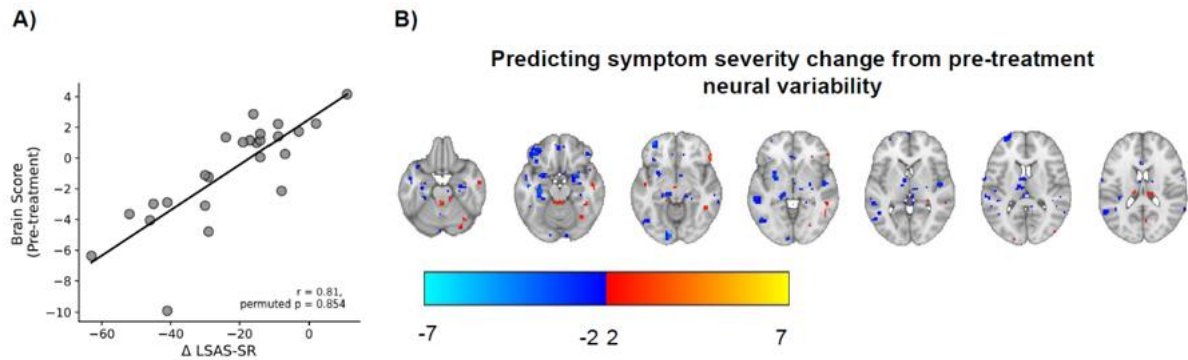


Figure 13. A) Relationship between pre-treatment brain scores (LV1) during anticipatory speech anxiety (relative to baseline) and change in LSAS-SR scores following treatment. B) Bootstrap ratio map of suprathreshold voxels for the SD_{BOLD} vs. symptom severity model. **Abbreviations:** SAD, social anxiety disorder; LV1, latent variable 1; LSAS-SR, Liebowitz Social Anxiety Scale – Self-Report; BSR, bootstrap ratio.

Question 2: Does moment-to-moment neural variability during anticipatory speech anxiety relative to baseline change from pre- to post-treatment?

Behavioral PLS analysis did not reveal an effect (permuted $p = 0.283$), with the first latent variable (LV1) accounting for 100% of the cross-block covariance.

Question 3: Do changes in moment-to-moment neural variability during anticipatory speech anxiety relative to baseline from pre- to post-treatment correlate with treatment-related changes in LSAS-SR scores?

Behavioral PLS analysis did not reveal an effect (permuted $p = 0.106$), with LV1 accounting for the observed cross-block covariance.

Question 4: Does symptom severity change differ between treatment subgroups (ABM vs iCBT)?

There was no statistically significant difference in symptom severity change between the ABM and iCBT groups ($\beta = -5.89$, $p = 0.42$). After controlling for age and sex, there was still no statistically significant difference in symptom severity change between ABM and CBT groups ($\beta = -5.29$, $p = 0.45$).

3.4.4. Discussion

Our study aimed to extend current models of SAD by probing additional underlying processes using an ecologically valid task with potential relevance for predicting symptom severity change. A deeper understanding of clinical heterogeneity and underlying neurobiology is a critical first step toward advancing translational approaches and improving treatment outcomes (Drzewiecki & Fox, 2024).

While prior work has suggested that task-based neural variability is a reliable and sensitive marker of treatment response (Månsson et al., 2022), outperforming resting-state variability and conventional mean-based measures (Tsikonofilos et al., 2025), the present findings do not support a robust or generalizable association between moment-to-moment neural variability and treatment-related symptom change in social anxiety disorder. Behavioral PLS analyses revealed no significant multivariate effects, indicating that neural variability during anticipatory speech anxiety neither predicted symptom change nor captured pre- to post-treatment alterations. However, consistent positive correlations between brain scores and symptom change suggest that weak or spatially restricted associations may exist.

Rather than reflecting a simple failure to replicate, these findings highlight the context-dependent nature of neural variability. While prior studies employed highly controlled, low-demand tasks (Månsson et al., 2022), the present anticipatory speech paradigm was designed to enhance

ecological validity by capturing clinically relevant anticipatory anxiety in social anxiety disorder. However, increased task complexity may introduce greater cognitive and affective heterogeneity, potentially reducing signal reliability and obscuring consistent brain–behavior relationships. Consistent with this, task selection has been shown to differentially influence reliability, enhancing it in task-engaged regions while introducing variability across networks (Rai et al., 2024). Together, these findings suggest that neural variability may not function as a universal biomarker of treatment-related symptom change, but rather as a context-dependent signal whose predictive utility is contingent on task structure.

Methodological factors may further account for the observed discrepancy. Although multivariate approaches can enhance sensitivity by integrating information across distributed brain regions (Kragel et al., 2020), the PLS method used here is primarily exploratory and does not directly assess predictive validity or reliability (McIntosh & Lobaugh, 2004). This may explain the absence of significant multivariate effects despite relatively strong correlations between brain scores and symptom change. In contrast, prior work demonstrating robust predictive utility combined multivariate modeling with cross-validation and test–retest reliability assessments (Månsson et al., 2022). Consistent with this, recent evidence suggests that multivariate brain-behavior associations can be replicable in moderate sample sizes when appropriate validation strategies, such as cross-validation, are applied; without such approaches, effect sizes may be inflated and less likely to replicate (Spisak et al., 2023).

Taken together, the present findings do not negate a role for neural variability in treatment-related symptom change, but instead delineate important boundary conditions under which such effects may emerge. Specifically, they suggest that the predictive utility of neural variability is likely constrained by task design, measurement reliability, and analytical approach. From this perspective, neural variability may represent a promising but context-sensitive biomarker, requiring careful alignment between experimental paradigm and clinical phenotype to yield meaningful predictions.

3.4.5. Limitations and future directions

A key limitation is the lack of validation of predictive performance, as the observed brain–behavior associations were not tested for generalizability beyond the current sample. Consistent with recent methodological work, neuroimaging findings should be evaluated based on their ability to predict clinically relevant outcomes in independent data. Future studies should therefore incorporate cross-validation and out-of-sample prediction approaches, examine transdiagnostic generalizability, and use longitudinal designs to better establish clinically meaningful biomarkers.

3.4.6. Conclusions

While neural variability remains a promising candidate marker, the present findings offer only modest evidence for its clinical utility in predicting treatment-related symptom change in social anxiety disorder. Interpretation is limited by several methodological factors, and the results should not be viewed as conclusive. Future work integrating task optimization, reliability assessment, and predictive validation will be essential to determine whether neural variability during anticipatory anxiety can serve as a clinically meaningful biomarker.

4. GENERAL CONCLUSIONS AND IMPLICATIONS

4.1. General Conclusions

The growing interest in anxiety disorders is driven by their high prevalence, early onset, frequently during childhood or adolescence, persistent course, and the significant impairment they impose on individuals, as well as on families and society (Bandelow & Michaelis, 2015; Rapee et al., 2023). However, they remain underprioritized in mental health care worldwide, receiving less attention and resources than conditions like cancer or cardiovascular disease (Wu et al., 2025).

While standardized interviews are used to improve consistency, the diagnosis of anxiety disorders still relies largely on subjective symptom reports and clinician judgment, guided by the DSM-5 and ICD-11, which may introduce variability and limit diagnostic precision (Liu et al., 2024; Penninx et al., 2021). This challenge is compounded by the disorder's poorly understood etiology and its often subtle, insidious onset, which can delay early identification and intervention (Lisboa et al., 2023; Liu et al., 2024). Consequently, treatment outcomes remain suboptimal (Higa-McMillan et al., 2016; Lucken et al., 2016), with a considerable proportion of patients exhibiting chronic or progressively worsening symptoms despite available psychological and pharmacological approaches (Scholten et al., 2013). This limitation highlights the need for reliable biomarkers capable of predicting treatment response and guiding personalized interventions. A deeper understanding of dysfunctional brain circuits is considered essential for improving the diagnosis and treatment of psychiatric disorders, including anxiety disorders. Advances in neuroimaging have provided increasingly refined insights into their structural and functional underpinnings. Since the introduction of MRI into clinical psychiatry, a key aim has been to identify neural correlates, measurable alterations in brain structure or function compared to healthy individuals, often conceptualized as biomarkers (Nosari et al., 2024).

Accordingly, this thesis aimed to investigate neural correlates of anxiety across the lifespan as potential biomarkers, contributing to more targeted and effective interventions. Additionally, a secondary objective focused on cognitive processes, such as interpretation bias and anticipatory processing, in social anxiety across adults and adolescents, emphasizing the need for a comprehensive understanding of psychopathology.

The first step of this research was to systematically synthesize neuroimaging evidence on neural changes associated with CBT in youth with anxiety disorders, as well as to identify potential neural predictors of treatment response (Study 1). Identifying reliable neural markers capable of predicting treatment outcomes is critical for the development of personalized interventions in anxiety disorders (Williams & Whitfield Gabrieli, 2024). Across fifteen studies published up to 27 October 2025, findings indicated that task-related neural activity increased from pre- to post-treatment in key regions, particularly the anterior cingulate cortex (ACC; 2/8, 25%) and, to a lesser extent, the insula (1/8, 12.5%), and were associated with symptom improvement. Furthermore, pre-treatment activity or connectivity within the ACC and amygdala predicted CBT outcomes in a subset of studies (3/13, 23%), while a smaller proportion (2/13, 15%) identified additional regions, including the insula, precuneus/cuneus, postcentral gyrus, and nucleus accumbens, as potential predictors. Notably, across studies and regardless of whether analyses focused on pre-post changes or predictive markers, the ACC, insula, and amygdala emerged as the most consistently reported regions. These patterns likely reflect the distinct functional contributions of regions involved in emotion regulation, salience processing, threat processing, and reward. Overall, the findings support a network-based model in which CBT response is shaped by interactions among these systems. Notably, the ACC emerged as the most consistently implicated region, in line with prior meta-analytic evidence demonstrating increased dorsal ACC activity in anxious youth relative to healthy controls (Ashworth et al., 2021), underscoring its central role in both anxiety-related neural dysfunction and treatment-related brain changes.

Next, an empirical study (Study 2) was conducted to examine the network structure of interpretation biases (hostile, threatening, and neutral) and their associations with social anxiety symptoms in adolescents, as well as the invariance of these networks across age and sex. The sample included 1,431 Romanian adolescents ($M_{age} = 12.87$, range = 10–17). Network models were estimated using Gaussian Graphical Models, and the edge stability and centrality indices were assessed via bootstrapping procedures. Our subscale-level network indicated that threatening interpretations showed positive associations across all social anxiety dimensions, with the strongest connection emerging between threatening interpretations and fear of negative evaluation. Moreover, threatening interpretations exhibited the highest bridge expected influence within the network. This is consistent with developmental evidence highlighting increased sensitivity to peer evaluation during adolescence (Blakemore & Mills, 2014). In contrast, hostile interpretations showed fewer and less stable associations with social anxiety symptoms, suggesting they may represent correlates or consequences of social anxiety rather than a primary underlying mechanism (Patel et al., 2026). Neutral interpretations were linked to social avoidance and distress, indicating that even neutral or non-threatening cues may possibly contribute to the persistence of anxiety-related behaviors. At the same time, some neutral and hostile interpretations were negatively associated with social anxiety symptoms, suggesting a potential buffering role of benign social appraisals; however, these associations are correlational, and causality cannot be inferred. Finally, the network structure was largely consistent across age and sex, suggesting similar interpretation-bias processes and supporting shared intervention targets among adolescents.

In the third study, we examined neural variability in SAD compared to healthy controls during an anticipatory public speaking task. The findings show that individuals with SAD exhibit reduced neural variability across multiple cortical regions, including frontal, temporal, parietal, and occipital areas, as well as subcortical structures such as the amygdala/hippocampus and insula, and sensorimotor regions, suggesting a stable and widespread alteration in neural dynamics that is not limited to a specific task context. At the same time, both patients and healthy controls demonstrated increased neural variability during speech anticipation, with no significant group differences, indicating that this context-dependent modulation is preserved and may reflect a general neural response to socio-evaluative threat (Garrett et al., 2013b; Waschke et al., 2021). However, our findings indicate that neural variability was not significantly associated with symptom severity. Overall, these results highlight neural variability as a relevant measure for capturing alterations in large-scale brain dynamics, with potential utility for future longitudinal and treatment-focused research (Månsson et al., 2022).

The last study investigated the role of moment-to-moment neural variability during anticipatory speech anxiety in relation to treatment response in social anxiety disorder. Across all analyses, no significant effects were observed. Pre-treatment neural variability did not predict symptom improvement, neural variability did not change following treatment, and changes in variability were not associated with symptom change. Additionally, no differences in treatment-related symptom reduction were found between the ABM and iCBT groups. However, the results should be interpreted cautiously and viewed as an initial step that opens avenues for further investigation in this domain.

4.2. Implications of the Thesis

4.2.1. Theoretical Implications

The main theoretical contributions of this thesis emerge from Studies 1-3, each advancing current models of anxiety from complementary perspectives. Study 1 supports a network-based model of CBT response, indicating that treatment-related changes is associated with changes in distributed systems involved in emotion regulation and salience and threat processing, particularly the ACC, insula and amygdala. To our knowledge, this represents the first critical review focusing specifically on neural predictors and changes related to CBT in pediatric anxiety disorders diagnosed according to DSM-5 criteria.

Study 2 provides an important refinement of cognitive models of social anxiety by demonstrating that interpretation bias is not a unitary construct, but rather a set of content-specific processes with different associations to symptom domains. Our findings suggest that threat-related interpretations are most strongly connected with social anxiety, particularly fear of negative evaluation, underscoring their importance in the cognitive network underlying social anxiety (Chen et al., 2020; Subar et al., 2022).

Study 3 highlights neural variability as a complementary dimension of brain function that may not be captured by conventional mean-activation approaches. By demonstrating reduced neural variability in SAD alongside preserved context-related increases during socio-evaluative threat across cortical (e.g., frontal, temporal, parietal, and occipital), subcortical (e.g., amygdala/hippocampus and insula), and sensorimotor regions (e.g., supplementary motor area), these findings suggest that altered neural dynamics may represent a stable, disorder-related feature of the condition.

4.2.2. Methodological Implications

Several important methodological implications emerged from the second and third study included in this thesis.

Study 2 has methodological relevance through the use of a network analytic framework to examine interpretation biases and social anxiety symptoms in a large community sample of Romanian adolescents. The examination of invariance across age and sex further strengthens the methodological contribution of this study, as it moves beyond average group differences and evaluates whether the broader architecture of symptom-bias associations remains stable across developmental subgroups.

Study 3 introduced a whole-brain PLS framework to investigate moment-to-moment neural variability during anticipatory public speaking task. This represents a methodological contribution because it extends the application of neural variability metrics to a clinically relevant, ecologically informed socio-evaluative task in SAD. In contrast to conventional mean-based analyses, the use of SD_{BOLD} as an index of neural variability captures fluctuations in ongoing neural signal amplitude and therefore provides complementary information about brain dynamics.

4.2.3. Practical Implications

In addition to its theoretical and methodological contributions, the present thesis also has several practical implications.

First, the findings of Study 1 are relevant for the development of more targeted interventions in youth anxiety in the future. Identifying neural correlates associated with CBT response may contribute to the longer-term goal of personalizing treatment by helping distinguish which patients are more likely to benefit from particular therapeutic approaches.

In Study 2, the network structure showed substantial invariance across age and sex, indicating that interpretation-bias mechanisms associated with social anxiety may function similarly across these demographic groups. This finding has practical implications, as it points to the potential for common intervention targets among adolescents regardless of age or sex.

Finally, Study 4 has practical implications for biomarker development and treatment research. More broadly, this study highlights the need for future translational research to combine neural, behavioral, and clinical indicators when developing clinically useful models of treatment response.

4.3. Limitations and Future Directions of Research

While this thesis offers meaningful contributions at the theoretical, methodological, and practical levels, several limitations should be considered when interpreting its main findings.

Overall, in the first study, findings remain heterogeneous, likely reflecting substantial methodological variability across studies. Differences in task paradigms, sample composition, with a

predominance of GAD, and treatment protocols limit comparability. Taken together, although neuroimaging markers of CBT response in youth anxiety show promise, the evidence remains preliminary. Future work should emphasize larger, well-characterized samples, greater methodological standardization, and more reliable measures (e.g., moment-to-moment neural variability) (Garrett et al., 2011; Garrett et al., 2010b; Garrett et al., 2013b).

In the second study, its cross-sectional, self-report design limits causal inference and may be influenced by shared method variance, as well as by socially desirable responses from participants. Future research should replicate these findings using longitudinal designs and behavioral measures. Future studies should assess whether our findings extend to clinical populations and different cultural contexts.

In the third study, the small sample size may have reduced power to detect reliable group and brain-behavior effects, and the cross-sectional design limits conclusions about causality. Also, neural variability was assessed using SD_{BOLD} , capturing only a single facet of brain dynamics, and the inclusion of medicated participants may have attenuated group differences. Future research should employ larger longitudinal designs, integrate complementary measures of neural dynamics, and examine links with behavioral, physiological and treatment-related outcomes.

In the fourth study, key limitations include the absence of predictive validation, the short task duration of only two minutes, and the small sample size. In line with recent methodological recommendations, neuroimaging findings should be judged by their capacity to predict clinically meaningful outcomes in independent datasets (Scheinost et al., 2019). Accordingly, future research should incorporate cross-validation and out-of-sample prediction methods, explore generalizability across diagnostic categories, and employ longitudinal designs to strengthen the development of clinically relevant biomarkers.

4.4. Summary of General Conclusions

Based on the findings of the studies included in this thesis, and in light of the limitations outlined above, several overarching conclusions can be drawn.

1. Neural markers of treatment response in pediatric anxiety appear to involve a distributed brain network rather than a single isolated region. Across the reviewed neuroimaging studies, pre-treatment activity and connectivity in the anterior cingulate cortex and amygdala were associated with treatment prediction, while treatment-related neural changes in the anterior cingulate cortex and insula were linked to symptom improvement following CBT, highlighting their relevance in treatment-related neural processes.

2. The network analysis revealed that the strongest association between interpretation bias and social anxiety was the association between threatening interpretations and fear of negative evaluation. Their centrality and stable associations across symptom dimensions suggest that maladaptive interpretive processes may represent an important target for intervention.

3. The cognitive network structure underlying interpretation biases showed substantial invariance across age and sex, indicating that these processes may function similarly across adolescent developmental stages and between sexes, and may represent common targets for intervention.

4. Social anxiety disorder was associated with reduced neural variability across widespread cortical and subcortical regions, indicating a disorder-related feature of the condition.

5. Neural variability did not demonstrate utility as a treatment-response biomarker in the investigated context. It neither predicted symptom improvement nor showed treatment-related changes, indicating that its clinical relevance may depend on specific task contexts, measurement approaches, or analytical strategies.

To summarize, the findings of this thesis support the importance of integrating neural and cognitive approaches in understanding anxiety disorders across the lifespan. Although these findings

are not yet directly translatable into clinical practice, they provide an important foundation for future longitudinal and translational research aimed at improving personalized interventions and biomarker-guided treatment strategies in anxiety disorders.

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