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Corrélatés cérébraux de l'anxiété catégorielle et dimensionnelle

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Neural correlates of categorical and dimensional anxiety

Corrélatés cérébraux de l'anxiété catégorielle et dimensionnelle

Thèse de doctorat de l'Université Paris-Saclay
et de Humboldt-Universität zu Berlin

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Contribution of brain magnetic resonance imaging to individual-level prediction of prospective anxiety onset and treatment response

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Résumé : Les troubles anxieux sont très répandus et représentent une lourde charge de morbidité. Cependant, malgré une abondante littérature sur la neuro-imagerie à l'échelle du groupe, des marqueurs cérébraux robustes de vulnérabilité ou de réponse thérapeutique peinent à émerger. Ces dernières années, les approches de prédiction à l'échelle individuelle utilisant l'apprentissage automatique sont devenues de plus en plus populaires dans la recherche en santé mentale, et certains résultats prometteurs ont été rapportés dans des études de neuro-imagerie à petite échelle (généralement avec $N_{\text{total}} < 60$ participants). Ces résultats n'ont pas encore été reproduits dans des échantillons plus importants et multisites.

Le présent projet de doctorat impliquait l'utilisation de l'apprentissage automatique supervisé pour prédire prospectivement le développement de troubles anxieux chez les adolescents en utilisant un jeu de données longitudinales de la population générale, IMAGEN, ainsi que pour prédire la réponse au traitement psychothérapeutique chez les patients phobiques en utilisant le jeu de données SPIDER-VR.

Avec les données IMAGEN, des analyses d'apprentissage automatique ont été réalisées à partir de questionnaires et de données neuroanatomiques d'adolescents non anxieux, afin de prédire le développement d'un futur trouble anxieux ($N = 156$) par rapport à un statut de contrôle sain ($N = 424$). L'étude a souligné le potentiel prédictif des données sociodémographiques et issues de questionnaires pour la prédiction de futurs troubles anxieux regroupés, et celui des volumes de matière grise pour la prédiction d'un trouble anxieux généralisé. Les mesures d'IRM fonctionnelle extraites d'une tâche de traitement émotionnel des visages n'ont pas produit de performance prédictive supérieure au niveau de chance.

Avec les données SPIDER-VR, des analyses d'apprentissage automatique ont été menées pour prédire la réponse des patients phobiques des araignées ($N = 190$) à une session de thérapie d'exposition en réalité virtuelle, en utilisant des données de questionnaires, des données d'IRM structurelle et diverses mesures d'IRM fonctionnelle extraites d'une tâche de provocation des symptômes. Contrairement aux attentes, l'étude n'a pas confirmé le potentiel prédictif des données sociodémographiques et de questionnaires, ni des données de neuro-imagerie, à l'exception de la variance du signal BOLD qui a produit une performance prédictive modérée.

Dans l'ensemble, ce travail de doctorat remet en question les résultats optimistes d'études antérieures à plus petite échelle sur la prédiction de l'anxiété par apprentissage automatique basé sur la neuro-imagerie. Néanmoins, les résultats corroborent le fait que des questionnaires faciles à administrer présentent une performance prédictive prometteuse pour la prédiction de l'apparition de l'anxiété et que l'IRM structurelle puisse apporter une valeur prédictive supplémentaire. Divers autres biomarqueurs de l'anxiété sont apparus dans la littérature avec le potentiel d'améliorer la précision des prédictions relatives à l'anxiété, et d'autres recherches multimodales utilisant des jeux de données à grande échelle ainsi qu'une méthodologie rigoureuse d'apprentissage automatique sont nécessaires pour atteindre l'utilité clinique.

Title : Neural correlates of categorical and dimensional anxiety

Keywords : Anxiety, Neuroimaging, MRI, Machine-learning

Abstract : Anxiety disorders are highly prevalent and represent a heavy burden of disease. However, despite a large group-level neuroimaging literature, robust brain markers of vulnerability or therapeutic response struggle to emerge. In recent years, individual-level prediction approaches using machine-learning have become increasingly popular in mental health research, and some promising results have been reported in small-scale neuroimaging studies (usually with $N_{total} < 60$ participants). These prediction results have yet to be replicated in larger, multisite samples.

The present doctoral project involved the use of supervised machine-learning to prospectively predict the development of anxiety disorders in adolescents using a longitudinal dataset from the general population, IMAGEN, as well as to predict the response to psychotherapeutic treatment in phobic patients using the SPIDER-VR dataset.

With IMAGEN data, machine-learning analyses were conducted using questionnaire and neuroanatomical data of non-anxious adolescents, to predict the development of a future anxiety disorder ($N = 156$) vs. healthy control status ($N = 424$). The study supported the predictive potential of sociodemographic and questionnaire data for the future onset of pooled anxiety disorders, and of gray matter volumes for future generalized anxiety disorder onset. Functional MRI metrics extracted from an emotional face processing task did not yield any above-chance level predictive performance.

With SPIDER-VR data, machine learning analyses were conducted to predict the response of patients with spider phobia ($N = 190$) to a virtual reality exposure therapy session, using questionnaire data, structural MRI data, and various functional MRI metrics extracted from a symptom provocation task. Contrastingly to expectations, the study did not support the predictive potential of sociodemographic and questionnaire data nor neuroimaging data, with the exception of BOLD signal variance which yielded moderate predictive performance.

Overall, this doctoral work challenges optimistic results from earlier smaller-scale neuroimaging-based machine-learning prediction studies in anxiety. Nonetheless, findings substantiate that easy-to-administer questionnaires show promising predictive performance for anxiety onset prediction and that structural MRI might bring incremental predictive value. Various other anxiety biomarkers have emerged in the literature with potential to improve the accuracy of anxiety-relevant predictions, and further multimodal research using large-scale datasets alongside rigorous machine-learning methodology are needed in an effort to reach clinical utility.

Kurzfassung

Angststörungen sind weit verbreitet und stellen eine große Krankheitslast dar. Trotz einer umfangreichen Literatur zur Neurobildung auf Gruppenebene ist es jedoch schwierig, robuste Hirnmarker für Anfälligkeit oder therapeutische Reaktion zu finden. In den letzten Jahren sind Vorhersageansätze auf individueller Ebene unter Verwendung von maschinellem Lernen in der Forschung zur psychischen Gesundheit immer beliebter geworden, und einige vielversprechende Ergebnisse wurden in kleinen Neurobildungsstudien (in der Regel mit einer Gesamtzahl von weniger als 60 Teilnehmern) berichtet. Diese Vorhersageergebnisse müssen noch in größeren, standortübergreifenden Stichproben repliziert werden.

Das vorliegende Promotionsprojekt umfasste den Einsatz von überwachtem maschinellem Lernen zur prospektiven Vorhersage der Entwicklung von Angststörungen bei Jugendlichen unter Verwendung eines Längsschnittdatensatzes aus der Allgemeinbevölkerung, IMAGEN, sowie zur Vorhersage der Reaktion auf psychotherapeutische Behandlung bei Phobiepatienten unter Verwendung des SPIDER-VR-Datensatzes.

Anhand von IMAGEN-Daten wurden maschinelle Lernanalysen unter Verwendung von Fragebogen- und neuroanatomischen Daten nicht ängstlicher Jugendlicher durchgeführt, um die Entwicklung einer zukünftigen Angststörung (N = 156) im Vergleich zu einem gesunden Kontrollstatus (N = 424) vorherzusagen. Die Studie untermauert das Vorhersagepotenzial von soziodemografischen und Fragebogendaten für das künftige Auftreten von Angststörungen und von Volumina der grauen Substanz für das künftige Auftreten einer generalisierten Angststörung. Funktionelle MRT-Metriken, die aus einer emotionalen Gesichtsverarbeitungsaufgabe extrahiert wurden, erbrachten keine über dem Wahrscheinlichkeitsniveau liegende Vorhersageleistung.

Mit SPIDER-VR-Daten wurden maschinelle Lernanalysen durchgeführt, um die Reaktion von Patienten mit Spinnenphobie (N = 190) auf eine Virtual-Reality-Expositions-Therapie-Sitzung vorherzusagen, wobei Fragebogendaten, strukturelle MRT-Daten und verschiedene funktionelle MRT-Metriken, die aus einer Symptom-Provokationsaufgabe gewonnen wurden, verwendet wurden. Im Gegensatz zu den Erwartungen unterstützte die Studie weder das Vorhersagepotenzial der soziodemografischen und Fragebogendaten noch der Neuroimaging-Daten, mit Ausnahme der BOLD-Signalvarianz, die eine moderate Vorhersageleistung erbrachte.

Insgesamt stellt diese Doktorarbeit die optimistischen Ergebnisse früherer kleinerer Studien zur Vorhersage von Angstzuständen auf der Grundlage von Neuroimaging und maschinellem Lernen in Frage. Nichtsdestotrotz belegen die Ergebnisse, dass einfach zu handhabende Fragebögen eine vielversprechende Vorhersagekraft für die Vorhersage des Angstausschlags haben und dass die strukturelle MRT einen zusätzlichen Vorhersagewert haben könnte. In der Literatur sind verschiedene andere Angst-Biomarker aufgetaucht, die das Potenzial haben, die Genauigkeit angstrelevanter Vorhersagen zu verbessern. Um einen klinischen Nutzen zu erreichen, sind weitere multimodale Forschungsarbeiten erforderlich, bei denen große Datensätze und strenge Methoden des maschinellen Lernens eingesetzt werden.

Erklärung / Declaration

Hiermit erkläre ich, die Dissertation selbstständig und nur unter Verwendung der angegebenen Hilfen und Hilfsmittel angefertigt zu haben.

I hereby declare that I completed the doctoral thesis independently based on the stated resources and aids.

.....

Datum, Unterschrift

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“Never, in his brief cave-life, had he encountered anything of which to be afraid. Yet fear was in him. [...] Fear! – that legacy of the Wild which no animal may escape nor exchange for pottage.”

Jack London (1906), “The Wall of the World”, *White Fang*.

List of Abbreviations

MRI: Magnetic resonance imaging

CBT: Cognitive-behavioural therapy

GAD: Generalized anxiety disorder

SAD: Social anxiety disorder

PD: Panic disorder

AG: Agoraphobia

PD/AG: Panic disorder with or without agoraphobia

SpP: Specific phobia

fMRI: Functional magnetic resonance imaging

tb-fMRI: task-based functional magnetic resonance imaging

rs-fMRI: resting-state functional magnetic resonance imaging

FC: Functional connectivity

BNST: Bed nucleus of the stria terminalis

PAG: Peri-aqueductal gray

PFC: Prefrontal cortex

ROI: Region of interest

SVM: Support Vector Machine

AUC: Area under the curve

MSE: Mean Squared Error

FUA: Future anxiety participants

BLA: Baseline anxiety participants

mAD: Multiple anxiety disorders group

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1. Introduction

Anxiety can be an adaptive behaviour, but excessive feelings of anxiety can also impair individuals in their everyday lives and require medical attention. Indeed, anxiety disorders are the most prevalent group of mental disorders in contemporary nosology (Penninx *et al.*, 2021). Biomarker identification has potential to inform prevention, early detection and treatment stratification strategies for anxiety disorders. The widespread use of both structural and functional magnetic resonance imaging (MRI) techniques in the past 25 years has produced an abundant neuroimaging literature identifying group-level regions of interest involved in anxiety, both in adults and in youth, but to date the literature has not led to any significant clinical breakthrough. However, machine-learning approaches allow to produce individual-level predictions and are becoming increasingly popular in the field of neuropsychiatry. The present doctoral work thus leveraged machine-learning approaches to investigate the potential of structural and functional metrics in previously identified brain regions in the prospective prediction of risk of onset and therapeutic response in anxiety disorders.

1.1. Anxiety disorders

Due to their high prevalence, comorbidity and chronicity, anxiety disorders represent a considerable burden of disease and substantial healthcare costs (Gustavsson *et al.*, 2011; Wittchen *et al.*, 2011). First-line treatment options include pharmacotherapy and cognitive-behavioural therapy (CBT), but treatment resistance and relapse are common. This section will describe each point in further detail.

1.1.1. Classification and epidemiology of anxiety disorders

1.1.1.1. Phenomenology and classification of anxiety disorders

The word anxiety is derived from Latin roots (from *anxiētās*, anxiety, itself derived from *angō*, to constrict, to hurt). Anxiety, defined as the aversive anticipation of a perceived but uncertain and unpredictable threat, can be an adaptive behaviour with a clear benefit for survival. It is prevalently seen as distinct from fear, which is defined as the response to a perceived threat that is immediate and certain. Anxiety enhances vigilance and primes

defensive mechanisms, allowing individuals to detect and deal with threats more efficiently (Bateson, Brillot and Nettle, 2011). Anxiety can occur naturally in many situations, such as meeting a stranger, walking down a dark alley at night, or general life transitions. However, when feelings of anxiety are severe, disproportionate to the perceived threat, and negatively impact daily functioning, they can require clinical attention.

Mentions of anxiety and its pathological states date back to the Greek and Latin medicine and philosophy, followed by centuries of the term being absent from the medical literature (Crocq, 2015). However, cultural and religious representations of anguish (French: *angoisse*, also derived from Latin *angō*), which encompassed both acute emotional distress, bodily sensations of constriction, and existential worry, were still abundant (see paintings such as *The Garden of Early Delights* or *Tondal's Vision* from Hieronymus Bosch). Then, in the late 19th and early 20th century nosology, anxiety was listed as one of the core symptoms of neurasthenia. The Diagnostic and Statistical Manual of Mental Disorders (DSM) classification, in the mid-20th century, led to the emergence of the anxiety neurosis diagnosis (American Psychiatric Association, 1968), which was subsequently refined in later editions.

The main disorder classifications, the fifth edition of the DSM (DSM-V) (American Psychiatric Association, 2013) and the 11th edition of International Classification of Diseases (ICD-11) (World Health Organization, 2022), currently define distinct anxiety disorder diagnoses (Penninx *et al.*, 2021). Arranged by increasing typical age of onset, the list of anxiety disorders in these classifications is as follows: separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder (see Table 1 for core characteristics of each disorder).

While formal classifications of categorical disorders have clinical use, they also have well-known limitations. For instance, anxiety disorders as defined by the DSM or ICD are highly comorbid with each other, and with depression. In a large adult sample from the Netherlands, 48-68% of participants with a current anxiety disorder fulfilled criteria for another anxiety disorder, and 63% of participants with a current anxiety disorder also reached clinical threshold for a depression disorder (Lamers *et al.*, 2011). Large within-disorder heterogeneity also subsists (Galatzer-Levy and Bryant, 2013). Moreover, subclinical anxiety symptoms commonly occur and can still impair functioning. In adults, subthreshold anxiety disorder was reported to persist 3 years later for 29.0% of participants and transition to a full-blown anxiety disorder for 13.8% of participants (Bosman *et al.*, 2019).

1. Introduction

	Core emotions or cognitions	Physical symptoms	Behaviour	Required symptom duration	Median age of onset
Selective mutism	Consistent failure to speak in situations for which there is an expectation to speak, despite language competence	No physical symptoms	Disturbance interferes with (educational) achievement or social communication	>1 month (beyond first school month)	Childhood (<5 years)
Separation anxiety	Unrealistic, persistent fear or anxiety about separation from, or loss of, attachment figure, or adverse events occurring to them	Nightmares and symptoms of distress	Reluctance to leave attachment figure; Disturbance impairs social, school, or other functioning	>1 month (childhood; 4–18 years) >6 months (adulthood; 18 years or older)	Childhood (around 6 years)
Specific phobia	Marked, excessive, and unreasonable fear or anxiety of circumscribed objects or situations (e.g., animals, natural forces, blood injection, or places)	No physical symptoms	Avoidance of circumscribed objects or situations; disturbance impairs social, school, work, or other functioning	>6 months	Childhood (around 8 years)
Social anxiety disorder	Marked, excessive, and unreasonable fear or anxiety of scrutiny or negative judgement by other people	Blushing, fear of vomiting, urgency or fear of micturition or defaecation	Avoidance of social interactions and situations; disturbance impairs social, school, work, or other functioning	>6 months	Early adolescence (around 13 years)
Agoraphobia	Marked, excessive, and concerning fear of leaving home, entering closed or open public places, crowds, or transportation	No physical symptoms	Avoidance of fear-inducing situations; disturbance impairs social, school, work, or other functioning	>6 months	Late adolescence (around 20 years)
Panic disorder	Recurrent, unexpected panic attacks with sustained mental (e.g., fear, fear of losing control, or feeling of alienation) manifestations	Multiple symptoms (e.g., palpitations, dyspnoea, diaphoresis, chest pain, dizziness, paraesthesia, or nausea)	Changed behaviour in maladaptive ways related to the attacks; disturbance impairs social, school, work or other functioning	>1 month	Adulthood (around 25 years)
Generalized anxiety disorder	Marked, uncontrollable, and anxious worry and fears about everyday events and problems	Restlessness, fatigue, irritability, difficulty concentrating, muscle tension, sleep disturbance, or autonomic arousal	Disturbance impairs social, school, work, or other functioning	>6 months	Adulthood (around 30 years)

Table 1: Core diagnostic features and characteristics for anxiety disorders (Penninx *et al.*, 2021).

As such, dimensional frameworks such as the Research Domain Criteria (RDoC) (Insel *et al.*, 2010; Cuthbert and Insel, 2013), and quantitative nosology approaches such as the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov *et al.*, 2017), have emerged. While the former was designed to establish links between biological mechanisms and

psychopathology, the latter focuses on targeting clinical shortcomings of existing diagnoses, and both have potential to bring complementary perspectives.

1.1.1.2. Prevalence and burden of anxiety disorders

Epidemiological studies report lifetime prevalence rates for anxiety disorders in the general population ranging from 14.5% to 33.7% (Bandelow and Michaelis, 2015). The variability in prevalence rates in these studies may be attributed to various methodological differences, and putative biological or cultural differences across investigated populations may also be a factor. Despite the heterogeneity across studies, however, prevalence rates of anxiety disorders in women have consistently be shown to be approximately twice as high as in men. This has been extensively discussed in the literature, mostly focusing on biological factors using animal studies (Bangasser and Cuarenta, 2021), but recent work has also introduced the gender and socialization perspective (Farhane-Medina *et al.*, 2022). During the recent COVID-19 pandemic, a 25% increase in prevalence for anxiety disorders was reported around the globe, including up to 50% in youth, highlighting the urgency in addressing the burden of disease they represent (Racine *et al.*, 2021; Santomauro *et al.*, 2021).

Anxiety disorders were ranked as the 9th cause of years lived with disability worldwide in 2016 (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016; Yang *et al.*, 2021). Direct and indirect costs of anxiety disorders represent on average around 2% of healthcare costs, and 0.58% of total gross domestic product (GDP) (Konopka and König, 2020). In 2010, anxiety disorders in 30 European countries were reported to cost approximately €74.4 billion in total (Gustavsson *et al.*, 2011). As an example, the average cost per person with an anxiety disorder, weighted for all diagnoses and age groups, was €1199 in France and €1357 in Germany on that year.

1.1.1.3. Age of onset and naturalistic course of anxiety disorders

The average age of onset for anxiety disorders predates 15 years old (y.o.) for social anxiety disorder (14.3 y.o.) and specific phobia (11.0 y.o.), whereas agoraphobia (21.1 y.o.), panic disorder (30.3 y.o.) and generalized anxiety disorder (34.9 y.o.) tend to emerge later in life, with no gender difference in the age of onset (Lijster *et al.*, 2017).

Anxiety symptoms are generally persistent. In early adolescence, 56.4% and 32.3% persistence rate of total anxiety symptom score were reported at 1-year and 3-year follow-ups respectively (Voltas *et al.*, 2017). At a 10-year follow-up in a sample of 14-24 y.o. with social anxiety disorder, 56.7% of participants still had symptoms and 15.5% fully met clinical criteria (Beesdo-Baum *et al.*, 2012).

Indeed, a continuity from childhood to adulthood has been reported for anxiety disorders : they predict themselves over time, but they also predict depression (Costello, Copeland and Angold, 2011). In an adolescent sample (average age at baseline = 14.3 y.o.), 22.6 % of participants meeting diagnostic criteria for an anxiety disorder at first assessment still met criteria 15 months later, and 17.7% met criteria for depression (Essau, Conradt and Petermann, 2002). Thus, prevention, early detection, and effective therapeutic intervention for anxiety disorders are essential.

1.1.2. Treatment of anxiety disorders

1.1.2.1. Access to care and existing treatments

Less than half (41.3%) of individuals with an anxiety disorder perceive a need for treatment, and only two thirds of those that do report a need for treatment will receive it (i.e. only 27.6% of all individuals with an anxiety disorder) (Alonso *et al.*, 2018). It was reported that only a third of treated cases receive possibly appropriate level of care. However, effective treatments for anxiety disorders do exist, and both pharmacotherapy and CBT are the first-line treatment options.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are commonly prescribed to treat anxiety disorders, and they have shown efficacy in children and adolescents (Locher *et al.*, 2017). Benzodiazepines are also an efficacious anxiolytic treatment (Gomez, Barthel and Hofmann, 2018). However, as benzodiazepines can be addictive and act acutely, prescribing guidelines currently recommend them only to mitigate the adverse effects during the first few weeks of first-line SSRI or SNRI treatment, with strict monitoring (Reinhold and Rickels, 2015).

Pregabalin has also garnered interest and is licensed as a treatment for anxiety disorders in several countries (Generoso *et al.*, 2017). A few other pharmacological options exist,

including buspirone, opipramol and quetiapine, but their use is limited by yet insufficient evidence or adverse effects (Maneeton *et al.*, 2016).

A large range of psychotherapies are also first-line treatment options for anxiety disorders. Among them, CBT has the largest body of literature, reporting moderate efficacy when controlled against care-as-usual and pill placebo (Cuijpers *et al.*, 2016; Carpenter *et al.*, 2018; van Dis *et al.*, 2020). CBT for anxiety disorders is a short-term therapy aimed at disrupting the vicious circle of maladaptive emotional responses and avoidance behaviours, oftentimes involving a fear-inhibitory learning process through some form of exposure to the feared stimuli. Alternative psychotherapies, such as psychodynamic therapy, have weaker evidence of efficacy in comparison with CBT (Tolin, 2010). Current response rates to CBT as a first-line treatment average at 50% or lower for most anxiety disorders (Hofmann *et al.*, 2012; Loerinc *et al.*, 2015).

1.1.2.2. Relapse and treatment resistance

A meta-analysis found no difference in efficacy between medication and psychotherapy for anxiety disorders and depression, and reported that the effects of both persisted up to a 2-year follow-up, although there was substantial heterogeneity between studies and methodological differences make it difficult to compare pharmacotherapy and CBT (Bandelow *et al.*, 2018). Another recent meta-analysis reported improved outcome of CBT compared to various control groups for patients with anxiety disorders up until 12 months after treatment completion, but found improved outcome after 12-month follow-up only for GAD and SAD (van Dis *et al.*, 2020). It is important to note that, both for psychotherapy and pharmacotherapy, a substantial proportion of the treated population sees no symptom improvement.

Furthermore, therapeutic gains for both treatment options on the long-term are less maintained. A naturalistic study of long-term (7-year) effects of CBT, pharmacotherapy and the combination of both in youth with anxiety disorders reported similarly modest persistence for all treatment arms, with an average of 22% of participants in stable remission, 48 % relapsing, and 30 % chronically ill (Ginsburg *et al.*, 2018). Another study in adults reported that 54.8% of participants with anxiety disorder(s) diagnosed at baseline without depression had overall recurrence (re-occurrence of the same anxiety disorder(s), or newly diagnosed anxiety or depressive disorder(s)) within 4 years of reaching remission (Scholten *et al.*, 2016).

The literature substantiates that early identification of patients with a high risk of treatment non-response, resistance and relapse is of ample interest.

1.2. Adolescence and the brain

In the context of a global search for mental health biomarkers that can help diagnose patients, give mechanistic insight to disorders, predict treatment response and risk of onset and relapse, adolescence is a key target for investigation. Indeed, adolescence is a critical time period for the emergence of psychopathology, including anxiety disorders, and it is also a time of profound morphological and physiological change, the brain being no exception (Arain *et al.*, 2013).

In this search for biomarkers, the possibility of non-invasively measuring brain structure and function using Magnetic Resonance Imaging (MRI) has held a lot of promise (see Appendix for the general principles of MRI and functional MRI). Notably, investigating the developing brain during adolescence has potential to yield crucial biomarkers for mental health.

The following section substantiates the vulnerability of adolescents to mental health disorders and briefly describes the cortical maturation occurring throughout adolescence that MRI and fMRI have brought to light.

1.2.1. Vulnerability to mental health disorders

The increased risk of psychopathology during adolescence is well-established in the literature. Cumulative incidence of psychiatric disorders before 18 years of age, including depression, anxiety disorders and psychosis, was reported to be around 15% (Dalsgaard *et al.*, 2020). Other studies reported that anxiety disorders impacted nearly one in three individuals during adolescence (Beesdo, Knappe and Pine, 2009; Merikangas *et al.*, 2010) and that approximately 11% of 13-18 y.o. had already experienced a depressive episode (Avenevoli *et al.*, 2015). As such, adolescence is known as a window of vulnerability for mental health disorders, including anxiety disorders, and biomarkers would be of particular interest in this age range to inform prevention and early detection, as well as treatment stratification. Indeed, adolescents suffering from a mental health disorder are also more likely

to have not yet received any treatment, and thus are the ideal target population for treatment stratification strategies *via* early identification of putative non-responders.

1.2.2. Brain maturation during adolescence

The emergence of MRI as a noninvasive brain imaging technique with high spatial resolution enabled, among other research avenues, a detailed investigation of brain development in youth. After the second surge of synaptogenesis and neural growth occurring in late childhood, significant structural and functional development occur throughout adolescence (between 10 and 24 y.o.) (Arain *et al.*, 2013). Both myelination and dendritic pruning processes take place during that time, and consolidate regional neurocircuitry. The resulting change in total gray matter volume over time has an inverted U-shaped pattern. In male adolescents, mean total cerebral volume is approximately 10% larger than in females, as is the case in adults, although this does not demonstrate any functional advantages or disadvantages (Goldstein *et al.*, 2001; Giedd, 2008). Remarkably, total brain volume shows to be highly heterogeneous, with up to 50 % difference between children at the same age.

The age of peak gray matter volume is generally earlier for females, and maturation does not occur homogeneously in all brain regions (Giedd, 2008). The limbic system structures (amygdala, hippocampus, nucleus accumbens), which are involved in emotional processing, develop earlier than prefrontal control regions (Casey, Jones and Hare, 2008). This imbalance, as well as the still-developing functional connectivity between the two systems, has traditionally been postulated as an explanation for the emotional reactivity and impulsive behaviour in adolescents (Hare *et al.*, 2008). Brain maturation during adolescence is regulated by, and can be altered by, multiple factors such as physical and psychological stress, drug consumption, sex hormones, pubertal development, nutrition, sleep, heredity, and pre-and post-natal environments (Arain *et al.*, 2013).

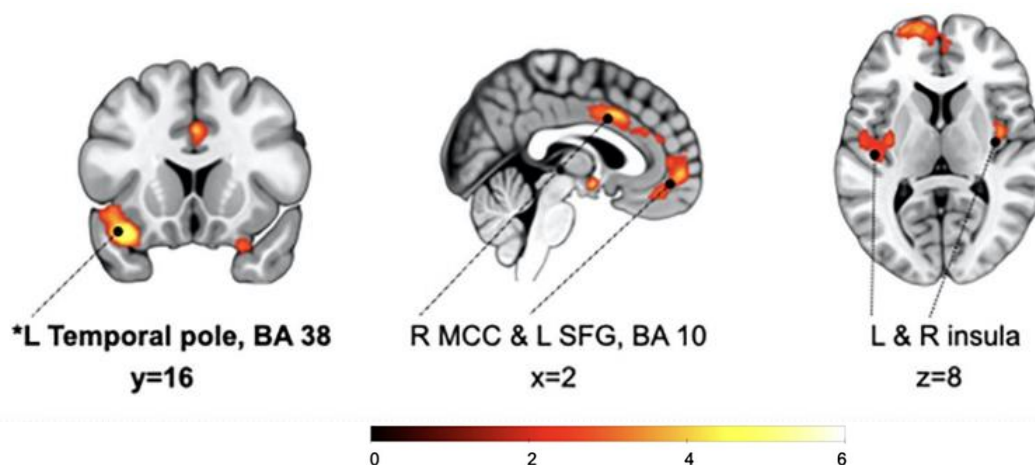
1.3. MRI correlates of cross-sectional anxiety disorders

The following section will describe the large body of work investigating structural and functional differences in the brains of adult and paediatric patients with anxiety disorders, compared with non-anxious controls. A well-established literature shows corticolimbic circuitry to be altered in anxiety disorders.

1.3.1. Cross-sectional correlates in adults

1.3.1.1. Structural correlates

Gray matter volume alterations in the bilateral putamen (Radua *et al.*, 2010), left superior temporal, left orbitofrontal, left inferior frontal, left dorsolateral and bilateral cingulate gyri, as well as in the bilateral insula (Serra-Blasco *et al.*, 2021; Liu *et al.*, 2022) have been reported in anxiety disorders at the meta-analytical level (Figure 1). These regional alterations are common overlaps between distinct anxiety diagnoses, with the strongest evidence for anterior cingulate and insula alterations. Divergences between diagnoses, such as between GAD and SAD, PD and SpP, have also been reported in the left insula and left inferior frontal gyrus in one meta-analysis (Liu *et al.*, 2022). The involvement of the temporal pole points to alteration of the ventral attention network, which plays a role in stimulus-driven attention (Sylvester *et al.*, 2012). Of note, these meta-analytic results are based on group-level whole-brain studies, which generally have high smoothing and may thus have reduced sensitivity to volumetric variations in small limbic structures, in addition to heterogeneous methodology overall (e.g. high variability in the control groups and control strategies used in MRI processing).



* Brain regions that reach $p < 0.05$ TFCE correction in bold

Figure 1: Results of structural MRI whole-brain meta-analysis between patients with anxiety disorders and healthy controls (Serra-Blasco *et al.*, 2021).

L: left; R: right; MCC: middle cingulate gyrus; SFG: superior frontal gyrus; BA: Brodmann area.

Structural alterations in anxiety disorders using other metrics, such as cortical thickness, have also been reported in similar regions (Syal *et al.*, 2012; Kang, Lee and Lee, 2017). This literature, however, is much less abundant and no meta-analytic results have emerged to our knowledge, thus leaving less robust findings overall.

1.3.1.2. Functional correlates

Functional differences between patients with anxiety and control have been investigated in a very large body of work. Systematic reviews and meta-analyses of task-based functional activation in specific anxiety disorders (Ipser, Singh and Stein, 2013; Brühl *et al.*, 2014; Sobanski and Wagner, 2017; Goossen, van der Starre and van der Heiden, 2019), reported that regions such as the anterior cingulate cortex, the medial prefrontal cortex, the bed nucleus of the stria terminalis (BNST), the peri-aqueductal grey (PAG), the amygdala, the striatum and the insula have been implicated. A recent meta-analysis of both functional activation during emotional tasks (i.e. exposure to phobic, traumatic, socioemotional or strongly aversive stimuli) further supports the implication of the middle and superior temporal gyri, insula, amygdala, frontal and medial frontal gyri, parahippocampal gyrus, hippocampus, thalamus, anterior and mid-cingulate gyri, and caudate in pooled anxiety disorders (Chavanne and Robinson, 2021) (Figure 2), although some heterogeneity was found between specific disorders.

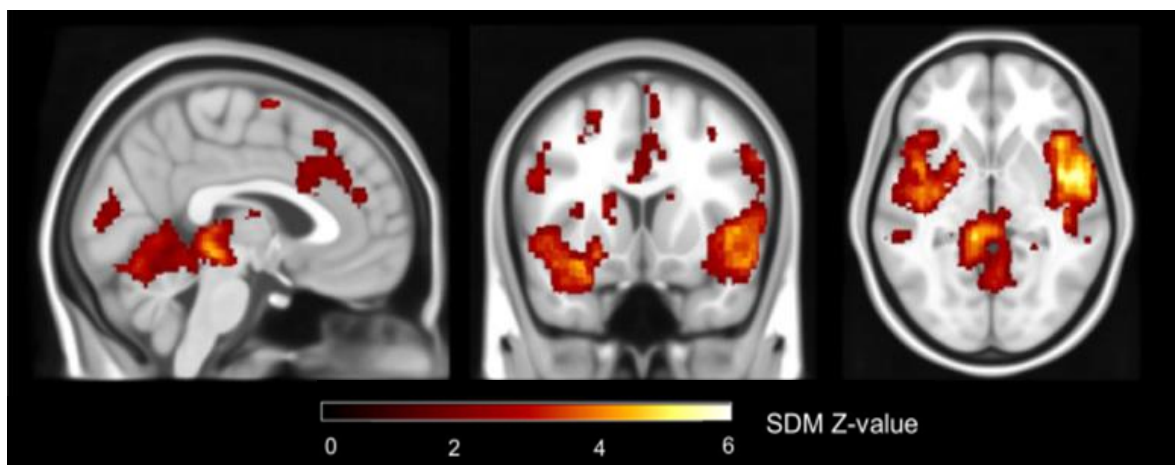


Figure 2: Functional activation differences between 2554 anxious patients and 2348 non-anxious controls across pooled pathological anxiety studies (Chavanne and Robinson, 2021).

Seed-based d-Mapping (SDM) Z-value of activation in yellow-red.

Insula and cingulate functional activation has also been found significantly altered in a meta-analysis of Pavlovian fear-conditioning neural activation studies (Fullana *et al.*, 2016). These regions have been argued to form part of a fear-conditioning and/or salience network (Yeo *et al.*, 2011) driving interoception (Paulus and Stein, 2006), and may thus play a role in promoting avoidant responses to negatively salient stimuli. Of note, the amygdala alterations were scarce in both meta-analyses (Fullana *et al.*, 2016; Chavanne and Robinson, 2021), which might be a result of the exclusion of studies using region-of-interest approaches, but could also reflect insufficient power of amygdala findings in whole-brain studies. An extensive literature points to the central extended amygdala and BNST being key hubs for the response to sustained and uncertain threats (Fox and Shackman, 2019), but it is important to note that the very amygdalo-centric view of human fear and anxiety, mostly initiated by rodent research and likely to be at risk from confirmation bias, has been largely challenged (Fullana *et al.*, 2019; Radua and Fullana, 2022).

Overall, these meta-analytic results, alongside two decades of translational anxiety research (Shackman and Fox, 2021), show that anxiety disorders are associated with increased reactivity in an extended subcortico-cortical circuitry, including (but not limited to) the amygdala, anterior insula, middle cingulate, BNST and PAG during emotional tasks.

A systematic review and meta-analysis of seed-based rs-fMRI findings in anxiety disorders reported a reduced functional connectivity between the amygdala and the medial frontal, cingulate and anterior cingulate gyri (Zugman *et al.*, 2023), although findings were largely heterogenous did not hold against publication bias correction. Other metrics derived from functional connectivity, such as those obtained using graph theory and reflecting functional networks organisation, have also been used to differentiate between patients with anxiety disorders and non-anxious controls (Makovac *et al.*, 2018). However, these metrics currently remain exploratory.

1.3.2. Cross-sectional correlates in children and adolescents

1.3.2.1. Structural correlates

Studies investigating structural correlates of anxiety disorders in youth are less common than in adults. Nonetheless, in line with the literature in adults, cross-sectional differences in gray matter volume were reported in the amygdala, hippocampus, insula, cingulate cortex,

ventromedial prefrontal cortex (vmPFC), nucleus accumbens and temporal gyri in adolescents diagnosed with anxiety disorders (Gold *et al.*, 2017; Merz *et al.*, 2018; Auerbach *et al.*, 2022).

Additionally, the striatum was highlighted as a critical subcortical region of interest (ROI) for the onset of anxiety disorders in adolescence (Lago *et al.*, 2017). A model of anxious temperament has also been shown to involve the central amygdala, orbitofrontal cortex, BNST and PAG in young primates (Kalin, 2017; Fox and Shackman, 2019).

1.3.2.1. Functional correlates

A recent meta-analysis of fMRI results in adolescents with anxiety disorders reported functional activation alterations in the bilateral amygdala, parahippocampal gyri, putamen and globus pallidus, suggesting that regional functional activation alterations in youth with anxiety disorder are similar to those that have been observed in adults (Ashworth, Brooks and Schiöth, 2021). This is in line with an older review, that also reported recurrent alterations of the PFC in youth with anxiety disorders (Blackford and Pine, 2012).

1.4. Longitudinal correlates of anxiety

Although the abundant MRI and fMRI literature has identified brain regions robustly involved in cross-sectional anxiety, these findings have not led to clinical breakthrough for the diagnosis or treatment of anxiety disorders. However, they have informed longitudinal studies which are, by nature, well-equipped to investigate potential markers of risk of onset, and of treatment response. The following section will describe findings for both.

1.4.1. Anxiety disorder onset and prevention

1.4.1.1. Sociodemographic and questionnaire correlates

Many sociodemographic, psychosocial, as well as physical and mental health factors have been reported as risk factors of anxiety disorders (Moreno-Peral *et al.*, 2014; Strawn *et al.*, 2021). Personality scores such as neuroticism and anxiety sensitivity have been established as pre-existing risk factors for future anxiety disorders (Schmidt, Zvolensky and Maner, 2006; Jeronimus *et al.*, 2016). Early-life anxious temperament and behavioural inhibition are also

strong risk factors for anxiety disorders later in life (Clauss and Blackford, 2012; Hardee *et al.*, 2013; Sandstrom, Uher and Pavlova, 2020; Goldsmith *et al.*, 2022).

An attempt was made to implement a statistical model using a limited number of variables (general sociodemographic information, family history of psychiatric illness, current physical and mental health scores) to predict onset of generalized anxiety and panic symptoms (King *et al.*, 2011). The model was developed using data from four European countries (the UK, Spain, Slovenia and Portugal), and was validated with data from the Netherlands, Estonia and Chile. However, a more recent study used this algorithm in an external sample from the US with limited success, and do not encourage its use (Nigatu and Wang, 2019). Thus, the field has turned to other (bio)markers to improve the detection and prevention anxiety disorders.

1.4.1.2. Structural MRI correlates

Neuroimaging data, jointly with psychometric and clinical data, shows promise to identify at-risk populations (Linden, 2012). Only a few longitudinal studies have investigated neurostructural correlates of anxiety from a developmental perspective, often using a ROI approach (Jones *et al.*, 2017; Haller *et al.*, 2018). It was reported that amygdala volume measured up to three times at 2-year intervals in non-clinical participants between age 4 and 18 was longitudinally and positively associated with anxio-depressive symptoms (Albaugh *et al.*, 2017). Another study found no association of amygdala or nucleus accumbens gray matter volume with prospective generalized and social anxiety symptoms after a 6-month follow-up in a mixed sample of healthy and depressed-anxious adolescents (Auerbach *et al.*, 2022). One study reported that larger pituitary volume at age 12-13 preceded an increase in anxiety symptoms two to three years later (Zipursky *et al.*, 2011). Another study reported that larger right middle temporal gyrus cortical thickness in non-clinical participants aged 13 to 20 was associated with prospective symptoms of generalized anxiety disorder two years later (Busso *et al.*, 2017). It was also reported that gray matter volumes in the medial PFC and hippocampus were associated with prospective anxiety symptoms one year later in a sample of 18-22 y.o. participants (Gorka *et al.*, 2014).

1.4.1.3. fMRI correlates

Several studies have also investigated functional activation and connectivity group-level correlates of prospective anxiety symptoms, most often using ROI approaches. In preschool

children, amygdala activation to emotional faces was associated with negative affect 12 months later (Gaffrey, Barch and Luby, 2016). It was reported that a diminished difference between amygdala responses to trustworthy vs. untrustworthy faces in children was associated with separation anxiety symptoms up to 2 years later (Green *et al.*, 2016). Functional activation to a fear-conditioning task in the ventromedial PFC was associated with anxiety symptoms up to 30-month later in participants aged 18-19 (Peng *et al.*, 2022). Another study found no association of the nucleus accumbens functional activation during a reward incentive task with generalized and social anxiety symptoms after a 6-month follow-up in a mixed sample of healthy and depressed-anxious adolescents (Auerbach *et al.*, 2022).

In 20 y.o. men, amygdala-inferior frontal gyrus connectivity during emotional faces viewing was associated with internalizing symptom increase 2 years later (Gard *et al.*, 2018). Functional connectivity between the amygdala and the posterior cingulate cortex, caudate, and postcentral gyrus was also associated with change in GAD symptomatology one year later in adults diagnosed with GAD (Makovac *et al.*, 2016).

Overall, MRI and fMRI longitudinal correlates of anxiety onset share similarities with cross-sectional correlates of anxiety, involving structural and functional alterations in the amygdala and PFC, as well as in broader limbic circuitry. However, this literature is sparser and no meta-analytic investigation has been published to our knowledge, with most findings not having been replicated and thus being vulnerable to sample-specific biases.

1.4.2. Psychotherapy response

Although both pharmacotherapy and CBT were mentioned in section 1.1.2 to give a full overview of first-line treatment options for anxiety disorders, the present doctoral work was focused on CBT, for data availability reasons. Thus, CBT will be the focus of the treatment response correlates described hereafter.

1.4.2.1. Sociodemographic and questionnaire correlates

Prospectively distinguishing treatment-responding from nonresponding patients has potential to guide clinical decisions and improve prognosis (Bzdok, Varoquaux and Steyerberg, 2021). A number of psychosociodemographic factors associated with prospective psychotherapy response in anxiety disorders have been investigated. Despite small sample sizes and

replication difficulties, some factors associated with poor response to therapy in adults have been reported as consistent across studies, such as non-adherence to therapeutic homework, a hostile interpersonal environment, greater severity of the treated disorder and/or greater severity of comorbid mental disorders (Stein *et al.*, 2009; Taylor, Abramowitz and McKay, 2012; Skriner *et al.*, 2019). Similar factors have been reported in youth (Pegg *et al.*, 2022). However, these findings have not resulted in impactful clinical improvement for psychotherapy stratification in anxiety disorders, still leaving nearly half of patients receiving therapy with no significant symptom improvement (Loerinc *et al.*, 2015). Neuroimaging techniques have thus been used to explore potential markers of prospective therapeutic outcome and help treatment stratification. Indeed, several studies have reported significant differences in neural correlates before and after CBT for anxiety disorders, which substantiates the promise of neuroimaging to provide biomarkers for personalized therapy (Goldin *et al.*, 2014; Yang, Kircher and Straube, 2014).

1.4.2.2. Structural MRI and fMRI correlates

A recent whole-brain meta-analysis reported that, across a variety of tasks, functional activation in regions involved in salience and interoceptive networks such as the inferior frontal gyrus, anterior insula, dorsomedial PFC, anterior cingulate cortex, was associated with positive CBT outcome in anxiety disorders (Picó-Pérez *et al.*, 2022). Although overlapping regions were associated with prospective CBT outcome in youth patients with anxiety disorders, the direction of association between functional activation and outcome may not be the same as in adults (Pegg *et al.*, 2022).

Other MRI modalities have also been explored for potential prospective markers of therapeutic response. Significant association with clinical outcome after therapy was reported for the amygdala sustained response to threatening stimuli (Woody *et al.*, 2019), the hippocampal and nucleus accumbens gray matter volumes (Reinecke *et al.*, 2014; Burkhouse *et al.*, 2020; Suarez-Jimenez *et al.*, 2020), and the amygdala-PFC FC (Young *et al.*, 2019). To our knowledge, however, these findings remain exploratory due to the small number of published studies.

Several studies have reported rs-fMRI markers associated with clinical outcome in anxiety disorders. One study reported that rs-FC of the insula with the superior parietal lobe, and rs-FC of the anterior medial PFC with the precuneus and the occipital cortex were significantly

associated with post-treatment clinical outcome in patients with GAD (Fresco *et al.*, 2017). Five studies investigated resting-state factors associated with therapy response in SAD. One reported a significant association of CBT response with rs-FC of the cerebellum with the angular gyrus and dorsolateral frontal cortex (MinlanYuan *et al.*, 2017). In another study, bilateral amygdala - PFC rs-FC was positively associated with CBT response in patients with SAD (Klumpp *et al.*, 2014). One study reported that rs-FC of the amygdala with a subgenual ACC/caudate/putamen cluster, as well as with the bilateral central sulcus and an inferior temporal/occipital cluster, was significantly associated with post-CBT symptom change for patients with SAD (Whitfield-Gabrieli *et al.*, 2016). A replication attempt reported that the statistical model using rs-FC in the previous study did predict CBT outcome in a replication sample of patients with SAD, but did so with marginal statistical significance (Ashar *et al.*, 2021). Finally, a recent study reported that early changes of rs-FC between the dorsolateral PFC and regions of the default mode network, salience network and executive control network were associated with later symptom improvement during therapy in SAD patients (Zhu *et al.*, 2023).

Overall, the literature of MRI and fMRI longitudinal correlates of psychotherapy response in anxiety disorders points to alterations in frontolimbic circuitry, broadly similar to cross-sectional correlates of anxiety disorders. However, an earlier review of biomarkers associated with psychotherapy and pharmacotherapy response in anxiety disorders reported the highly variable methodological quality across studies, and underlined the potential of machine-learning individual-level prediction approaches with robust cross-validation schemes to help treatment stratification (Lueken *et al.*, 2016).

1.5. Machine-learning in mental health research

A number of vulnerability or prognostic markers have been detected at group level in the anxiety literature. However, statistical association does not necessarily translate into cross-sectional classification or prospective prediction, the second and third implying an ability to generalize findings to new, unseen data (Poldrack, Huckins and Varoquaux, 2020). Indeed, a large gap has remained between group-level findings and clinical relevance, and in the last decade, research on mental disorders and their treatment has progressively incorporated machine-learning approaches in an effort to bridge that gap. The following section will briefly

describe the general principles of some supervised machine-learning classification approaches from a practical perspective.

1.5.1. General principles of supervised machine-learning approaches

1.5.1.1. Main definitions

Machine learning is a term that describes automated, flexible and computationally intense approaches to identifying patterns in complex data (Jiang, Gradus and Rosellini, 2020). In particular, supervised learning corresponds to machine-learning approaches used to classify a particular outcome of interest.

Classification is defined herein as the partitioning of a set of observations into several categorical groups (i.e. classes) with distinct characteristics (Lemm *et al.*, 2011). Based on a set of previous observations, the machine-learning algorithm has to find a rule to assign an unseen observation x to a class y . The observations consist in a set of predictor variables, usually termed features, measured for each example in the dataset (e.g. each participant). While classification predicts categorical classes, regression approaches can also be used in machine-learning to predict continuous outcomes. Of note, the present dissertation only includes binary classification analyses.

The algorithm is always trained using one subset of the data (i.e. the training set) to find an optimal decision rule, then is used to predict classes in a separate set of the data (i.e. the testing set) to evaluate how well the decision rules generalizes to unseen data. Comparing the predicted classes with the true classes in the testing set thus measures the predictive performance of the algorithm. Notably, training and testing sets never overlap, and must always be kept separate, to ensure that the algorithm is tested in a truly unseen (sub-) sample.

1.5.1.2. Common pitfalls of machine-learning prediction

Machine-learning prediction analyses are based on complex pipelines, often involving several preprocessing steps embedded in cross-validation (further discussed in section 1.5.1.4 below), which make them vulnerable to several pitfalls that require vigilance.

A common but insidious mistake in machine-learning is data leakage, which occurs when the testing data have been contaminated by the training data, thus resulting in overinflated

performance estimation of the algorithm (Kapoor and Narayanan, 2023). Many types of data leakage exist, some obvious and others subtle, including (but not limited to) any preprocessing step (data imputation, normalization, over/under sampling, data-driven feature selection) performed on the whole dataset before train-test split, the use of features ‘from the future’ to make predictions about a future outcome, non-independence between train and test samples or duplicate observations, etc.

Another common pitfall of machine-learning prediction is overfitting, which occurs when the decision rule fits too closely to the training data and has started learning from the noise rather than from meaningful information, thus failing to generalize to new data. Underfitting, on the other hand, occurs when the decision rule is too simple to capture the complexity of the data, and does not effectively adapt to the training data (Lemm *et al.*, 2011). As such, although complex models might better adapt to details of the data, and be able to produce a more accurate prediction, they are also more at risk of overfitting. Overfitting becomes more likely to occur when the number of features used (i.e. the dimensionality) is too large in comparison with the number of observations in the data. This is the bias-variance trade-off, where an equilibrium has to be found through a model that is sufficiently complex to identify underlying patterns in the data, but not so complex that it uses noise to predict outcomes. As such, machine-learning usually requires relatively large samples. Furthermore, the raw data are rarely used directly in the machine-learning pipeline, and specific features are often selected before training the classifier(s), either manually using prior knowledge, or using automated approaches (Heinze, Wallisch and Dunkler, 2018).

1.5.1.3. Frequently used supervised machine-learning algorithms

Logistic regression, which is standard in statistical analyses, is also used in machine-learning (Jiang, Gradus and Rosellini, 2020). Designed for linear binary classification problems, logistic regression calculates the probability P that the observation belongs to a given class using a sigmoid function (also called a logistic function) and determines the coefficients of each feature (also called weights). The decision boundary between classes can then be $P = 0.5$.

Other common variants of linear or logistic regression also come with a regularization strategy to limit model complexity and prevent overfitting. Those include Least Absolute Shrinkage and Selection Operator (LASSO), also known as L1 regularization, Ridge

regularization, also known as L2 regularization, and Elastic Net. Both LASSO and Ridge introduce a penalization factor to constrain the feature coefficients. In LASSO, the penalization factor takes the magnitude of the coefficient, while in Ridge it takes the square. The Elastic Net regularization combines both the L1 and L2 regularization and is usually preferred over each (Zou and Hastie, 2005).

Support Vector Machines (SVMs) use a kernel function to transform the input features onto a multidimensional space where they are linearly separable. Then, SVMs identify an optimal separating hyperplane (i.e. decision boundary) between two classes by maximizing the margin between the points most similar in both classes (also called support vectors) and the decision boundary (Muller *et al.*, 2001) (Figure 3A). Various kernels allow SVMs to capture linear and nonlinear associations between features.

Random Forests are also popular classifiers in machine-learning, and are based on multiple decision tree classifiers (Breiman, 2001). A decision tree classifier is a flowchart-like structure built by splitting the input training set (the root node) into subsets recursively, using a split criterion dividing all possible values of a feature into non-overlapping regions. This process is called recursive partitioning and can also detect non-linear effects. Each internal node denotes a choice regarding a feature, each branch of the tree denotes a decision rule, and each terminal node (also called leaf node) denotes the result from the classifier (Figure 3B). Decision trees can use a large range of criteria to decide to split a node into two or more sub-nodes. The recursion completes when the data subsets at all leaf nodes are sufficiently homogeneous, or when splitting no longer adds predictive value. Observations will then be predicted to belong to the most frequently occurring class in the node they have been placed in.

Random Forests involve a combination of a large number of individual decision tree classifiers. This uses bagging (i.e. bootstrap aggregation), which consists in randomly sampling from the full dataset with replacement (i.e. bootstrapping, akin to drawing balls from a bag and then putting them back) numerous times, and training a classifier on each subset of data. The final output of a bagging strategy results from a majority vote or averaging between all classifiers.

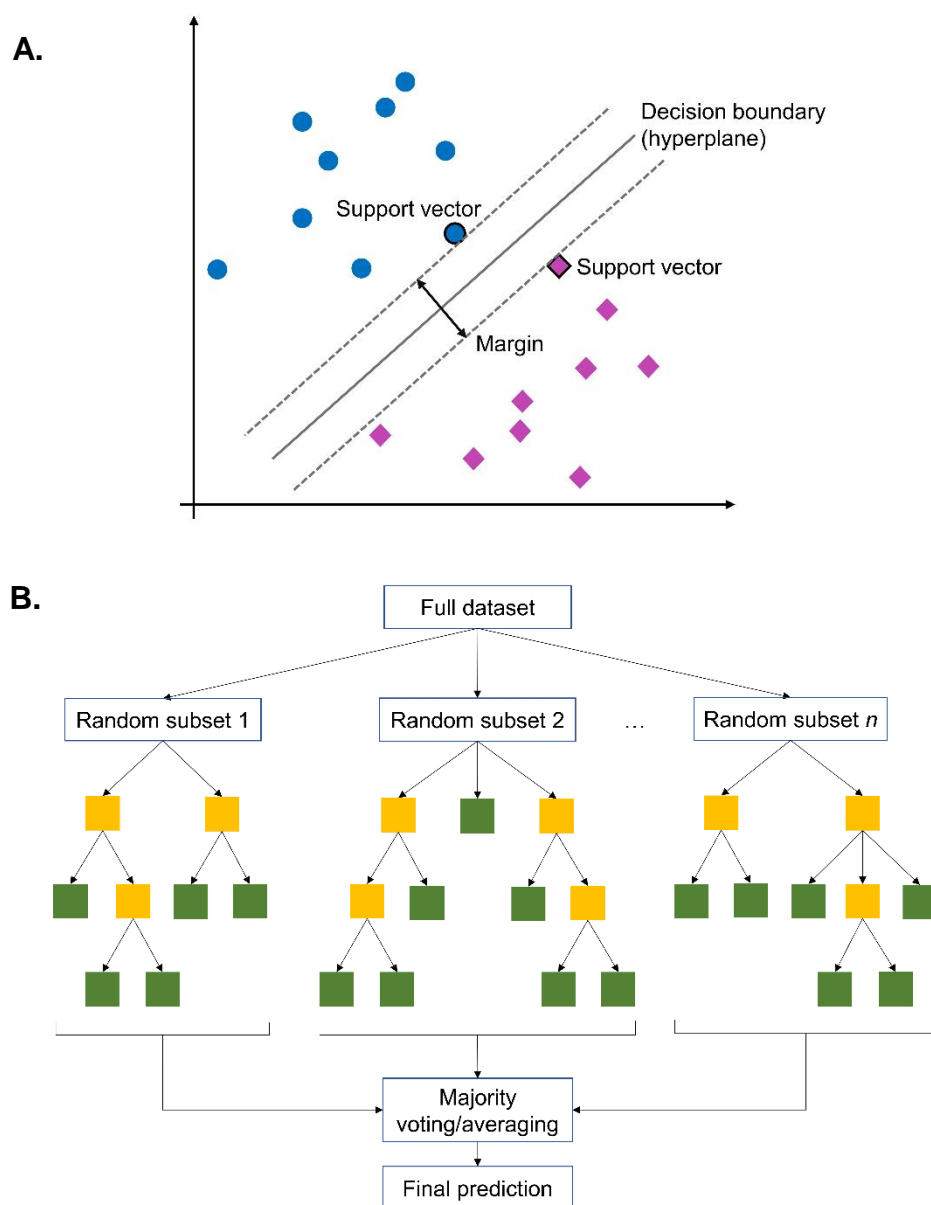


Figure 3: Graphical representation of example supervised machine-learning classifications.

A: Support Vector Machine classification; B: Random Forest classification. Decision nodes are represented in yellow and terminal nodes in green.

Most supervised machine-learning algorithms can be applied to complex data that include both categorical and continuous features, but some methods might perform better than others, and each has inherent limitations. For instance, logistic regression results are usually easily interpretable but tends to overfit when dealing with collinear features. Both SVMs and Random Forest classification strategies also have variants for regression, and usually perform

well when dealing with a large number of predictors for a limited sample, but have somewhat poorer interpretability. Of note, composite approaches, also called stacking or ensemble approaches, that use more than one of the above-mentioned algorithms in parallel can also be implemented to optimize prediction performance at a higher computational cost

1.5.1.4. Cross-validation

The ideal case in machine-learning involves training a classifier using a sample and then testing its predictive performance using an external and completely independent sample (i.e. hold-out sample). In practice, however, an external sample is rarely available. Standard practice thus involves the embedding of the learning process (training and testing) into an internal validation scheme, also called cross-validation. Cross validation consists in an iterative resampling procedure, where each iteration involves one split of the dataset into training and testing and the subsequent training and testing of the classifier. The overall predictive performance is then averaged over all iterations of the cross-validation scheme. Additional cross-validation procedures can be implemented within the overall cross-validation (i.e. nested cross-validation), to tune the hyperparameters of learning algorithms.

K-fold cross-validation, one of the most popular cross-validation approaches, consists in randomly dividing the dataset into k subsets (i.e. folds) of the same size, then in the classifier being trained using $k-1$ folds and tested on the remaining fold, and this procedure is repeated k times such that each fold has been used a testing set once. Leave-one-out cross-validation, where only one observation serves as the testing set, is another common cross-validation scheme but its use is not usually recommended, as it presents a higher risk of bias in the estimation of predictive performance (Varoquaux, 2018).

1.5.2. Interest of machine-learning use in mental health research

As shown in section 1.5.1 above, machine-learning approaches are inherently well-equipped to tackle research questions in mental health research in meaningful ways. Machine-learning models can produce predictions at the individual level, i.e. for one given patient, which is particularly useful in a medical field where clinical profiles are highly heterogenous (Nielsen *et al.*, 2020). Although they also come with their own methodological tradeoffs (Poldrack, Huckins and Varoquaux, 2020), machine-learning models can learn from multimodal data

and incorporate both categorical and continuous variables into prediction pipelines that use cross-validation to improve the generalisability of results. An increasing number of studies have used machine learning to investigate predictors of diagnosis, prognosis and treatment outcome in mental health (Chekroud *et al.*, 2021; Iyortsuun *et al.*, 2023).

1.6. Machine-learning prediction of anxiety

This section will give an overview of the existing literature using machine-learning in anxiety disorders using easy-to-collect sociodemographic and questionnaire data, as well as neuroimaging data, for the prediction of current symptoms or diagnosis, the prediction of prospective symptoms or disorder onset, and the prediction of prospective psychotherapeutic outcome.

1.6.1. Cross-sectional prediction of patients with an anxiety disorder

1.6.1.1. Prediction using sociodemographic and questionnaire data

Cross-sectional prediction of anxiety disorders or anxiety symptoms levels using only sociodemographic information and/or questionnaire scores as features in large samples has potential to inform screening practices in vulnerable populations. One study reported prediction accuracies of 0.7275 to 0.784 for the classification of anxiety symptom level in $N=3984$ youth aged 10 to 15 y.o., (Qasrawi *et al.*, 2022), another study reported $AUC = 0.73$ for classification of GAD using non-psychiatric routine general health assessment features in $N = 4184$ undergraduate students (Nemesure *et al.*, 2021). Two studies investigated anxiety classification in the elderly, one reporting an accuracy of 0.874 for severe anxiety symptoms classification in $N_{\text{patients}} N = 1558$ people (Byeon, 2021), the other reporting an area under the curve (AUC) ranging between 0.79 and 0.85 for the classification of high symptom levels of anxiety, depression or dementia vs healthy controls in $N= 15173$ people (Liu *et al.*, 2023). One study reported a machine-learning regression of anxiety symptom scores with $r^2 = 0.19$ in $N = 4029$ working nurses (Havaei *et al.*, 2021). However, to our understanding, some methodological shortcomings in these studies can be noted, such as (Qasrawi *et al.*, 2022) that did not use cross-validation over the whole dataset, (Liu *et al.*, 2023) that refitted classifiers on features selected *a posteriori* based on their predictive contribution, and (Havaei

et al., 2021) that regressed out covariates of non-interest on the whole dataset before cross-validation.

A recent body of literature also examined cross-sectional machine-learning prediction of anxiety symptoms during COVID-19, with sample sizes ranging from $N= 329$ to $N= 29841$, predictive accuracies ranging from 0.6364 to 1.0, and one study reporting $r^2 = 0.387$ (Hueniken *et al.*, 2021; Albagmi *et al.*, 2022; Caldirola *et al.*, 2022; Simjanoski *et al.*, 2022; Mahalingam *et al.*, 2023; Tian *et al.*, 2023).

In line with the overall performances reported in the literature, an AI-enriched cross-sectional diagnosis tool for mental health clinicians was recently proposed to aid in the screening and decision-making processes, based on supervised learning and using only a few sociodemographic variables and $N= 6000$ observations, with a predictive accuracy of 0.89 (Tutun *et al.*, 2023). However, this framework has yet to be applied to other, larger datasets to test its full generalisability, and diagnostic accuracy should still be improved. Thus, many studies have tried to explore other data modalities to improve the predictive performance of anxiety cross-sectional classification, neuroimaging data being the most common.

1.6.1.2. Prediction using MRI and fMRI data

Indeed, machine-learning techniques have shown promise in single-subject patient classification using neuroimaging data, and there has been a recent effort to use larger samples and multisite data to overcome inherent limitations of such analyses (Arbabshirani *et al.*, 2017; Rashid and Calhoun, 2020). A first step in the use of neuroimaging data with machine-learning in anxiety consisted in investigating whether previously identified group-level cross-sectional brain markers of anxiety disorders were indeed predictive of individual-level current anxiety symptoms.

Prediction in adults

Few studies in adults have attempted single-participant classification of clinical anxiety using neuroimaging data, with limited sample sizes, heterogenous performance metrics and non-prospective designs. In adults, two studies investigated classification of social anxiety disorder with very small clinical sample sizes ($N_{\text{patients}} = 14$ and 20, with accuracies of 0.845 and 0.825 respectively) (Frick *et al.*, 2014; Liu *et al.*, 2015), one other study did so with

moderately larger sample size ($N_{\text{patients}} = 47$, area under the curve = 0.72)(Xing, Fitzgerald and Klumpp, 2020), and another investigated spider phobia classification ($N_{\text{patients}} = 59$, accuracy ranging from 0.62 to 0.88) (Lueken, Hilbert, *et al.*, 2015). In each study, classification performance tended not to rely on a few select structures of the fear circuitry or other networks, but rather relied on widespread predictors across the brain. Of note, one study that was not published at the start of the dissertation work reported an AUC of 0.84 for the classification of patients with anxiety disorders using deep learning and functional activation in 10 ROIs classically involved in anxiety during a fear learning task ($N_{\text{patients}} = 92$) (Wen *et al.*, 2021). Other fMRI measures, including Regional Homogeneity (ReHo; local temporal correlation of the BOLD signal timeseries between a voxel and its nearest neighbours during resting state) and functional Amplitude of Low Frequency Fluctuations (ALFF; fluctuations of spontaneous BOLD signal intensity within the 0.01 and 0.1 Hz during resting-state) have also been investigated. Indeed, one study recently reported ReHo and fALFF to have predictive value (balanced accuracy ranging from 0.644 to 0.777) for a high vs. low social anxiety group classification, in a study using $N = 116$ median-split participants (Kim *et al.*, 2022).

Machine-learning prediction of self-reported anxiety scores in non-clinical samples using neuroimaging data has also been recently attempted, with moderate success, with several studies reporting significant, albeit modest, predictive performances. One study predicted trait anxiety score using whole-brain tb-fMRI features in $N = 154$ young adults and reported a significant $r_{(\text{predicted}, \text{observed})} = 0.28$ (Portugal *et al.*, 2019), another reported $r^2 = 0.27$ using neurostructural features in a sample of $N = 158$ (Baggio *et al.*, 2023). It was also reported that FC derived from an interoceptive attention task significantly predicted self-reported anxiety during the task with $r_{(\text{predicted}, \text{observed})} = 0.247$ in $N = 122$ participants (Wu *et al.*, 2019). Amygdala-based ROI-to-ROI rs-FC was found to be predictive of negative emotionality dimension score, comprised of self-reported feelings of fear, anger and neuroticism, with up to $r_{(\text{predicted}, \text{observed})} = 0.224$ in a $N = 393$ sample, with an out-of-sample performance of $r_{(\text{predicted}, \text{observed})} = 0.219$ and a $N = 97$ sample (Klein-Flügge *et al.*, 2022). However, other studies of machine-learning prediction of anxiety scores using neuroimaging data reported non-significant regressions. One study predicted a composite trait anxiety score in $N = 531$ participants with $r^2 = 0.06$, then in a fully held out sample of $N = 348$ with a nonsignificant $r^2 = -0.04$ (Boeke, Holmes and Phelps, 2020). Another study investigated the prediction of self-reported anxiety scores using rs-FC data from $N = 10,343$ healthy individuals from the

UKBIOBANK cohort, but found predictive performance at chance-level (Maglanoc *et al.*, 2020).

Of note, some studies have also attempted to use machine-learning classification to disentangle comorbidity between anxiety disorders and depression, both using tb-fMRI (Lueken, Straube, *et al.*, 2015), cognitive tasks without neuroimaging (Richter *et al.*, 2020, 2021), and symptom questionnaire scores (Liu, Droncheff and Warren, 2022).

Prediction in youth

To our knowledge, only three studies have investigated cross-sectional machine-learning prediction of anxiety using neuroimaging data in youth. The first study used fMRI features from an emotional faces task from the whole brain and conducted classification of anxiety disorder vs. control with an accuracy of 0.81 in a sample of 6-8 y.o. children with $N_{\text{patients}}=22$ (Sawalha *et al.*, 2021). Another study found the basolateral amygdala volumes and the left amygdala rs-FC with various brain regions to be significantly predictive of anxiety scores in $N = 60$ children aged 7-9 y.o. ($r_{(\text{predicted}, \text{observed})}=0.40$ and $r_{(\text{predicted}, \text{observed})}=0.22$ for the left and right basolateral amygdala volume respectively, r up to 0.56 for amygdala rs-FC) (Qin *et al.*, 2014). Finally, a third study found a moderate predictive value ($r_{(\text{predicted}, \text{observed})} = 0.09$) of the cerebrum and cerebrocortical ROIs gray matter in a prediction of anxiety symptom dimension using a sample of $N = 1401$ youth aged 8-23 years (Moberget *et al.*, 2019).

Overall, studies investigating cross-sectional machine-learning prediction of categorical or dimensional anxiety using neuroimaging data were highly heterogeneous in sample sizes, cross-validation strategies and predictive performance, both in adults and in youth. Nonetheless, neuroimaging data appears to have some cross-sectional predictive value for anxiety, although studies have yet to fully investigate the potential of neuroimaging data to bring incremental predictive value compared to inexpensive and easy-to-collect questionnaires and sociodemographic information. The potential incremental predictive value of neuroimaging data could be particularly useful for longitudinal predictions, such as predictions of risk and therapeutic response, to address clinical needs.

1.6.2. Prospective prediction of anxiety symptoms or disorder onset

1.6.2.1. Prediction using sociodemographic and questionnaire data

Few studies have used questionnaire data to predict individual-level prospective onset of anxiety disorders in longitudinal samples. One study used psychosociodemographic data and physical health features to predict prospective GAD ($N_{\text{patients}} = 1,123$; $N_{\text{total}} = 33,018$), PD ($N_{\text{patients}} = 647$; $N_{\text{total}} = 32,714$) or SAD ($N_{\text{patients}} = 560$; $N_{\text{total}} = 32,902$) 3 to 4 years later in adults, and reported AUC = 0.7991 for GAD, 0.7813 for PD, 0.7990 for SAD (Rosellini *et al.*, 2020). Another predicted anxiety disorders at age 15 in $N = 374$ youth from the community followed up between ages 3 and 15, both using questionnaire, physiological and environmental data from individual timepoints (ages 3, 6, 9, 12) and also combined from several timepoints (Hawes *et al.*, 2022). A third study predicted 10-year risk of anxiety onset using sociodemographic, physiometric and questionnaire data collected digitally, in $N = 477,100$ UKBIOBANK participants with a concordance index of 0.77 (Morelli *et al.*, 2021).

Several recent longitudinal studies investigated machine-learning prospective prediction of anxiety symptoms during COVID-19, a time of increased vulnerability to mental health problems. One study used pre-pandemic mental health and sleep questionnaire data from $N = 3,193$ adolescents aged 11-14 in the Adolescent Brain Cognitive Development Study (ABCD) to predict anxiety symptoms during the pandemic and reported an AUC ranging between 0.740-0.755 (Kiss *et al.*, 2022). Another study used demographic and survey data to predict high psychological distress corresponding to mood and anxiety symptoms a year later, in a sample of $N = 3,561$ Japanese students, with an AUC ranging between 0.696-0.796 (Baba and Bunji, 2023). Finally, a third study used pre-pandemic clinical and demographic data to predict lockdown-induced anxiety and depression symptoms in a mixed sample of $N = 29$ healthy controls, $N = 46$ obsessive-compulsive disorder and $N = 19$ adjustment disorder patients ($N_{\text{total}} = 94$), and reported predictive accuracies ranging between 0.67-0.75 (D'Urso *et al.*, 2022).

Predictive performances of prospective anxiety symptoms or disorder onset using only sociodemographic and mental and physical health questionnaire data are encouraging but heterogenous, and require improvement.

1.6.2.2. Prediction using MRI and fMRI data

Although neuroimaging data has potential to bring incremental predictive value, longitudinal designs allowing the investigation of prospective individual-level anxiety symptoms in vulnerable populations are very rare in the literature.

In adults, one study predicted anxiety symptom levels in $N = 22$ physically healthy survivors two years after they had lived through an earthquake using anxiety symptoms level and rs-fMRI data at baseline, and reported $r_{(\text{predicted}, \text{observed})} = 0.727$ ($\text{MSE} = 37.24$) (Long *et al.*, 2014). Another study used prepandemic rs-FC to predict trait anxiety scores in undergraduate students during the acute phase of the pandemic in China ($r_{(\text{predicted}, \text{observed})} = 0.215$, $N = 589$), and although the identified FC pattern was not predictive of trait anxiety in an external validation sample ($r_{(\text{predicted}, \text{observed})} = -0.045$, $N = 149$) it significantly predicted cross-sectional GAD vs. HC in a clinical sample (accuracy = 0.6872, $N_{\text{patients}} = 24$) (He *et al.*, 2021). In adolescents, to our knowledge, only one prospective machine-learning prediction of anxiety has been attempted, in which orbitofrontal cortex volume and orbitofrontal-amygdala functional connectivity in a dot-probe task at age 7-17 were found to be predictive of social anxiety score a year later in a healthy adolescent sample (support vector regression $r_{(\text{predicted}, \text{observed})} = 0.301$, $N = 66$) (Mao *et al.*, 2020). Thus, to date, attempts to predict prospective anxiety scores at the individual-level using neuroimaging data have been exploratory, and no prediction of anxiety disorder onset has been found in literature.

1.6.3. Prospective prediction of clinical outcome for patients with an anxiety disorder

Machine-learning approaches can predict at the individual-level on unseen samples, and are well-suited for predicting individual therapeutic outcomes, particularly with the high-dimensional data collected in clinical research and practice (Fusar-Poli *et al.*, 2018, p.). This is crucial in psychiatric prognosis, where many factors can influence the course of the disease and therapeutic outcome.

1.6.3.1. Prediction of naturalistic course of anxiety disorders

Predicting long-term course of anxiety disorders can be an important step towards personalised medicine. Three studies used the Netherlands Study of Depression and Anxiety

(NESDA), an adult cohort including both healthy controls and patients diagnosed with anxiety and/or depression, to predict the naturalistic course of patients with anxiety disorders using various sociodemographic and questionnaire data with a follow-up of up to 9 years. The first study used baseline demographic and clinical questionnaire data to investigate classification performance for health outcomes at each follow-up, and reported (2-year follow-up: $N = 2,596$, balanced accuracy for anxiety 0.592–0.612; 4-year follow-up: $N = 2,402$, balanced accuracy for anxiety 0.536–0.596; 6-year follow-up: $N = 2,256$, balanced accuracy for anxiety 0.226–0.584; 9-year follow-up: $N = 2,068$, balanced accuracy for anxiety 0.509–0.598) (van Eeden *et al.*, 2021). The second NESDA study used questionnaires, blood markers and physiological health features to predict increased severity (Mean Squared Error, $MSE = 0.057$) or recovery ($MSE = 0.095$) from anxiety disorder symptoms over the 9-year course ($N = 1,693$) ($N =$ (Wardenaar *et al.*, 2021)). The third NESDA study investigated prediction of recovery in $N = 887$ patients with anxiety disorders (GAD, SAD or PD/AG) after two years using sociodemographic, clinical, physiological health and lifestyle questionnaire data, and reported an $AUC = 0.67$ (Bokma *et al.*, 2022).

1.6.3.2. Prediction of psychotherapy outcome using sociodemographic and questionnaire data

A promising literature of machine-learning treatment outcome prediction has also emerged across mental disorders (see (Chekroud *et al.*, 2021) for a general review), including a rapidly increasing number of psychotherapy outcome prediction studies (Vieira *et al.*, 2022).

However, recent large-scale efforts to predict individual-level psychotherapy treatment response for patients with anxiety disorders based on sociodemographic and/or clinical data alone resulted only in moderate prediction accuracies, ranging from $N = 2147$, accuracy = 0.59, $N = 1236$, accuracy = 0.71; $N = 174$ and $AUC = 0.58-0.62$ (Hilbert *et al.*, 2020; Hornstein *et al.*, 2021; Leehr *et al.*, 2021).

Other studies with large samples that were not published at the beginning of this doctoral work reported similarly moderate prediction performances on average. One study predicted relapse over the 12-months following completion of a low-intensity CBT-based intervention in $N = 317$ participants with anxiety and depression using demographic and clinical features, reporting AUC between 0.72-0.84 (Lorimer *et al.*, 2021). Two studies of session-by-session prediction of anxiety symptom reduction during psychotherapy using routine clinical data in

adult patients diagnosed with anxiety and/or depression disorder yielded, respectively, AUCs ranging from 0.577 to 0.822 (training set $N = 2317$, validation in external test set $N = 2036$), and AUCs ranging from 0.500 to 0.859 (training set $N = 42,992$, held-out test set $N = 30,026$) (Bone *et al.*, 2021). One study used clinical and self-report questionnaires to predict CBT outcome in $N = 1210$ patients with anxiety and depression disorders (principal diagnosis remission AUC = 0.71, principal diagnosis improvement AUC = 0.61) (Rosellini *et al.*, 2023). Another study predicted anxiety symptom change after a digital psychotherapy in $N = 632$ participants using pre-treatment questionnaires and reported $r_{(\text{predicted}, \text{observed})}$ between 0.548 and 0.569 (Jacobson and Nemesure, 2021).

Overall, this literature shows promising but still limited predictive accuracies of psychotherapy outcome using clinical data and questionnaires, despite increasing sample sizes. As such, other data modalities, such as neuroimaging, have been explored in an effort to find incremental predictive performance.

1.6.3.3. Prediction of psychotherapy outcome using MRI and fMRI data

Neuroimaging data has shown promise to predict treatment outcomes for patients with anxiety disorders in previous attempts, but those have been exploratory and reported small clinical sample sizes (Chekroud *et al.*, 2021) (see (Vieira *et al.*, 2022) for a recent review).

Indeed, to our knowledge, two studies conducted individual CBT outcome prediction using tb-fMRI in patients with panic disorder, with $N = 49$ and accuracy = 0.82, and $N = 59$ and accuracy = 0.54 respectively (Hahn *et al.*, 2015; Sundermann *et al.*, 2017). One study predicted CBT outcome using tb-fMRI and clinical data in a mixed sample of $N = 25$ patients with panic disorder or generalized anxiety disorder, reporting an accuracy = 0.82 (Ball *et al.*, 2014). One study used rs-fMRI data to predict CBT outcome in $N = 38$ SAD patients and reported an accuracy of 0.81 (Whitfield-Gabrieli *et al.*, 2016). Two studies predicted psychotherapy outcome using tb-fMRI in patients with social anxiety disorder (Månsson *et al.*, 2015; Frick *et al.*, 2020), reporting respectively accuracy = 0.92 ($N = 23$), accuracy = 0.83 ($N = 47$). One recent study used clinical data, tb-fMRI and rs-fMRI to predict CBT outcome in $N = 45$ patients with social anxiety disorder, and reported $r_{(\text{predicted}, \text{observed})} = 0.77$, with neuroimaging features outperforming questionnaire data in the prediction (Månsson *et al.*, 2022).

Overall, predictive performances were encouraging but the incremental value of neuroimaging compared to questionnaire data only has only been investigated in two of the above-mentioned studies, with divergent results. Moreover, sample sizes remained small, which a review of machine-learning psychiatric prognosis prediction studies using neuroimaging data has warned could lead to an increased risk of overoptimistic predictive performance estimates (Janssen, Mourão-Miranda and Schnack, 2018).

1.7. Aims and hypotheses

Recent individual-level predictions using sociodemographic, clinical and questionnaire data have yielded moderate predictive accuracies in large samples, both for the prediction of prospective anxiety symptom levels and of prospective psychotherapy outcome for anxiety disorders. Only one study has explored symptom level prediction during adolescence, which is a window of vulnerability for anxiety disorders, and future anxiety disorder onset prediction using neuroimaging has not yet been attempted in adults nor adolescents. Furthermore, an exploratory, small-scale literature has already investigated future psychotherapy outcome prediction in anxiety disorders using neuroimaging data and reported promising prediction performances, but the robustness of these performances in larger samples has not yet been shown. Additionally, studies generally investigated a single neuroimaging modality both for prospective anxiety levels prediction and psychotherapy outcome prediction.

Thus, this doctoral work aimed at explored multimodal neuroimaging data at various information levels for prospective individual-level predictions in anxiety disorders. Specifically, it focused on investigating the incremental contributions of structural MRI and tb-fMRI data compared to questionnaire data alone in machine-learning predictions of anxiety disorder onset, and of psychotherapy response in spider phobia. Detailed aims and hypotheses will be described in the relevant sections, but a brief overview is given here.

Given the lack of previous literature in anxiety disorder onset prediction using neuroimaging data, we hypothesized that questionnaire data would be predictive of future anxiety onset, and that MRI and tb-fMRI features from brain regions classically impacted in anxiety might have incremental predictive value compared to questionnaire data alone (sections 2. and 3.).

Regarding our prediction of psychotherapy response in spider phobia, given that a previous study using only sociodemographic and questionnaire data had already been published using

an overlapping patient sample (Leehr *et al.*, 2021), our work focused on exploring the potential incremental predictive value of structural MRI and tb-fMRI features extracted from brain regions classically impacted in anxiety, compared with questionnaire data alone (section 4). Our hypotheses were that neuroimaging data would have above-chance predictive value for psychotherapy outcome prediction, and that an ensemble prediction approach leveraging both neuroimaging and questionnaire data would outperform the prediction using questionnaire data alone.

2. Anxiety onset prediction in adolescents using structural MRI

This section corresponds to the first publication of the thesis (Chavanne, Paillère Martinot, *et al.*, 2023), in the *Molecular Psychiatry* journal. It has been cited in the 2023 National Health Strategy Report of the French *Haut Conseil de la Santé Publique* (HCSP, 2023).

Abstract

Recent longitudinal studies in youth have reported MRI correlates of prospective anxiety symptoms during adolescence, a vulnerable period for the onset of anxiety disorders. However, their predictive value has not been established. Individual prediction through machine-learning algorithms might help bridge the gap to clinical relevance. A voting classifier with Random Forest, Support Vector Machine and Logistic Regression algorithms was used to evaluate the predictive pertinence of gray matter volumes of interest and psychometric scores in the detection of prospective clinical anxiety. Participants with clinical anxiety at age 18-23 (N = 156) were investigated at age 14 along with healthy controls (N = 424). Shapley values were extracted for in-depth interpretation of feature importance. Prospective prediction of pooled anxiety disorders relied mostly on psychometric features and achieved moderate performance (area under the receiver operating curve = 0.68), while generalized anxiety disorder (GAD) prediction achieved similar performance. MRI regional volumes did not improve the prediction performance of prospective pooled anxiety disorders with respect to psychometric features alone, but they improved the prediction performance of GAD, with the caudate and pallidum volumes being among the most contributing features. To conclude, in non-anxious 14 y.o. adolescents, future clinical anxiety onset 4 to 8 years later could be individually predicted. Psychometric features such as neuroticism, hopelessness and emotional symptoms were the main contributors to pooled anxiety disorders prediction. Neuroanatomical data, such as caudate and pallidum volume, proved valuable for GAD and should be included in prospective clinical anxiety prediction in adolescents.

2.1. Introduction

Anxiety disorders have been reported to have a high impact on the global burden of disease (Yang *et al.*, 2021). Anxiety disorders are the most prevalent psychiatric condition in adolescence, impacting nearly one in three individuals (Beesdo, Knappe and Pine, 2009; Merikangas *et al.*, 2010). The average age of onset predates 15 y.o. for social anxiety disorder and specific phobia, whereas panic disorder and generalized anxiety disorder tend to emerge slightly later in life (Lijster *et al.*, 2017). Moreover, anxiety disorders can remain unstable in adolescence, before consolidating further in young adulthood. Therefore, detecting individuals at elevated risk of developing clinical anxiety is crucial.

Many sociodemographic, psychosocial, as well as physical and mental health factors have been reported as risk factors of generalized anxiety disorder and panic disorder (Moreno-Peral *et al.*, 2014). Personality scores such as neuroticism and anxiety sensitivity have also been established as pre-existing risk factors for future anxiety disorders (Schmidt, Zvolensky and Maner, 2006; Jeronimus *et al.*, 2016). Early-life anxious temperament is also a strong risk factor for anxiety disorders later in life (Clauss and Blackford, 2012). Furthermore, neuroimaging data, jointly with psychometric and clinical data, show promise to identify at-risk populations (Linden, 2012).

In adolescent patients with anxiety disorders, cross-sectional differences in gray matter volume have been reported using magnetic resonance imaging (MRI) in the amygdala, hippocampus, insula, cingulate cortex, ventromedial prefrontal cortex (vmPFC), and temporal gyri (Merz *et al.*, 2018). Additionally, the striatum was highlighted as a critical subcortical region of interest for the onset of anxiety disorders in adolescence (Lago *et al.*, 2017). A model of anxious temperament has also been shown to involve the central amygdala, orbitofrontal cortex, bed nucleus of the stria terminalis (BNST) and periaqueductal gray in young primates (Kalin, 2017; Fox and Shackman, 2019).

However, only few longitudinal studies have investigated neurostructural correlates of anxiety in adolescents from a developmental perspective (14, see 15 for a review). It was reported that amygdala volume measured up to three times at 2-year intervals in non-clinical participants between age 4 and 18 was longitudinally and positively associated with anxiety-depressive symptoms (Albaugh *et al.*, 2017). Two studies were based on regions of interest (ROIs) but did not include limbic structures. One reported that larger pituitary volume at age 12-13 preceded an increase in anxiety symptoms two to three years later (Zipursky *et al.*,

2011). The other found that larger right middle temporal gyrus cortical thickness in non-clinical participants aged 13 to 20 predicted symptoms of generalized anxiety disorder two years later (Busso *et al.*, 2017).

Nonetheless, statistical association does not necessarily translate into cross-sectional classification or prospective prediction, the second and third implying an ability to generalize findings to new, unseen data (Poldrack, Huckins and Varoquaux, 2020). In the last decade, research in psychiatry has progressively incorporated machine-learning approaches in an effort to bridge the gap between diagnostic or prognostic markers detected at group level, and clinical relevance. Machine-learning techniques have shown promise in single-subject patient classification using neuroimaging data, and there has been a recent effort to use larger samples and multisite data to overcome inherent limitations of such analyses (Arbabshirani *et al.*, 2017). Few studies in adults have attempted single-participant classification of clinical anxiety using neuroimaging data, with limited sample sizes, heterogenous performance metrics and non-prospective designs. In adults, two studies investigated classification of social anxiety disorder with very small clinical sample sizes ($N_{\text{patients}} = 14$ and 20 , with accuracies of 0.845 and 0.825 respectively) (Frick *et al.*, 2014; Liu *et al.*, 2015), one other study did so with moderately larger sample size ($N_{\text{patients}} = 47$, area under the curve = 0.72) (Xing, Fitzgerald and Klumpp, 2020), and another investigated spider phobia classification ($N_{\text{patients}} = 59$, accuracy ranging from 0.62 to 0.88) (Lueken, Hilbert, *et al.*, 2015). In each study, classification performance tended not to rely on a few select structures of the fear circuitry or other networks, but rather relied on diffuse predictors across the brain.

In adolescents, to our knowledge, only one prospective prediction of anxiety has been attempted, in which orbitofrontal cortex volume and orbitofrontal-amygdala functional connectivity in a dot-probe task at age 7-17 were found to be predictive of social anxiety score a year later in a healthy adolescent sample (support vector regression $r_{(\text{predicted, observed})} = 0.301$) (Mao *et al.*, 2020).

Therefore, the first aim of the current study was to predict prospective clinical anxiety at the individual level at ages 18 and/or 23, both pooled and disorder-specific, based on gray matter volumes as well as psychometric features such as neuroticism and anxiety sensitivity scores at age 14. The second aim was to assess the respective contributions of both gray matter volumes and psychometric feature categories to the prediction performance. These analyses were conducted under the *a priori* hypotheses that gray matter volumes in subcortical and

frontomedial regions might have, and that psychometric features would have, a predictive value for the onset of anxiety in adolescence.

2.2. Methods

2.2.1. Dataset and sample description

All data originated from the IMAGEN database (Schumann *et al.*, 2010) that includes neuroimaging data collected in community adolescents at age 14, as well as several questionnaires evaluating mental disorders, emotional functioning and alcohol and substance consumption. Written informed consent was obtained from all participants and their legal guardians.

Diagnostic data were collected at baseline, at age 18-19 (first follow-up, FU1), and age 22-23 (FU2) using the DAWBA (Development And Well-Being Assessment), a computerized self-report assessment that generates DSM-IV and ICD-10 diagnoses (Goodman *et al.*, 2000). These diagnoses were subsequently evaluated by trained clinicians, as previously described (Paillère Martinot *et al.*, 2014). Alcohol and cannabis consumption were respectively evaluated using the AUDIT (Alcohol Use Disorders Identification Test) and the ESPAD (European School survey Project on Alcohol and other Drugs) (Saunders *et al.*, 1993; Molinaro *et al.*, 2012). Other clinical assessments included negative thinking, anxiety sensitivity subscales from the Substance Use Risk Profile Scale (SURPS) (Woicik *et al.*, 2009); emotional symptoms score in the Strength and Difficulties Questionnaire (SDQ) (Goodman, 1997); autonomy, accidents, distress, family, and relocation subscales from the Life Events Questionnaire (LEQ) (adapted from 33); neuroticism, and extraversion subscales from the revised NEO Personality Inventory (NEO-FFI) (Costa Jr. and McCrae, 2008); novelty-seeking as measured by the revised Temperament and Character Inventory (TCI-R) (Cloninger, 1994). A more detailed description of the questionnaires is presented in machine-learning methods.

Participants with T1 data at baseline were assessed for eligibility in our analyses. Visual quality control was conducted for each MRI T1 scan and participants with excessive noise, motion artefacts or abnormal brain anatomy were excluded. Participants with AUDIT scores equal to or greater than 7 at baseline were excluded, as alcohol disorder may interfere with brain structure development (Kühn *et al.*, 2019) (inclusion flowchart in Figure 4).

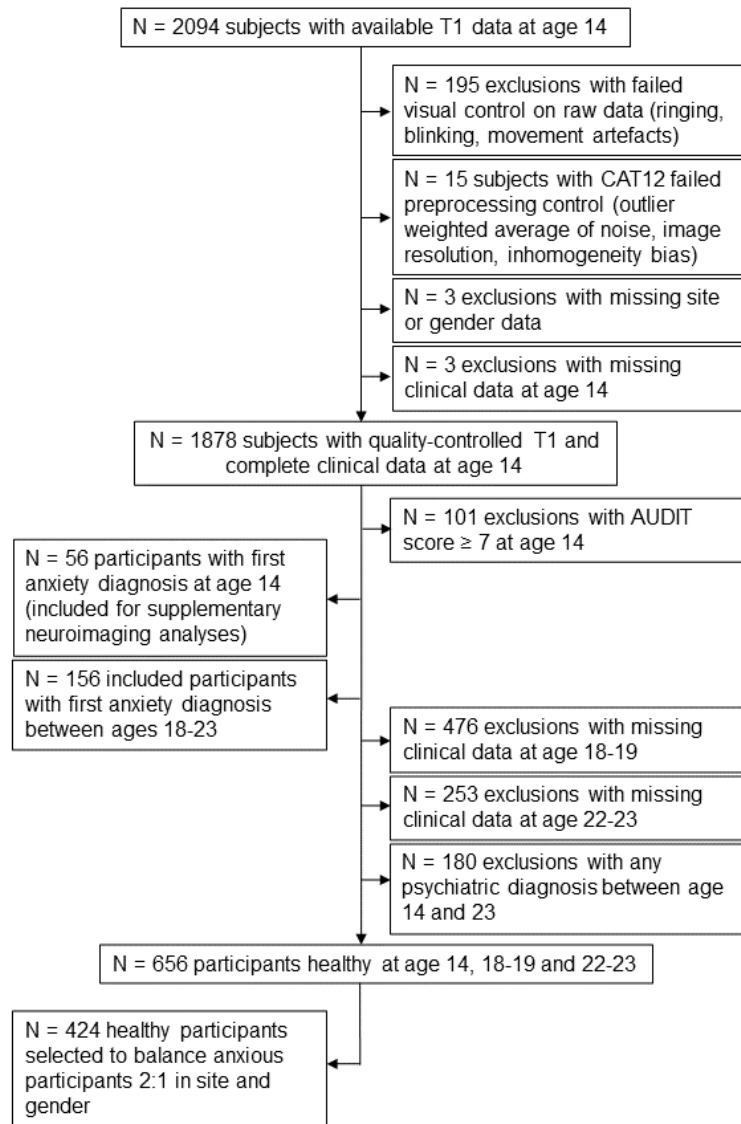


Figure 4: Inclusion flowchart.

AUDIT: Alcohol Use Disorders Identification Test.

Participants with DAWBA anxiety diagnoses of generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobia (SpP), panic disorder (PD), agoraphobia (AG) and other anxiety (OA) at baseline, FU1 or FU2 were included. They were subdivided between those who had at least one anxiety diagnosis at baseline (BLA) at age 14 (N=56, only used in neuroimaging group analyses in section 2.3.4.1), and future anxiety-onset participants, whose first anxiety diagnosis was reported at either FU1 or FU2 (future anxiety, FUA). FUA participants were then allocated to 5 mutually exclusive groups. Those who had only one anxiety disorder diagnosis at 18-23 (one stable diagnosis at both FU1 and FU2, or one diagnosis at either FU1 or FU2) were split into GAD, SAD, SpP and PD/AG diagnostic

2. Anxiety onset prediction in adolescents using structural MRI

groups, while participants with multiple anxiety disorders (mAD) at any timepoint at ages 18 and/or 23 (i.e., two or more distinct anxiety diagnoses, simultaneous or not) were allocated to a mAD group (see Tables 2 and 3 for details about the FUA or BLA sample respectively).

Group	SpP	SAD	PD/Ag	GAD	Multiple anxiety diagnoses ^a	Total FUA	HC	FUA vs. HC
N participants	25	25	22	42	42	156	424	
N major or other depression diagnoses at age 14	2	2	2	0	1	7		
Gender (m/f)	3/22	10/15	5/17	12/30	10/32	40/116	131/293	n.s.
Age (years) (SD)	14.6 (0.5)	14.4 (0.4)	14.4 (0.3)	14.4 (0.3)	14.4 (0.5)	14.4 (0.4)	14.4 (0.4)	n.s.
AUDIT score (SD)	1.2 (1.7)	0.9 (1.5)	2.0 (1.9)	1.4 (2.0)	1.4 (1.5)	1.4 (1.8)	0.9 (1.4)	1.0e-3*
ESPAD-year score (SD)	0.3 (1.1)	0.1 (0.4)	0	0.1 (0.4)	0.1 (0.5)	0.1 (0.6)	0.1 (0.4)	2.9e-2*
Neuroticism NEO score (SD)	26.7 (8.0)	28.0 (7.2)	25.0 (8.5)	24.9 (6.6)	29.5 (7.7)	27.0 (7.7)	22.6 (6.7)	5.4e-10*
Anxiety sensitivity SURPS score (SD)	11.5 (2.9)	12.6 (2.0)	11.2 (2.5)	12.1 (2.5)	12.6 (2.5)	12.1 (2.5)	11.2 (2.1)	2.5e-5*
SDQ emotional score (SD)	4.0 (2.4)	3.7 (2.5)	2.9 (2.5)	3.2 (1.8)	4.4 (2.3)	3.7 (2.3)	2.5 (1.8)	1.1e-8*
Transversal TIV (mm ³) (SD)	1 461.1 (132.5)	1 460.2 (144.6)	1 428.9 (118.9)	1 498.9 (133.5)	1 441.8 (140.4)	1 461.5 (135.7)	1 453.0 (133.5)	n.s.

Table 2: Sample description at age 14 of participants with future anxiety.

SpP: Specific phobia; SAD: social anxiety disorder; PD/Ag: panic disorder and/or agoraphobia; GAD: generalized anxiety disorder; HC: healthy controls; anxiety diagnosed at age 18-19 or age 22-23 follow-ups.

* $p < 0.05$; Kruskal-Wallis test for continuous variables, Chi² test for categorical variables.

^a Group included participants meeting criteria for at least two diagnoses (SpP, SoPh, PD/Ag, GAD, or other clinical anxiety (OA)), simultaneously or not, at any of FU1 or FU2 timepoints: 42 participants had a first anxiety onset at FU1/FU2 (9 SpP, 24 SoPh, 16 PD/Ag, 25 GAD and 12 OA current or future diagnoses).

PD and AG were combined because they are highly comorbid disorders (Kikuchi *et al.*, 2005), and our sample size did not allow the investigation of standalone agoraphobia. Participants that had missing DAWBA data at FU1 or FU2 but did have one anxiety diagnosis at the other follow-up timepoint (FU2 or FU1 respectively) were included, as this latter criterion was sufficient for allocation to the FUA (32 participants) or BLA (24 participants) groups. A total of $N = 156$ FUA participants were available for prediction analyses.

2. Anxiety onset prediction in adolescents using structural MRI

Group	SpP	SAD	PD/Ag	GAD	Multiple anxiety diagnoses ^a	Total BLA	HC	p-value BLA vs. HC
N participants	8	10	8	7	23	56	424	
N depression diagnoses at age 14	1	4	4	4	3	16		
Gender (m/f)	2/6	3/7	2/6	1/6	4/19	12/44	131/293	n.s.
Age (years) (SD)	14.3 (0.3)	14.3 (0.4)	14.3 (0.2)	14.2 (0.3)	14.3 (0.4)	14.3 (0.3)	14.4 (0.4)	n.s.
AUDIT score (SD)	0.8 (1.2)	0.8 (1.4)	0.8 (1.0)	1.9 (1.7)	1.3 (1.7)	1.1 (1.5)	0.9 (1.4)	n.s.
ESPAD-year score (SD)	0	0	0	0	0.0 (0.2)	0.0 (0.1)	0.1 (0.4)	n.s.
Neuroticism NEO score (SD)	27.1 (11.0)	32.1 (8.1)	35.0 (7.1)	28.0 (7.5)	32.4 (5.9)	31.4 (7.7)	22.6 (6.7)	1.1e-13*
Anxiety sensitivity SURPS score (SD)	11.6 (2.9)	12.1 (1.5)	11.8 (2.4)	12.1 (2.1)	12.9 (2.8)	12.3 (2.5)	11.2 (2.1)	4.3e-3*
SDQ emotional score (SD)	4.1 (2.2)	5.6 (2.5)	5.8 (1.9)	5.0 (1.9)	5.6 (1.6)	5.3 (1.9)	2.5 (1.8)	3.6e-18*
Transversal TIV (mm ³) (SD)	1 463.1 (128.9)	1 542.2 (156.3)	1 442.1 (95.1)	1 374.5 (148.5)	1 435.3 (123.5)	1 451.7 (134.8)	1 453.0 (133.5)	n.s.

Table 3: Sample description at age 14 of participants with current anxiety.

SpP: Specific phobia; SAD: social anxiety disorder; PD/Ag: panic disorder and/or agoraphobia; GAD: generalized anxiety disorder; HC: healthy controls; BLA: anxiety diagnosed at age 14.

* $p < 0.05$; Kruskal-Wallis test for continuous variables, Chi² test for categorical variables.

^a Group included participants meeting criteria for at least two diagnoses (SpP, SoPh, PD/Ag, GAD, or other clinical anxiety (OA)), simultaneously or not: 23 participants had a first anxiety onset at baseline (10 SpP, 18 SoPh, 10 PD/Ag, 14 GAD and 4 OA current or future diagnoses).

In the FUA group, data were collected in Berlin for N = 15 participants, in Dresden for N = 16 participants, in Dublin for N = 17 participants, in Hamburg for N = 17 participants, in London for N = 33 participants, in Mannheim for N = 6 participants, in Nottingham for N = 29 participants, and in Paris for N = 23 participants.

Among the 89 FUA participants that had a first anxiety diagnosis at FU1, 9 had the same anxiety disorder(s) diagnosed at FU2, 2 had the same diagnosis and one additional anxiety disorder diagnosed at FU2, 7 had a different anxiety diagnosis at FU2, 51 had no anxiety diagnosis at FU2, and 20 did not have clinical data at FU2.

Eligible controls were typical adolescents with no DAWBA diagnosis at baseline, FU1 and FU2. Participants with incomplete DAWBA data at any timepoint were excluded from

eligible controls. Then, we randomly selected controls amongst eligible participants to balance scanning acquisition sites and gender with participants with anxiety disorders by a 2:1 ratio.

2.2.2. MRI acquisition and preprocessing

All scans were obtained on 3T scanners (Siemens, Philips, General Electrics) across the 8 IMAGEN European sites, based on an Alzheimer's Disease Neuroimaging Initiative Magnetization-Prepared Rapid Acquisition Gradient Echo (ADNI-MPRAGE) standardized acquisition sequence (sagittal plane, repetition time = 2.3ms, echo time = 2.93 ms, flip angle = 8°, matrix: $256 \times 256 \times 160$, voxel size: $1.1 \times 1.1 \times 1.1$ mm) (Schumann *et al.*, 2010). MRI data were preprocessed with the CAT12 toolbox version 12.6 (<http://www.neuro.uni-jena.de/cat/>) in SPM12 (Statistical Parametric Mapping, <https://www.fil.ion.ucl.ac.uk/spm/>) in Matlab (<https://fr.mathworks.com>). T1-weighted images were segmented, normalized, and modulated. They were smoothed with a statistical 8 mm Full-Width Half-Maximum Gaussian filter (final voxel size: $1.5 \times 1.5 \times 1.5$ mm).

CAT12 provides TIV (Total Intracranial Volume) measures and calculates image quality ratings (noise, inhomogeneity bias, image resolution, and a weighted average rating of these measures, obtained with a root mean square equation to accentuate the impact of a mediocre measurement). The weighted average rating was examined, and the worse scoring participants (D and C-) at baseline were excluded from all analyses.

2.2.3. Machine-learning prediction

2.2.3.1. Feature extraction

Extraction was conducted with SPM12. ROIs classically involved in clinical anxiety were extracted from the AAL atlas (Tzourio-Mazoyer *et al.*, 2002) and combined from the left and right hemispheres with the WFU_PickAtlas toolbox (https://www.nitrc.org/projects/wfu_pickatlas/). ROIs included the amygdala, hippocampus, parahippocampal gyrus, mid- and anterior cingulate cortex, gyrus rectus, medial orbitofrontal cortex, putamen, pallidum, caudate nucleus, thalamus, insula, as well as the periaqueductal gray (PAG) from a 6 mm sphere centered on $x = 0$, $y = -29$, $z = -12$ (Linnman *et al.*, 2012), and the BNST (Neudorfer *et al.*, 2020). Gray matter volumes for each ROI were extracted

from preprocessed scans with the MarsBar toolbox (Brett *et al.*, 2002) with no additional scaling, for a total of 14 neuroimaging features at age 14.

IMAGEN questionnaire subscales relevant to anxiety phenomenology were selected *a priori*. In particular, the life-event questionnaire (LEQ) assesses a range of potentially stressful activities or experiences in adolescents, and the family, autonomy, distress, accident and relocation frequencies subscales (lifetime frequency score for distress, family and accident, past year score for autonomy and relocation) were included as predictive features. The revised temperament and character inventory (TCI-R) measures excitability, disorderliness, impulsivity and extravagance for a sum score of novelty seeking which was used as a feature. The strength and difficulties questionnaire (SDQ) measures conduct problems, peer problems, prosocial behaviour, hyperactivity, as well as emotional symptoms which was included in our analysis. The substance use risk profile scale (SURPS) assesses dimensions of sensation-seeking, impulsivity, hopelessness and anxiety sensitivity, and the last two were included as features. Finally, the revised NEO personality inventory (NEO-FFI is a well-known personality assessment based on the five-factor model, and measures openness, agreeableness, conscientiousness, extraversion and neuroticism subscales, with the last two being included in our analysis. While age is not a specific predictor of anxiety, age at baseline (in days) was included in our analysis to account for its potential interactions with other features, which could also provide predictive value, resulting in a total of 13 psychometric features at age 14.

2.2.3.2. Machine-learning pipeline

Classifications were conducted with scikit-learn 0.24.2 (<https://scikit-learn.org/dev/versions.html>) in Python. A majority voting algorithm between Logistic Regression (LR), Support Vector Machine (SVM) and Random Forest (RF) classifiers was used.

Three separate binary class prediction analyses were conducted with baseline neuroimaging and psychometric data. The first analysis was the prediction of any FUA (N = 156) vs. healthy controls (N=424). The second analysis was the prediction of FUA GAD diagnosis (N=42) vs. healthy controls, and the third prediction of FUA mAD (N=42) vs. healthy controls. Only the GAD and mAD groups had more than 30 FUA participants. Thus, no other specific diagnosis group could be explored. As the data were moderately imbalanced between FUA participants

and healthy controls, additional functions from imbalanced-learn 0.8.0 (Lemaître, Nogueira and Aridas, 2017) were used. The FUA SpP, SAD and PD/Ag groups all included $N < 30$ subjects and could not be explored separately ($N = 25$, $N = 25$, and $N = 22$ respectively). The three above-mentioned predictions were first conducted with the 27 features together, then only with the 13 psychometric features, and only with the 14 regional gray matter volume features, to evaluate their respective contributions.

A leave-3-groups-out cross-validation strategy was used: in each cross-validation fold, 5 acquisition sites were chosen as training data and the remaining 3 sites as testing data, such that no two participants from the same site could be in both the training and testing sets. All possible splits of the 8 sites resulted in 56 cross-validation folds in total, and in each fold a nested stratified 5-fold hyperparameter optimization to maximize area under the receiver operating curve (AUROC) was conducted. Inside each nested fold, missing psychometric data (0.02% of questionnaire scores in the whole sample, including FUA and healthy controls, $N=580$) were imputed with the feature median, then data were scaled and resampled with a combination of over- and under-sampling (synthetic minority oversampling technique and edited nearest neighbours cleaning with default parameters) so that both groups would have equal size (Batista, Prati and Monard, 2004). The analysis pipeline and reported metrics (i.e. 10-fold cross-validation, nested preprocessing to avoid data leakage, AUROC reported as a performance metric insensitive to relative class frequencies) were chosen according to recommended practices (Poldrack, Huckins and Varoquaux, 2020). Mean performance metrics over the 56 folds are reported in the results section.

The ‘liblinear’ library was set as the solver parameter of the LR classifier, and the class weight parameter was set to ‘balanced’ for all three classifiers. Optimized hyperparameters included the number of maximum iterations, penalty and C from the LR classifier, the gamma and C from the SVM classifier, and the maximum depth and maximum number of features from the RM classifier. Scikit-learn default values were used for all remaining classifier parameters.

To examine each feature contribution to individual predictions more closely, we also used the recent Shapley additive explanation (SHAP) module, version 0.39.0 (Lundberg and Lee, 2017). SHAP uses a game theoretic approach to assign an importance value to each feature for an individual prediction and allows visualization of the contribution of each feature value to its final classification for each participant.

A more traditional 10-fold stratified cross-validation repeated 10 times was also explored for completeness, with the nested optimization and all other classifier parameters kept identical.

2.2.3.3. Neuroimaging group-level analysis

All analyses were conducted with SPM12 and CAT12. Gray matter volume analyses were conducted within an anatomical mask encompassing bilateral regions classically involved in clinical anxiety, built from the AAL atlas with the WFU_PickAtlas toolbox (https://www.nitrc.org/projects/wfu_pickatlas/). The gray matter volume (GMV) mask included the amygdala, hippocampus, parahippocampal gyrus, mid- and anterior cingulate cortex, gyrus rectus, medial orbitofrontal cortex, putamen, pallidum, caudate nucleus, thalamus, insula, midbrain (the latter taken from the TD Lobes atlas) and BNST (Neudorfer *et al.*, 2020) regions of interest (ROIs).

Cross-sectional one-way ANOVA analyses were conducted with a group factor over the GM images at baseline with age, gender, IMAGEN acquisition sites, TIV, DAWBA depressive comorbidity, AUDIT score, and ESPAD cannabis consumption score as covariates of no interest. A six-level group factor was used for FUA participants (SpP, SAD, PD/AG, GAD, mAD or controls) and pairwise contrasts were examined. As only mAD had N>20 BLA participants, a two-level group factor was used (mAD or controls).

Results were obtained using the TFCE toolbox (<http://www.neuro.uni-jena.de/tfce/>) for non-parametric permutation-based statistics on each contrast, with a family-wise error-corrected $p_{FWE} \leq 0.05$ threshold and more than 10 voxels. TFCE parameters were set as 5000 permutations with the Smith method, with default weights H (height) and E (extent) ($H = 2$, $E = 0.5$ for GMV). Anatomical location of significant clusters was determined with the AAL atlas and manually verified with MRICron (<https://www.nitrc.org/projects/mricron>) for GMV.

2.3. Results

2.3.1. Sample characteristics

FUA participants did not differ from healthy controls for age, gender and TIV at baseline, but they had significantly higher AUDIT, ESPAD, neuroticism, anxiety sensitivity and emotional symptoms scores (see Table 2). Additionally, significantly higher neuroticism and emotional

symptoms scores were detected in FUA mAD participants compared to FUA participants with only one diagnosed disorder (p-value = 5.5e-3 and 2.3e-2 respectively).

At baseline, no significant difference was observed between BLA participants and healthy controls for age, gender, TIV, AUDIT or ESPAD score. BLA participants had significantly higher neuroticism (NEO), anxiety sensitivity (SURPS) and emotional symptoms (SDQ) scores.

2.3.2. Machine-learning diagnostic predictions

2.3.2.1. Main analysis using leave-3-groups-out cross-validation

Trained classifiers for all cross-validation iterations of all analyses are available online (<https://osf.io/pdmrv/>). Prediction of any future anxiety disorder vs. healthy control class resulted in an AUROC = 0.68 (standard deviation (SD) = 0.03) (Table 4).

Features that most differentiated between classes included neuroticism, hopelessness, emotional symptoms and family events (Figure 5). Higher values were interpreted by the trained classifier as contributing to clinical anxiety outcome classification, rather than to the healthy control class. Greater bilateral BNST volume supported healthy control classification outcome.

Classification metric	AUROC (SD)			Balanced accuracy (SD)			Sensitivity (SD)			Specificity (SD)		
	N+P	N	P	N+P	N	P	N+P	N	P	N+P	N	P
Any future anxiety (N=156) vs. HC (N=424)	0.68 (0.03)	0.52 (0.04)	0.69 (0.03)	0.60 (0.04)	≤0.5 ^a (0.03)	0.63 (0.04)	0.81 (0.13)	0.79 (0.17)	0.67 (0.15)	0.38 (0.15)	0.21 (0.17)	0.58 (0.12)
Future GAD (N=42) vs. HC (N=424)	0.69 (0.07)	0.63 (0.06)	0.62 (0.08)	0.62 (0.08)	0.59 (0.04)	0.57 (0.07)	0.53 (0.23)	0.49 (0.21)	0.38 (0.26)	0.71 (0.12)	0.69 (0.16)	0.76 (0.16)
Future mAD (N=42) vs. HC (N=424)	0.71 (0.06)	≤0.5 ^a (0.06)	0.74 (0.05)	0.65 (0.06)	≤0.5 ^a (0.05)	0.67 (0.07)	0.63 (0.20)	0.44 (0.24)	0.59 (0.12)	0.67 (0.14)	0.51 (0.22)	0.75 (0.10)

Table 4: Mean performance metrics of both pooled and disorder-specific future anxiety vs. healthy controls predictions.

HC: healthy controls; GAD: generalized anxiety disorder; mAD: multiple anxiety disorder; AUROC: area under the receiver operating curve; N: analysis conducted using neurostructural (regional gray matter volumes) features; P: analysis conducted using psychometric features.

^a: Equal to or below chance level.

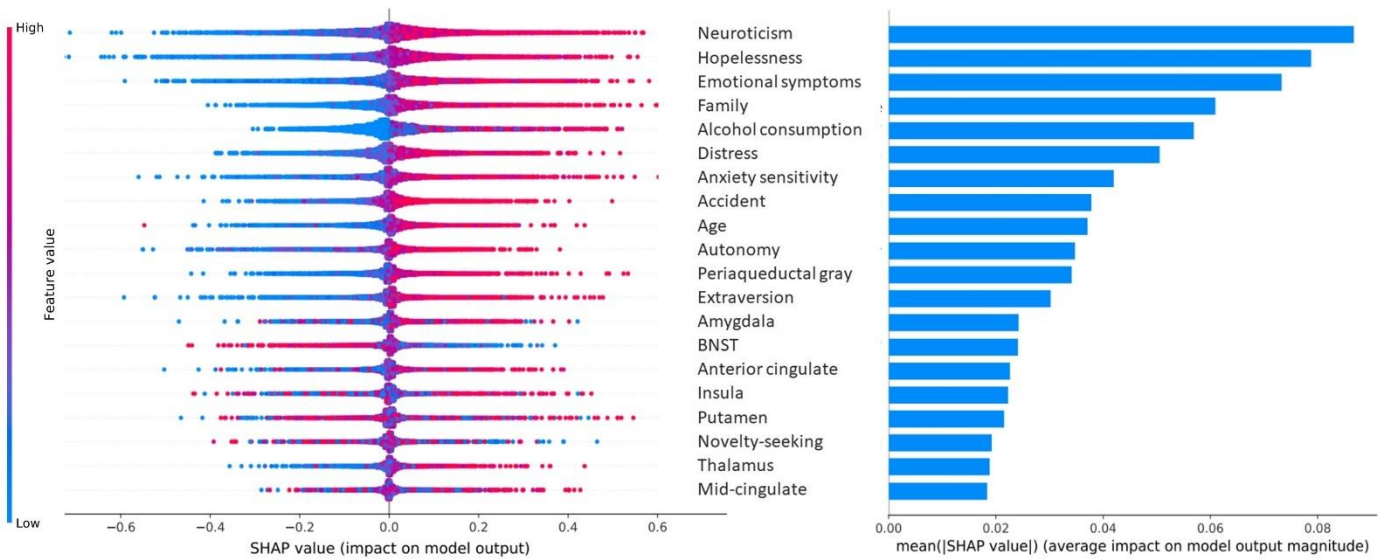


Figure 5 : SHAP values and importance of features at age 14 in the prediction of any future anxiety (N=156) vs. healthy control (N=424).

Each dot represents an individual in a given cross-validation iteration. Positive Shapley values indicate contribution of a feature value in favour of the positive class (future anxiety) prediction, negative Shapley values are in favour of the negative class (healthy control) prediction. Larger absolute Shapley values indicate larger impact on the model output. The 20 most contributing features are shown. BNST: bed nucleus of the stria terminalis.

Prediction of FUA GAD resulted in an AUROC = 0.69 (SD = 0.07). Most contributing features included bilateral caudate volume, autonomy, bilateral pallidum volume, extraversion, accident score, emotional symptoms and anxiety sensitivity, with higher values supporting FUA GAD outcome classification (Figure 6). Larger bilateral insula, BNST and mid-cingulate volumes, as well as higher novelty-seeking and relocation scores, contributed to healthy control classification outcome.

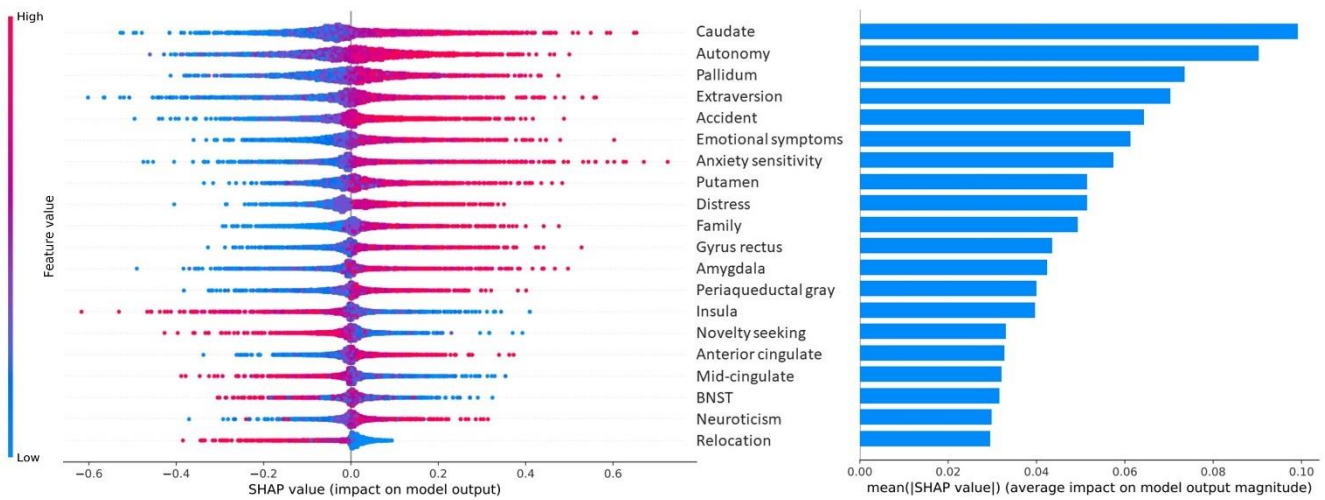


Figure 6: SHAP values and importance of features at age 14 in the prediction of future generalized anxiety disorder (N=42) vs. healthy control (N=424).

Each dot represents an individual in a given cross-validation iteration. Positive Shapley values indicate contribution of a feature value in favour of the positive class (future generalized anxiety) prediction, negative Shapley values are in favour of the negative class (healthy control) prediction. Larger absolute Shapley values indicate larger impact on the model output. The 20 most contributing features are shown. BNST: bed nucleus of the stria terminalis.

Prediction of FUA mAD resulted in an AUROC = 0.71 (SD = 0.06). Most impacting features included neuroticism, emotional symptoms and PAG volume, with higher values supporting FUA mAD outcome classification (Figure 7). Larger bilateral putamen, caudate, BNST, hippocampus and insula volumes, as well as age, generally supported healthy control classification outcome.

A prediction of FUA GAD vs. FUA mAD is presented in Figure 8.

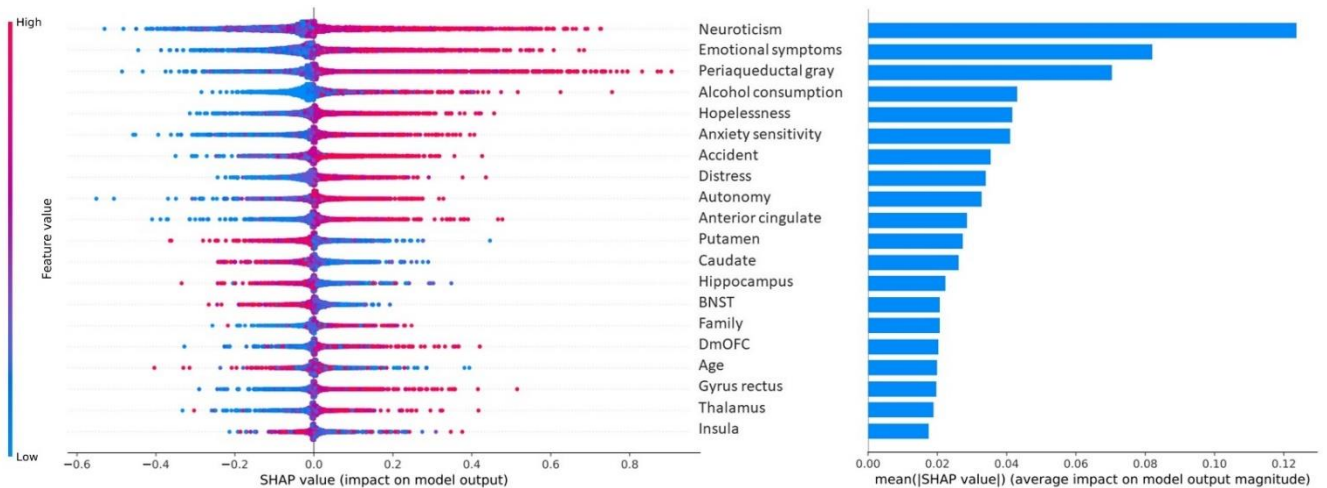


Figure 7: SHAP values and importance of features at age 14 in the prediction of future multiple anxiety diagnoses (N=42) vs. healthy control (N=424).

Each dot represents an individual in a given cross-validation iteration. Positive Shapley values indicate contribution of a feature value in favour of the positive class (future multiple anxiety diagnoses) prediction, negative Shapley values are in favour of the negative class (healthy control) prediction. Larger absolute Shapley values indicate larger impact on the model output. BNST: bed nucleus of the stria terminalis; DmOFC: dorsomedial orbitofrontal cortex. The 20 most contributing features are shown.

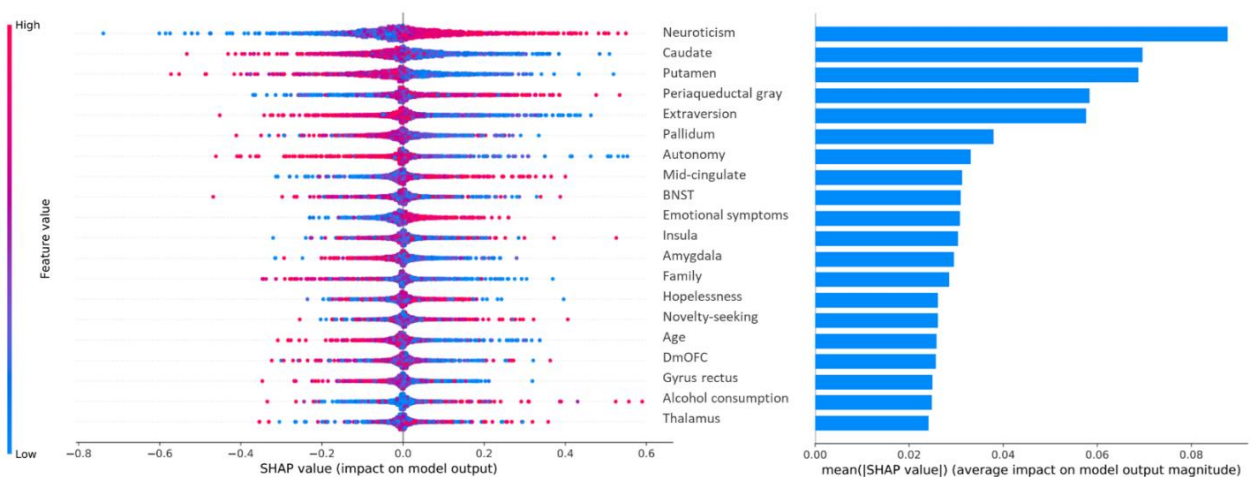


Figure 8 : SHAP values of features and importance at age 14 in the generalized anxiety (N=42) vs. multiple anxiety (N=42) prediction.

Each dot represents an individual in a given cross-validation iteration. Positive Shapley values indicate contribution of a feature value in favour of the positive class (multiple anxiety) prediction, negative Shapley values are in favour of the negative class (generalized anxiety) prediction. Larger absolute Shapley values indicate larger impact on the model output. BNST: bed nucleus of the stria terminalis; DmOFC: dorsomedial prefrontal cortex. The 20 most contributing features are shown.

2.3.2.2. Additional analysis using 10-fold stratified cross-validation

When using a 10-fold stratified cross-validation, the prediction of any anxiety disorder vs. healthy control resulted in an AUROC = 0.69 (SD = 0.06), with sensitivity = 0.82 (SD = 0.11) and specificity = 0.42 (SD = 0.13) and balanced accuracy = 0.62 (SD = 0.06). Prediction of GAD vs. healthy control resulted in an AUROC = 0.71 (SD = 0.11), with sensitivity = 0.63 (SD = 0.28), specificity = 0.66 (SD = 0.12) and balanced accuracy = 0.65 (SD = 0.12). Prediction of mAD vs. healthy control resulted in an AUROC = 0.77 (SD = 0.13) with sensitivity = 0.67 (SD = 0.28), specificity = 0.69 (SD = 0.12) and balanced accuracy = 0.68 (SD = 0.12).

2.3.3. Contribution of neuroimaging features

Predicting any future anxiety vs. healthy control based on gray matter volumes alone resulted in an AUROC = 0.52 (SD = 0.04), and the same prediction based only on psychometric features resulted in an AUROC = 0.69 (SD = 0.03).

Predicting FUA GAD vs. healthy control based on gray matter volumes alone resulted in an AUROC = 0.63 (SD = 0.06) and predicting based only on psychometric features resulted in an AUROC = 0.62 (SD = 0.08).

Predicting FUA mAD vs. healthy control based on gray matter volumes alone resulted in an AUROC \leq 0.50 (SD = 0.06) and predicting based only on psychometric features resulted in an AUROC = 0.74 (SD = 0.05).

2.3.4. Neuroimaging group analyses

2.3.4.1. Early adolescence anxiety onset

At age 14, a larger volume in the periaqueductal gray ($p_{\text{FWE}} = 0.039$) was detected in participants with early onset of mAD compared to healthy controls (see Figure 9A and Table 5A for details). Contrasting all pooled participants with anxiety disorders (SpP, SoPh, PD/Ag, GAD and mAD together) with first onset at age 14 compared with healthy controls yielded no significant differences.

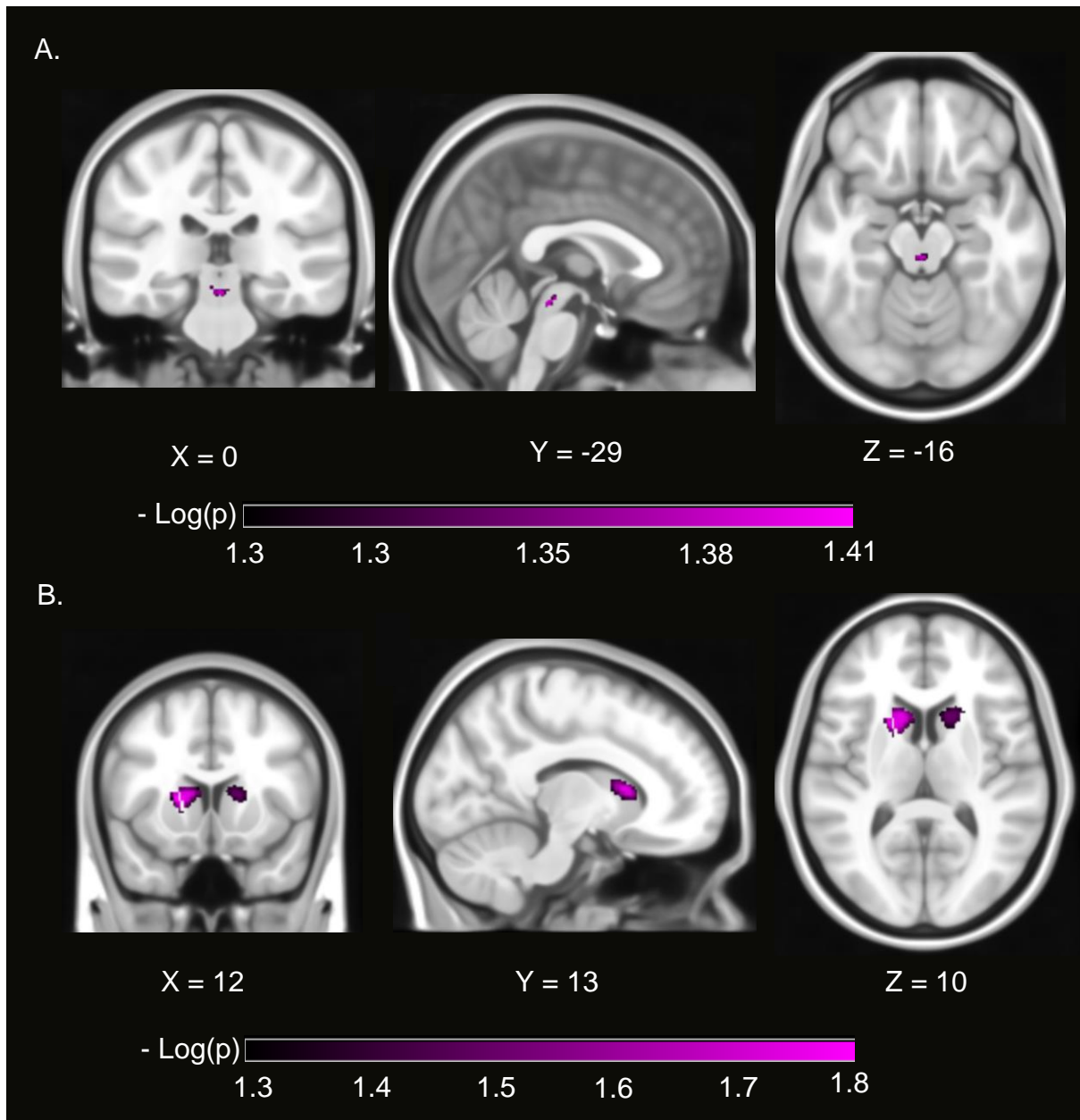


Figure 9: Gray matter volume differences at age 14 between participants with current or future anxiety and healthy controls.

A: Brain regions larger at age 14 in participants with current first onset of multiple anxiety disorders (N = 23) than in healthy controls (N = 424); B: Brain regions larger at age 14 in participants with future onset of generalized anxiety disorder (N = 42) than in healthy controls (N = 424).

$p_{FWE} \leq 0.05$, clusters > 10 voxels reported.

2. Anxiety onset prediction in adolescents using structural MRI

Contrast			Combined cluster-peak					
	k	Region	TFCE	p _{uncorr}	p _{FWE}	MNI coordinates		
						x	y	z
A. BLA								
Mixed anxiety > controls	37	Periaqueductal gray	497.12	6.0e-4	0.039	0	-27	-15
Controls > mixed anxiety		n.s.						
B. FUA								
GAD > controls	560	L. Putamen	608.17	2.0e-4	0.016	-18	12	8
		L. Caudate	602.27	2.0e-4	0.017	-15	16	9
	261	R. Caudate	521.66	4.0e-4	0.032	16	16	9
Controls > GAD		n.s.						

Table 5: Gray matter volume differences at age 14 between participants with current or future anxiety and healthy controls.

A: Volume differences between participants with onset of mAD at age 14 (N=23) and healthy controls (N=424); B: Volume differences at age 14 between participants with future onset of GAD (N=42) and healthy controls (N=424).

BLA: anxiety diagnosed at age 14; FUA: anxiety diagnosed at age 18-19 or age 22-23 follow-ups; GAD: generalized anxiety disorder; mAD: multiple anxiety disorders, simultaneous or not.

P<0.05 FWE-corr. Clusters >10 voxels reported. No significant volume difference was found between the FUA GAD and FUA mAD groups at age 14.

2.3.4.2. Late adolescence/early adulthood anxiety onset

At age 14, a larger volume in the caudate nucleus was detected bilaterally (p_{FWE} = 0.017 for the left and 0.032 for the right hemisphere) in participants with future GAD compared to controls (see Figure 9B and Table 5B for details). Contrasting all FUA participants together (SpP, SoPh, PD/Ag, GAD and mAD) with healthy controls yielded no significant differences, and neither did separate SpP, SoPh, PD/Ag and mAD analyses.

2.4. Discussion

This is the first report of anxiety onset prediction in European adolescents at age 18-23, using regional gray matter volumes and clinical features obtained at age 14. The predictive value of gray matter volumes alone for future anxiety disorders was also investigated. Prediction performance was above chance level when all future anxiety diagnoses were pooled together, with the most contributing features being neuroticism and hopelessness scores. No

contribution of neuroimaging features in classical regions of interest for anxiety was found in the prediction of *pooled* anxiety disorders. However, bilateral caudate and pallidum volumes at age 14 were major contributors to the specific prediction of pure GAD at age 18-23, with larger volumes in both regions indicating future GAD diagnosis. Additionally, prediction of future multiple anxiety disorders (mAD) across late adolescence involved a larger periaqueductal gray volume.

2.4.1. Predictive features for GAD, mAD and pooled diagnoses

As there is no pre-existing prediction study of future anxiety in adolescents, our prediction performance can only be put in perspective with two recent predictions of prospective depression and bipolar disorder (AUROC = 0.72 and 0.76 respectively) (Hafeman *et al.*, 2017; Toenders *et al.*, 2021). Indeed, using psychometric and neuroimaging features together, our prediction performance of pooled anxiety diagnoses was close (AUROC = 0.68), while our follow-up period was longer (8 years vs. 5 years follow-up in both studies). However, the performance should still be improved for prospective anxiety individual prediction to be clinically useful.

Regional gray matter features showed no incremental contribution to the prediction of pooled anxiety in comparison with psychometric data alone in our analysis. Additionally, regional gray matter features alone were poorly predictive of pooled diagnoses or mAD (AUROC = 0.52 and ≤ 0.50 respectively). One possible explanation for the lack of incremental accuracy could be the limited number of features used in our analysis (discussed in the limitations). Indeed, several predictive studies of anxiety using neuroimaging data report diffuse contributions to the prediction performance across the brain (Frick *et al.*, 2014; Liu *et al.*, 2015; Lueken, Hilbert, *et al.*, 2015; Xing, Fitzgerald and Klumpp, 2020). An alternative explanation could be that, although many neuroimaging similarities have been reported in clinical anxiety across diagnoses, heterogeneities remain between anxiety disorders (Shackman *et al.*, 2013; Chavanne and Robinson, 2021). Herein, larger caudate and pallidum volumes were predictive of pure GAD, but reduced volumes of the same regions were predictive of mAD, and these volumes were among the most contributing features for a GAD vs. mAD prediction (Figure 8). This heterogeneity might explain why regional gray matter volumes alone were better predictors of a specific diagnosis like GAD (AUROC = 0.63).

The striatum is frequently overlooked in the anxiety literature in comparison to the amygdala, anterior insula, bed nucleus of the stria terminalis, hippocampus and vmPFC. However, its potential importance, particularly in the emergence of anxiety during adolescence, has been highlighted in the past (Lago *et al.*, 2017), and striatal volumes have also been associated with the intolerance of uncertainty (Kim *et al.*, 2017).

Our findings are in line with that vision, and caudate and pallidum volumes were also significantly larger in future GAD participants compared with healthy controls in a voxel-based morphometry group analysis (Figure 9B and Table 5B).

Additionally, the periaqueductal gray was significantly larger in baseline mAD participants (see Figure 9B and Table 5B). We also found a significantly larger gray matter volume in the bilateral caudate of non-anxious participants at age 14 that were going to develop a generalized anxiety disorder (GAD) in the next 8 years (see Figure 9A and Table 5A). The periaqueductal gray is involved in defensive behaviour and pain processing but has also been implicated in fear, anxiety and anxious temperament for more than two decades despite being often eclipsed by other nodes such as the amygdala, vmPFC, and BNST (Graeff *et al.*, 1993; Fox and Shackman, 2019). However, its predictive value to prospective mAD was only moderate in comparison to the psychometric questionnaires, when all 27 features were used.

Neuroticism was the most predictive feature of future anxiety in the pooled anxiety sample. Still, although neuroticism was the psychometric subscale most relevant to anxiety in our dataset, it is not a plain measure of clinical severity and anxiety symptoms. Rather, neuroticism is a personality trait strongly associated with experiencing intense negative emotions and with internalizing disorders (Kotov *et al.*, 2010; Hur *et al.*, 2019). Herein, participants with mAD at age 18-23 had higher neuroticism and emotional symptoms mean scores at age 14 (before anxiety onset) than participants who were going to develop only one disorder. Our findings further confirm that neuroticism plays a role in anxiety onset during adolescence, perhaps denoting broad vulnerability to multiple anxiety disorders.

Following decades of MRI and fMRI group analyses, machine-learning individual predictions with neurofunctional and neuroanatomical markers show promise as one of the next steps towards targeted monitoring and treatment of psychiatric disorders (Arbabshirani *et al.*, 2017; Bzdok and Meyer-Lindenberg, 2018). The above-mentioned features most important to our prediction could contribute to the identification of a teenage population at

risk of developing anxiety disorders in the following years, and to an early detection of disease.

2.4.2. Strengths

Generalisability is a traditional issue in individual prediction, some concerns of which were addressed here. First, the IMAGEN cohort includes data from community adolescents collected from multiple acquisition sites across Europe and has an 8-years follow-up time that covers a window of vulnerability from teenage to young adulthood, leading to a good ecological validity. To our knowledge, IMAGEN is the largest neuroimaging cohort currently available spanning a period from puberty to early adulthood. Secondly, our machine-learning analysis included a state-of-the-art pipeline with appropriate nested cross-validation procedures to circumvent for the limited sample size and data imbalance. Our cross-validation strategy in particular was preferred over a more traditional K-fold one (see section 2.3.2.2) to capitalize on the multicentric nature of the IMAGEN dataset in an effort to improve the generalisability of prediction performance. Finally, SHAP was used to maximize interpretability.

2.4.3. Limitations

The sample sizes for anxiety disorder groups were the main limitation as a consequence of the long follow-up interval, and made separate prediction for social anxiety disorder, panic disorder with and without agoraphobia as well as specific phobia, impossible. In order to reduce the risk of overfitting with the limited sample sizes, we did not use nested feature selection (to avoid the risk of the algorithm selecting features based on very few GAD or mAD participants) and restricted our a priori selection to a small number of features (Hua *et al.*, 2005). For the neuroimaging group-level analysis specifically, the limited patient sample size led to the use of covariates of no interest, such as depressive comorbidity, rather than exclusion. It must be noted that, as the database included no medication nor psychotherapy data at age 14, their potential confounding effects could not be considered.

Regional gray matter features, which are of specific interest during adolescence, were chosen over neurofunctional data in our analysis and measures from both hemispheres were combined, but future studies are also encouraged to explore neurofunctional predictors of

anxiety onset whenever possible. One other possible limitation may be that IMAGEN participants were recruited in the general population and not through any clinical institution. It was, however, a necessary design to investigate *prospective* psychiatric disorders.

The IMAGEN cohort was not designed for the investigation of clinical anxiety, particularly not at age 14, and, as such, does not include targeted and specific clinical constructs assessing overall and diagnosis-specific anxious severity, such as the LSAS for social anxiety (Heimberg *et al.*, 1999). One could hypothesize that using questionnaires specific to clinical anxiety as features would improve the performance of both pooled and separate diagnosis prediction. Moreover, although the DAWBA, used to determine diagnostic status in the database, is a clinically valid diagnostic instrument (Goodman *et al.*, 2000), it does not optimally assess the exact time of symptom onset.

Finally, it must be noted that gender and site were not used as predictive features, despite the well-known gender difference in anxiety disorders (Donner and Lowry, 2013), as they were the initial balancing criteria between participants with anxiety and healthy groups.

2.4.4. Conclusion

The present study substantiates that clinical anxiety could be prospectively and individually predicted in teenagers using a multisite approach, albeit with moderate performance. Prediction performance showed that easily collected psychometric features, mainly neuroticism, hopelessness, and emotional symptoms at 14, greatly contributed to the prediction of pooled anxiety diagnoses. Thus, the present findings further support the idea that self-screening of these clinical features in teenagers could contribute to the early detection of anxiety disorders. Additionally, specific anxiety diagnosis prediction relied on some regional gray matter features such as striatal volumes, warranting further investigation of their involvement in developmental anxiety.

The predictive value of structural neuroimaging in anxiety onset also encourages the investigation of additional MRI modalities in the prediction, such as task-based functional MRI data.

3. Anxiety onset prediction in adolescents using task-based fMRI

This section builds on the previous prediction analyses of anxiety onset in section 2 and investigates the putative predictive value of tb-fMRI in the IMAGEN dataset.

3.1. Introduction

Several task-based fMRI correlates of prospective anxiety symptoms have been reported in the literature, usually with a ROI-based approach. Ventromedial PFC response during a fear-conditioning task was associated with anxiety symptoms up to 30-month later in participants aged 18-19, and amygdala-inferior frontal gyrus connectivity during emotional faces viewing was predictive of internalizing symptom increase 2 years later in 20 y.o. men (Gard *et al.*, 2018; Peng *et al.*, 2022). In children, amygdala response to emotional faces was associated with negative affect 12 months later and separation anxiety symptoms up to 2 years later (Gaffrey, Barch and Luby, 2016; Green *et al.*, 2016).

One study conducted individual-level cross-sectional classification of patients with anxiety disorders vs. controls using tb-fMRI data from the whole brain during an emotional faces task in a sample of 6-8 y.o. children with $N_{\text{patients}} = 22$ (Sawalha *et al.*, 2021). Although functional activation and connectivity are the most commonly investigated data modalities in the tb-fMRI literature anxiety disorders, additional modalities could also provide predictive value, such as connectivity-derived graph metrics, which has been used to investigate functional network dysfunctions (Yang *et al.*, 2019), and BOLD signal variability, which has recently garnered interest as an indicator of neural adaptability and efficacy (Månsson *et al.*, 2022).

To our knowledge, only one individual-level prediction of prospective anxiety using tb-fMRI has been attempted in adolescents, in which orbitofrontal-amygdala functional connectivity in a dot-probe task at age 7-17 were found to be predictive of social anxiety score a year later in a healthy adolescent $N = 66$ sample (Mao *et al.*, 2020), and none was attempted in adults. To date, no individual-level prospective anxiety disorder onset prediction using tb-fMRI data in youth has been found in the literature.

Therefore, the aim of this section was to predict prospective clinical anxiety at the individual level at ages 18 and/or 23, based on fMRI data during an emotional faces task at age 14 and.

This analysis was conducted under the *a priori* hypotheses that functional metrics such as activation, connectivity, connectivity-derived graph metrics and BOLD signal variance in subcortical and frontomedial regions might have predictive value for the onset of anxiety in adolescence.

3.2. Methods

3.2.1. Dataset and sample description

As with the previous study (in section 2), all data originated from the IMAGEN database (Schumann *et al.*, 2010). Written informed consent was obtained from all participants and their legal guardians.

Diagnostic data were collected at baseline, at age 18-19 (first follow-up, FU1), and age 22-23 (FU2) using the DAWBA (Goodman *et al.*, 2000). These diagnoses were subsequently evaluated by trained clinicians, as previously described (Paillère Martinot *et al.*, 2014). Alcohol and cannabis consumption were respectively evaluated using the AUDIT (and the ESPAD (Saunders *et al.*, 1993; Molinaro *et al.*, 2012).

Participants with available functional MRI data of the face task (described below in section 3.2.3) at baseline were assessed for eligibility in our analyses. Visual quality control was conducted for each fMRI scan and participants with excessive movement, signal dropout, or processing errors were excluded. Participants with AUDIT scores equal to or greater than 7 at baseline were excluded (Kühn *et al.*, 2019) (inclusion flowchart in Figure 10).

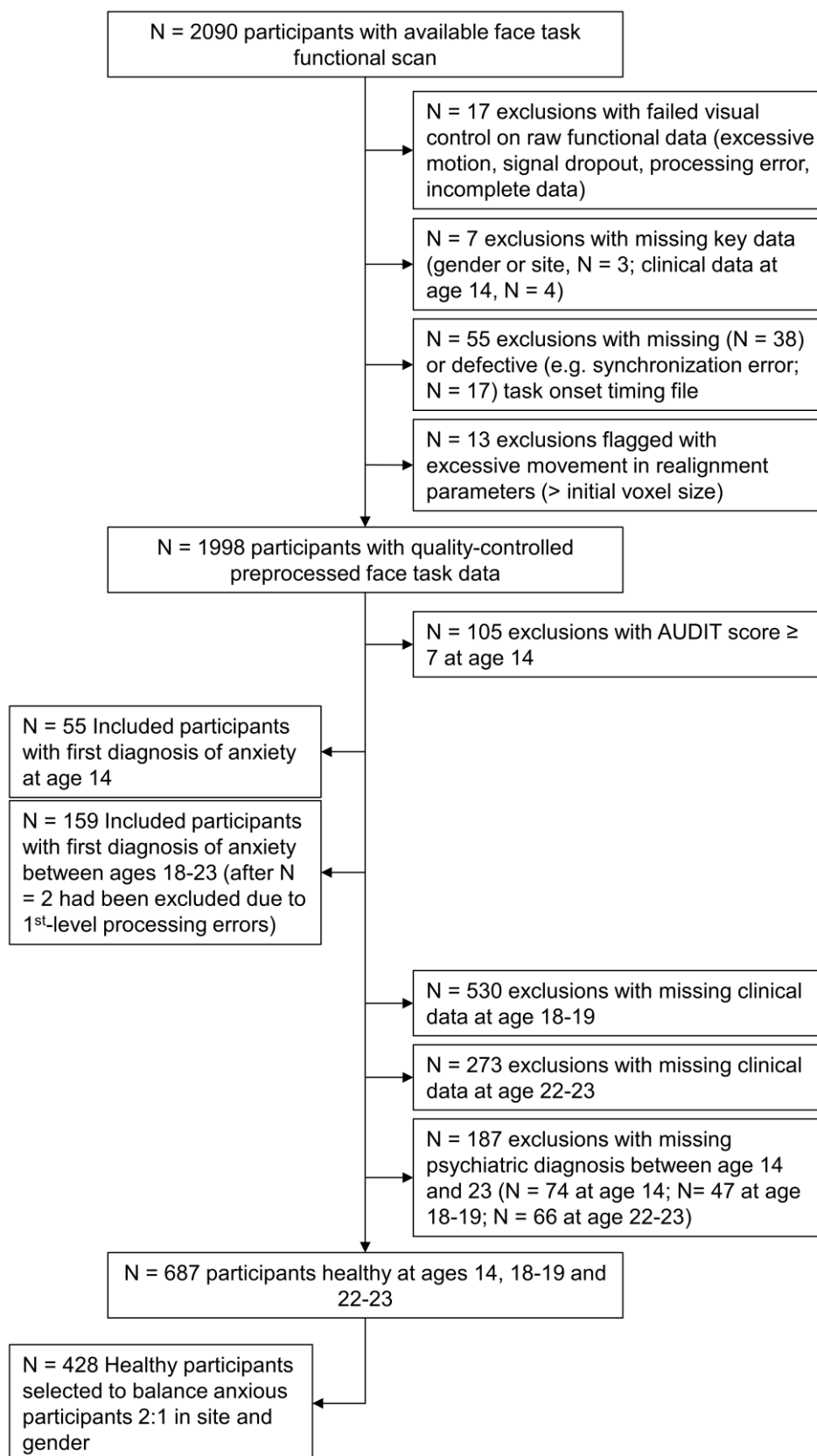


Figure 10: Inclusion flowchart.

AUDIT: Alcohol Use Disorders Identification Test.

3. Anxiety onset prediction in adolescents using task-based fMRI

Participants with DAWBA anxiety diagnoses of GAD, SAD, SpP, PD, AG and other anxiety at baseline, FU1 or FU2 were included. They were subdivided between those who had at least one anxiety diagnosis at baseline (BLA) at age 14 (N=55, only used in a supplementary analysis), and future anxiety-onset participants, whose first anxiety diagnosis was reported at either FU1 or FU2 (future anxiety, FUA). FUA participants were then allocated to 5 mutually exclusive groups. Those who had only one anxiety disorder diagnosis at 18-23 (one stable diagnosis at both FU1 and FU2, or one diagnosis at either FU1 or FU2) were split into GAD, SAD, SpP and PD/AG diagnostic groups, while participants with multiple anxiety disorders (mAD) at any timepoint at ages 18 and/or 23 (i.e., two or more distinct anxiety diagnoses, simultaneous or not) were allocated to a mAD group (see Tables 6 and 7 for details about the FUA or BLA sample respectively).

Group	SpP	SAD	PD/Ag	GAD	Multiple anxiety diagnoses ^a	Total FUA	HC	FUA vs. HC
N participants	25	25	22	40	47	159	428	
N major or other depression diagnoses at age 14	2	2	2	0	1	7		
Gender (m/f)	3/22	11/14	4/18	11/29	11/36	40/119	136/292	n.s.
Age (years) (SD)	14.6 (0.5)	14.4 (0.4)	14.4 (0.3)	14.4 (0.3)	14.4 (0.5)	14.4 (0.4)	14.4 (0.4)	n.s.
AUDIT score (SD)	1.3 (1.7)	0.9 (1.5)	2.0 (1.9)	1.2 (1.8)	1.3 (1.4)	1.3 (1.6)	0.9 (1.5)	1.1e-2*
ESPAD-year score (SD)	0.3 (1.1)	0.1 (0.4)	0	0.1 (0.3)	0.1 (0.5)	0.1 (0.6)	0.1 (0.4)	n.s.
Neuroticism NEO score (SD)	26.0 (8.8)	26.9 (7.3)	23.9 (8.6)	24.5 (6.8)	29.1 (7.5)	26.4 (7.8)	22.5 (6.9)	8.7e-8*
Anxiety sensitivity SURPS score (SD)	11.5 (3.0)	12.4 (2.1)	11.0 (2.6)	11.9 (2.5)	12.5 (2.4)	12.0 (2.5)	11.2 (2.1)	8.5e-3*
SDQ emotional score (SD)	3.8 (2.6)	3.4 (2.3)	2.6 (2.5)	3.2 (1.7)	4.3 (2.2)	3.6 (2.3)	2.5 (1.9)	1.4e-7*

Table 6: Sample description at age 14 of participants with future anxiety.

SpP: Specific phobia; SAD: social anxiety disorder; PD/Ag: panic disorder and/or agoraphobia; GAD: generalized anxiety disorder; HC: healthy controls; BLA: anxiety diagnosed at age 14.

* $p < 0.05$; Kruskal-Wallis test for continuous variables, χ^2 test for categorical variables.

^a Group included participants meeting criteria for at least two diagnoses (SpP, SoPh, PD/Ag, GAD, or other clinical anxiety (OA)), simultaneously or not: 47 participants had a first anxiety onset at FU1/FU2 (9 SpP, 27 SoPh, 20 PD/Ag, 28 GAD and 12 OA current or future diagnoses).

3. Anxiety onset prediction in adolescents using task-based fMRI

PD and AG were combined because they are highly comorbid disorders (Kikuchi *et al.*, 2005), and our sample size did not allow the investigation of standalone agoraphobia. Participants that had missing DAWBA data at FU1 or FU2 but did have one anxiety diagnosis at the other follow-up timepoint (FU2 or FU1 respectively) were included, as this latter criterion was sufficient for allocation to the FUA (32 participants) or BLA (24 participants) groups. A total of N = 156 FUA participants were available for prediction analyses.

Group	SpP	SAD	PD/Ag	GAD	Multiple anxiety diagnoses ^a	Total BLA	HC	FUA vs. HC
N participants	8	10	8	5	24	55	428	
N major or other depression diagnoses at age 14	1	4	4	4	4	17		
Gender (m/f)	2/6	3/7	2/6	0/5	4/20	11/44	136/292	n.s.
Age (years) (SD)	14.3 (0.3)	14.4 (0.4)	14.3 (0.2)	14.2 (0.3)	14.3 (0.4)	14.3 (0.4)	14.4 (0.4)	n.s.
AUDIT score (SD)	0.8 (1.2)	0.7 (1.3)	0.8 (1.0)	2.4 (1.7)	1.2 (1.7)	1.1 (1.5)	0.9 (1.5)	n.s.
ESPAD-year score (SD)	0	0	0	0	0.0 (0.2)	0.0 (0.1)	0.1 (0.4)	n.s.
Neuroticism NEO score (SD)	27.1 (11.0)	31.8 (5.8)	35.0 (7.1)	27.4 (8.3)	32.5 (6.0)	31.5 (7.4)	22.5 (6.9)	2.9e-12*
Anxiety sensitivity SURPS score (SD)	11.6 (2.9)	12.6 (2.0)	11.8 (2.4)	12.8 (2.2)	13.0 (2.8)	12.5 (2.5)	11.2 (2.1)	5.6e-3*
SDQ emotional score (SD)	4.1 (2.2)	5.9 (1.7)	5.8 (1.9)	5.0 (2.2)	5.7 (1.6)	5.4 (1.8)	2.5 (1.9)	3.4e-17*

Table 7: Sample description at age 14 of participants with current anxiety.

SpP: Specific phobia; SAD: social anxiety disorder; PD/Ag: panic disorder and/or agoraphobia; GAD: generalized anxiety disorder; HC: healthy controls; BLA: anxiety diagnosed at age 14.

* $p < 0.05$; Kruskal-Wallis test for continuous variables, χ^2 test for categorical variables.

^a Group included participants meeting criteria for at least two diagnoses (SpP, SoPh, PD/Ag, GAD, or other clinical anxiety (OA)), simultaneously or not: 24 participants had a first anxiety onset at baseline (10 SpP, 19 SoPh, 10 PD/Ag, 14 GAD and 3 OA current or future diagnoses).

In the FUA group, data were collected in Berlin for N = 14 participants, in Dresden for N = 16 participants, in Dublin for N = 16 participants, in Hamburg for N = 17 participants, in London for N = 32 participants, in Mannheim for N = 8 participants, in Nottingham for N = 32 participants, and in Paris for N = 24 participants.

Among the 94 FUA participants that had a first anxiety diagnosis at FU1, 12 had the same anxiety disorder(s) diagnosed at FU2, 2 had the same diagnosis and one additional anxiety disorder diagnosed at FU2, 7 had a different anxiety diagnosis at FU2, 52 had no anxiety diagnosis at FU2, and 21 did not have clinical data at FU2.

Eligible controls were typical adolescents with no DAWBA diagnosis at baseline, FU1 and FU2. Participants with incomplete DAWBA data at any timepoint were excluded from eligible controls. Then, we randomly selected controls amongst eligible participants to balance scanning acquisition sites and gender with participants with anxiety disorders by a 2:1 ratio. Overall, 89.8 % of participants in the main analysis overlapped with the sample used previously (in section 2), including 91.1% of FUA participants and 89.3% of healthy control participants (in the supplementary analysis, 92.7% of BLA overlapped with the previous sample).

3.2.2. MRI data acquisition

IMAGEN MRI scans were obtained on 3T scanners (Siemens, Philips, General Electric) across 8 European sites based on a Gradient-Echo Echo-Planar-Imaging (GE-EPI) sequences (matrix: $64 \times 64 \times 40$; voxel size = $3.4 \times 3.4 \times 3.4$ mm; slice thickness = 2.4 mm; TR = 2200 ms; TE = 30 ms; flip angle = 75°). The full details of the acquisition protocol are described elsewhere (Schumann *et al.*, 2010). Standardized hardware (goggles) for visual and auditory stimulus presentation (Nordic Neurolabs, Bergen Norway) was used.

3.2.3. Face task

The task involved passive viewing of short black-and-white videoclips (2-5 s) with actors displaying ambiguous facial expressions (emotionally neutral but including facial movement, e.g. nose twitching, opening mouth, blinking eyes) or angry facial expressions, and videoclips with nonbiological motion stimuli (i.e. control) (Grosbras and Paus, 2006). The control stimuli consisted of black- and white- concentric circles of various contrasts, expanding and contracting at various speeds, adapted from a previous study (Beauchamp *et al.*, 2003). The videoclips were arranged into 19 blocks of 18s; each block included seven to eight videoclips (5 neutral blocks, 5 angry blocks, 9 control blocks). Neutral, angry and control conditions were intermixed, and the total task duration was 6 minutes.

3.2.4. Task-based fMRI features extraction

Data preprocessing and processing steps described below were conducted for each participant individually. Initial visual quality control was conducted for overall image quality of raw functional scans, and participants with problematic (signal dropout, excessive motion) or missing scans were excluded (as mentioned in Figure 10).

Task fMRI data were preprocessed with SPM12 and associated toolbox CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012). Functional volumes were realigned and unwarped, and potential outlier scans were detected in CONN with conservative parameters (i.e. flagging scans with within-subject global BOLD signal change ≥ 3 standard deviations or framewise displacement 0.5 mm). Volumes were then segmented and normalized onto MNI template space, then smoothed with 8 mm full width at half-maximum Gaussian kernel. Subjects with movement-correction realignment parameters ≥ 3.4 mm (initial voxel size) in any direction were excluded. Functional measures described below were extracted for a set of 30 bilateral anxiety-relevant ROIs derived from recent meta-analyses and reviews (Chavanne and Robinson, 2021), to restrict dimensionality of features for the main prediction analysis.

ROIs for the fMRI data included the amygdala, hippocampus, anterior and posterior insula, periaqueductal gray, bed nucleus of the stria terminalis, the dorsal, pregenual and subgenual anterior cingulate cortex, as well as the dorsomedial, ventromedial, dorsolateral and orbitofrontal cortices (all were taken from the Brainnetome atlas (Fan *et al.*, 2016) with the exception of periaqueductal gray, taken from Keuken *et al.* (Keuken *et al.*, 2017), and bed nucleus of the stria terminalis, taken from Neudorfer *et al.* (Neudorfer *et al.*, 2020)).

Given that some of the previous literature reported widespread brain regions to have predictive value in anxiety disorder classification, an exploratory prediction analysis was also conducted in which functional measures were extracted for every ROI in the CONN default atlas, covering the whole brain (combining cortical and subcortical areas from the FSL Harvard-Oxford atlas and the AAL cerebellar areas for a total of 132 ROIs).

3.2.4.1. Activation features

Condition effects were modeled using the general linear model in SPM with separate conditions for angry faces, neutral faces, and control blocks. The six movement-correction

parameters from the realignment procedure were used as regressors of no interest. Default 1st-level SPM analysis parameters were used. Three contrasts of interest were computed per subject (angry blocks vs. control blocks, neutral blocks vs. control blocks, angry blocks vs. neutral blocks). All SPM design matrixes and 1st-level activation maps for these contrasts were visually inspected to ensure that no errors in the functional preprocessing and 1st-level analysis, due to defective condition onset data or otherwise, had occurred. For each contrast per subject, the MarsBar toolbox (Brett *et al.*, 2002) was then used to extract median effect sizes in every ROI, which were included as features.

3.2.4.2. BOLD variance features

All preprocessing described above was kept identical apart from smoothing, which was absent. According to (Garrett *et al.*, 2010), realigned unwarped normalized unsmoothed volumes, as well as the 1st-level SPM model described above, were used as input in VarTbx (<https://github.com/LNDG/vartbx>) and a boxcar model was used to model the task design. To correct for block offsets from the concatenated blocks, all blocks were normalized to have a four-dimensional mean of 100. The block mean was then subtracted from each voxel, and detrended variance of each condition was extracted voxelwise, producing whole-brain BOLD variance maps. For the angry faces, neutral faces and control conditions, the MarsBar toolbox was then used to extract average variance in every ROI, which were included as features.

3.2.4.3. Functional connectivity features

Preprocessed functional volumes were denoised with the standard CONN pipeline (linear regression of potential confounding effects including noise components from cerebrospinal fluid and white matter, and temporal band-pass filtering [0.008 - 0.09 Hz]). ROI-to-ROI task-modulated effective connectivity matrices were computed with generalized psychophysiological interaction (gPPI) for all ROIS both in the angry faces and neutral faces conditions and were included as features.

3.2.4.3. Graph-theoretic connectivity features

The above-mentioned gPPI matrices were used in the BCT toolbox (Rubinov and Sporns, 2010). The gPPI matrices for angry and neutral faces (i.e. weighted directed graphs) were

thresholded with $r = 0.3$ to avoid spurious edges. All global and ROI-specific metrics available in the toolbox for directed graphs were extracted (degree, strength, density, clustering coefficient, transitivity, global and local efficiency, assortativity, characteristic path length, betweenness centrality, K-core centrality, flow coefficient, as well as the fingerprint, intensity and coherence of structural and functional motifs), with the exception of communities-related metrics (due to the varying number of communities detected among subjects preventing their use as comparable predictive features), and included as features.

3.2.5. Ensemble machine-learning prediction

All prediction analyses were conducted with scikit-learn (version 0.24.2) in Python (version 3.6.9). A binary classification prediction between FUA ($N = 159$) and healthy controls ($N = 428$) was conducted using an ensemble learning approach, with six 1st-level classifiers each using different feature modalities (functional activation, gPPI connectivity for both angry and neutral faces, gPPI-derived graph-theoretic metrics, BOLD variance; see Figure 11) from which the output (i.e. predictions) was used as feature by a 2nd-level classifier, the latter producing the final prediction. A random shuffle cross-validation was repeated 100 times with an 80-20 train-test split used in every iteration, and included scaling, median imputation and feature selection using a logistic regression stochastic gradient descent learning classifier with mean feature importance as selection threshold (log-loss, Elastic Net penalisation, grid search tuning of l1 ratio between 0 and 1 with default 5-fold nested cross-validation, all other default classifier parameters were kept identical). All classifiers used were Random Forests (1000 estimators, out-of-bag score true, class weight balanced, all other default parameters kept identical). An alternative 2nd-level classifier (soft voting with sum of 1st-level predictions) was also examined for completeness. Additional control analyses were also conducted for male and female participants separately.

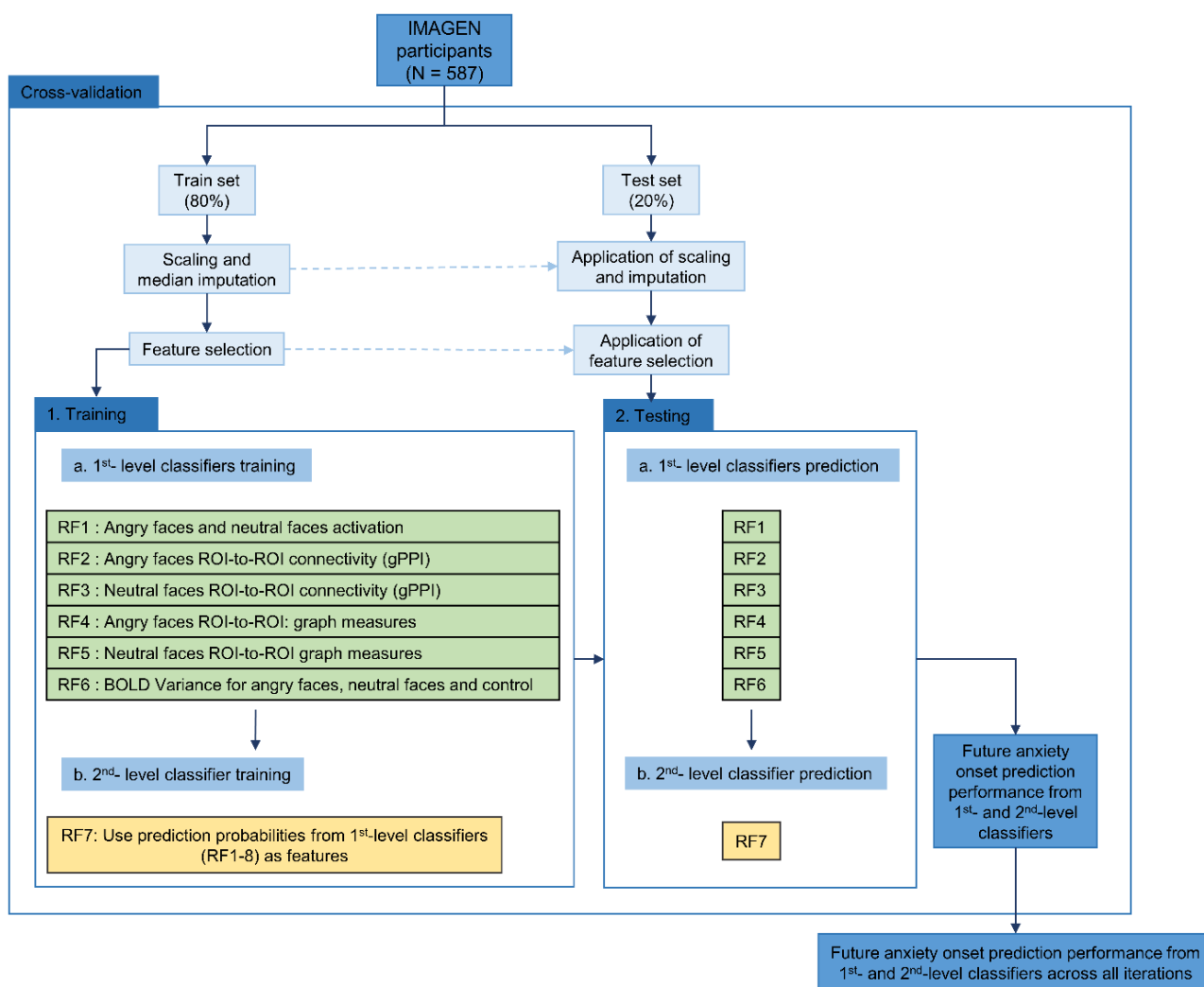


Figure 11: Ensemble machine-learning classification pipeline.

RF: Random Forest; ROI: region of interest; gPPI: generalized psychophysiological interaction; MRI: magnetic resonance imaging; BOLD: blood-oxygen-level-dependent.

Mean performance metrics across the 100 cross-validation folds are reported in the results section. A corrected resampled t-test (Nadeau and Bengio, 2003; Bouckaert and Frank, 2004) between the balanced accuracy of classifiers of interest and the one of a dummy classifier always predicting the majority class was used to investigate above-chance classification accuracies.

To explore individual feature contribution to predictions, the Shapley additive explanation (SHAP) module was used (version 0.39.0) (Lundberg and Lee, 2017). SHAP uses a game theoretic approach to assign an importance value to each feature for an individual prediction.

3.3. Results

3.3.1. 1st-level future anxiety onset prediction results

The prediction analysis of future anxiety onset based on functional activation, gPPI connectivity, gPPI-derived graph metrics for both angry faces and neutral faces conditions and BOLD signal variance did not perform above chance level (balanced accuracy = 0.5 for all classifiers, AUROC ranging from 0.49 to 0.53) (Table 8, Figure 12A). No significant difference emerged between any 1st-level or 2nd-level classifier and the dummy classifier using the corrected resampled t-test.

1 st -level classifier	Balanced accuracy (SD)	AUROC (SD)
<i>Functional features extracted from a-priori selected 30 ROIs</i>		
Functional activation	0.50 (0.01)	0.53 (0.05)
Angry faces gPPI	0.50 (0)	0.50 (0.05)
Neutral faces gPPI	0.50 (0)	0.51 (0.05)
Angry faces graph measures	0.50 (0)	0.49 (0.05)
Neutral faces graph measures	0.50 (0)	0.50 (0.05)
BOLD variance	0.50 (0.01)	0.51 (0.05)
<i>Functional features extracted from ROIs across the whole brain (exploratory)</i>		
Functional activation	0.50 (0)	0.48 (0.05)
Angry faces gPPI	0.50 (0)	0.49 (0.05)
Neutral faces gPPI	0.50 (0)	0.50 (0.05)
Angry faces graph measures	0.50 (0)	0.48 (0.05)
Neutral faces graph measures	0.50 (0)	0.47 (0.05)
BOLD variance	0.51 (0.01)	0.53 (0.05)

Table 8: Prediction results of the 1st-level classifiers of post-treatment response (N=159 FUA vs N=428 healthy controls).

ROI: region of interest; AUROC: Area under the receiving operator curve; gPPI: generalized psychophysiological interaction.

*: $p < 0.05$, corrected resampled t-test against the accuracy of a dummy classifier, two-tailed.

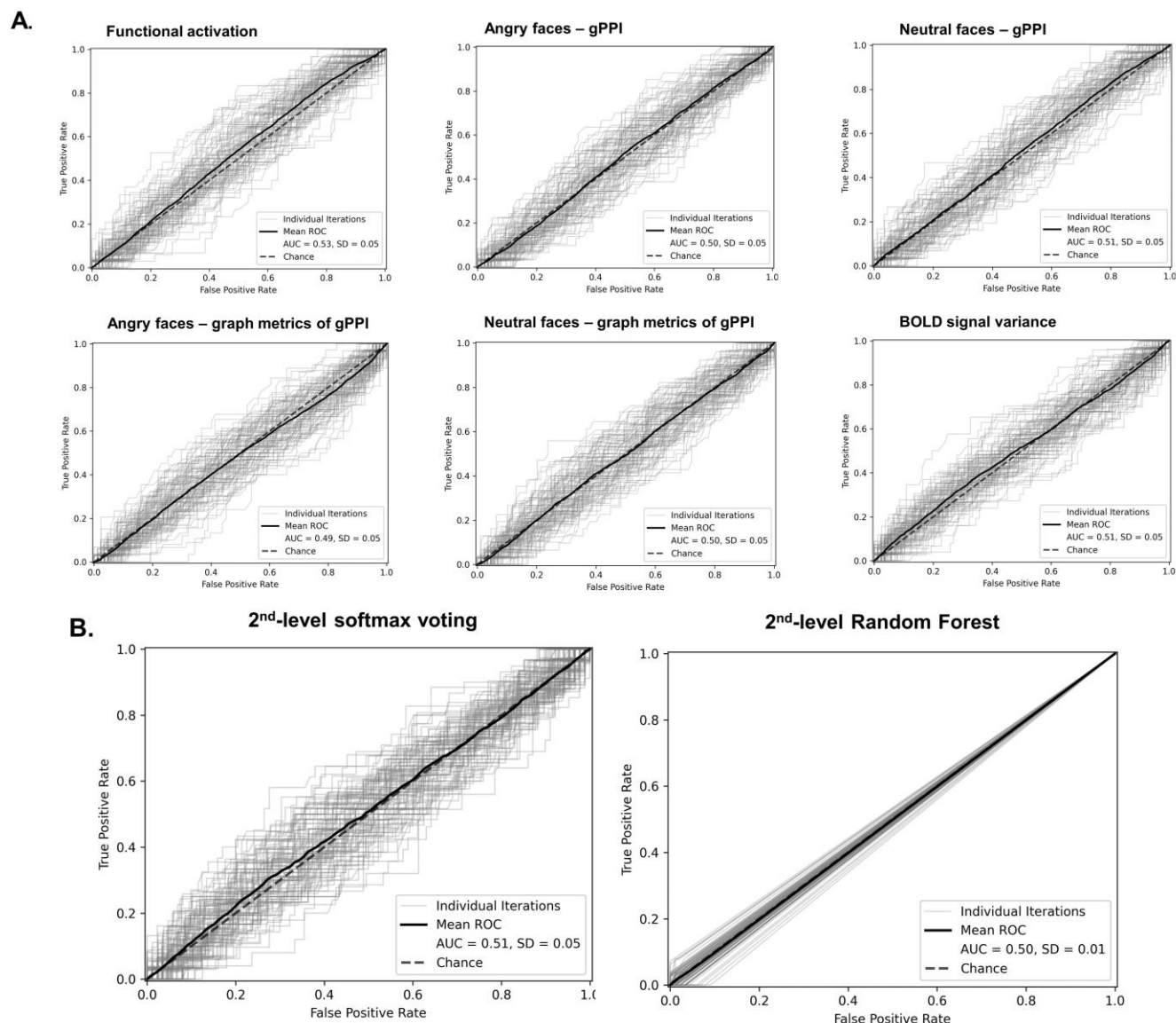


Figure 12: Area under the receiving operating curves for treatment outcome classification.

A: 1st-level classification results; B: 2nd-level classification results. gPPI: generalized psychophysiological interaction.

Female-specific prediction analyses yielded no 1st- or 2nd- level above-chance prediction performances, with all balanced accuracies = 0.50, AUC of 1st- level classifiers ranging from 0.51 to 0.56, Male-specific prediction analyses yielded similar results for 1st-level, with all balanced accuracies = 0.50 and AUCs ranging from 0.48 to 0.55.

The exploratory analysis in which functional features were derived from ROIs across the whole brain instead of an a-priori selected set resulted in nonsignificant prediction

performances, with all balanced accuracies = 0.50. The supplementary cross-sectional classification analysis of BLA participants vs. HC did not result in any above chance-level prediction, also with balanced accuracies = 0.50.

3.3.2. 2nd-level future anxiety onset prediction results

The 2nd-level classifiers using prediction probabilities of all 1st-level classifiers as input features failed to predict treatment outcome above chance level in the main prediction analysis (Figure 12B). The 2nd-level voting classifier prediction resulted in a balanced accuracy = 0.50 (SD = 0) and AUROC = 0.51 (SD = 0.05). The 2nd-level Random Forest classifier resulted in a balanced accuracy = 0.50 (SD = 0) and AUROC = 0.50 (SD = 0.01).

Female-specific 2nd-level analyses yielded nonsignificant balanced accuracy = 0.50 (SD = 0) and AUCs = 0.57 (SD = 0.07) for the voting classifier, and balanced accuracy = 0.50 (SD = 0) and AUC = 0.50 (SD = 0.03) for the Random Forest classifier. Male-specific 2nd-level analyses yielded balanced accuracy = 0.50 (SD) and AUC = 0.56 (SD = 0.09) for the voting classifier, and balanced accuracy = 0.50 (SD = 0) and AUC = 0.50 (SD = 0) for the Random Forest classifier.

Comparable results were obtained with the exploratory analysis in which functional features were derived from ROIS across the whole brain instead of an a-priori selected set, with the voting classifier resulting in a balanced accuracy = 0.50 (SD = 0) and AUROC = 0.49 (SD = 0.05), and the Random Forest classifier resulting in a balanced accuracy = 0.50 (SD = 0) and AUROC = 0.51 (SD = 0.01).

3.4. Discussion

The present section investigated the incremental predictive value of tb-fMRI data collected at age 14 for individual-level anxiety disorder onset prediction at age 18-23. Contrary to expectations, prediction performance did not go beyond chance-level for all distinct functional data modalities during an emotional faces task, including condition-specific activation, connectivity, connectivity-derived graph metrics and BOLD signal variance.

3.4.1. Perspective on prediction performance

Despite previous studies reporting group-level and cross-sectional individual-level predictive value of tb-fMRI activation and connectivity for anxiety symptoms, the present findings did not support a predictive contribution of tb-fMRI in anxiety disorder onset prediction, using an emotional faces task.

Several methodological aspects could have contributed to the chance-level predictive performances, including limitations intrinsic to the emotional faces task that was used, the feature selection strategy, or to possible heterogeneity of tb-fMRI correlates between participants with distinct future anxiety disorders (see limitations in 3.4.3.).

To our knowledge, the only study investigating the cross-sectional predictive value of tb-fMRI in youth anxiety disorders reported an accuracy of 0.81, but used a child sample of $N_{\text{patients}} = 22$ (Sawalha *et al.*, 2021). The only study investigating prospective predictive value of tb-fMRI in youth anxiety symptoms reported $r_{(\text{predicted}, \text{observed})} = 0.301$ using a sample of $N_{\text{total}} = 66$ healthy adolescents (Mao *et al.*, 2020). In both cases, sample sizes were small, and it was reported in the literature that prediction accuracies for classification based on medical imaging features appear to be decreasing as sample sizes increase, perhaps reflecting performance evaluation or cross-validation biases in the neuroimaging literature (Varoquaux, 2018; Hosseini *et al.*, 2020; Poldrack, Huckins and Varoquaux, 2020; Varoquaux and Cheplygina, 2022). Furthermore, our FUA sample size, although relatively large with respect to already-published studies, was still modest in terms of machine-learning methodology.

Overall, given the exploratory nature of this work, and the lack of other tb-fMRI machine-learning prediction of anxiety disorder onset in the literature, the predictive potential of fMRI data using an emotional face task cannot be ruled out. However, other fMRI tasks or neuroimaging modalities might be better able to bring incremental predictive value to the prediction of future anxiety disorder onset. For instance, as the gray matter volumes of striatal regions were found to be predictive of future GAD disorder in section 2 (see results in section 2.3.2.1), fMRI metrics extracted from a task broadly targeted toward reward brain circuitry might provide some predictive value to for future GAD prediction in adolescence.

3.4.2. Strengths

As in section 2.4.2, much of the strength of this analysis is intrinsic to the IMAGEN dataset, that includes data from community adolescents collected from multiple acquisition sites across Europe and has an 8-years follow-up time covering a window of vulnerability from teenage to young adulthood. Furthermore, our machine-learning analysis included a state-of-the-art stacking pipeline with appropriate nested cross-validation procedures to circumvent for the limited sample size and data imbalance, designed to incorporate respective predictive contributions of distinct data modalities.

3.4.3. Limitations

Limitations inherent to the IMAGEN dataset, described in section 2.4.3, also apply in this analysis. Briefly, those include small diagnostic-specific sample sizes for anxiety disorder groups, the fact that IMAGEN participants were recruited in the general population and not through any clinical institution, and that the DAWBA, used to determine diagnostic status in the database, does not optimally assess the exact time of symptom onset. The long follow-up period (up to 8 years) Finally, as in section 2, it must be noted that gender and site were not used as predictive features, as they were the initial balancing criteria between participants with anxiety and healthy groups.

Critically, our feature selection strategy precluded additional analyses specific to diagnostic subgroups, which would have small sample sizes (FUA PD/AG, SAD, and SpP all had $N < 30$ participants, and GAD had $N = 42$), and induced loss of information in comparison to more fine-tuned, voxel-wise approaches, particularly for variance-based measures. However, this strategy was chosen to allow the exploration of various tb-fMRI data modalities in a number of selected ROIs while keeping a reasonable feature dimensionality.

The emotional faces task was used in our analysis because emotional face processing tasks were the most commonly used tasks in previous literature investigating developmental anxiety tb-fMRI predictors (Gaffrey, Barch and Luby, 2016; Green *et al.*, 2016; Sawalha *et al.*, 2021; Peng *et al.*, 2022). However, although it is a broadly ‘affective’ stimulus, emotional faces as presented during the task might not produce similar functional activation in participants with future SAD and in participants with future SpP for instance, thus possibly resulting in considerable heterogeneity between diagnostic subgroups.

3.4.4. Conclusion

The present study found no evidence of the predictive potential of fMRI metrics during an emotional faces task, including activation, connectivity, connectivity-derived graph-theoretical metrics or BOLD signal variance, for the prediction of anxiety disorder onset in adolescence. Further research could explore other tasks and other neuroimaging modalities in the search for incremental predictive value in anxiety disorder onset prediction. Additionally, tb-fMRI data might have predictive value for other clinically relevant predictions in anxiety disorders, such as psychotherapy response prediction.

4. Psychotherapy outcome prediction in spider phobia using structural MRI and task-based fMRI

This section corresponds to the second publication of the thesis (Chavanne, Meinke, *et al.*, 2023), in the *Depression and Anxiety* journal.

Abstract

Machine-learning prediction studies have shown potential to inform treatment stratification, but recent efforts to predict psychotherapy outcomes with clinical routine data have only resulted in moderate prediction accuracies. Neuroimaging data showed promise to predict treatment outcome, but previous prediction attempts have been exploratory and reported small clinical sample sizes. Herein, we aimed to examine the incremental predictive value of neuroimaging data in contrast to clinical and demographic data alone (for which results were previously published), using a two-level multimodal ensemble machine-learning strategy. We used pre-treatment structural and task-based fMRI data to predict virtual reality exposure therapy outcome in a bicentric sample of $N = 190$ patients with spider phobia. First, eight 1st-level Random Forest classifications were conducted using separate data modalities (clinical questionnaire scores and sociodemographic data, cortical thickness and gray matter volumes, functional activation, connectivity, connectivity-derived graph metrics and BOLD signal variance). Then, the resulting predictions were used to train a 2nd-level classifier that produced a final prediction. No 1st-level or 2nd-level classifier performed above chance level except BOLD signal variance, which showed potential as a contributor to higher-level prediction from multiple regions across the brain (1st-level balanced accuracy = 0.63). Overall, neuroimaging data did not provide any incremental accuracy for treatment outcome prediction in patients with spider phobia with respect to clinical and sociodemographic data alone. Thus, we advise caution in the interpretation of prediction performances from small-scale, single-site patient samples. Larger multimodal datasets are needed to further investigate individual-level neuroimaging predictors of therapy response in anxiety disorders.

4.1. Introduction

Anxiety disorders are amongst the most prevalent mental disorders (Penninx *et al.*, 2021) with a considerable burden of disease (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Current response rates to cognitive-behavioural therapy (CBT) as a first-line treatment average at 50% or lower for most anxiety disorders (Hofmann *et al.*, 2012; Loerinc *et al.*, 2015). Prospectively distinguishing treatment-responding from nonresponding patients could help guide clinical decisions and improve prognosis (Bzdok, Varoquaux and Steyerberg, 2021). Machine-learning approaches can predict at the individual-level on unseen samples, and are well-suited for predicting individual therapeutic outcomes, particularly with the high-dimensional data collected in clinical research and practice (Fusar-Poli *et al.*, 2018, p.). A promising literature of machine-learning outcome prediction has emerged across mental disorders (see (Chekroud *et al.*, 2021) for a general review), including a rapidly increasing number of psychotherapy outcome prediction studies (Vieira *et al.*, 2022).

However, recent large-scale efforts to predict individual-level psychotherapy treatment outcomes for patients with anxiety disorders based on routine clinical data alone resulted only in moderate prediction accuracies (Hilbert *et al.*, 2020; Hornstein *et al.*, 2021; Leehr *et al.*, 2021). Neuroimaging data has shown promise to predict treatment outcomes for patients with anxiety disorders in previous attempts, but those have been exploratory and reported small clinical sample sizes (Chekroud *et al.*, 2021).

To our knowledge, two studies conducted individual CBT outcome prediction using task-based fMRI in patients with panic disorder (Hahn *et al.*, 2015; Sundermann *et al.*, 2017), three in patients with social anxiety disorder (Månsson *et al.*, 2015, 2022; Frick *et al.*, 2020), and one in a mixed sample of patients with panic disorder or generalized anxiety disorder (Ball *et al.*, 2014) (see (Vieira *et al.*, 2022) for a recent review). However, no study had a sample with $N > 60$. It has been reported that studies using small sample sizes present a considerable risk for overestimating prediction performance, in part because they are limited to much less robust cross-validation schemes (Varoquaux *et al.*, 2017; Varoquaux, 2018, p. ; Flint *et al.*, 2021). A recent review encouraged the use of larger sample sizes to disentangle the contribution of neuroimaging data to psychotherapy response prediction from the effect of small sample sizes on reported prediction performance (Vieira *et al.*, 2022).

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In all but one of the above-mentioned CBT outcome prediction studies, predictive features were extracted from symptom-related fMRI tasks. Indeed, symptom-related task-based functional activation and connectivity are commonly used in anxiety disorders studies and they, along with structural MRI, have been associated with prospective treatment response of patients with anxiety disorders at the group level (see (Santos *et al.*, 2019) for a review). Graph-theoretical measures derived from functional connectivity, reported to have overall good reproducibility (Welton *et al.*, 2015), have also been used in recent years for fine-tuned investigation of functional network dysfunctions in anxiety disorders (Yang *et al.*, 2019; Guo *et al.*, 2021). Additionally, BOLD signal variability measures have recently been reported as promising individual-level predictors for therapeutic outcomes in anxiety disorders (Månsson *et al.*, 2015, 2022).

Therefore, the aim of the present study was to build upon previous literature using a fairly large, bicentric and clinically well-characterized sample of patients with spider phobia to investigate the incremental performance of structural MRI and symptom-related task-based fMRI measures over routine clinical data in predicting psychotherapy outcome with a state-of-the-art ensemble machine-learning pipeline. We hypothesized that structural and task-based (f)MRI measures would predict post-treatment and 6-month follow-up psychotherapy outcomes significantly beyond chance level, and that an ensemble approach using clinical, sociodemographic and neuroimaging modalities would produce higher predictive performance than clinical and sociodemographic data alone.

4.2. Methods

4.2.1. Dataset and sample description

The bicentric clinical study SPIDER-VR was part of the Transregional Collaborative Research Centre 58 “Fear, Anxiety, Anxiety Disorders” (clinical trial registration at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03208400): NCT03208400). It includes a sample of untreated patients with spider phobia according to DSM-IV criteria (*Diagnostic and statistical manual of mental disorders (4th ed.)*, 1994) aged 18-65 without major comorbidities (low to moderate depression was tolerated unless currently treated, as well as other animal phobias) and with a total Spider Phobia Questionnaire (SPQ) (Klorman *et al.*, 1974) score > 19 (clinical cut-off). See (Schwarzmeier *et al.*, 2019) for a complete study description, and (Böhnlein *et al.*, 2021;

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Leehr *et al.*, 2021; Siminski *et al.*, 2021; Roesmann, Elisabeth Johanna Leehr, Böhnlein, *et al.*, 2022; Roesmann, Toelle, *et al.*, 2022) for other studies using the SPIDER-VR data. Bicentric recruitment was conducted in Würzburg (WÜ) and Münster (MS), Germany. The SPIDER-VR study protocol has been reviewed by the Ethics Committees of the Medical Faculties of Münster University (proposal 216-212-b-S) and Würzburg University (proposal 330/15), and written informed consent was obtained from all participants.

Clinical and neuroimaging data were acquired before treatment. Patients were then invited for a one-session virtual reality exposure therapy (VRET) and primary outcome (responder/non-responder status at post-treatment and at 6-month follow-up [FU]) was based on a 30% SPQ score reduction between pre-treatment and post-treatment or FU respectively.

Of note, clinical effects of VRET and prediction results based only on sociodemographic and clinical data using the original sample of SPIDER-VR patients (N = 171 for the prediction) have been previously published (Leehr *et al.*, 2021). Herein, we investigate the incremental value of neuroimaging data using an extended sample of SPIDER-VR patients (due to the continuation of patient recruitment in MS). In this extended sample, N = 211 patients had complete post-treatment data, but twelve did not have available functional MRI data, three were excluded for structural MRI artefacts or abnormalities, five were excluded due to substantial movement during the task, and one was excluded due to absent visual activation (see section 4.2.4 below for quality control details). Thus, N = 190 patients in total (81.6 % overlap with the sample in (Leehr *et al.*, 2021)) were included for analysis at post-treatment (see Table 1 for sample description). Primary treatment response (30% SPQ score reduction between pre-treatment and post-treatment) was observed in 54% of patients. A sample description of follow-up responders and non-responders is presented in Table 10 (see section 4.3.3 for prediction analyses on primary outcome at follow-up).

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Variables	Post-treatment responders N =103	Post-treatment non-responders N=87	p-value
<i>Demographic characteristics at pre-treatment</i>			
Gender (m/f)	13/90	12/75	n.s.
Site distribution	WÜ:54 MS:49	WÜ:29 MS: 58	1.3e-2*
Age (SD)	26.6 (7.5)	30.4 (9.9)	3.6e-3*
Years of education (SD)	14.6 (3.0)	14.5 (3.0)	n.s.
<i>Clinical characteristics at pre-treatment</i>			
Age of onset spider phobia (SD)	7.2 (4.6)	6.4 (4.6)	n.s.
Comorbid depression (%)	3 (2.9)	3 (3.4)	n.s.
SPQ (SD)	20.8 (3.5)	19.9 (4.2)	n.s.
LSAS (SD)	22.4 (16.0)	26.1 (18.6)	n.s.
ASI-3 (SD)	14.6 (7.0)	16.2 (8.1)	n.s.
STAI trait (SD)	34.7 (8.4)	35.8 (8.2)	n.s.
BDI-II total (SD)	3.0 (3.6)	3.3 (3.9)	n.s.
UI-18 (SD)	37.5 (12.4)	39.9 (13.3)	n.s.
Promis specific phobia (SD)	11.3 (8.4)	11.0 (8.9)	n.s.
FEAS anxiety (SD)	102.3 (13.5)	100.6 (10.8)	n.s.
FAS (SD)	83.6 (12.7)	83.3 (11.7)	n.s.
Final BAT distance (cm) (SD)	175.7 (61.4)	158.1 (69.2)	n.s.
<i>Post-treatment</i>			
SPQ (SD)	13.2 (2.4)	17.8 (2.0)	< 2.2e-16*
<i>Follow-up</i>			
SPQ (SD)	12.2 (2.8)	15.3 (3.2)	1.5e-10*

Table 9: Pre-treatment sample description of post-treatment responders and non-responders.

Statistical tests were two-sided t-test for continuous variables and chi-squared tests for categorical variables. WÜ: Würzburg; MS: Münster; SPQ: Spider Fear Questionnaire; LSAS: Liebowitz Social Anxiety Scale; ASI-3; Anxiety Sensitivity Scale 3; STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; UI-18: Unsicherheitsintoleranz (intolerance of uncertainty) 18 scale; PROMIS = Patient-Reported Outcomes Measurement Information System (PROMISPHO: specific phobia); FEAS: Fragebogen zur Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); FAS: Fragebogen zur Angst von Spinnen (questionnaire regarding the fear of spiders); BAT: Behavioural avoidance test.

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Variables	Follow-up responders N=143	Follow-up non-responders N=40	p-value
<i>Demographic characteristics at pre-treatment</i>			
Gender (m/f)	19/124	5/35	n.s.
Site distribution	WÜ: 67 MS: 76	WÜ: 16 MS: 23	n.s.
Age (SD)	28.6 (9.2)	27.9 (8.1)	n.s.
Years of education (SD)	14.7 (3.0)	14.7 (3.0)	n.s.
<i>Clinical characteristics at pre-treatment</i>			
Age of onset spider phobia (SD)	7.2 (4.7)	6.2 (4.4)	n.s.
Comorbid major depression n%			n.s.
SPQ (SD)	20.3 (3.9)	20.9 (3.8)	n.s.
LSAS (SD)	23.8 (17.3)	26.3 (18.3)	n.s.
ASI-3 (SD)	15.0 (7.4)	16.3 (8.4)	n.s.
STAI trait (SD)	34.6 (8.3)	37.9 (7.9)	n.s.
BDI-II total (SD)	2.9 (3.4)	4.3 (4.5)	n.s.
UI-18 (SD)	37.5 (12.4)	42.5 (14.1)	4.6e-2*
Promis specific phobia (SD)	11.1 (8.8)	10.7 (7.6)	n.s.
FEAS anxiety (SD)	101.9 (11.7)	100.7 (14.8)	n.s.
FAS (SD)	83.2 (12.6)	85.2 (10.7)	n.s.
Final BAT distance (cm) (SD)	169.1 (67.2)	165.5 (60.6)	n.s.
<i>Post-treatment</i>			
SPQ (SD)	14.5 (3.1)	17.8 (1.9)	1.8e-12*
<i>Follow-up</i>			
SPQ (SD)	12.4 (2.6)	17.7 (1.6)	< 2.2e-16*

Table 10: Pre-treatment patient sample description of follow-up responders and nonresponders

Continuous variables with two-sided t-test. Categorical variables with chi-squared test. WÜ: Würzburg; MS: Münster; SPQ: Spider Fear Questionnaire; LSAS: Liebowitz Social Anxiety Scale; ASI-3; Anxiety Sensitivity Scale 3; STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; UI-18: Unsicherheitsintoleranz (intolerance of uncertainty) 18 scale; PROMIS = Patient-Reported Outcomes Measurement Information System (PROMISPHO: specific phobia); FEAS: Fragebogen zur Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); FAS: Fragebogen zur Angst von Spinnen (questionnaire regarding the fear of spiders); BAT: Behavioural avoidance test.

4.2.2. MRI data acquisition

The full acquisition procedure is described in (Schwarzmeier *et al.*, 2019). Briefly, all scans were obtained with 3T MRI scanners (WÜ: Siemens Skyra, MS: Siemens Prisma). A structural T1 dataset was collected using an MPRAGE acquisition sequence ($256 \times 256 \times 176$ matrix, FOV = 256, voxel size = $1 \times 1 \times 1$ mm, TE = 2.26 ms [WÜ], TE = 2.28 ms [MS], TR = 1.9 s [WÜ], TR = 2.13 s [MS], flip angle = 9° [WÜ], flip angle = 8° [MS]). Functional images were collected with a T2* weighted EPI sequence in ascending order ($64 \times 64 \times 33$ matrix, FOV = 210, voxel size = $3.3 \times 3.3 \times 3.8$ mm, slice thickness = 3.8 mm, 10% slice gap, TE = 30 ms [WÜ], TE = 29 ms [MS], TR = 2.0 s, flip angle = 90°). Slices covered the whole brain and were positioned transaxially parallel to the anterior–posterior commissural line with a tilted angle of 20° . Stimuli were presented via MR-compatible LCD goggles (WÜ) or via a back-projection monitor (MS).

4.2.3. Sustained and Phasic Fear (SPF) task

The SPF task is a suitable paradigm to measure activation in relevant networks for fear processing, and has been used in previous literature to detect significant differences of functional activation in patients with spider phobia compared to non-anxious controls during both phasic fear and sustained fear conditions (Münsterkötter *et al.*, 2015). Of note, analyses of the activation patterns during sustained and phasic fear in patients with spider phobia revealed increased anterior cingulate cortex activation during sustained rather than phasic fear, whereas amygdala and insula activation were of particular relevance for phasic fear processing (see Breede *et al.*, in prep.). Though lacking a healthy control group, these results can be seen in line with the results in (32).

The task employed a block design including 15 active and 14 inactive blocks. During inactive blocks, a fixed dot was displayed on the middle of the screen for 15s. Active blocks included 10 successive trials in which a picture was shown for 1.7s and followed by 300ms of fixation dot. Each active block was followed by an inactive block. Active blocks were split between three fear conditions in pseudorandomized order: 1) a sustained fear condition, during which participants were informed that a spider could appear; pictures of empty rooms were shown and in three of the five sustained fear blocks, a spider was shown instead of an empty room in the last quarter of the block, 2) a phasic fear condition in which participants were told they

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would see spiders and were shown spider pictures, and 3) a no fear (safety) condition during which participants were shown pictures of empty rooms. After each active block, participants had to rate their experience from very pleasant to very unpleasant. The total task duration was 9:45 min.

4.2.4. Feature extraction

Sociodemographic, clinical, structural MRI and fMRI data were used as features, and each is described in detail below. The fMRI data provided phasic and sustained fear activation, BOLD variance and functional connectivity features, and graph-theoretical features were then derived from functional connectivity matrices.

4.2.4.1. Sociodemographic data and clinical questionnaires

The pre-treatment sociodemographic and clinical features included in the prediction analysis were previously described in (Leehr *et al.*, 2021). Briefly, they included age, gender, years of education, age at phobia onset, family history of mental health conditions, comorbidities, lifetime suicidal intent, smoking, consumption of alcohol, cannabis and coffee, distance and salience of a standardized behavioural avoidance test (a live bird spider was placed in a closed box that patients had to drag as close as possible to themselves), as well as sum scores and subscales of a battery of anxiety-relevant questionnaires.

The complete list of questionnaires used for the clinical and sociodemographic classifier included: Specific Phobia Questionnaire (Klorman *et al.*, 1974), Anxiety Sensitivity Index (Kemper, Ziegler and Taylor, 2009), Liebowitz Social Anxiety Scale (Heimberg *et al.*, 1999), Uncertainty Intolerance questionnaire (Gerlach, Andor and Patzelt, 2008), State-Trait Anxiety Inventory (Laux L, no date), Questionnaire regarding the fear of spiders (Fragebogen zur Angst vor Spinnen) (Rinck M, Bundschuh S, Engler S, Muller A, Wissmann J, Ellwart T, Becker ES, 2002), Questionnaire regarding the disgust and fear of spiders (Fragebogen zu Ekel und Angst vor Spinnen) (Schaller E., Gerdes A., Alpers G. W., no date), Positive And Negative Affect Schedule (Krohne HW, Egloff B, Kohlmann CW, Tausch A, 1996), Penn State Worry Questionnaire (Stöber, 1998), Social Phobia and Anxiety Inventory (Fydrich T, no date), Agoraphobic Cognitions Questionnaire (Ehlers A, Margraf J, Chambless, 2001), Beck Depression Inventory (Hautzinger M, Keller F, Kühner C, 2006), General scale of

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depression (Allgemeine Depressionsskala) (Radloff, 1977), Short questionnaire about stresses and strains (Kurzer Fragebogen zur Belastungen) (Flor H., no date), Patient-Reported Outcome Information System (Cella *et al.*, 2010), Beck Anxiety Inventory (Beck *et al.*, 1988), Brief COPE (Carver, 1997), Childhood Trauma Questionnaire (Bernstein *et al.*, 1994), General Self-Efficacy scale (Schwarzer R. & Jerusalem M., 1995).

4.2.4.2. Structural MRI data

Structural data processing and quality control were conducted with Freesurfer (Fischl *et al.*, 2002) in accordance with ENIGMA protocols (<https://enigma.ini.usc.edu/protocols/imaging-protocols/>). Total intracranial volume was extracted, cortical surface area and cortical thickness were extracted for 68 cortical ROIs of the Desikan-Killiany atlas (Desikan *et al.*, 2006), and volume was extracted for 16 subcortical ROIs from the Freesurfer automatic segmentation (Fischl *et al.*, 2002). A visual control was conducted for segmentation failure or substantial over- or underestimation and the data from the affected regions were excluded.

4.2.4.3. Task-based fMRI data

Data preprocessing and processing steps described below were conducted for each subject individually. Initial visual quality control was conducted for structural and functional data and subjects with excessive noise, motion artefacts or abnormal brain anatomy were excluded (as mentioned above, N = 3 were excluded for structural MRI artefacts or abnormalities, N= 5 were excluded due to substantial movement during the task).

Task fMRI data were preprocessed with SPM12 and associated toolbox CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012). Functional volumes were realigned and unwarped, and potential outlier scans were detected in CONN with conservative parameters (i.e. flagging scans with within-subject global BOLD signal change ≥ 3 standard deviations or framewise displacement 0.5 mm). Volumes were then segmented and normalized onto MNI template space, then smoothed with 8 mm full width at half-maximum Gaussian kernel. Subjects with movement-correction realignment parameters ≥ 3.3 mm (initial voxel size) in any direction were excluded. The absence of occipital visual activation in the active vs. inactive blocks contrast was also an exclusion criterion. As in section 3.2.3, Functional measures described below were extracted for a set of 30 bilateral anxiety-relevant ROIs derived from recent meta-

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analyses and reviews (Santos *et al.*, 2019; Chavanne and Robinson, 2021), to restrict dimensionality of features for the main prediction analysis.

ROIs for the fMRI data included the amygdala, hippocampus, anterior and posterior insula, periaqueductal gray, bed nucleus of the stria terminalis, the dorsal, pregenual and subgenual anterior cingulate cortex, as well as the dorsomedial, ventromedial, dorsolateral and orbitofrontal cortices (all were taken from the Brainnetome atlas (Fan *et al.*, 2016) with the exception of periaqueductal gray, taken from Keuken *et al.* (Keuken *et al.*, 2017), and bed nucleus of the stria terminalis, taken from Neudorfer *et al.* (Neudorfer *et al.*, 2020)).

Given that some of the previous literature reported widespread brain regions to have predictive value in psychotherapy outcome prediction (Hahn *et al.*, 2015), an exploratory prediction analysis was also conducted in which functional measures were extracted for every ROI in the CONN default atlas, covering the whole brain (combining cortical and subcortical areas from the FSL Harvard-Oxford atlas and the AAL cerebellar areas for a total of 132 ROIs).

Activation features

Condition effects were modeled using the general linear model in SPM with separate conditions for phasic fear, sustained fear, no fear, instructions, rating and inactive blocks separately to map the entire experimental space. The six movement-correction parameters from the realignment procedure were used as regressors of no interest. Default 1st-level SPM analysis parameters were used. Three contrasts of interest were computed per subject (phasic fear vs. no fear, sustained fear vs. no fear, and active blocks vs. inactive blocks). For each contrast per subject, the MarsBar toolbox (Brett *et al.*, 2002) was then used to extract median effect sizes in every ROI, which were included as features.

BOLD variance features

BOLD variance features were extracted according to (Garrett *et al.*, 2010) using the 1st-level SPM model described above and VarTbx (<https://github.com/LNDG/vartbx>), just as in the previous study (section 3.2.4.2). For the phasic fear, sustained fear and no fear conditions, the MarsBar toolbox was then used to extract average variance in every ROI, which were included as features.

Functional connectivity features

As described in section 3.2.4.3, ROI-to-ROI task-modulated effective connectivity matrices were computed with generalized psychophysiological interaction (gPPI) using CONN for all ROIS both in the phasic fear and sustained fear conditions and were included as features.

Graph-theoretic connectivity features

As described in section 3.2.4.4, the above-mentioned gPPI matrices for phasic and sustained fear were used in the BCT toolbox (Rubinov and Sporns, 2010) to extract all global and ROI-specific metrics available in the toolbox for directed graphs, with the exception of communities-related, and included as features.

4.2.5. Ensemble machine-learning prediction

4.2.5.1. Post-treatment outcome ensemble prediction

All prediction analyses were conducted with scikit-learn (version 1.1.1) in Python. A binary classification prediction between responders (N = 103) and nonresponders (N = 87) at posttreatment was conducted using an ensemble learning approach, with eight 1st-level classifiers each using different feature modalities (demographic and clinical questionnaires, functional activation, gPPI connectivity for both phasic and sustained fear, gPPI-derived graph-theoretic metrics, BOLD variance; see Figure 13) from which the output (i.e. predictions) was used as feature by a 2nd-level classifier, the latter producing the final prediction. As with the previous study (see section 3.2.5 for details), a random shuffle cross-validation was repeated 100 times with an 80-20 train-test split, included scaling, median imputation and feature selection using a logistic regression stochastic gradient descent learning classifier. All classifiers used were Random Forest, and an alternative 2nd-level classifier (soft voting) was also examined. The prediction analysis code, as well as the code for neuroimaging measures extraction, has been made freely available online (https://github.com/avchavanne/SpiderPhobia_Treatment_response_prediction_multimodal)

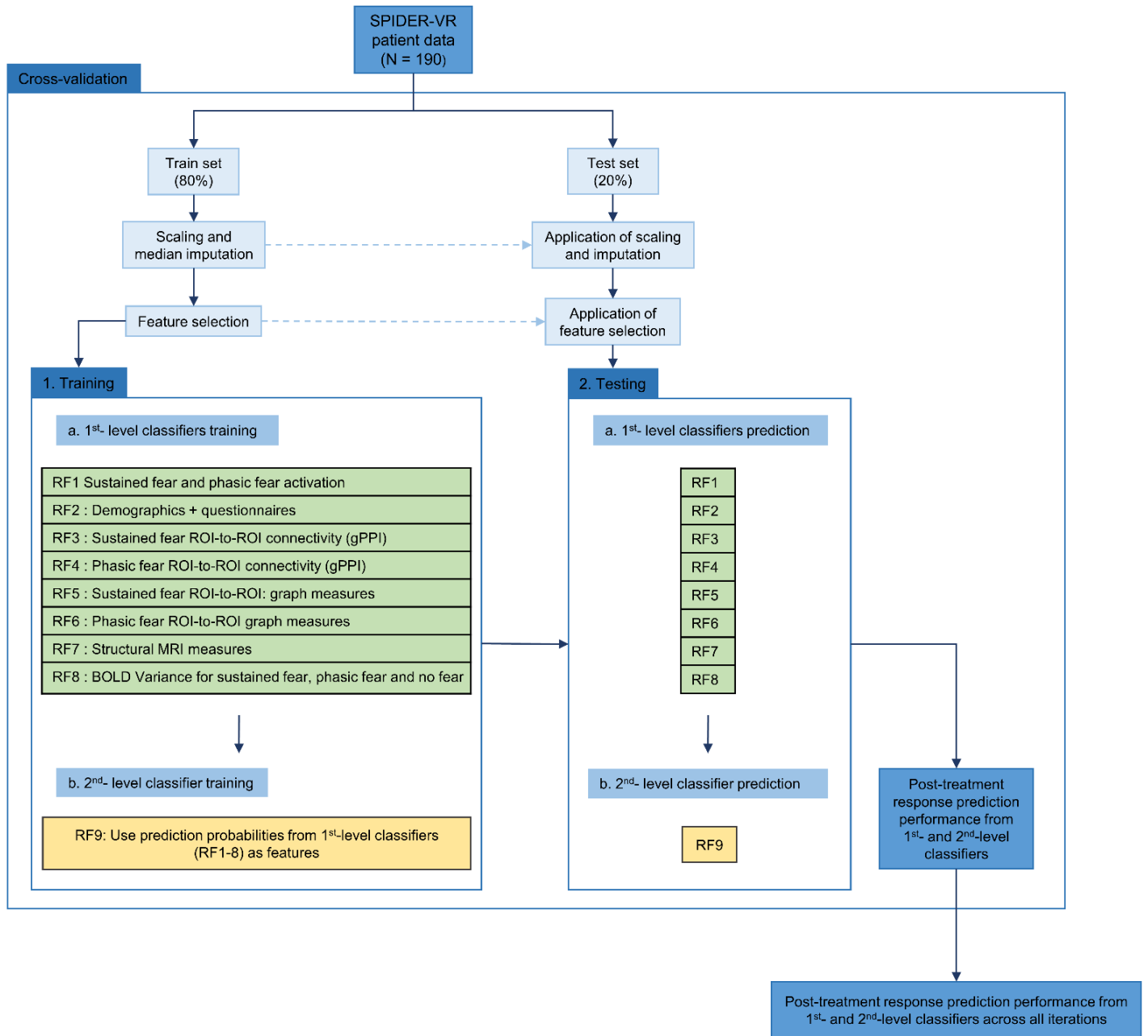


Figure 13: Ensemble machine-learning classification pipeline.

RF: Random Forest; ROI: region of interest; gPPI: generalized psychophysiological interaction; MRI: magnetic resonance imaging; BOLD: blood-oxygen-level-dependent.

The corrected resampled t-test (Nadeau and Bengio, 2003; Bouckaert and Frank, 2004) was again used to investigate classification accuracies, and the SHAP module (Lundberg and Lee, 2017) to explore individual feature contribution to predictions.

4.2.5.2. Follow-up outcome ensemble prediction

Sustained treatment outcome (30% SPQ score reduction between pre-treatment and FU) after 6 months was also analysed, including $N = 183$ patients with a response rate of 78%. Additional prediction analyses were conducted with an identical classification pipeline and features to the main analysis, to investigate the prospective prediction of responders ($N = 143$) vs. non-responders ($N = 40$) at FU.

4.2.5.3. Supplementary prediction strategies

With all other parameters kept identical, prediction analyses were re-performed *a posteriori* using a decision tree classifier as feature selection (with scikit-learn default parameters) instead of the gradient descent learning classifier.

The prediction analyses were also re-performed using alternative structural data, which was re-extracted from all subjects using the CAT12 toolbox (<https://neuro-jena.github.io/cat/>). Regional cortical thickness and gyrification were extracted from the Destrieux atlas, alongside regional volumes from the neuromorphometrics atlas.

4.3. Results

4.3.1. 1st-level post-treatment outcome prediction results

The main prediction analysis of post-treatment outcome based on demographic and clinical questionnaires resulted in a balanced accuracy = 0.60 (SD = 0.07) and AUROC = 0.64 (SD = 0.08) (Table 11, Fig. 14A). No significant difference emerged between the sociodemographic and clinical classifier and the dummy classifier using the corrected resampled t-test.

The main prediction analysis based on structural MRI measures, functional activation, gPPI connectivity, gPPI-derived graph metrics for both phasic and sustained fear conditions and BOLD signal variance did not perform above chance level (balanced accuracy ranging from 0.48 to 0.55, AUROC ranging from 0.48 to 0.59).

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1 st -level classifier	Balanced accuracy (SD)	AUROC (SD)
<i>Functional features extracted from a-priori selected 30 ROIs</i>		
Demographic and questionnaire data	0.60 (0.07)	0.64 (0.08)
Structural MRI	0.51 (0.07)	0.51 (0.08)
Functional activation	0.48 (0.08)	0.48 (0.09)
Phasic fear gPPI	0.52 (0.06)	0.53 (0.08)
Sustained fear gPPI	0.51 (0.06)	0.55 (0.08)
Phasic fear graph measures	0.52 (0.07)	0.54 (0.08)
Sustained fear graph measures	0.54 (0.07)	0.56 (0.09)
BOLD variance	0.55 (0.07)	0.59 (0.08)
<i>Functional features extracted from ROIs across the whole brain (exploratory)</i>		
Demographic and questionnaire data	0.60 (0.07)	0.64 (0.08)
Structural MRI	0.51 (0.07)	0.51 (0.08)
Functional activation	0.51 (0.06)	0.52 (0.08)
Phasic fear gPPI	0.49 (0.05)	0.49 (0.10)
Sustained fear gPPI	0.49 (0.05)	0.49 (0.09)
Phasic fear graph measures	0.48 (0.06)	0.50 (0.07)
Sustained fear graph measures	0.47 (0.06)	0.49 (0.08)
BOLD variance	0.63* (0.07)	0.67 (0.08)

Table 11: Prediction results of the 1st-level classifiers of post-treatment response (N=103 responders vs N=87 non-responders).

ROI: region of interest; AUROC: Area under the receiving operator curve; gPPI: generalized psychophysiological interaction.

*: $p < 0.05$, corrected resampled t-test against the accuracy of a dummy classifier, two-tailed.

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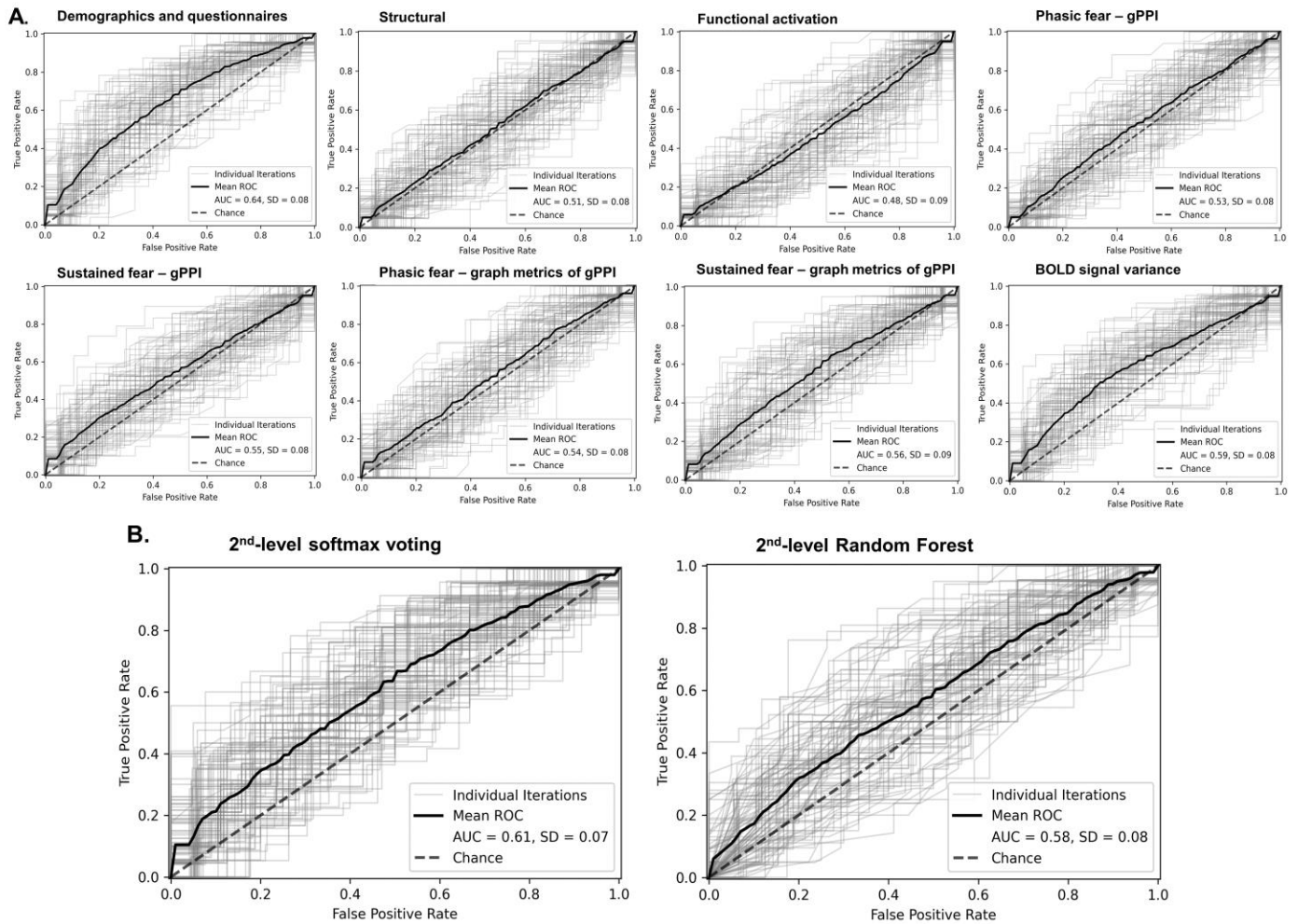


Figure 14: Area under the receiving operating curves for treatment outcome classification.

A: 1st-level classification results; B: 2nd-level classification results. gPPI: generalized psychophysiological interaction.

The exploratory prediction analysis, in which functional features were derived from ROIs across the whole brain instead of an a-priori selected set, produced similar results except for the 1st-level BOLD signal variance classifier, which resulted in a balanced accuracy = 0.63 (SD = 0.07) and AUROC = 0.67 (SD = 0.08) (Table 11, Figure 15A). A significant performance difference was found between the BOLD variance classifier and the dummy classifier using the corrected resampled t-test ($p = 0.041$).

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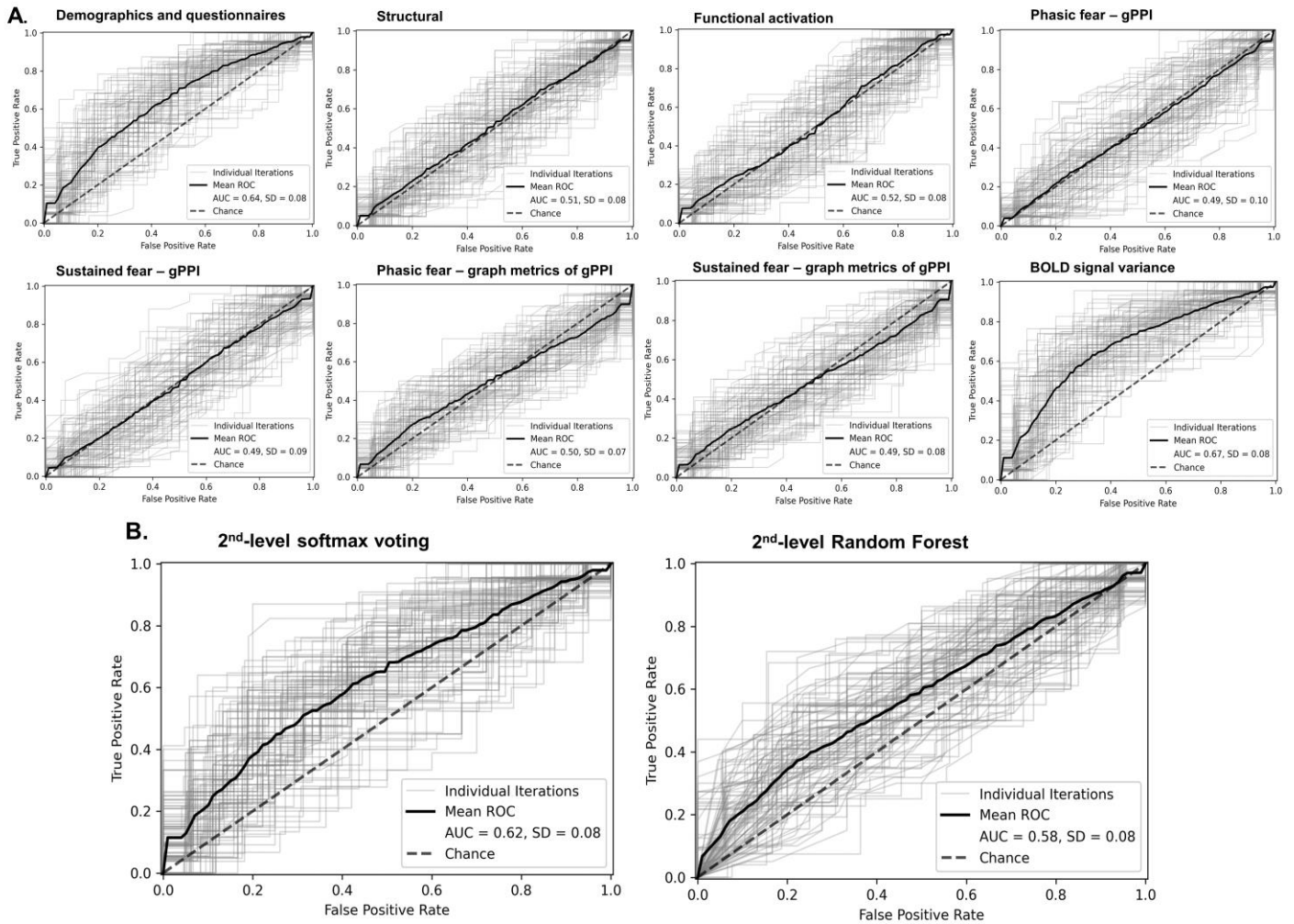


Figure 15: Area under the receiving operating curves for treatment outcome classification using functional features extracted for regions of interest across the whole brain.

A: 1st-level classification results; B: 2nd-level classification results. gPPI: generalized psychophysiological interactions.

Features that contributed most to this variance classifier prediction varied across conditions and brain regions, including for instance BOLD variance in the right supramarginal gyrus, left parahippocampal and angular gyri, and left intracalcarine cortex (Figure 16).

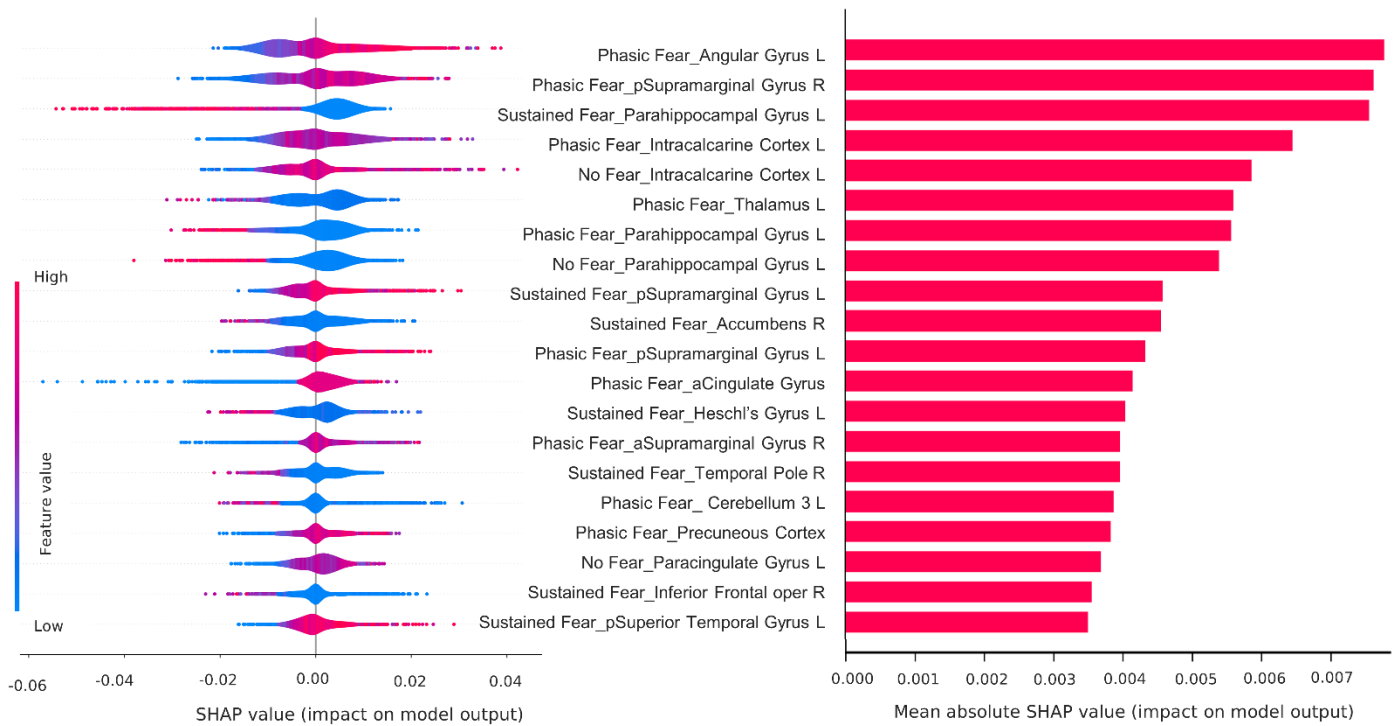


Figure 16: Shapley (SHAP) values and feature importance of the 1st-level variance classifier in the responder (N = 103) vs. nonresponder (N = 87) prediction using functional features across ROIs covering the whole brain.

Positive SHAP values indicate a contribution of feature value in favour of the positive class prediction (future responder), negative Shapley values are in favour of the negative class prediction (future non-responder). Larger absolute Shapley values indicate larger impact on the model output. The 20 most contributing features are shown, ranked in decreasing order of mean absolute SHAP value. Horizontal violin plots on the left represent the distribution of all individuals in the test set across all cross-validation iterations. For each feature, relative values are represented on the left by a colour gradient.

4.3.2. 2nd-level post-treatment outcome ensemble prediction results

The 2nd-level classifiers using prediction probabilities of all 1st-level classifiers as input features failed to predict treatment outcome above chance level in the main prediction analysis (Figure 14B). The 2nd-level voting classifier prediction resulted in a balanced accuracy = 0.55 (SD = 0.06) and AUROC = 0.61 (SD = 0.07). The 2nd-level Random Forest classifier resulted in a balanced accuracy = 0.54 (SD = 0.07) and AUROC = 0.58 (SD = 0.08).

Comparable results were obtained with the exploratory analysis in which functional features were derived from ROIS across the whole brain instead of an a-priori selected set, with the

voting classifier resulting in a balanced accuracy = 0.54 (SD = 0.06) and AUROC = 0.62 (SD = 0.08), and the Random Forest classifier resulting in a balanced accuracy = 0.52 (SD = 0.06) and AUROC = 0.58 (SD = 0.08) (Figure 14B).

4.3.3. Follow-up outcome ensemble prediction results

The main prediction analysis of follow-up treatment primary outcome based on any modality (functional activation, demographic and clinical data, functional connectivity gPPI and gPPI-derived graph metrics, structural measures, BOLD variance) did not perform above chance level (balanced accuracy = 0.5 for all 1st-level classifiers, AUROC ranging between 0.47 and 0.56). Similarly, both soft voting and Random Forest 2nd-level classifiers did not predict follow-up treatment outcome above chance level (balanced accuracy = 0.5 (SD = 0) for both, AUROC = 0.49 (SD = 0.11) and 0.5 (SD = 0.02) respectively).

The exploratory prediction analysis resulted in similar results, with no performance above chance level from any 1st- or 2nd-level classifier.

4.3.4. Supplementary machine-learning predictions

Re-performing the analyses using a non-linear (decision tree) classifier to select features did not impact prediction performance (AUROC of 1st-level classifiers ranging between 0.48 and 0.64; balanced accuracy between 0.49 and 0.60; 2nd-level voting classifier AUROC = 0.59 (SD = 0.09), balanced accuracy = 0.55 (SD = 0.07); 2nd-level Random Forest classifier AUROC = 0.58 (SD = 0.08), balanced accuracy = 0.55 (SD = 0.07)). No significant differences were found between prediction performances of the 1st- or 2nd-level classifiers and the dummy classifier using the corrected resampled t-test.

Re-performing the analyses using CAT12-extracted regional thickness and gyrification as structural data resulted in a 1st-level AUROC = 0.62 (SD = 0.08), balanced accuracy = 0.56 (SD = 0.06) (corrected resampled t-test $p = 0.56$). The 2nd-level voting classifier using prediction probabilities of all 1st-level classifiers as input features resulted in an AUROC = 0.64, (SD = 0.08), balanced accuracy = 0.56 (SD = 0.06) ($p = 0.48$). The 2nd-level Random Forest classifier resulting in an AUROC = 0.60 (SD = 0.08), balanced accuracy = 0.56 (SD = 0.06) ($p = 0.71$).

4.4. Discussion

The present study investigated the incremental predictive value of neuroimaging data in comparison with clinical data alone for individual-level psychotherapy outcome prediction in patients with spider phobia. Contrary to expectations, prediction performance did not go beyond chance-level for all distinct data modalities except BOLD variance, and the contribution of (f)MRI measures to the prediction did not outperform clinical and sociodemographic data alone. At post-treatment, clinical questionnaires and BOLD signal variance derived from ROIs across the whole brain showed potential to contribute to higher-level ensemble prediction with a balanced accuracy of 0.60 and 0.63 respectively. No predictive contribution was found for any data modality at follow-up.

4.4.1. Perspective on prediction performance

Overall, our findings challenge the existing literature reporting above-chance predictive accuracies for machine-learning psychotherapy outcome prediction using neuroimaging data in patients with anxiety disorders (Ball *et al.*, 2014; Hahn *et al.*, 2015; Månsson *et al.*, 2015, 2022; Whitfield-Gabrieli *et al.*, 2016; Sundermann *et al.*, 2017; Frick *et al.*, 2020). However, they echo a more recent body of methodological work underlining that, despite initial promise in the field, prediction accuracies for patient classification based on medical imaging features appear to be decreasing as sample sizes increase, perhaps reflecting unwitting biases in performance evaluation, overhyping and cross-validation error bars in the neuroimaging literature (Varoquaux, 2018; Hosseini *et al.*, 2020; Poldrack, Huckins and Varoquaux, 2020; Varoquaux and Cheplygina, 2022). The importance of general sample size and the size of test sets in particular to guard against misestimation of prediction accuracy was underlined in a study using a very large sample of patients with depression to mimic small-scale sampling results in machine-learning classification using structural neuroimaging (Flint *et al.*, 2021). In line, another recent prospective prediction of pharmacotherapy outcome in a relatively large sample of patients with depression using baseline cross-sectional functional MRI connectivity yielded no prediction above chance level, although using changes in connectivity from baseline to week two as predictive features instead yielded accuracies up to 0.696 (Harris *et al.*, 2022). This study pointed out that many previous studies reporting high classification or prediction accuracies were based on single-site, small samples of patients that do not generalize well, and that although more heterogeneous and larger multisite

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datasets may yield lower prediction performances, they were more representative of the target population. While our sample was bicentric and fairly larger than previously published studies, it is not large per machine-learning standards. Efforts to collaboratively build multisite samples with very large sizes, such as the ENIGMA consortium initiative (Thompson *et al.*, 2020), should be bolstered to address this recurring concern. Performance of machine-learning models can also vary depending on the initial choice of various prediction pipeline elements, and can also be affected by the incorporation of distinct data modalities in the prediction.

The clinical demographic classifier showed close performance to a previous prediction study using the original SPIDER-VR sample (Leehr *et al.*, 2021), however it was not significantly above chance level in our study (possible causes include distinct balancing and cross-validation strategies between the two studies, and the use of an extended sample herein). The BOLD variance classifier did reach above-chance predictive performance on its own at post-treatment in our exploratory analysis with features extracted from ROIs across the whole brain, but with moderate performance. It could be a promising contributor to 2nd-level prediction alongside other feature modalities. Indeed, in the field of neuroimaging, interest in BOLD signal variability has been increasing with mounting evidence that it could be a promising correlate of cognitive performance with good measurement reliability, of a more flexible brain state allowing more accurate processing, complementary to the traditional BOLD signal mean (Garrett *et al.*, 2011; Garrett, Kovacevic, *et al.*, 2013; Garrett, Samanez-Larkin, *et al.*, 2013). Regional BOLD signal variability has been related to regional functional integration in the whole-brain network (Garrett *et al.*, 2018), and inter-regional BOLD signal variability was closely associated with inter-regional functional connectivity (Baracchini *et al.*, 2023). BOLD signal variability has also been reported to differ significantly between patients with generalized anxiety disorder and healthy controls in widespread brain regions, with a non-linear relationship between anxiety level and variability, showing promise as a potential clinical biomarker (Li *et al.*, 2019).

Critically, given the recent and sparse literature in the predictive value of BOLD variability both in resting-state and task-based fMRI in anxiety disorders (Månsson *et al.*, 2015, 2022), our study supports further investigation of BOLD variability as a predictive feature of clinical outcome.

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Additionally, other psychological, neuroimaging and biological measures could also be explored for individual-level predictive purposes. For instance, early response to psychotherapy is a well-established group-level predictor of post-treatment response in patients with internalizing disorders (Bradford *et al.*, 2011; Lutz *et al.*, 2014; Schlagert and Hiller, 2017; Rech *et al.*, 2020; Roesmann, Elisabeth J. Leehr, Böhnlein, *et al.*, 2022), and early functional connectivity variation during psychotherapy was also reported to be predictive of individual-level clinical outcome (Harris *et al.*, 2022). The promise of ecological momentary assessments to measure symptom dynamics and inform clinical decisions in patients with anxiety disorders has been recently underlined (Lutz *et al.*, 2018; Robinaugh *et al.*, 2020).

Epigenetic markers have also been noticed as promising group-level prospective biomarkers for psychotherapy response in patients with stress-related and anxiety disorders in the recent literature (Schiele, Gottschalk and Domschke, 2020).

Based on our results as well as the mentioned previous literature, we encourage caution in the interpretation of promising neuroimaging prediction results with small patient sample sizes. Further investigation with large and multisite samples is still needed to elucidate the potential contribution of (f)MRI measures to the prediction of anxiety disorders therapy response.

4.4.2. Strengths

The clinical outcome prediction was based on targeted, anxiety-specific standardized questionnaires and on multimodal MRI data, including both structural as well as several functional neuroimaging measures. Additionally, our investigation included a state-of-the-art machine-learning pipeline designed to incorporate respective predictive contributions of distinct data modalities, and to maximize feature interpretability.

4.4.3. Limitations

As in section 3, limitations to our study include the ROI-based approach, which induced loss of information in comparison to voxel-wise approaches, particularly for variability-based measures, but was necessary to keep a more reasonable feature dimensionality.

Our sample also included quite homogeneous spider phobic patients without major comorbidities, and might not be fully representative of a diverse clinical population of patients with anxiety disorders. It was, however, crucial for the internal validity to investigate clinical effects of VRET in previous SPIDER-VR publications.

4.4.4. Conclusion

The present study found no evidence of incremental contribution of structural MRI and symptom-relevant task-based fMRI measures to psychotherapy outcome prediction in a fairly large and bicentric sample of patients with spider phobia, with the exception of BOLD signal variance which performed moderately above chance. As such, our findings invite further investigation of BOLD signal variability as a contributor to higher level prediction. However, even the BOLD signal variability prediction performance was lower than in previous single-site, small-sample literature. Thus, the present study also warrants caution in interpreting previous small-scale psychotherapy outcome prediction studies and underline the need for larger, multisite and multimodal datasets to further examine the predictive contribution of neuroimaging measures to psychotherapy response in anxiety disorders.

5. General discussion and perspectives

The present doctoral work leveraged supervised machine-learning approaches to prospectively predict risk of onset and therapeutic outcome in anxiety disorders, using neuroimaging data. In particular, this work investigated the potential individual-level predictive value of structural MRI and tb-fMRI during adolescence in the prediction of anxiety disorder onset 4 to 8 years later (sections 2 and 3), and in the prediction of psychotherapeutic response for patients with spider phobia (section 4). Given the paucity of longitudinal investigations of anxiety onset as well as treatment non-response, and in light of the importance of such investigations for prevention, early identification, and treatment stratification, this doctoral work is of particular interest to both researchers and clinicians.

The studies yielded the following main findings: Regarding the prediction of future pooled anxiety disorder, findings resulted in above-chance predictive performances for psychometric and questionnaire data, but MRI and tb-fMRI data did not show any predictive contribution on their own. However, for the subgroup-specific future GAD prediction, both questionnaires and structural MRI data showed modest predictive value separately, and predictive performance was increased when both data modalities were used in the same prediction. The prediction of psychotherapy outcome in spider phobia did not yield any above-chance prediction results using sociodemographic and questionnaire data, nor MRI and fMRI data except for BOLD signal variance, which yielded modest predictive performance.

Overall, findings in sections 2, 3 and 4 point to a moderate to nonsignificant individual-level predictive value of structural MRI and tb-fMRI data extracted from ROIs classically involved in clinical anxiety, despite an abundant group-level literature. Section-specific results are discussed in detail in the corresponding sections, and an overarching discussion is presented below, including methodological considerations on mental health machine-learning prediction using neuroimaging data, and an overview of additional biomarkers of anxiety with potential to complement multimodal prediction approaches.

5.1. Methodological considerations

5.1.1. Sample size, multisite consortia and generalisability

Sufficient sample sizes are crucial to discover robust brain-behaviour associations. This has been a regular concern in neuroimaging group-level literature, recently underlined in a review recommending that thousands of participants and multivariate strategies should be used to obtain replicable results (Marek *et al.*, 2022). However, this review largely focused on rs-fMRI studies. A wave of responses has emerged, defending the potential utility of samples in the hundreds (Cecchetti and Handjaras, 2022; DeYoung *et al.*, 2022), especially in the case of structural MRI and tb-MRI (Makowski *et al.*, 2023), and emphasized the importance of maximizing the generalisability of findings, which is not always guaranteed by sample size alone (Rosenberg and Finn, 2022). Although datasets with thousands of subjects are obviously costly and may not always be required to produce reproducible research, data collected in multiple sites is essential to improve ecological validity of findings.

Multisite samples from the general population with large to very large sizes, such as the UKBIOBANK (<https://biobank.ndph.ox.ac.uk/>), the Adolescent Brain Cognitive Development (ABCD) study (Casey *et al.*, 2018), and IMAGEN (Schumann *et al.*, 2010), have emerged in the past 15 years. The former is one of the largest biomedical databanks in the world, and the latter two are longitudinal datasets with children or adolescent data. The ENIGMA consortium initiative (Thompson *et al.*, 2020) is also a very large collaborative effort of pooling neuroimaging and genetic data across projects and laboratories worldwide. Furthermore, neuroimaging datasets of patients with anxiety disorders have also emerged via multicentre randomized controlled clinical trials, such as PANIC-NET (Gloster *et al.*, 2009), PROTECT-AD (Heinig *et al.*, 2017) and SPIDER-VR (Schwarzmeier *et al.*, 2019), to address specific clinical prediction questions. The increasing availability of larger-scale neuroimaging and clinical datasets will allow for sophisticated machine-learning approaches and collaborative efforts should continue to be bolstered in that direction.

This doctoral work, through the use of the IMAGEN and SPIDER-VR datasets, was conducted within this multisite framework, thus improving the ecological validity and generalisability of our findings. However, it bears repeating that the available sample sizes of both datasets were still quite modest in terms of machine-learning methodology, and, in the case of IMAGEN, prevented diagnosis-specific predictions for all disorders but GAD. As

such, it remains essential to determine how replicable the present findings are, as well as those from earlier literature.

5.1.2. Sample diversity

Another complex obstacle to the generalisability of neuroscience findings is the gap between a heterogenous general population and the limited representativity and inclusivity of experimental samples, even larger ones (Kopal, Uddin and Bzdok, 2023). This potential mismatch between the distribution in the population used to identify a biomarker and the distribution in the target population that should benefit from it, is also a well-known problem in machine-learning prediction (Dockès, Varoquaux and Poline, 2021). Field-standards and availability of research funding have constrained the inclusion of marginalized communities in neuroscience studies, including individuals with low socio-economic status as well as racial and ethnic minorities (Edmiston and Juster, 2022; Garcini *et al.*, 2022; Ricard *et al.*, 2023). Frequent methodological problems have also been identified in the LGBT (lesbian, gay, bisexual and transgender) neuroimaging literature (Levin *et al.*, 2023). It is difficult to even quantify the depth and scope of the inclusion problem, as race and ethnicity were reported 10% of the time or less in MRI studies (Sterling *et al.*, 2022). Building large and diverse multisite datasets through collaborations and consortia does tackle at least some of these issues. However, further effort still has to be undertaken in the field. Notably, several recommendations to improve scientific practices in fair and appropriate ways at multiple levels, from interpersonal to systemic, have emerged in the literature (Falk *et al.*, 2013; Rowley and Camacho, 2015; Garcini *et al.*, 2022). They include, but are not limited to, involving community partners in study planning, using culturally sensitive methods, and ensuring that some of the research staff is from a similar background as the target population.

This doctoral work was based on already-collected large datasets in which race and ethnicity were not fully documented, although the IMAGEN project explicitly aimed to recruit Caucasian participants, to maximise ethnic homogeneity for genetic studies (Schumann *et al.*, 2010). The lack of documentation is at least partly attributable to European and national regulations (e.g. race and ethnicity data collection is prohibited by French law, and even the collection of proxy data is very heavily constrained). As such, the samples used herein are vulnerable to an overrepresentation of participants of European ancestry with higher socio-

economic status, which is a general bias in the neuroimaging literature (Henrich, Heine and Norenzayan, 2010), and findings may generalize less well to underrepresented populations.

5.1.3. Clinical heterogeneity and clinical constructs

A recent review emphasized that, while moving to larger consortia datasets could help address concerns of small samples sizes and inadequate statistical power, it would still have limited impact unless the precision of psychopathology phenotyping is improved (Tiego *et al.*, 2023). Indeed, although the traditional psychiatric nosology framework is based on practical interests to help clinical decision-making (Kraepelin, 1992; American Psychiatric Association, 2013), the overlapping symptoms between disorders, the manifestation of most disorders on a continuum (instead of a binary diagnosis), and the substantial heterogeneity within disorders make the investigation of biological mechanisms underlying mental health conditions challenging (Markon, Chmielewski and Miller, 2011; Feczko *et al.*, 2019). As clinical phenotypes may often have multidimensional and hierarchical structures, different subsets of individuals might have different biological mechanisms driving one same diagnosis, and biological measures might differ between subsets. Psychometric assessments may also lack coverage (i.e. phenotypic resolution) on the lower end of symptom questionnaire scales where most individuals in non-clinical cohorts from the general population will score, which could be problematic to investigate individual differences even in large consortia (Tiego *et al.*, 2023).

These limitations have sparked the RDoC initiative (Insel *et al.*, 2010) and, more recently, the HiTOP model (Kotov *et al.*, 2017) (see Figure 15 for both), including specific considerations for youth psychopathology (Forbes *et al.*, 2023). Leveraging both RDoC and HiTOP approaches has potential to bring the field closer to bio-behaviourally and psychometrically grounded nosology (Michelini *et al.*, 2021). It is important to note, however, that a richer phenotyping with higher dimensionality also warrants careful feature reduction steps for data used in machine-learning prediction (Bzdok, Nichols and Smith, 2019).

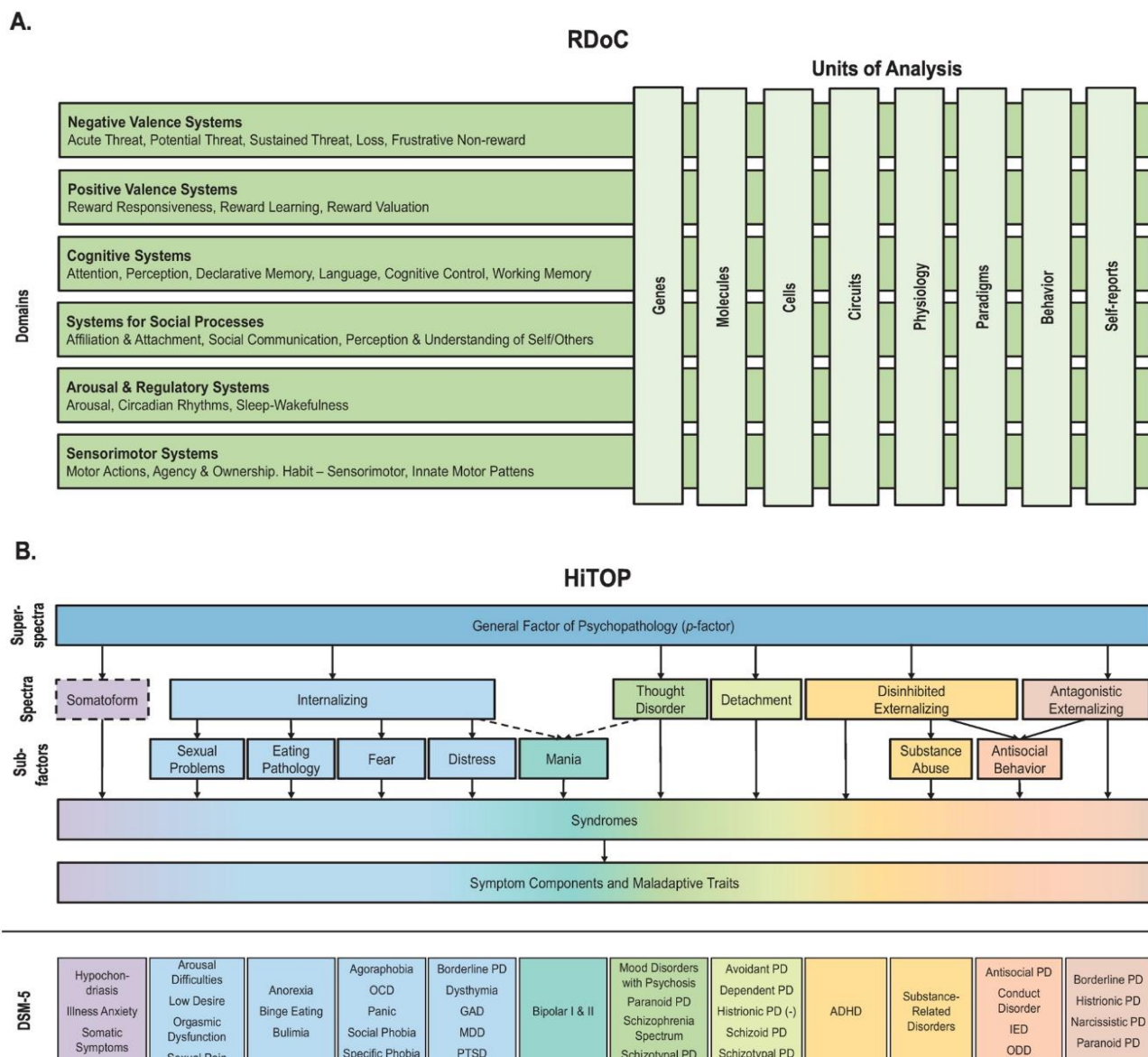


Figure 15: RDoc and HiTOP (Michellini *et al.*, 2021).

A: the RDoC matrix includes six domains (rows) and their respective constructs, which can be characterized on the basis of eight units of analysis (columns). B: HiTOP dimensions span from super-spectra (more general) to symptoms components and maladaptive traits (more specific). Dashed lines indicate provisional elements requiring more study. DSM diagnoses mapping onto more than one HiTOP spectrum or subfactor are listed in multiple places. (–) indicates negative association between histrionic personality and the Detachment spectrum. ADHD: attention-deficit/hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; GAD: generalized anxiety disorder; IED: intermittent explosive disorder; MDD: major depressive disorder; OCD: obsessive–compulsive disorder; ODD: oppositional defiant disorder; PD: personality disorder; PTSD: posttraumatic stress disorder.

Alternatively, data-driven approaches have emerged to tackle heterogeneity in psychopathology by distinguishing putative subtypes, using both supervised models,

unsupervised clustering, and hybrid methods incorporating both (Feczko *et al.*, 2019). Normative modelling is another data-driven conceptual framework that consists in the longitudinal modelling of biological variation across either a large healthy sample or the general population (including healthy and clinical samples), thus allowing to relate deviation from the biological norm to clinical symptoms (Marquand *et al.*, 2016, 2019) (Figure 16). Normative deviation features have shown promise to be better than the corresponding raw neuroimaging measures at distinguishing patients with schizophrenia from controls in both group-level and individual-level benchmarks (Rutherford *et al.*, 2022, 2023). They have also started to shed light on the considerable within-group heterogeneity in neuroimaging that is usually obscured by case-control frameworks in schizophrenia and bipolar disorder (Wolfers *et al.*, 2021), attention deficit disorder (ADHD) (Wolfers *et al.*, 2020) and autism (Zabihi *et al.*, 2020).

Although the IMAGEN sample used in this doctoral work was clinically heterogeneous, the SPIDER-VR sample, due to internal validity constraints to investigate clinical effects of VRET in previous publications, included quite homogeneous spider phobic patients that might not be fully representative of a diverse clinical population. Furthermore, predictions herein were articulated around traditional DSM-IV diagnoses for both samples, thus regrouping individuals with potentially different underlying symptoms and biological driving mechanisms. The limited contribution of neuroimaging features to anxiety-relevant predictions in our findings and to depression predictions in other recent large-scale work (Winter *et al.*, 2022) further supports the implementation of initiatives such as RDoC, HiTOP and data-driven alternatives in mental health research. Overall, various efforts to move beyond case-control designs and to tackle the long-standing problem of clinical heterogeneity in meaningful ways are ongoing, and may contribute to prospective individual-level prediction of anxiety-relevant symptoms in the close future.

5.1.4. Machine-learning considerations and alternatives to supervised learning for MRI data

One of the core components of machine-learning is the systematic use of cross-validation, which is one of the suggested approaches to enhance generalisability of neuroimaging findings (Rosenberg and Finn, 2022). However, cross-validation does not completely protect against overinflated results and unrepresentative samples. It was noted that, contrarily to

expectations, prediction accuracy generally decreased in studies using larger sample sizes in the neuroimaging machine-learning literature (Varoquaux, 2018), and that small-sample studies ($N < 50$) tended to report highly variable prediction performance estimates, suggesting a risk of overoptimistic claims in the neuroimaging literature (Poldrack, Huckins and Varoquaux, 2020). The importance not only of sample size, but of test set size, to protect against overinflated estimation of predictive performance was recently underlined (Flint *et al.*, 2021). Furthermore, pernicious overfitting was also shown to occur despite the use of cross-validation through a phenomenon termed overhyping, which is overfitting due to the (typically unintentional) manual adjustment of analysis hyperparameters, a problem akin to multiple testing (Hosseini *et al.*, 2020; Radua and Koutsouleris, 2023). This is a possible explanation for the moderate to chance-level prediction performances obtained from neuroimaging data in our analyses, both for anxiety onset and therapeutic outcome predictions, contrastingly to earlier smaller-scale work. Based on the findings in this doctoral work, we further encourage caution in the interpretation of optimistic small-scale predictive performances using neuroimaging data.

Deep learning is a fast-developing field that could provide alternative machine-learning classification approaches. The availability of very large neuroimaging consortia has made possible the use of deep learning to investigate brain-based phenotype predictions. However, evidence that deep learning yields improved performance compared to supervised learning for neuroimaging-based classification is yet unclear (He *et al.*, 2020; Schulz *et al.*, 2020). Deep learning models require much larger sample sizes (likely tens of thousands of observations) to be fully trained and with a much higher computational cost, in comparison with supervised learning (Radua and Koutsouleris, 2023). They are also considerably more complex, which makes their interpretability challenging (Scheinost *et al.*, 2019), although post-hoc methods such as LIME (Ribeiro, Singh and Guestrin, 2016) or SHAPley (Lundberg and Lee, 2017) can provide some insight to feature contribution, similarly to nonlinear supervised machine-learning approaches.

A recent meta-analysis reported that deep learning approaches showed generally improved predictive performance in comparison with supervised machine-learning when applied to psychiatry-relevant cross-sectional predictions, but noted several methodological concerns in the studies reviewed, including a risk of publication bias in favour of deep-learning findings (Quaak *et al.*, 2021). Some other promising findings emerged recently, such as the (not yet peer-reviewed) prospective prediction of anxiety, depression and somatic symptom disorders

at ages 11-12 using MRI, fMRI and psychosocial data collected at ages 9-10 in N = 5355 youth from the ABCD cohort, with an accuracy = 0.933 for anxiety onset prediction, and accuracy = 0.75 for the same prediction using only neuroimaging data (Lacy and Ramshaw, 2023). Overall, deep learning methods have shown some promise in better predicting psychiatry-relevant outcomes compared with more simple learning approaches, but evidence is mixed and methodological challenges remain. Transfer learning, also termed pre-training, which consists in re-using the knowledge gained by a model in a task for another related task or problem, could be one way of reducing the sample size requirements of deep learning (Koppe, Meyer-Lindenberg and Durstewitz, 2021; Kalmady *et al.*, 2022).

Large multisite consortia are also facilitating prediction analyses based on multimodal data, which have been postulated to be a good candidate to bridging the gap to clinical utility (Koutsouleris *et al.*, 2021; Dwyer and Koutsouleris, 2022). A recent review also underlined the necessity of multimodal data integration using machine-learning in the search for robust markers of treatment response in anxiety (Khosravi *et al.*, 2022). Overall, the limited success of using single neuroimaging data modalities and brain markers previously identified at group-level to predict individual-level anxiety onset or therapeutic response, as was further demonstrated in this doctoral work, encourages the field to move towards multimodal data-based predictions to improve predictive accuracy.

5.2. Non-MRI brain markers of anxiety

MRI is by far the most commonly explored neuroimaging data modality in anxiety disorders, but some promising findings have emerged from non-MRI neuroimaging approaches. For example, several studies have used electroencephalography (EEG) to cross-sectionally predict either anxiety symptoms in a non-clinical N = 97 sample (Kato *et al.*, 2022), or classify patients with anxiety disorders vs. healthy controls (Park *et al.*, 2021; Shen *et al.*, 2022). One other study used error-related negativity, which is a robust group-level EEG marker of anxiety (Moser *et al.*, 2013), to prospectively predict GAD onset over 1.5 years in N = 457 adolescent girls (Meyer *et al.*, 2018). A recent review also underlined the potential of error-related negativity in youth as a developmental risk marker for anxiety (Meyer, 2022).

Functional near-infrared spectroscopy (fNIRS) studies have also yielded some putative group-level markers of pathological anxiety (Rosenbaum *et al.*, 2020; Kir *et al.*, 2021;

Papasideris, Ayaz and Hall, 2021; Zhang *et al.*, 2022), and one study used fNIRS data to cross-sectionally predict state anxiety levels using machine-learning (Duan *et al.*, 2020). To our knowledge, no prospective prediction has been attempted in anxiety using fNIRS data, and fNIRS findings remain exploratory.

Overall, both EEG and fNIRS hold some promise to produce anxiety-relevant biomarkers with predictive value. However, although they are less expensive approaches to extract brain measures in comparison with MRI, EEG and fNIRS currently lack the sample sizes available with existing large-scale MRI consortia, and efforts to build large-scale collaborations should be bolstered.

5.3. Beyond the brain: other potentially predictive markers of anxiety

Neuroimaging data, and MRI data in particular, can usually only be collected in experimental settings and is expensive. In the search for incremental predictive value, prediction analyses using multimodal data are progressively developing. To this end, various other non-invasive markers have recently shown potential to predict cross-sectional or prospective outcomes in anxiety, an overview of which is presented below.

5.3.1. Genetic and epigenetic data

An abundant literature has investigated group-level genetic markers of anxiety, which are believed to be polygenic, with small effect sizes from common genetic variants (Meier and Deckert, 2019). Twin studies have yielded heritability estimates ranging around 30-50% for anxiety disorders (Hettema, Neale and Kendler, 2001). However, although genome-wide association studies (GWAS) have identified several variants associated with susceptibility to both binary anxiety disorders and anxiety symptom dimensions, many were not significant at the meta-analytic level and/or lacked replication in larger studies (Shimada-Sugimoto, Otowa and Hettema, 2015; Meier and Deckert, 2019). Epigenetic and epigenome-wide studies have become increasingly popular in the past decade and have also yielded promising anxiety-relevant markers, mostly DNA methylation patterns (Schiele and Domschke, 2018). Modest genetic and epigenetic group-level correlates of psychotherapeutic response have been

identified in small samples of patients with anxiety disorders (Coleman *et al.*, 2016; Lueken *et al.*, 2016; Schiele, Gottschalk and Domschke, 2020).

A few attempts to predict anxiety at the individual level using genetic markers have emerged. One study used circadian genes expression profiles to cross-sectionally predict anxiety symptom score (Zafar *et al.*, 2022). Another study used genetic markers, alongside neuroimaging data, to predict CBT response in patients with SAD, but sample size of genetic data was limited and no predictive contribution of genetic data was found (Frick *et al.*, 2020). To our knowledge, no study has yet investigated the predictive value of epigenetic data in anxiety, which could be a promising complementary research avenue to predictions using genetic and other multimodal data.

5.3.2. Physiological biomarkers and wearables

Various physiological biomarkers have been associated with anxiety disorders or anxiety symptoms at group-level, including, but not limited to, gut microbiota composition (Simpson *et al.*, 2020), cortisol levels, skin conductance, heartrate variability (HRV) (Chesnut *et al.*, 2021), gait (Feldman *et al.*, 2019) and sleep patterns (Pastre and Lopez-Castroman, 2022), with some mixed evidence and heterogeneous directions of effects. Physiological measures collected at regular intervals via wearable assessments, such as HRV or sleep patterns, show potential as a means to help detect symptoms and allow for a window of possible preventive intervention before they escalate to full-fledged disorders (Gomes *et al.*, 2023).

Several studies have investigated the predictive value of physiological markers for anxiety using machine-learning. For example, two studies used gait data to cross-sectionally predict anxiety symptom scores (Zhao *et al.*, 2019; Wen *et al.*, 2023), one study used HRV to predict weekly anxiety and depression scores (Coutts *et al.*, 2020), one study used dynamic emotional arousal, electrocardiogram data and electrodermal activity to predict state anxiety scores (Ding *et al.*, 2022), and another used HRV and skin conductance to predict social anxiety symptoms in real-time (Shaukat-Jali, van Zalk and Boyle, 2021). Kinematical measures obtained with wearable equipment during a 90 s fear induction task in children aged 3-7 were found to be cross-sectionally predictive of anxiety disorders (McGinnis *et al.*, 2019), and passive movement data was also found cross-sectionally predictive of GAD symptom severity (Jacobson and Feng, 2022). Finally, one study reported that actigraphy (movement and sleep) data was predictive of prospective degradation of GAD and PD symptoms more

than a decade later (Jacobson *et al.*, 2021). Overall, physiological data that is less expensive and relatively easy-to-collect in comparison with neuroimaging has shown potential to yield incremental predictive performance for individual-level anxiety-relevant outcomes.

5.3.3. Smartphone data and social media use

Regular smartphone use has become ubiquitous in the past fifteen years, providing opportunities to collect sensor data in a less-intrusive and more realistic setting than specialized sensing devices and resulting in a growing interest from the field (Cornet and Holden, 2018; Gillan and Rutledge, 2021). Smartphones can also collect new behavioural data with potential predictive relevance to anxiety and other mental health disorders, such as app usage and online social contact, as well as environmental data, such as light and sound exposure, temperature and location. Of note, other environmental markers related to urbanicity, such as air pollution and green space proximity, have been also been reported as promising group-level risk markers for anxiety disorders (Ventimiglia and Seedat, 2019; Xu *et al.*, 2023).

Several studies attempted to use digital data to cross-sectionally predict anxiety symptoms. For instance, one predicted real-time anxiety and sadness levels in adolescents using physical activity, location and phone state data (Ren *et al.*, 2023), another study used movement, text messages and phone calls data to predict social anxiety symptom severity in participants with SAD and subclinical SAD (Jacobson, Summers and Wilhelm, 2020), one study used GPS movement patterns to predict social anxiety levels in college students (Boukhechba *et al.*, 2018), and another predicted used nonidentifiable smartphone app usage data to predict generalized anxiety score in the general population (Choudhary *et al.*, 2022). One last study found no value of phone keystroke behaviour for anxiety score prediction in adolescents, despite modest group-level correlations (Braund *et al.*, 2023).

A few longitudinal (short-term) prediction attempts using smartphone data have also emerged, including one study that used heartrate, light exposure, social contact and GPS data to longitudinally predict next-hour anxiety symptoms in participants with GAD or SAD (Jacobson and Bhattacharya, 2022), and another study that predicted next-day anxiety symptoms increase in healthy participants using app usage, light exposure and movement data (Fukazawa *et al.*, 2019).

Increasing social media usage has yielded further opportunities to access digital behaviours that are potentially relevant to, and predictive of, mental health. Despite a growing interest, anxiety has, to date, received little attention in comparison with suicidality or depression predictions, as was shown in two recent reviews of mental health prediction studies based on social media data (Ahmed *et al.*, 2022; Di Cara *et al.*, 2023). Nonetheless, these reviews emphasized that machine-learning prediction of anxiety and depression using freely available social media data was a fast-growing field with potential to inform early detection of disorders and provide complementary screening strategies to the traditional clinical route.

A majority of cross-sectional studies predicting anxiety symptoms or disorders used text features extracted from social media posts or messages (Gruda and Hasan, 2019; Kumar, Sharma and Arora, 2019; Mori and Haruno, 2021; Singh and Singh, 2022; Yu, Li and Liu, 2023), although one used profile pictures and posted pictures (Guntuku *et al.*, 2019). To our knowledge, two studies attempted longitudinal predictions, one using daily social media usage before and during lockdown due to COVID-19 to predict post-lockdown anxiety symptoms (Ryu *et al.*, 2021), and the other using Google search prompts and YouTube history data pre-pandemic to predict the worsening of anxiety and depression symptoms during the pandemic (Zhang *et al.*, 2020).

Despite the developing literature, it is important to mention current methodological challenges, such as the questionable validity of symptoms classifications that were used (Chancellor and De Choudhury, 2020), and the non-specificity of social media language features, for which comparable predictive performances have been reported for distinct mental health problems (Kelley *et al.*, 2022). Attempts to detect mental illness through smartphone data and social media also come with privacy concerns that the field will have to address while moving forward (Arora, Yttri and Nilsen, 2014; Brundage *et al.*, 2018). In spite of these challenges, digital phenotyping has shown potential to complement current screening strategies and bring inexpensive incremental predictive accuracy to anxiety-relevant outcomes.

5.4. Conclusion

This doctoral work investigated machine-learning prediction of future anxiety onset and psychotherapy response in patients with spider phobia using sociodemographic and

questionnaire data, as well as structural and fMRI data. Although sociodemographic and questionnaire data showed moderate predictive value for any future anxiety onset at 4-8 years follow-up, no predictive value of either structural MRI or tb-fMRI was found for this prediction. Of note, structural MRI did show moderate predictive contribution in the diagnosis-specific prediction of future generalized anxiety onset. Contrastingly to the previous smaller-scale literature, neither structural MRI or tb-fMRI showed above-chance level predictive performance for psychotherapeutic response in patients with spider phobia, with the exception of BOLD signal variance which showed a modest predictive contribution.

The field of mental health machine-learning prediction is evolving at a fast pace, with the increasing availability of multisite consortia datasets and a progressive shift in favour of multimodal data usage. Various other (epi)genetic, physiological, environmental and behavioural markers of anxiety, many of which can be passively and nonexpensively collected, also have potential to complement MRI data and bring incremental prediction accuracy to help inform anxiety disorder prevention, early detection, and treatment stratification.

However, the present findings also emphasize the current challenges of machine-learning methodology in mental health research, which are closely tied with sample size, diversity, clinical heterogeneity and generalisability considerations. After almost a decade of smaller-scale proof-of-concept prediction studies, the field is moving towards more robust and longitudinal predictions based on larger samples, with a noticeable decrease in predictive performance that is shedding light on the risk of bias in earlier literature. However, even moderate prediction accuracies could inform clinical decision-making, especially for predictions of prospective outcomes that chiefly depend on future life events. In comparison with other medical disciplines such as radiology, machine-learning approaches in mental health still struggle to produce results with clinical utility, which can be attributable to the twofold challenge of parsing out relevant individual-level biological markers for complex and heterogeneous clinical phenotypes. The field nonetheless holds promise and is maturing, now with clearly delineated guidelines for good scientific practice that should leave future studies less vulnerable to overoptimistic estimations of prediction performance (Radua and Koutsouleris, 2023).

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Appendix: MRI and fMRI

This appendix describes the principles of MRI and some of its most commonly used modalities in mental health research.

General principles

MRI is based on the magnetic properties of atomic nuclei, most often hydrogen nuclei, which consist of a single proton and are very abundant in water molecules (Rajan, 1998; van Geuns *et al.*, 1999). In the absence of an external magnetic field, hydrogen nuclei spin around their own axis and are oriented randomly in space. As such, under normal circumstances, the nuclear magnetic moments arising from the nuclear spins usually cancel each other out, resulting in a net zero magnetization vector.

When the nuclei are exposed to a constant and non-negligible external magnetic field B_0 (e.g. from a strong magnet), some spins align themselves either in a parallel or antiparallel fashion with respect to B_0 (Figure A1). The antiparallel state is the lower energy state and thus the preferred alignment, resulting in a net longitudinal magnetization vector M_z aligned to B_0 . Nuclear spins are not individually aligned to B_0 , but precess around its direction at the frequency of Larmor, each with their individual phase of precession, while still spinning around their own axis. In this equilibrium state, M_z is static and its signal is not measurable. Higher strength of the magnetic field (7 Tesla > 3 Tesla > 1.5 Tesla) will lead to a higher proportion of spins aligning themselves around B_0 .

The excitation phase consists in the alteration of the direction of the spin alignment by means of energy addition. Very short radiofrequency (RF) pulses of the Larmor frequency (also called resonance frequency) are applied using a second external magnetic field B_1 , orthogonal to B_0 and 10^6 times weaker. Protons thus absorb the energy and jump to the antiparallel state, spins precess in phase, and their alignment will flip from a positive z-axis to a transverse xy plane, resulting in a net transverse magnetization vector, M_{xy} .

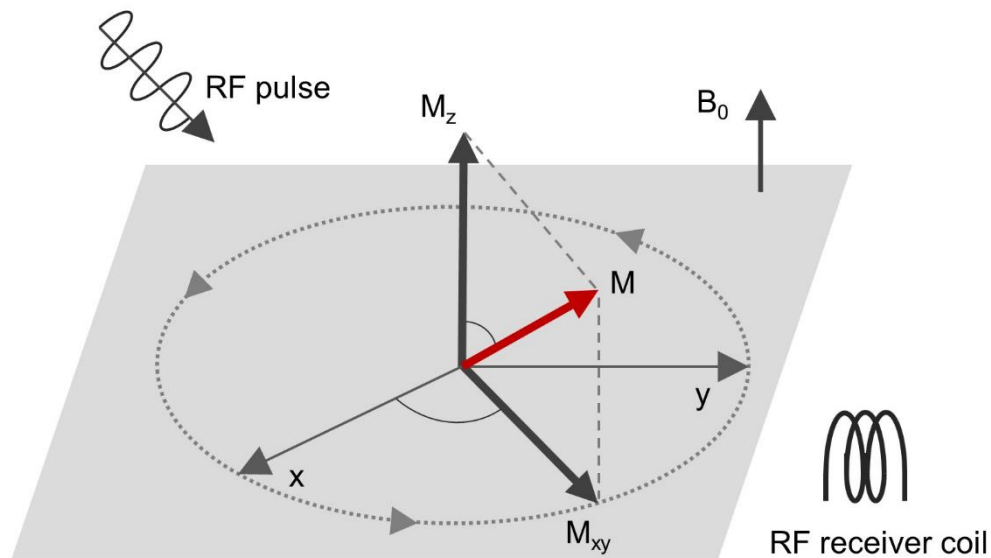


Figure A1: principle of the excitation and relaxation phases in magnetic resonance imaging. M_z : longitudinal magnetization vector; M_{xy} : transverse magnetization vector; B_0 : external magnetic field; RF: radiofrequency.

When the energy pulse from B_1 is interrupted, protons release the absorbed energy, spins will seek to restore equilibrium and will progressively take back their initial alignment. This is the relaxation process, and can be measured both in M_z and in M_{xy} via the receiver coil in the MRI scanner. A directional magnetic gradient is added along the main magnetic field, to enable a slice-specific excitation of spins through the body (3-8 mm slices) and thus obtain the spatial localisation of the signal.

The longitudinal relaxation (i.e. the process of realignment to B_0) is measured on the z-axis. The time it takes for M_z to recover 63% of its initial equilibrium value is named T1, the relaxation time. Additionally, following the RF pulse interruption, the spins progressively dephase due to global and local magnetic inhomogeneities and spin-spin interactions. This is the transverse relaxation process, and T2 is the time it takes for M_{xy} to decay to 37% of its initial value. Both T1 and T2 are tissue-dependent.

As such, parameters of an MRI scanning sequence can be calibrated in order to better capture tissues of interest. Those parameters include echo time (TE, defined as the time between the application of the RF pulse and the peak of the signal induced in the RF coil), and repetition time (TR, defined as time the from the application of the RF pulse to the application of the next pulse).

Brain structural MRI

Structural MRI sequences use short TEs and TRs to produce mostly T1-weighted images of brain tissue with quasi-millimetric resolution (Iorio-Morin *et al.*, 2022). Gray and white matter are distinguishable from one another, although the quality of the contrast depends from the MRI acquisition sequence parameters and from the MRI scanner. Specific structural parameters such as gray and white matter volumes, cortical thickness and cortical surface area can be extracted in post-processing.

Functional MRI

Functional MRI indirectly assesses cerebral activity through the proxy of the local haemodynamic response occurring while participants are completing a task (task-based fMRI, or tb-fMRI) or resting (resting-state fMRI, or rs-fMRI) (Iorio-Morin *et al.*, 2022). The haemodynamic response, also called Blood-Oxygen-Level-Dependent (BOLD) response, corresponds to an increase in cerebral blood flow and oxygen consumption as a result of increased local neural activity. The increase in blood flow surpasses the increase in oxygen consumption, thus increasing the ratio of oxygenated haemoglobin relative to deoxygenated haemoglobin in the active brain region. These haemoglobin variants have different magnetic properties, with deoxyhaemoglobin being paramagnetic and the nuclear spins of its atoms aligning themselves around the main magnetic field. The BOLD signal shows local changes in deoxyhaemoglobin concentration and can be measured using specific MRI T2*-weighted scanning sequences.

In a real MR setting, the transverse magnetization M_{xy} decays much faster than would be predicted by molecular mechanisms. This is mainly due to inhomogeneities in B_0 that can be attributed to the magnet itself or to susceptibility-induced field distortions produced by the tissue in the field (such as the BOLD response). T2* is the effective T2, and is always inferior

or equal to T2. T2*-weighted fMRI sequences use relatively long TEs, to accentuate local magnetic distortions (Chavhan *et al.*, 2009).

Specific functional metrics can be extracted from the fMRI BOLD signal in post-processing, such as task-based functional activation (task-specific changes in BOLD signal), Functional Connectivity (FC; temporal correlation of the BOLD signal timeseries between spatially distributed areas of the brain), Regional Homogeneity (ReHo; local temporal correlation of the BOLD signal timeseries between a voxel and its nearest neighbours during resting state), or Amplitude of Low Frequency Fluctuations (ALFF; fluctuations of spontaneous BOLD signal intensity within the 0.01 and 0.1 Hz during resting-state) (Lv *et al.*, 2018).

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Appendix: Synthèse de la thèse

Les troubles anxieux sont très répandus et représentent une lourde charge de morbidité, ainsi que des coûts sociétaux et économiques importants. La survenue de l'anxiété clinique est particulièrement fréquente à l'adolescence, laquelle pourrait être une fenêtre d'intervention pertinente pour des stratégies de prévention ou de stratification des traitements. De nombreux facteurs psychologiques et environnementaux ont été associés à l'anxiété pathologique, et l'émergence de l'IRM a permis l'exploration des corrélats cérébraux de l'anxiété. Cependant, malgré une abondante littérature sur la neuro-imagerie à l'échelle du groupe et des corrélats de l'anxiété pathologique bien identifiés, des marqueurs cérébraux robustes de vulnérabilité ou de réponse thérapeutique peinent à émerger. En outre, ces dernières années, les approches de prédiction à l'échelle individuelle utilisant l'apprentissage automatique sont devenues de plus en plus populaires dans la recherche en santé mentale, et certains résultats prometteurs de prédiction prospective ont été rapportés dans des études de neuro-imagerie sur l'anxiété à petite échelle (généralement avec $N_{\text{total}} < 60$ participants). Ces résultats n'ont pas encore été reproduits dans des échantillons plus importants et multisites.

Le présent projet de doctorat impliquait l'utilisation de l'apprentissage automatique supervisé pour prédire prospectivement le développement de troubles anxieux chez les adolescents en utilisant un jeu de données longitudinales de la population générale, IMAGEN, ainsi que pour prédire la réponse au traitement psychothérapeutique chez les patients phobiques en utilisant le jeu de données SPIDER-VR.

Avec les données IMAGEN, des analyses d'apprentissage automatique ont d'abord été réalisées à partir de questionnaires et de données neuroanatomiques d'adolescents non anxieux âgés de 14 ans, afin de prédire la survenue d'un futur trouble anxieux 4 à 8 ans plus tard ($N = 156$) par rapport à un statut de contrôle sain ($N = 424$). Les données neuroanatomiques utilisées étaient les volumes de matière grise, extraits pour un ensemble de régions cérébrales d'intérêt traditionnellement impliquées dans l'anxiété. Cette étude a souligné le potentiel prédictif des données sociodémographiques et issues de questionnaires pour la prédiction de futurs troubles anxieux regroupés, et celui des volumes de matière grise, en particulier des régions du striatum, pour la prédiction d'un futur trouble anxieux généralisé.

La prédiction de futurs troubles anxieux chez les adolescents de 14 ans d'IMAGEN a aussi été explorée en extrayant des mesures d'IRM fonctionnelle ($N = 159$ futurs anxieux, $N = 428$

contrôles sains). Ces mesures fonctionnelles ont été extraites d'une tâche de traitement émotionnel des visages. Toutefois, aucune mesure fonctionnelle n'a produit de performance prédictive supérieure au niveau de chance.

Avec les données SPIDER-VR, des analyses d'apprentissage automatique ont été menées pour prédire la réponse des patients phobiques des araignées (N = 190) à une session de thérapie d'exposition en réalité virtuelle, en utilisant des données issues de questionnaires, des données d'IRM structurelle et diverses mesures d'IRM fonctionnelle extraites d'une tâche de provocation des symptômes. Une méthode d'apprentissage automatique ensembliste a également été utilisée pour examiner séparément la contribution prédictive de chaque modalité de données. Contrairement aux attentes, l'étude n'a pas confirmé le potentiel prédictif des données sociodémographiques et de questionnaires, ni des données de neuro-imagerie, à l'exception de la variance du signal BOLD qui a produit une performance prédictive modérée.

Dans l'ensemble, ce travail de doctorat remet en question les résultats optimistes d'études antérieures menées avec de plus petits échantillons, sur la prédiction de l'anxiété par apprentissage automatique basé sur la neuro-imagerie. Nos résultats, ainsi que d'autres travaux récents, soulignent le risque de surestimation de la performance prédictive dans ces précédentes études. Néanmoins, nos résultats corroborent le fait que des questionnaires faciles à administrer présentent une performance prédictive prometteuse pour la prédiction de l'apparition de l'anxiété et que l'IRM structurelle puisse apporter une valeur prédictive supplémentaire.

La littérature récente a souligné que l'utilisation de multiples modalités IRM pouvait améliorer la performance pour des prédictions relatives à la santé mentale. Plusieurs autres biomarqueurs avec le potentiel d'améliorer la précision des prédictions relatives à l'anxiété sont également apparus dans la littérature ces dernières années. Ils comprennent, par exemple, des modalités de neuroimagerie autres que l'IRM, la génétique et l'épigénétique, des variables physiologiques mesurant le mouvement ou le sommeil, ou encore celles mesurant l'usage des smartphones. De façon générale, d'autres recherches multimodales utilisant des jeux de données à grande échelle ainsi qu'une méthodologie rigoureuse d'apprentissage automatique sont nécessaires pour atteindre l'utilité clinique dans les prédictions relatives à l'anxiété.