The transdiagnostic value of self-referent memory bias in psychopathology

Fleur Duyser

DONDERS SERIES

RADBOUD UNIVERSITY PRESS

Radboud Dissertation Series

The transdiagnostic value of self-referent memory bias in psychopathology

Fleur Duyser

The transdiagnostic value of self-referent memory bias in psychopathology
Fleur Duyser

Radboud Dissertation Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Proefschrift AIO | Guntra Laivacuma
Printing: DPN Rikken/Pumbo

ISBN: 9789465150963
DOI: 10.54195/9789465150963
Free download at: https://doi.org/10.54195/9789465150963

RADBOUD
UNIVERSITY
PRESS

The transdiagnostic value of self-referent memory bias in psychopathology

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 25 juni 2025
om 14:30 uur precies

door

Fleur Anne-Wil Duyser

Promotoren:
Prof. dr. I. Tendolkar
Dr. J.N. Vrijsen

Copromotoren:
Dr. P.F.P. van Eijndhoven
Dr. R.M. Collard

Manuscriptcommissie:
Prof. dr. J.B. Prins
Prof. dr. J.R. Homberg
Dr. J. Everaert (Tilburg University)

Table of contents

1

Introduction

Thinking outside the box: alternative classification systems for mental disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2022) and the International Classification of Diseases (ICD-11; World Health Organization, 2021) are the two main classification and diagnostic systems for mental disorders. These handbooks contain descriptions, symptoms, criteria, and other relevant information for mental disorders like depression, anxiety disorders, substance use disorders, autism spectrum disorder, and hundreds more. Before World War II, the ICD only covered physical illnesses, but when its sixth edition was released in 1948 it also included a section on mental disorders for the first time. Soon after, the first edition of the DSM (DSM-I) was published, which even exclusively focused on mental disorders. Throughout the years, both systems have been extensively revised, updated, and expanded to match new insights and developments. While they offer invaluable guidance and a common language to mental health professionals and researchers around the world, there are also relevant criticisms and issues. The DSM is not based on the underlying aetiology of disorders, but on the descriptions of their symptoms. A main concern is that the artificial boundaries between disorders and between 'disordered' and 'non-disordered' are often not as clear as the current classification systems imply. Similar clinical presentations can have different underlying mechanisms and causes and at the same time, disorders that seem clinically different might have the same underlying biological, cognitive, and/or environmental factors. This could explain why many disorder categories have a wide range of possible treatments and why some treatments are effective for disorders other than their intended target. In addition, people often have symptoms that cut across multiple different categories and multimorbidity (the co-occurrence of multiple mental disorders) is highly prevalent. So, there seems to be a misalignment between the descriptive disorder categories and their possibly shared underlying mechanisms and vulnerabilities. This results in difficulties with diagnosing, suboptimal treatment effectiveness, and hinders the successful implementation of research findings into clinical practice.

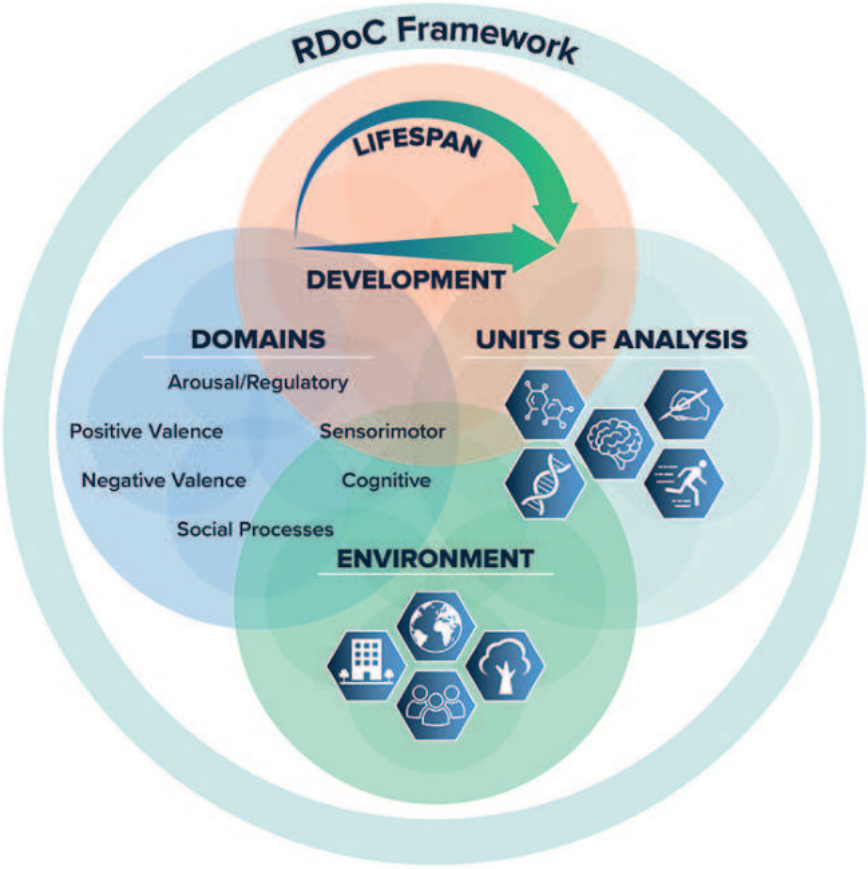

Figure 1. A conceptual overview of the RDoC framework (US National Institute of Mental Health).

In response, alternative approaches to characterising psychopathology have emerged that address these limitations of the traditional classification systems. An important initiative is the US National Institute of Mental Health's Research Domain Criteria project (RDoC; Insel *et al.*, 2010). RDoc adopts a 'thinking outside the box' dimensional approach that aims to uncover the fundamental biological, cognitive, and emotional mechanisms that contribute to psychopathology across different units of analysis and domains (**Figure 1**). The intention is not to serve as a diagnostic guide or to replace the current classification systems. Rather, the aim is to identify shared mechanisms and biomarkers and to understand the core processes that occur across different disorder categories. This understanding hopefully eventually provides systems like the DSM and ICD with transdiagnostic targets for personalised, more effective interventions.

The processing of negative, emotional information is an important part of the negative valence domain in the RDoC framework. Many mental disorders are characterised by negatively biased information processing related to attention, interpretation, and memory. For example, anxiety disorders and anxiety vulnerability have long been associated with an attentional bias for threatening stimuli (Mathews & MacLeod, 2005; Koster *et al.*, 2006; MacLeod *et al.*, 2019). And negative interpretation bias, where ambiguous social events are interpreted negatively and even small negative social events are easily catastrophised, is considered a key maintenance factor in social anxiety disorder (Chen *et al.*, 2020). In depression, negative events are often remembered better and more frequently than neutral or positive events. Depressed individuals will likely remember a critical comment from their supervisor that played into their negative self-image, but easily forget a compliment from a colleague. This negative memory bias is the focus of this thesis.

What is negative self-referent memory bias?

Negative self-referent memory bias refers to the better and more frequent recall of negative information that is personally relevant compared to other information (Gotlib & Joormann, 2010). While non-depressed individuals are usually biased towards positive information, negative self-referent memory bias is a well-known cognitive symptom of depression (Bradley & Mathews, 1983; LeMoult & Gotlib, 2019). In addition to being a strong characteristic of depression, it is also considered a vulnerability or risk factor for its development and a contributor to the maintenance and recurrent of depression symptoms (Johnson *et al.*, 2007; LeMoult *et al.*, 2016), existing beyond current depressive episodes (Joormann & Arditte, 2015; Everaert *et al.*, 2022). This is explained by the cognitive model of depression in **Figure 2** (Beck, 1974; Beck 1987; Beck & Haigh, 2014; Beck & Bredemeier, 2016).

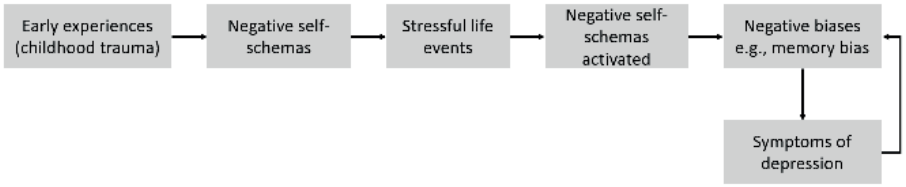

Figure 2. A schematic overview of Beck's cognitive model of depression.

To illustrate this model, let's imagine someone who experienced emotional abuse in their childhood. As a result, they might develop dysfunctional beliefs about

themselves ("I am worthless"), the environment ("nobody loves me"), and the future ("I will never achieve anything") which are stored in negative self-schemas. These negative self-schemas form a latent characteristic and cognitive vulnerability and can be activated under stressful conditions later in life, such as the end of a relationship or a work conflict, resulting in schema-congruent processing in the attention, interpretation, and especially memory (Marchetti *et al.*, 2018) domains. This means that their attention is predominantly focused on negative information, ambiguous events are interpreted negatively, and negative situations are remembered better and more often, especially when they match their negative beliefs and previous experiences. All this can contribute to a depressed mood.

Biased information processing in the cognitive domain of attention has been found in different mental disorders like substance use disorders, anxiety disorders, and eating disorders (Mathews & MacLeod, 2005; Koster *et al.*, 2006; MacLeod *et al.*, 2019), while self-referent memory bias has predominantly been associated with depression. However, there is emerging evidence that it might actually play a role in a broader range of mental disorders. For example, a better recall for negative self-referent information has been found in highly socially anxious individuals (Kalengaza & Jouhaud, 2018), in adolescents with disruptive behaviour disorders (Alloy *et al.*, 2012), and has been associated with the presence of psychiatric multimorbidity and the number of diagnoses (Vrijsen *et al.*, 2018a). In healthy individuals, a stronger negative self-referent memory bias has been related to stronger ADHD symptom severity while differences in negative depressotypic state were controlled for (Vrijsen *et al.*, 2017). Unfortunately, research findings can be difficult to compare due to differences in methodologies and choice of outcome measures.

Measuring (self-referent) memory bias

(Self-referent) memory bias is most commonly assessed in research with a self-referent encoding task (SRET; Derry & Kuiper, 1981; Dobson & Shaw, 1987). There are variations, but they consist of self-referent encoding followed by free recall. During the self-referent encoding phase, individuals have to indicate for positive and negative words such as 'loving' and 'worthless' whether or how well they describe them, this is also referred to as the 'endorsement phase'. When a five-point scale is used, words rated as 4 or 5 are typically considered endorsed as self-referent. Then, after a brief distracting task usually consisting of puzzles, participants are asked to freely recall as many of the words that were presented during the encoding phase within a time limit, which is also called the 'recall phase' (**Figure 3**).

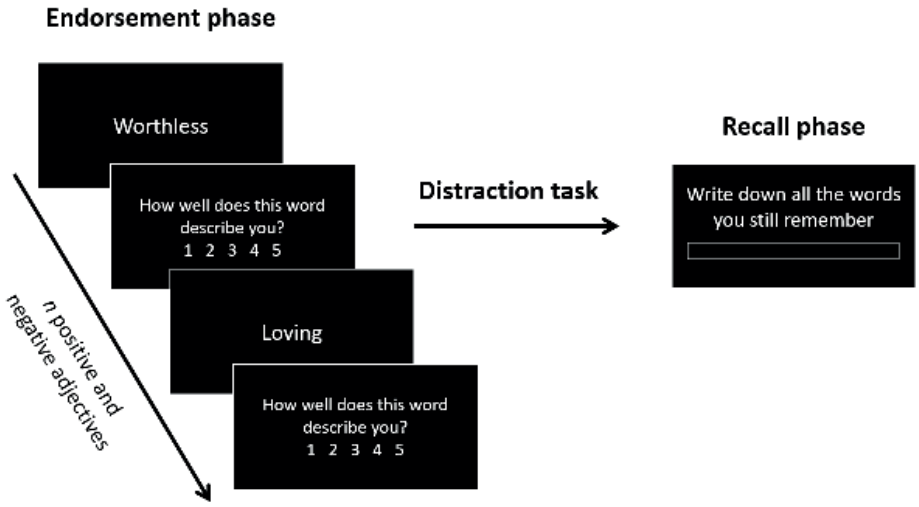

Figure 3. Overview of the Self-Referent Encoding Task (SRET) used in this thesis.

The SRET is a relatively short and simple task, but a large number of possible outcomes can be calculated. While this shows the task's flexibility, the choice for a certain outcome in studies seems arbitrary, since there are no standard or recommendations, which limits comparability. A frequently used outcome is the proportion of negative self-referent recalled words (Bradley & Mathews, 1983; Gotlib *et al.*, 2004), i.e., the number of negative words that was endorsed as self-referent and subsequently recalled divided by the total number of self-referent recalled words. When using the example below, the negative self-referent memory bias score is ¾ or 0.75.

Example outcome from the self-referent encoding task

Total number of words endorsed as self-referent during the endorsement phase: 8
- Of which positive: 3
- Of which negative: 5

Total number of words recalled during the recall phase: 6
- Of which positive: 2
- Of which negative: 4

Number of words recalled that were also endorsed as self-referent: 4
- Of which positive: 1
- Of which negative: 3

The number of negative words that was endorsed as self-referent and subsequently recalled can also be divided by the total number of endorsed words, resulting in a score of ⅜ or 0.38, or divided by the total number of recalled words, giving a score of ⅗ or 0.50 (Goldstein *et al.*, 2015; Allison *et al.*, 2021). In addition, only the number or proportion of negative words endorsed as self-referent or only the number or proportion of negative recalled words are used to assess negative self-referent processing (Dozois & Dobson, 2001; Moulds *et al.*, 2007; Romero *et al.*, 2014) or negative memory (Hakamata *et al.*, 2022). Using the same example above, this would result in scores of ⅝ or 0.63 and ⅘ or 0.67, respectively. Despite these differences in outcomes, research findings are generally consistent: depressed individuals have a higher negative (self-referent) memory bias than non-depressed individuals.

Recently, computational modelling has allowed researchers to get even more information out of the SRET. The reaction times (RTs) from the endorsement phase, i.e., when individuals indicate with button presses whether or how well words describe them, can provide information about the cognitive mechanisms involved in attributing positive and negative information to oneself. In the past, the faster endorsement of negative words as self-referent was already proposed as a characteristic of depression (McDonald & Kuiper, 1985), but the findings have been mostly inconsistent (Bradley & Mathews, 1983; Dozois & Dobson, 2001; Gotlib *et al.*, 2004). However, the application of the drift diffusion model (DDM; Ratcliff & Rouder, 1998) on SRET data has gained popularity. The DDM uses the responses from the endorsement phase, the RTs, and their distribution to offer a deeper understanding of the cognitive process underlying schema-(in)congruent self-referent processing and decision-making. The drift rate is one of the possible parameters and reflects the ease at which the decision was made to endorse positive or negative words as self-referent. It has therefore been proposed as a good proxy of self-schema activation (Disner *et al.*, 2017; Dainer-Best *et al.*, 2018a; Allison *et al.*, 2021). In healthy adults with increased levels of depression symptoms, negative drift rate has been associated with stronger depression severity (Disner *et al.*, 2017; Dainer-Best *et al.*, 2018; Cataldo *et al.*, 2023), but evidence from clinical samples is lacking.

Neural correlates of self-referent memory bias

The original cognitive model of depression (Beck, 1974) was eventually updated and expanded with neurobiological evidence focusing on genetic predisposition, amygdala hyperactivity, and a maladaptive stress response (Beck, 2008; Disner *et al.*, 2011). It is well-known that the amygdala plays a crucial role in the enhancement of any highly emotional memories, both positive and negative (e.g., Phelps & LeDoux,

2005). In depression, the amygdala shows a hyperreactive response to negative information and contributes to the encoding of this information (Siegle *et al.*, 2002, Siegle *et al.*, 2007; Surguladze *et al.*, 2005; Hamilton *et al.*, 2012). For example, depressed individuals have higher amygdala reactivity during the encoding of negative information that is later recalled and that this reactivity is associated with depressive symptom severity (Hamilton & Gotlib, 2008). When associating amygdala reactivity and self-referent memory bias specifically, individuals vulnerable for depression relapse show increased amygdala reactivity that is related to a stronger negative self-referent memory bias (Ramel *et al.*, 2007). Even though increased amygdala reactivity in response to negative information is considered a neural marker of depression and negative self-referent memory bias is a well-known cognitive characteristic of depression likely influenced by amygdala modulation, the relationship between the two has never been studied before.

Psychiatric multimorbidity and the importance of naturalistic samples

Psychiatric multimorbidity is very common; around 28% of individuals who are diagnosed with one mental disorder also have another diagnosis and 17% even have two or more diagnoses at the same time (Kessler *et al*, 2005). The available prevalence rates of common comorbidities vary greatly. For example, the prevalence of co-occurring ADHD and ASD ranges between 14% and 78% (Gargaro *et al.*, 2011), for depression and anxiety disorders this is between 40% and 80% (De Graaf *et al.*, 2003), and for ASD and depression this is 53% to 77% (Hofvander *et al.*, 2009; Joshi *et al.*, 2013). As mentioned before, these high multimorbidity rates and overlap in symptoms point towards shared underlying (neuro)biological, cognitive, and emotional mechanisms that require transdiagnostic research to uncover. Such transdiagnostic approaches have increasingly been applied, but samples often still consist of single, clearly delimited disorders. This does not reflect the clinical reality accurately and complicates the implementation of research findings.

Therefore, two naturalistic psychiatric cohorts were used for the research in this thesis. First, the MIND-Set cohort (Van Eijndhoven *et al.*, 2021) from the Department of Psychiatry of the Radboud University Medical Centre. The MIND-Set study aimed to understand the unique and shared mechanisms of neurodevelopmental and stress-related mental disorders across different dimensions derived from the RDoC framework. Adults with diagnosed depression, anxiety disorders, substance use disorders, ADHD, ASD, and their comorbidities as well as other non-psychotic mental disorders and somatic comorbidities completed extensive biological,

neuroimaging, cognitive, and behavioural testing that focused on dysfunction associated with either or both neurodevelopmental and stress-related mental disorders. Second, the MATCH cohort (Koekkoek *et al.*, 2016) from the Social Psychiatry and Mental Health Nursing Research Group of the HAN University of Applied Sciences. The MATCH study aimed to gain insight in long-term mental healthcare service use of individuals with common mental disorders as well as the long-term course of these disorders. In addition, we utilised a cohort of remitted depressed individuals from the Info in Genes study, and two sets of non-disordered controls. Together, these datasets cover a wide range of the psychopathological spectrum and its comorbidities.

The aims of this thesis and an overview of its chapters

Negative self-referent memory bias is a well-known feature of depression that is also considered a contributor to its onset, maintenance, and recurrence. Evidence for its presence in a broader range of (multimorbid) mental disorders suggests that it might reflect a transdiagnostic mechanism of psychopathology. However, research now too often focuses on single, well-delimited disorders rather than the broader spectrum of psychopathology, including multimorbidity, meaning that the transdiagnostic value of self-referent memory bias is still unclear. In this thesis, I therefore investigate self-referent memory bias as a potential transdiagnostic mechanism within the negative valence domain of the RDoC framework, with three main focus points. The first focus is the (transdiagnostic) presence and strength of self-referent memory bias in a range of mental disorders and the association with their symptom severity (**Chapter 2**). The second focus is the relationship between self-referent memory bias and amygdala reactivity, which has a known role in emotional information processing and has been considered a neural correlate of memory bias (**Chapter 3**). The final point of focus is the self-referent memory bias task itself. Specifically its different possible outcome measures and how they differentiate depression status and how they are associated with depressive symptom severity (**Chapter 4**). The overarching goal of this thesis is to gain insights in whether self-referent memory bias can be a novel transdiagnostic cognitive marker and future intervention and prevention target. The final chapter, **Chapter 5**, places the findings from these chapters into a broader context and discusses strengths, limitations, and importantly, the clinical implications of this work. The thesis is concluded with recommendations for future research.

2

Self-referent negative memory bias as a transdiagnostic cognitive marker for depression symptom severity

Duyser, F.A., Van Eijndhoven, P.F., Bergman, M.A., Collard, R.M., Schene, A.H., Tendolkar, I., & Vrijsen, J.N. (2020). Negative memory bias as a transdiagnostic cognitive marker for depression symptom severity. *Journal of Affective Disorders*, 274, 1165 – 1172, doi.org/10.1016/j.jad.2020.05.156

Abstract

Negative memory bias is a strong risk factor for the development and maintenance of depression. Recent evidence also found negative memory bias in other mental disorders. Here, we aim to: 1) assess the presence and strength of negative memory bias in a range of (comorbid) mental disorders, 2) investigate which disorder-specific symptoms are associated with negative memory bias, and 3) test whether negative memory bias might be a transdiagnostic mechanism. We measured negative memory bias in patients with at least one diagnosis of a stress-related disorder (n = 86), a neurodevelopmental disorder (n = 53), or both (n = 68), and 51 controls. Depression, anxiety, attention-deficit/hyperactivity disorder, and autism spectrum disorder symptom severity was assessed using questionnaires. Groups were compared on negative memory bias and the associations between negative memory bias and symptom severity were made using linear regression models. All patient groups showed stronger negative memory bias than the controls. Negative memory bias was individually associated with all symptom severity indices, but when added into a single model, only the association with depressive symptom severity remained. This persisted after controlling for diagnostic group. Negative memory bias thus seems characteristic of a depressotypic processing style and present in different mental disorders. It might play a mechanistic role in the development of (subclinical) co-occurrence between mental disorders.

Introduction

The prevalence of mental disorders is high; approximately 46% of the general population will be affected by a mental disorder at some point during their life (Kessler *et al.*, 2005). Moreover, co-occurrence of different mental disorders is more the rule than the exception: about 28% of psychiatric patients is diagnosed with two or more mental disorders and 17% of patients meet the criteria for three or more diagnoses (Kessler *et al.*, 2005). The most common mental disorders can roughly be categorised into two groups. Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are disorders that develop in early childhood and frequently persist into adulthood and are therefore considered neurodevelopmental disorders (Thapar *et al.*, 2017). Mood, anxiety, and substance use disorders are considered stress-related disorders, because they are all associated with an atypical response to stress (Sharma *et al.*, 2016).

There is high, but not well-defined, comorbidity within and between these categories. For example, studies have shown that the comorbidity between ADHD and ASD ranges between 14-78% (Gargaro *et al.*, 2011), for depression and anxiety disorders this is 40-80% (De Graaf *et al.*, 2003), and for ASD and depression this is 53-77% (Hofvander *et al.*, 2009; Joshi *et al.*, 2013). This suggests that different mental disorders might have common causes (Harkin *et al.*, 2016). Given this high prevalence and comorbidity, as well as the consequential personal and societal burden of mental disorders (Vigo *et al.*, 2016), it is important to identify mechanisms involved in the development and maintenance of different mental disorders.

In this study, we examined negatively biased memory processing as a potential shared underlying mechanism in both stress-related and neurodevelopmental disorders. Negative cognitive biases are defined as the involuntary, preferential processing of negative information and occur in different cognitive domains, such as attention, interpretation, and memory (Gotlib and Joormann, 2010). These negative cognitive biases have most frequently been studied in depressed individuals (Beck and Bredemeier, 2016; Joormann and Stanton, 2016; LeMoult and Gotlib, 2019; Miskowaik and Carvalho, 2014) and have been associated with greater depressive symptom severity and increased risk of relapse (Johnson *et al.*, 2007). Beck's original cognitive model of depression explains the link between negative cognitive biases and depression (Beck, 1974; Beck, 2008). According to this model, adverse experiences in childhood lead to the development of dysfunctional cognitive schemas, which form the core of cognitive vulnerability. This cognitive

vulnerability is a latent characteristic that can be activated by stressful events and contributes to the development of mental disorders.

In depression, the most stable type of negative cognitive bias is memory bias (Gotlib & Krasnoperova, 1998; Gupta and Kar, 2012; Marchetti *et al.*, 2018; Matt *et al.*, 1992; Watkins *et al.*, 1996), meaning that negative information is recalled better and more frequently than neutral or positive information (Gotlib and Joormann, 2010). This is especially true for self-relevant information such as self-descriptive adjectives (Benau *et al.*, 2019; Del Valle and Mateos, 2018; Matt *et al.*, 1992; Symons and Johnson, 1997). Negative memory bias is considered an important risk factor for the development and maintenance (Hamilton and Gotlib, 2008) as well as the recurrence (LeMoult *et al.*, 2016) of depression (Bradley *et al.*, 1995; Bradley and Mathews, 1983; Harmer *et al.*, 2009; Matt *et al.*, 1992; Vrijsen *et al.*, 2014).

Although mostly studied in depression, negative memory bias is also present in other mental disorders, such as anxiety disorders (Coles and Heimberg, 2002; Kalenzaga and Jouhaud, 2018), eating disorders (Nikendei *et al.*, 2008), ASD (Henderson *et al.*, 2009; Freeth *et al.*, 2010), and substance use disorder (Wiers *et al.*, 2015), and it has also been related to ADHD symptom severity (Vrijsen *et al.*, 2018a). In addition, Vrijsen and colleagues (2017) found that a stronger negative memory bias is associated with a higher number of current mental disorders. This implicates that negative memory bias can be a transdiagnostic marker and possible mechanism involved in the development of different mental disorders and their comorbidity.

So far, the majority of studies on negative memory bias have focused on single mental disorders, defined according to the classic International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic systems. In order to be able to translate research findings into targeted treatments, it is important to look beyond the traditional classifications and explicitly focus on possible common causes and causes of comorbidity (Cuthbert and Insel, 2013; Insel, 2014; Watkins, 2015).

In order to so do, we require more research in large, naturalistic patient samples. Therefore, we recruited a heterogenic, naturalistic psychiatric patient sample. Comorbidity was allowed and assessed and we did not sample on specific disorders (see Methods). This sample consists of patients with one or more stress-related disorders (mood, anxiety, and substance use disorders) and/or neurodevelopmental disorders (ADHD and ASD), as well as a healthy control group. The three aims of our exploratory study were: 1) to assess the presence and strength of negative

memory bias in different mental disorders, 2) to investigate the associations between different disorder-specific symptom severity indices (depression, anxiety, ADHD, and ASD) and negative memory bias, and 3) to investigate whether negative memory bias is related to disorder-specific symptom severity above and beyond diagnostic classifications and depressive symptoms.

First we examined if negative memory bias was also present in neurodevelopmental disorders. If that would be the case, there would be evidence for its transdiagnostic nature. Patients were divided into three different groups based on their clinical classification: a group of patients with only stress-related disorders, a group of patients with only neurodevelopmental disorders, and a group of patients with both types of disorders. This allowed us to study negative memory bias in comorbid disorders whilst still keeping in line with the current research tradition of categorising disorders based on shared characteristics and underlying (genetic) mechanisms. For the second and third research aims, we examined negative memory bias across the classifications – and hence taking a transdiagnostic approach – by examining the association between bias strength and symptom levels in all patients.

Methods

Participants

This study was part of a naturalistic psychiatric cohort called MIND-Set (Measuring Integrated Novel Dimensions in Neurodevelopmental and Stress-related mental disorders). The aim of the MIND-Set cohort is to gain a better understanding of unique and shared mechanisms in stress-related and neurodevelopmental mental disorders by studying these disorders on different biological, neurocognitive, and behavioural levels using the same methodology. MIND-Set was initiated by the Department of Psychiatry of the Radboud University Medical Centre and the Donders Institute for Brain, Cognition, and Behaviour in Nijmegen, The Netherlands.

All patients at the outpatient clinic of the Department of Psychiatry who were 18 years or older and with a clinical diagnosis of a current mood disorder and/or anxiety disorder and/or substance use disorder and/or ADHD and/or ASD were eligible to participate. Patients with a current psychosis, sensorimotor handicaps, inadequate command of the Dutch language, a full-scale IQ estimate of below 70, and/or mental incompetence to sign the informed consent form were excluded from participation.

To answer the research aims as formulated in the introduction, patients ($N = 207$) were divided into three groups based on their diagnoses: 1) a stress-related disorders group (SR group, $n = 86$), only consisting of patients with one or more mood and/or anxiety and/or substance use disorders, 2) a neurodevelopmental disorders group (ND group, $n = 53$), only consisting of patients with ADHD and/or ASD, and 3) a comorbid group (CM group, $n = 68$), consisting of patients with at least one stress-related and at least one neurodevelopmental disorder. See **Table 1** for an overview of the (comorbid) diagnoses in each group.

In addition, a control group ($n = 51$) was included, consisting of individuals without a current or past mental disorder. The control participants were matched to the patients in terms of gender identification, age, and educational level. The absence of mental disorders was assessed through a telephonic screening interview, using the same diagnostic instruments as for the patients (see below). The total patient group and control group did not differ significantly in gender identification ($\chi^2(1) = 2.74$, $p = .098$), age ($t(256) = 0.67$, $p = .504$), or education level ($\chi^2(3) = 2.71$, $p = .438$). The SR, ND, CM, and control group also did not differ significantly in gender identification ($\chi^2(3) = 2.82$, $p = .420$) or education level ($\chi^2(9) = 11.37$, $p = .251$), but they did differ significantly in age ($F(3) = 3.20$, $p = .024$). Control participants received a monetary compensation of €66 for participation. Written informed consent was obtained from all participants. The MIND-Set study was approved by the local ethical committee ('Commissie Mensgebonden Onderzoek Arnhem-Nijmegen') in July 2017.

Diagnostic procedure

Patients were diagnosed by trained clinicians. Mood and anxiety disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First & Gibbon, 2004). Substance use disorder was diagnosed according to the DSM-IV with the Measurements in the Additions for Triage and Evaluation and Criminality (MATE-Crimi, subsections 1, 3, 4, 9 and Q1; Schippers and Broekman, 2010). ADHD was diagnosed according to the DSM-IV with the Diagnostic Interview for Adult ADHD (DIVA; Kooij, 2010), and ASD was diagnosed using the Dutch Interview for Diagnosing Autism Spectrum Disorders (in Dutch: 'Nederlands Interview ten behoeve van Diagnostiek Autismespectrumstoornissen'; NIDA; Vuijk, 2016) according to the DSM-V.

Disorder-specific symptoms

All patients and control participants filled out an online self-report questionnaire that has previously been proven to be useful to assess demographics (Stronks *et al.*,

2013) as well as several other self-report questionnaires to assess different disorder-related symptoms. Depressive symptom severity was assessed using the 30-item Inventory of Depressive Symptomatology – Self Rating questionnaire (IDS-SR; Rush *et al.*, 1996), which had good internal consistency in our sample: Cronbach's α = .87. The 16-item Anxiety Sensitivity Index questionnaire (ASI; Rodriguez *et al.*, 2004) was used as a measure for anxiety sensitivity. The ASI has adequate psychometric properties to assess an individual's concerns about the negative consequences associated with anxiety, even in individuals without an anxiety disorder (Powers *et al.*, 2016). Anxiety sensitivity has been linked to the presence (Allan *et al.*, 2014) and development (Deacon and Abramowitz, 2006) of anxiety disorders as well as to cognitive biases (Clerkin *et al.*, 2015). Furthermore, it is linked to the negative valence domain domain of the RDoC matrix. In our sample, the ASI had good internal consistency: α = .87. ADHD symptom severity was assessed using the 26-item Conners' Adult ADHD Rating Scale (CAARS; Conners *et al.*, 1999) and ASD symptom severity was measured with the 50-item Autism Spectrum Quotient (AQ-50; Baron-Cohen *et al.*, 2001). They respectively showed good (α = .88) and excellent (α = .90) internal consistency in our sample. Higher scores on the questionnaires indicate more severe symptoms. The total score of each questionnaire was used for the data analyses.

Negative memory bias

The computerised Self-Referent Encoding Task (SRET; Derry and Kuiper, 1981) was used to assess self-referent negative memory bias (Derry and Kuiper, 1981; Dobson and Shaw, 1987). This is an implicit learning task that consists of an encoding phase followed by a recall phase. During the encoding phase, twelve positive and twelve negative possibly self-descriptive adjectives (Dutch translations of the Affective Norms for English Words database; ANEW; Bradley and Lang, 1999) were individually presented on a computer screen in a fixed randomised order. These words were aimed at triggering positive and negative cognitive schemas (Beck, 1987; Young, 1990). An example of a positive word is 'loving' and an example of a negative word is 'useless'. The valence of these words was confirmed by 99 independent volunteers (79% female, *M* age = 29 years, *SD* age = 15.12 years) who rated all words on a scale of 1 (*extremely negative*) to 10 (*extremely positive*). The valence of the positive words (M = 6.02, SD = 0.49) was significantly more positive than the valence of the negative words (M = 2.69, SD = 0.72), $t(98) = -34.57$, $p < .001$).

In the current study, we instructed participants to indicate how well each word described them on a five-point scale ranging from 1 (*not very well*) to 5 (*extremely well*). If a word was scored with a 4 or a 5, it was considered to be endorsed as

self-descriptive. After a two-minute distraction task (Digit Symbol Substitution Task; Royer, 1971), the recall phase started. Participants were asked to type in as many words they remembered from the encoding phase (spelling mistakes were permitted and all responses that did not exactly match the presented words were checked by the experimenter).

The first 112 participants performed the task without a time restriction. To ensure that our version of the task was in line with other studies using the SRET (Gotlib *et al.*, 2004; Gerritsen *et al.*, 2012; Van Oostrom *et al.*, 2012; Vogel *et al.*, 2014; Vrijsen *et al.*, 2017, Vrijsen *et al.*, 2018a) and since we noticed that participants typed in their answers within minutes after the start of the recall phase, we added a time restriction of three minutes to create more uniformity in the procedure. To account for primacy and recency effects, the first and last two words of the encoding phase were excluded from the task results.

In line with a broad range of studies using the SRET (Gerritsen *et al.*, 2012; Gotlib *et al.*, 2004; Van Oostrom *et al.*, 2012; Vogel *et al.*, 2014; Vrijsen *et al.*, 2017, Vrijsen *et al.*, 2018a), a negative memory bias index score was calculated by dividing the number of endorsed and correctly recalled negative words by the total number of endorsed and recalled words. The advantage of calculating the negative memory bias index in this way, is that it controls for differences in overall rates of endorsement (Symons and Johnson, 1997).

Statistical analyses

An ANCOVA was used to test for differences in mean negative memory bias score between the SR, ND, CM, and control group whilst controlling for gender identification, age, and education level. Partial correlation analyses, controlling for age, gender identification, and education level, were used to look at the correlations between the symptom severity questionnaires. We used linear regression models to examine the associations between the different disorder-related symptom severity indices and negative memory bias. Then, we further explored these relationships by examining the associations between the disorder-specific symptom severity indices and negative memory bias whilst controlling for diagnostic category and depressive symptoms. The partial correlation and all linear regression models were only performed in patients and included gender identification, age, and education level as covariates.

Results

Self-referent negative memory bias across the groups

See **Table 1** for an overview of gender identification, age, and education level per group. The mean number of positive and negative endorsed and recalled words per group are also presented in the table as they were used to calculate the negative memory bias index score.

The four groups (SR, ND, CM, and controls) differed significantly in strength of negative memory bias, $F(6, 238) = 6.70$, $p < .001$, Cohen's $f = .42$. A Tukey post-hoc test revealed that the SR group had the highest mean negative memory bias score, which was significantly higher than the ND group ($p < .01$, Cohen's $d = .54$) and the control group ($p < .001$, $d = 1.23$). Both the CM and ND groups had significantly higher negative memory bias scores than the control group ($p < .001$, $d = .94$ and $p < .05$, $d = .84$, respectively), see **Figure 1**.

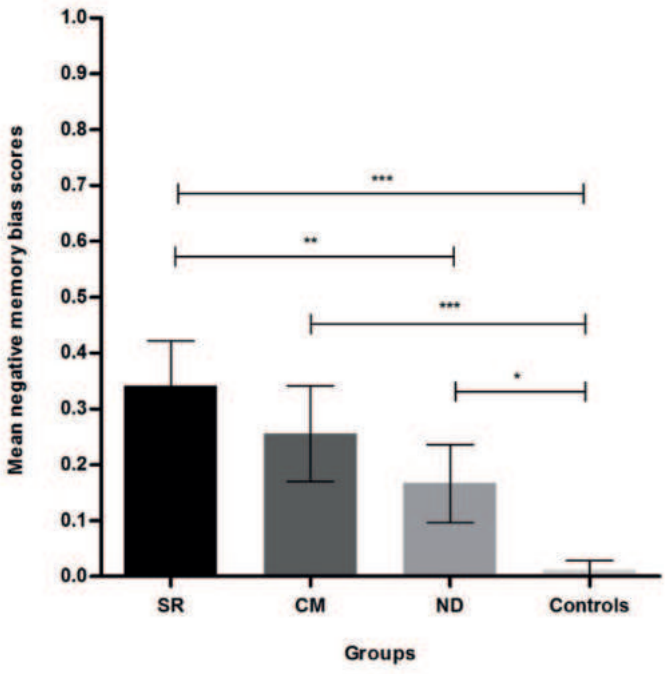

Figure 1. Mean negative memory bias scores for the stress-related (SR), comorbid (CM), neurodevelopmental (ND), and control group. The error bars show the standard error of the mean.
* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 1. Overview of the (comorbid) disorders, gender identification, age, education level, and mean depressive (IDS-SR), anxiety (ASI), ADHD (CAARS), and ASD (AQ-50) symptom severity scores in the stress-related (SR), neurodevelopmental (ND), comorbid (CM), and control group. SUD = substance use disorder, ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder. The mean number of positive and negative endorsed and recalled words that were used to calculate the negative memory bias index score are also presented for each group.

	SR	**ND**	**CM**	**Controls**
Stress-related disorders (n)	86	-	-	-
Mood (n)	43	-	-	-
Anxiety (n)	9	-	-	-
SUD (n)	1	-	-	-
Mood and anxiety (n)	18	-	-	-
Mood and SUD (n)	10	-	-	-
Anxiety and SUD (n)	1	-	-	-
Mood, anxiety, and SUD (n)	4	-	-	-
Neurodevelopmental disorders (n)	-	53	-	-
ADHD (n)	-	27	-	-
ASD (n)	-	17	-	-
ADHD and ASD (n)	-	9	-	-
Stress-related and neurodevelopmental disorders (n)	-	-	68	-
Mood and ADHD (n)	-	-	7	-
Mood and ASD (n)	-	-	3	-
Anxiety and ADHD (n)	-	-	6	-
Anxiety and ASD (n)	-	-	9	-
SUD and ADHD (n)	-	-	6	-
SUD and ASD (n)	-	-	1	-
Mood, anxiety, ADHD (n)	-	-	2	-
Mood, anxiety, and ASD (n)	-	-	8	-
Mood, SUD, and ADHD (n)	-	-	5	-
Anxiety, SUD, and ADHD (n)	-	-	1	-
Mood, anxiety, SUD, and ADHD (n)	-	-	4	-
Mood, SUD, ADHD and ASD (n)	-	-	2	-
Mood, ADHD, and ASD (n)	-	-	5	-
Anxiety, ADHD, and ASD (n)	-	-	2	-
Mood, anxiety, ADHD, and ASD (n)	-	-	4	-
Controls (n)	-	-	-	51
Gender (% female)	44%	45%	43%	57%
Mean age (SD)	45 (14.8)	40 (12.4)	38 (12.5)	40 (15.3)

Table 1. Continued

	SR	ND	CM	Controls
Education level[a]				
None	4%	4%	6%	0%
Low	11%	10%	16%	10%
Medium	32%	44%	48%	44%
High	53%	42%	30%	46%
Mean IDS-SR score (SD)	40 (13.7)	24 (9.5)	35 (10.8)	5 (4.4)
Mean ASI score (SD)	18 (10.3)	13 (8.9)	16 (8.9)	7 (4.9)
Mean CAARS score (SD)	38 (12.9)	39 (12.5)	43 (10.0)	11 (7.7)
Mean AQ-50 score (SD)	118 (18.0)	123 (25.6)	131 (19.3)	94 (11.0)
Mean number positive endorsed words (SD)	4.6 (2.1)	6.1 (2.0)	5.2 (2.0)	8.7 (1.3)
Mean number negative endorsed words (SD)	3.4 (2.6)	1.4 (1.7)	2.7 (2.8)	0.1 (0.4)
Mean number positive recalled words (SD)	2.8 (1.3)	2.8 (1.5)	3.0 (1.6)	3.8 (1.6)
Mean number negative recalled words (SD)	2.5 (1.5)	2.4 (1.6)	2.5 (1.5)	2.6 (1.4)
Mean negative memory bias index score (SD)	0.34 (0.37)	0.17 (0.25)	0.25 (0.35)	0.01 (0.06)

[a] Education level is the highest education someone finished with a diploma and is calculated conform the HELIUS study (Stronks *et al.*, 2013). * $p < .05$.

In order to control for the possible influence of individuals with remitted depression in the CM and ND groups on the mean negative memory bias score (LeMoult *et al.*, 2016), we repeated this analysis after removing the patients with remitted depression from the CM and ND groups. There was still a significant difference in negative memory bias strength between the four groups, $F(6,197) = 6.83$, $p < .001$, Cohen's $f = .46$. A Tukey-post hoc test revealed that the SR group still had the highest mean negative memory bias score, which was significantly higher than the ND ($p < .05$, $d = .69$), and control ($p < .001$, $d = 1.23$) groups. The CM group also had a significantly higher negative memory bias score than the control group ($p < .001$, $d = .96$). The mean negative memory bias score of the ND group was no longer significantly higher than the control group ($p = .439$, $d = .68$), which was most likely due to the smaller group size (ND group was now $n = 24$). However, the effect size was still medium and comparable to that of the SR versus ND pairwise comparison.

Considering the relatively large number of patients and control participants who did not show a negative memory bias at all (a negative memory bias score of 0), we explored if the diagnostic groups (SR $n = 47$, ND $n = 18$, and CM $n = 28$) differ on negative memory bias strength. We performed the same analysis as above again,

but only including the patients with a negative memory index score larger than 0. Interestingly, there was no significant difference between the groups anymore, $F(5,80) = 1.46$, $p = .212$.

Associations between negative memory bias and disorder-specific symptom severity

The mean scores of each symptom severity questionnaire are presented in **Table 1**. The correlations between the symptom severity questionnaires were as follows: IDS-SR and AQ-50, $r = .18$, $p < .05$, IDS-SR and ASI, $r = .50$, $p < .001$, IDS-SR and CAARS, $r = .47$, $p < .001$, ASI and AQ-50, $r = .08$, $p = .252$, ASI and CAARS, $r = .40$, $p < .001$, CAARS and AQ-50, $r = .30$, $p < .001$. To assess the associations between negative memory bias and the disorder-specific symptom severity indices in the patient groups, we performed five separate linear regression analyses. In the first four models, we associated either depressive symptoms (IDS-SR score), anxiety sensitivity (ASI score), ADHD symptoms (CAARS score), or ASD symptoms (AQ-50 score) with the strength of negative memory bias. In the fifth model, we associated negative memory bias with all the symptoms. Here, the order of the symptom severity scores was based on the results from the previous regression analyses.

The results showed that all psychiatric symptom severity indices were significantly associated with negative memory bias (**Table 2**, models 1-4). However, when all symptom severity scores were included in one model, only depressive symptoms were significantly associated with negative memory bias strength (**Table 2**, model 5).

Because only depressive symptom severity was significantly associated with negative memory bias, we looked at the distribution of depressive symptoms across the SR, CM, ND, and control group. We found that mean IDS-SR scores differed significantly between these groups, $F(6,238) = 65.32$, $p < .001$, Cohen's $f = 1.28$. The subsequent Tukey post-hoc test showed indeed that all groups differed significantly from each other, with the SR group showing the highest symptom scores, followed by the CM group, the ND group, and the control group showing the lowest depressive symptom scores (see **Figure 2**). The IDS-SR cut-off scores (Rush *et al.*, 1996) revealed that all patient groups (so even the ND group) had an average score indicating at least moderate depression.

Table 2. Results from the linear regression analyses relating IDS-SR (depressive symptoms), CAARS (ADHD symptoms), AQ-50 (ASD symptoms), and ASI (anxiety sensitivity) scores to negative memory bias. * $p < .05$, ** $p < .01$.

	B	SE B	β	p-value	R^2
Model 1				< .001	.383
Constant	-.216	.112		.055	
IDS-SR	.009	.002	.359	< .001	
Model 2				.001**	.093
Constant	-.249	.133		.062	
CAARS	.007	.002	.262	< .001	
Model 3				.046*	.050
Constant	-.242	.179		.180	
AQ-50	.002	.001	.155	.030*	
Model 4				.051	.048
Constant	-.025	.113		.827	
ASI	.005	.003	.154	.035*	
Model 5				< .001	.166
Constant	-.435	.177		.015*	
IDS-SR	.008	.002	.320	< .001	
CAARS	.003	.002	.118	.146	
AQ-50	.001	.001	.069	.331	
ASI	-.002	.003	-.060	.459	

Note: gender, age, and education level were also added to each model. Education level was a significant ($p < .05$) predictor for negative memory bias in all models.

Associations between negative memory bias and disorder-specific symptom severity, above and beyond diagnostic classification

To further explore the associations between the disorder-specific symptom severity indices and negative memory bias, we first assessed the relationship between negative memory bias and depressive symptoms whilst controlling for diagnostic category (SR, CM, and ND recoded into two dummy variables: CM vs. SR and ND vs. SR), which appeared significant (**Table 3**, model 1). We then performed three linear regression analyses to examine the relationships between the other disorder-specific symptoms and negative memory bias whilst controlling for diagnostic classification. In three additional models, we also added depressive symptom severity.

The results showed that without depressive symptoms added to the regression model, negative memory bias and ADHD symptoms, ASD symptoms, and anxiety

sensitivity were significantly associated above and beyond diagnostic category (**Table 3**, models 2a, 3a, and 4a). However, when depressive symptoms were added, only depressive symptom severity was significantly associated with negative memory bias (**Table 3**, models 2b, 3b, and 4b). Negative memory bias was thus associated with depressive symptoms above and beyond diagnostic category.

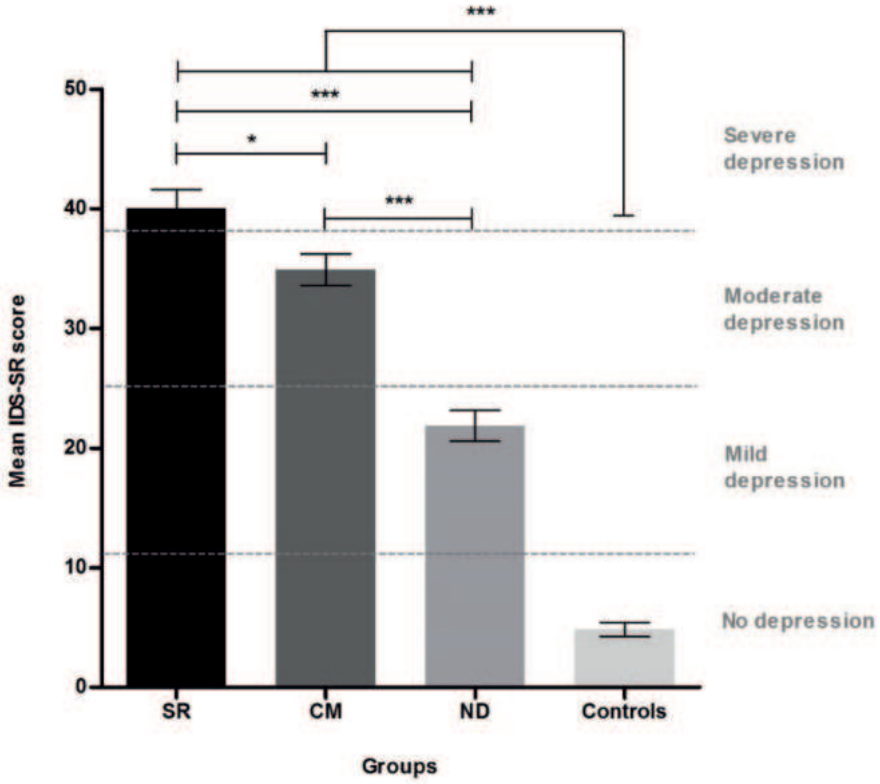

Figure 2. Mean IDS-SR scores (measuring severity of depression symptoms) for the stress-related (SR), the comorbid (CM), neurodevelopmental (ND), and control group, including the IDS-SR cut-off scores (Rush *et al.*, 1996). The error bars show the standard error of the mean. * $p < .05$, *** $p < .001$.

Table 3. Results from the linear regression analyses that examined the associations between IDS-SR (depressive symptom severity), CAARS (ADHD symptom severity), AQ-50 (ASD symptom severity), and ASI (anxiety sensitivity) and negative memory bias whilst controlling for diagnosis clusters (and IDS-SR in models 2a to 5b). * $p < .05$, ** $p < .01$.

	B	SE B	β	p-value	R^2
Model 1 (IDS-SR)				< .001	.355
Constant	40.018	3.816		< .001	
CM vs. SR	-14.684	2.060	-.473	< .001	
ND vs. SR	-4.727	1.933	-.164	.015	
Negative memory bias	10.369	2.385	.263	< .001	
Model 2a (CAARS)				< .001	.354
Constant	38.857	3.994		< .001	
CM vs. SR	2.248	2.156	.081	.298	
ND vs. SR	5.645	2.023	.217	.006**	
Negative memory bias	9.827	2.496	.277	< .001	
Model 2b (CAARS)				< .001	.593
Constant	17.535	4.340		< .001	
CM vs. SR	10.072	2.097	.361	< .001	
ND vs. SR	8.163	1.773	.314	< .001	
Negative memory bias	4.302	2.260	.121	.058	
IDS-SR	.533	.066	.593	< .001	
Model 3a (AQ-50)				.002**	.319
Constant	115.737	7.097		< .001	
CM vs. SR	7.351	3.830	.150	.056	
ND vs. SR	13.914	3.594	.306	< .001	
Negative memory bias	11.428	4.434	.184	.011*	
Model 3b (AQ-50)				< .001	.379
Constant	99.661	8.746		< .001	
CM vs. SR	13.250	4.226	.271	.002	
ND vs. SR	15.813	3.574	.347	< .001	
Negative memory bias	7.262	4.554	.117	.112	
IDS-SR	.402	.133	.255	.003**	
Model 4a (ASI)				.002**	.327
Constant	21.991	3.222		< .001	
CM vs. SR	-4.893	1.739	-.220	.005**	
ND vs. SR	-1.600	1.632	-.077	.328	
Negative memory	3.168	2.013	.112	.117	
Model 4b (ASI)				< .001	.538
Constant	6.712	3.628		.066	
CM vs. SR	.713	1.753	.032	.685	
ND vs. SR	.205	1.482	.010	.890	
Negative memory bias	-.791	1.889	-.028	.676	
IDS-SR	.382	.055	.532	< .001	

Note: gender identification, age, and education level were also added to each model. Education level was only significantly associated with ASI ($p < .01$).

Discussion

By examining negative bias in different mental disorders, we aimed to investigate whether negative memory bias is a potential shared neurocognitive mechanism involved in the development of (comorbidity between) different stress-related and neurodevelopmental disorders. Our first aim was to assess the presence and strength of negative memory bias in different mental disorders. We found that all patient groups showed a negative memory bias that was stronger than in the control group. Our second aim was to investigate the associations between different disorder-specific symptom severity indices and negative memory bias. We showed that while depressive symptoms, anxiety sensitivity, ADHD, and ASD symptoms were all associated with negative memory bias strength, only depressive symptoms showed a unique association with negative memory bias that was not explained by variance in the other symptom clusters. Our third aim was to investigate whether negative memory bias is related to disorder-specific symptom severity above and beyond diagnostic classifications and depressive symptoms. We found that only depressive symptoms were uniquely associated with negative memory bias regardless of the diagnostic group differences. The results thus indicate that negative memory bias is present in different mental disorders, independent of depression classification. Moreover, negative memory bias may be a transdiagnostic marker for depression, also in patients with neurodevelopmental disorders in which depression is often overlooked and difficult to diagnose (Chandrasekhar and Sikich, 2015).

Negative memory bias was present in all disorder groups, which is in line with previous findings showing that negative memory bias might be characteristic of multiple mental disorders (Coles and Heimberg, 2002; Dalgleish & Watts, 1990; Freeth *et al.*, 2010; Henderson *et al.*, 2009; Kalenzaga and Jouhaud, 2018; Nikendei *et al.*, 2008; Vrijsen *et al.*, 2017; Wiers *et al.*, 2015). When only selecting patients with at least some level of negative memory bias (i.e. a negative memory bias score larger than 0), the differences between the disorder groups disappeared. This could indicate that once the positive memory bias is missing, the negative memory bias might be independent of diagnostic classification. However, it is important to note that this was a post-hoc analysis in smaller subgroups, limiting the informativeness of this result.

When we looked at the relationships between negative memory bias and the different disorder-specific symptom severity indices, we found that only depressive symptom severity, as measured with the IDS-SR, was uniquely associated with negative memory bias. This is in line with the findings of Del Valle and Mateos

(2018) who showed that self-referent negative memory bias was present in individuals with subclinical depression independent of primary diagnosis. Our findings are also in line with a recent study by Beevers *et al*. (2019) who studied adults whose symptoms ranged from no symptoms of depression to clinical levels of depression. Using a similar task as we used here, they found that depression symptoms explained a large part (34-45%) of the variance in negative self-referent processing. Interestingly, this was not the case for negative attention bias, confirming the earlier notion that negative memory bias is the negative cognitive bias that is strongest related to depression and depressive symptoms (Marchetti *et al*., 2018). Further research is necessary to find out which specific factors in the IDS-SR are associated with negative memory bias.

On the one hand, our findings confirm the already well-established relationship between negative memory bias and depression (Bradley et al., 1995; Bradley and Mathews, 1983; Harmer et al., 2009; Matt et al., 1992; LeMoult and Gotlib, 2019). On the other hand, we showed that this relationship extends beyond the depression diagnosis border. Our study therefore ties in well with recent initiatives pushing a transdiagnostic or even classification-free approach to psychiatry and mental health. Recent initiatives, such as the National Institute of Mental Health's Research Domain Criteria project (RDoC), aim for a transdiagnostic approach to discover the fundamental underlying mechanisms of psychopathology with the ultimate goal to improve personalised healthcare (Insel, 2014; Cuthbert and Insel, 2013; Watkins, 2015).

The results from our study contribute to this step towards precision psychiatry. As Harmer and colleagues have shown, negative memory bias can be altered as a function of pharmacological treatment and these changes are visible way before subjective depression symptoms show a change (Harmer *et al*., 2003; Harmer *et al*., 2009; Harmer *et al*., 2017). Hence, we suggest that negative memory bias could be used to index depressive symptoms transdiagnostically. Since norm scores are not available for the SRET, its outcome cannot be used for screening. However, negative memory bias may be used as intraindividual screening of the course of an individual's treatment in a more objective way than (self-report) questionnaires can. In addition, non-pharmacological treatments to alter negative memory bias, such as memory bias modification (Hertel and Mathews, 2011; Lang *et al*., 2009; Vrijsen *et al*., 2018b) and neuromodulation of memory processes, might be strong candidates for transdiagnostic treatment and prevention of comorbid depression. Although these are promising possible clinical applications, more research is required.

This study has strengths and limitations. A strength is the large, naturalistic sample, facilitating the generalisation of the findings to the clinical population. Another strength is the use of the SRET to measure negative memory bias, which is frequently used and hence allows us to compare the current findings to other memory bias results. A limitation might be that the stress-related and comorbid disorders groups only included patients with *current* mood and anxiety disorders. This means that patients with remitted depression could be included in any of the three patient groups. Patients with remitted depression and ADHD and/or ASD were hence categorised into the neurodevelopmental disorders group. Given that individuals with remitted depression often still show a negative memory bias (LeMoult *et al.*, 2016), one might consider it a possibility that the patients with remitted depression caused the high negative memory bias scores in patients in the neurodevelopmental disorders group. However, we showed that the effect sizes remained the same after removing the patients with remitted depression from the comorbid and neurodevelopmental disorders groups, meaning that remitted depression most likely did not cause the stronger negative memory bias in this group. Second, due to the cross-sectional study design, we were only able to look at the associations between negative memory bias and disorder-specific symptoms and not at the direction of the effects. To gain more insight in the mechanistic role of negative memory bias in the development of psychiatric problems across mental disorders and the comorbidity between them, a longitudinal study predicting symptom development by negative memory bias over time in a heterogeneous sample is necessary.

In conclusion, negative memory bias appears to be driven by a depressotypic processing style, not only in patients with depression, but also in patients with (comorbid) neurodevelopmental disorders. We therefore propose negative memory bias as a transdiagnostic cognitive marker for (comorbid) depression in mental disorders in general.

3

Amygdala sensitivity for negative information as a neural marker for negative memory bias across psychiatric diagnoses

Duyser, F.A., Vrijsen, J.N., Van Oort, J., Collard, R.M., Schene, A.H., Tendolkar, I., Van Eijndhoven, P.F. (2022). Amygdala sensitivity for negative information as a neural marker for negative memory bias across psychiatric diagnoses. *Psychiatry Research: Neuroimaging*, 323, https://doi.org/10.1016/j.pscychresns.2022.111481

Abstract

Self-referent negative memory bias is a known risk factor for depression, but recent evidence suggests its function as a transdiagnostic cognitive depressotypic marker. The amygdala's sensitivity for negative information is considered a neurobiological depressotypic marker. However, their relationship remains unknown. We transdiagnostically investigated the association between the amygdala's sensitivity, self-referent negative memory bias and its two components: negative endorsement bias and negative recall bias. Patients (n = 125) with (multimorbid) stress-related and neurodevelopmental psychiatric disorders and healthy controls (n = 78) performed an fMRI task to assess the amygdala's sensitivity for negative information and a task outside the scanner for the biases. Linear regression models assessed their associations. The left amygdala's sensitivity to negative information was significantly positively associated with negative recall bias in patients, but not controls. There were no significant associations with self-referent negative memory bias or negative endorsement bias or between the two depressotypic markers. Thus, the left amygdala's sensitivity for negative information may be considered a neural marker of negative memory bias across psychiatric diagnoses. Further research on the interactons with known determinants such as genetic predisposition is required to fully understand the relationship between the amygdala's sensitivity for negative information and these biases.

Introduction

Enhanced memory for negative self-referent information (i.e. self-referent negative memory bias) is one of the main cognitive symptoms of depression (Bradley & Mathews, 1983; LeMoult & Gotlib, 2019) and is considered the result of negative schema-related memory processing. The cognitive model of depression (Beck, 1974; Beck, 2008; Beck & Bredemeier, 2016) states that negative schemas are the result of aversive childhood experiences that form the core of cognitive vulnerability; a latent characteristic that is activated by stressful events resulting in negative cognitive biases in interpretation, attention, and memory, that in turn increase the risk of developing depression. More negative memory bias is not only a symptom of and risk factor for the development of depression, but also contributes to its maintenance and recurrence (LeMoult *et al.*, 2016), while less negative memory bias is associated with lower depressive symptom severity (Johnson *et al.*, 2007). When looking at the neurocognitive evidence, we indeed see that new information can latch onto congruent pre-existing knowledge structures, also called memory schemas, which makes schema-congruent information easier to encode and retrieve (Gilboa & Marlatte, 2017; Fernández & Morris, 2018). In the case of depression, these schemas are predominantly negative, resulting in the preferential encoding and recall of negative information.

In addition to this cognitive depressotypic marker, several (neuro)biological ones have been identified. The extent to which the amygdala is activated during the processing of negative stimuli is a representation of the amygdala's sensitivity for negative information, which is often found to be higher in individuals with depression (Hamilton *et al.*, 2012; Siegle *et al.*, 2002; Siegle *et al.*, 2007; Surguladze *et al.*, 2005). According to Beck's developmental model of depression (Beck, 2008), increased amygdala sensitivity for negative information, following genetic predisposition, can result in negative cognitive biases. However, the evidence linking these two phenomena is sparse. One fMRI study found that depressed individuals showed more amygdala reactivity during the encoding of subsequently recalled negative, but not neutral or positive stimuli, and that this increased reactivity was associated with more severe depression symptoms (Hamilton & Gotlib, 2008). Another fMRI study showed that increased amygdala reactivity was associated with a higher self-referent negative memory bias in individuals vulnerable for depression relapse, suggesting that an amygdala-modulated arousal system contributes to the deeper encoding of negative self-referential information and subsequent recall in those who are vulnerable for depression (Ramel *et al.*, 2007).

Although these studies show that the amygdala plays a role in self-referent negative memory bias, the relationship between the cognitive depressotypic marker of self-referent negative memory bias on the one hand and the neurobiological marker of the amygdala's sensitivity for negative information on the other hand, as two separate concepts, has never been investigated independently. In other words, how do two depressotypic markers in different domains and at a different time relate to one another?

The self-referent encoding task (SRET; Derry & Kuiper, 1981; Dobson & Shaw, 1987) is widely used to assess self-referent negative memory bias and consists of two components: 1) endorsement, representing self-referential processing and indirectly the activation of aforementioned positive or negative schemas, and 2) recall, representing preferential memory for positive or negative information. Dainer-Best *et al.* (2018a) found that only negative endorsement and not negative recall was associated with depressive symptom severity, thereby suggesting that these two components reflect intrinsically distinct processes, one perhaps more clinically relevant than the other. It is thus important to not only look at the relationship between the amygdala's sensitivity to negative information and the composite self-referent negative memory bias score (as used in i.a. Gotlib *et al.*, 2004), but also examine the relationships with negative endorsement bias and negative recall separately.

Importantly, previous studies have mainly included (formerly) depressed individuals and/or healthy controls, even though there is increasing and compelling evidence for negative cognitive biases in other psychiatric disorders (Coles & Heimberg, 2002; Nikendei *et al.*, 2008; Freeth *et al.*, 2010; Wiers *et al.*, 2015) and it might even contribute to psychiatric multimorbidity (Vrijsen *et al.*, 2017). Previously, we showed that self-referent negative memory bias was present across a large variety of (multimorbid) psychiatric disorders (Duyser *et al.*, 2020). For example, patients with attention-deficit/hyperactivity disorder (ADHD) and/or autism spectrum disorder (ASD) and no mood or anxiety disorder showed more self-referent negative memory bias than healthy control participants, and depressive symptom severity was transdiagnostically linked to self-referent negative memory bias. It is therefore important to also investigate the relationship between the depressotypic cognitive marker of self-referent negative memory bias and the neurobiological marker of the amygdala's sensitivity to negative information transdiagnostically.

To summarise, the association between two independently assessed depressotypic markers – the amygdala's sensitivity for negative information and self-referent

negative memory bias – has never actually been investigated. Because self-referent negative memory bias appears to reflect a transdiagnostic depressotypic process (Duyser *et al.*, 2020), we aimed to investigate this association in a large sample of (multimorbid) stress-related and neurodevelopmental psychiatric disorders. Our second, more exploratory aim was to investigate this association for the two components of self-referent negative memory bias, negative endorsement bias and negative recall bias, separately.

Methods

Participants

This study was part of the MIND-Set cohort (Measuring Integrated Novel Dimensions in neurodevelopmental and stress-related psychiatric disorders; Van Eijndhoven *et al.*, 2021) that was initiated by the Department of Psychiatry of the Radboud university medical centre and the Donders Institute for Brain, Cognition, and Behaviour in Nijmegen, The Netherlands. MIND-Set was a cross-sectional study aiming to determine shared and specific mechanisms of neurodevelopmental and stress-related psychiatric disorders at different observational levels, such as physiology, neuroimaging, behaviour, self-report, and neuropsychology, as determined by the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013). The cohort consists of adults with a current mood disorder and/or anxiety disorder and/or substance use disorder and/or ADHD and/or ASD. Patients were diagnosed by trained clinicians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First & Gibbon, 2004), the Measurements in the Additions for Triage and Evaluation and Criminality (MATE-Crimi for DSM-IV; Schippers *et al.*, 2011), the Diagnostic Interview for Adult ADHD (DIVA for DSM-IV; Kooij, 2010), and the Dutch Interview for Diagnosing Autism Spectrum Disorders (NIDA for DSM-V; Vuijk, 2016), respectively. Exclusion criteria were a current psychosis, sensorimotor handicaps, inadequate command of the Dutch language, a full-scale IQ estimate of below 70, not being able to give informed consent, the presence of non-removable ferromagnetic objects in the upper body, previous brain surgery, epilepsy, claustrophobia, and (suspected) pregnancy.

Data of 125 patients were available for the current study. An overview of their diagnoses and multimorbidity frequencies are presented in **Figure 1**. We also included a control group of 78 volunteers without a current or past psychiatric disorder. The control group differed significantly from the patient group in gender, $\chi^2(1) = 4.917$, $p = .027$, age, $t(200) = -2.180$, $p = .031$, and education level, $\chi^2(3) = 9.099$,

p = .028, so they were added as covariates in (supplementary) analyses comparing patients and controls. Informed consent was obtained from all participants and the study was approved by the local medical-ethical committee.

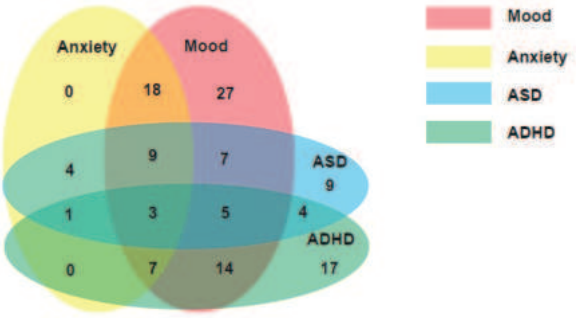

Figure 1. Overview of the psychiatric diagnoses and their multimorbidity in our total patient sample (n = 125). Adapted with permission from Brolsma *et al.* (2021).

Procedure

Patients were diagnosed and subsequently recruited at the outpatient clinic of the Department of Psychiatry of the Radboud university medical centre. Controls were recruited through advertisements and subsequently telephonically screened using the same diagnostic instruments as described above to confirm the absence of any current or past psychiatric disorders. Participants completed two appointments as part of the MIND-Set cohort study: an MRI scanning session that included the task to measure the amygdala's sensitivity for negative information and, on a different day, a neuropsychological assessment that included questionnaires to assess i.a. demographical information and the task to assess self-referent negative memory bias, negative endorsement bias, and negative recall bias.

The amygdala's sensitivity to negative information

Emotional faces processing task

Participants performed an emotional faces processing paradigm that is known to elicit robust amygdala activation in a wide range of samples (Hariri *et al.*, 2002; Geissberger *et al.*, 2020; Peluso *et al.*, 2009; Stein *et al.*, 2007; Tessitore *et al.*, 2005) and represents the amygdala's sensitivity to negative information. The task consisted

of two Faces and three Shapes blocks. During the Faces blocks, triangular trios of angry and fearful faces were presented and participants were asked to indicate which one of the bottom two faces matched the top face in terms of emotional expression. During the Shapes blocks, trios of elliptical shapes, consisting of pixelated faces, were presented and participants were asked to indicate which one of the bottom two shapes matched the top shape in terms of spatial orientation, see **Figure 2**. Each block consisted of six trials and lasted 30 seconds, resulting in a total task length of 150 seconds.

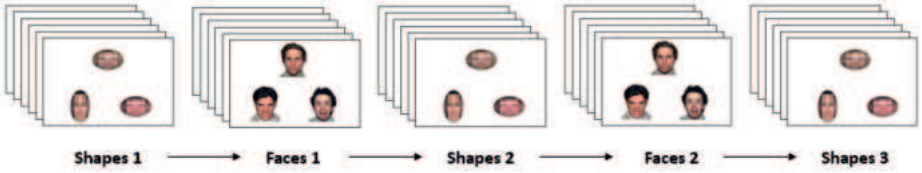

Figure 2. Schematic overview of the emotional faces processing task used to assess amygdala sensitivity for negative information. Each block consisted of six trials and had a duration of 30 seconds.

fMRI acquisition

During the emotional faces processing task, fMRI data were collected using a 3T Siemens Magnetom Prisma system with a 32-channel head coil. T2*-weighted echoplanar images with blood-oxygen-level-dependent contrast were acquired during the emotion processing task (repetition time [TR] = 1000 ms, echo time [TE] = 34 ms, slicing: interleaved ascending, voxel size: 2.0 × 2.0 × 2.0 mm, flip angle: 60°). Anatomical images were acquired using a T1-weighted MP-RAGE sequence (TR = 2300 ms, TE = 3.03 ms, voxel size: 1.0 × 1.0 × 1.0 mm, flip angle: 8°, GRAPPA acceleration factor: 2).

fMRI preprocessing and analysis

Statistical Parametric Mapping software (SPM12; Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used for the pre-processing and analysis of the fMRI data. To allow for T1 signal equilibration effects, the first five images, which were acquired during a buffer period before the task began, were discarded. Functional images were realigned, coregistered, spatially normalised to standard Montreal Neurological Institute space, and smoothed using a 6 mm full-width at half-maximum Gaussian kernel. The onsets and durations of the two conditions (Faces and Shapes) were modelled using a canonical haemodynamic response function. The model was corrected for serial correlations and a high-pass filter (128 s) was administered to decrease the amount of low frequency noise.

To confirm task-related amygdala activity during the Faces condition compared to the Shapes condition, we used the individual contrast images (Faces > Shapes) in a second-level analysis to determine mean condition-specific activity using a one-sample *t*-test (Faces > Shapes) with a statistical threshold of $p < .05$ with familywise error (FWE) correction and an extended threshold of 10 contiguous voxels. Next, MarsBaR (Brett *et al.*, 2002) was used to extract bilateral amygdala activation parameter estimates, giving the amount of activation in the left and right amygdala during the Faces condition in comparison to the Shapes condition, i.e. the left and right amygdala's sensitivity for negative information.

Self-referent negative memory bias, negative endorsement bias, and negative recall bias

The negative biases were assessed using the computerised self-referent encoding task (SRET; Derry and Kuiper, 1981; Dobson and Shaw, 1987), which consisted of an endorsement phase followed by a recall phase, separated by a two-minute digit symbol substitution distraction task. During the endorsement phase, twelve positive and twelve negative possibly self-descriptive adjectives were presented in a fixed randomised order. These words were chosen by a clinical neuropsychologist with expertise in schema-based memory using the Dutch translations of the Affective Norms for English Words database (Bradley & Lang, 1999) and the Dutch version of the Young Schema Questionnaire (Rijkeboer *et al.*, 2005) and their valence was subsequently validated (see Duyser *et al.*, 2020). Participants rated how well each word described them on a five-point scale, where a 4 or 5 meant that a word was endorsed as self-descriptive, from here on referred to as 'endorsed'.

Then, during the recall phase, participants had three minutes to type as many words as they remembered from the endorsement phase. They were stimulated to also include words they were not completely sure of and typographical errors were allowed. 43 patients performed the task without the three-minute time restriction that was added later to ensure that our version of the task was in line with other studies using the SRET (Gotlib *et al.*, 2004; Gerritsen *et al.*, 2012; Van Oostrom *et al.*, 2012; Vrijsen *et al.*, 2017). Unlimited recall time did not result in more recalled words as shown by an ANCOVA with gender, age, and education level as covariates, $F(1,197) = .222$, $p = .638$, $\eta^2 = .001$.

To account for primacy and recency effects, the first two and last two words that were presented during the endorsement phase were excluded from the recall results, conform i.a. Van Oostrom *et al.* (2012) and Vrijsen *et al.* (2017). Finally, in line

with i.a. Gotlib *et al.* (2004), Gerritsen *et al.* (2012), Van Oostrom *et al.* (2012), and Vrijsen *et al.* (2017), three scores were calculated:

1. Self-referent negative memory bias =

$$\frac{number\ of\ negative\ recalled\ words\ that\ were\ endorsed}{total\ number\ of\ recalled\ words\ that\ were\ endorsed}$$

2. Negative endorsement bias =

$$\frac{number\ of\ negative\ endorsed\ words}{total\ number\ of\ endorsed\ words}$$

3. Negative recall bias =

$$\frac{number\ of\ negative\ recalled\ words}{total\ number\ of\ recalled\ words}$$

Higher values indicated more negative bias.

Statistical analyses

IBM SPSS Statistics version 25 was used for the statistical analyses. Because the self-referent negative memory bias and negative endorsement scores were not normally distributed (right skewed), we applied log transformations to these scores. In addition to gender, age, and education level, current, verified antidepressant medication use (yes/no) was added as covariate in every analysis, since selective serotonin reuptake inhibitors can attenuate amygdala activation in response to negative emotional faces (Fu *et al.*, 2004; Godlewska *et al.*, 2012). In the analyses that included self-referent negative memory bias and negative recall bias, SRET version (i.e. with or without three-minute time restriction during the recall phase) was included. This was not necessary for the analyses including negative endorsement bias, because that score only included data from the endorsement phase of the SRET.

ANCOVAs were used to assess differences in left and right amygdala sensitivity to negative information between patients with and without self-referent negative memory bias (i.e. a score of 0 or > 0) and the association between left and right amygdala sensitivity to negative information and self-referent negative memory

bias was assessed with linear regression models. This was repeated for the associations with negative endorsement bias and negative recall bias.

In addition to the analyses related to the main aims of the study, we aimed to gain more insight in how the amygdala's sensitivity for negative information, self-referent negative memory bias, negative endorsement bias, and negative recall bias differed between patients and controls. These additional analyses are presented in the supplementary material.

Results

The amygdala's sensitivity to negative information and self-referent negative memory bias

The emotional faces processing task successfully evoked significant ($p_{FWE} < .001$) bilateral amygdala activation in both patients and control participants, see supplementary **Figure S1**. The patients with a self-referent negative memory bias (i.e. a score of > 0; $n = 61$) did not have a stronger left, $F(1,118) = .198$, $p = .657$, $\eta^2 = .002$, or right, $F(1,118) = 2.011$, $p = .159$, $\eta^2 = .017$, amygdala sensitivity to negative information than the patients without a self-referent negative memory bias (i.e. a score of 0; $n = 63$). The linear regression model to assess the association between the left amygdala's sensitivity to negative information and self-referent negative memory bias was not significant, $F(6,54) = .498$, $p = .807$, $R^2 = .052$, and the left amygdala's sensitivity to negative information was not significantly associated with self-referent negative memory bias, $\beta = -.145$, $p = .295$. The same was the case for the right amygdala's sensitivity to negative information, $F(6,54) = .560$, $p = .760$, $R^2 = .059$ and $\beta = -.168$, $p = .229$, see also **Figure 3A** and **B**. Note that as a result of the log transformation of the self-referent negative memory bias score, these linear regression models were performed in a subsample of patients ($n = 61$) who actually had a self-referent negative memory bias.

The amygdala's sensitivity to negative information and negative endorsement bias

The linear regression model to assess the association between the left amygdala's sensitivity to negative information and negative endorsement bias was not significant, $F(5,89) = 1.025$, $p = .408$, $R^2 = .054$, and the left amygdala's sensitivity to negative information was not significantly associated with negative endorsement bias, $\beta = -.006$, $p = .958$. The same was the case for the right's amygdala sensitivity to negative information, $F(5,89) = 1.110$, $p = .361$ and $\beta = -.067$, $p = .525$, see **Figure 3C**

and **D**. Note again that due to the log transformation of the negative endorsement score, these linear regression models were performed in a subsample of patients (n = 95) who actually had a negative endorsement bias.

The amygdala's reactivity to negative information and negative recall bias

The linear regression model to assess the association between the left amygdala's sensitivity to negative information and negative recall bias was significant, $F(6,118) = 3.037$, $p = .008$, $R^2 = .134$, and the left amygdala's sensitivity for negative information was significantly associated with negative recall bias, $\beta = .193$, $p = .028$, see **Figure 3E**. Two additional linear regression models showed that this association was driven by more negative recalled words, $F(6,118) = 2.011$, $p = .070$, $R^2 = .093$, $\beta = .274$, $p = .003$, rather than less positive recalled words, $F(6,118) = .523$, $p = .790$, $R^2 = .026$, $\beta = .051$, $p = .593$. A repetition of the model in only the control participants (n = 78) was not significant, $F(4,70) = .376$, $p = .825$. Left amygdala's sensitivity for negative information was also not significantly associated with negative recall bias, $\beta = .069$, $p = .568$.

The model with the right amygdala's sensitivity to negative information and negative recall bias was significant, $F(6,118) = 2.567$, $p = .023$, $R^2 = .115$, but the association between the right amygdala's sensitivity for negative information and negative recall bias was not, $\beta = .137$, $p = .125$, see **Figure 3F**.

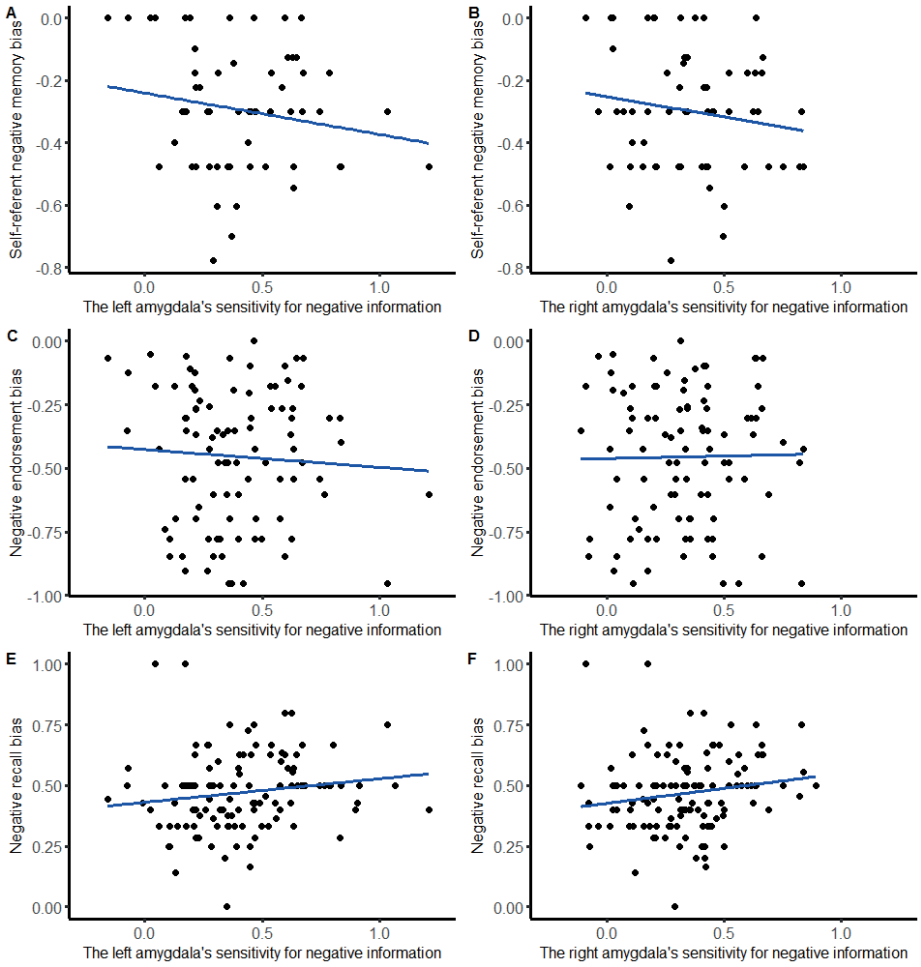

Figure 3. The relationships between the left and right amygdala's sensitivity for negative information and self-referent negative memory bias in a subsample of 61 patients **(A and B**), negative endorsement bias in a subsample of 95 patients **(B and C)**, and negative recall bias in the total sample of 125 patients **(E and F)**.

Discussion

In a naturalistic cohort of psychiatric patients, we associated the amygdala's sensitivity for negative information, a neurobiological depressotypic marker, with the independently measured cognitive depressotypic marker of self-referent negative memory bias. We found no significant association between self-referent negative memory bias and bilateral amygdala sensitivity to negative information. When we further investigated the two components of self-referent negative memory bias, there was a significant association between negative recall bias and the left amygdala's sensitivity to negative information, but we did not find this for negative endorsement bias. Together, these findings indicate that across different psychiatric disorders, but not in healthy controls, an increased left amygdala sensitivity for negative information seems to modulate a better recall of negative information, while the composite self-referent negative memory bias score did not bear a clear relationship with this amygdala sensitivity measure. Below, we discuss and interpret these findings in more detail.

Higher left amygdala sensitivity for negative information was associated with the better recall of negative words, regardless of whether or not they were endorsed as self-referential. We also showed that it was driven by a higher absolute number of negative recalled words rather than a lower absolute number of positive recalled words, which is in line with previous studies using the self-referent encoding task (SRET) in depressed individuals (LeMoult & Gotlib, 2019). Only finding this relationship in the left amygdala is also in line with the existing literature (Baas *et al.*, 2004, Wager *et al.*, 2003), although lateralisation of the amygdala remains a debated topic. We further showed that this association was specific to psychopathology as this association was not present in healthy control participants. We expect that this higher amygdala sensitivity is not solely limited to negative emotional faces, such as in the emotional faces processing task, but occurs in response to negative stimuli in general, including the negative words presented during the first part of the SRET, likely resulting in amygdala-enhanced memory encoding and retrieval (Dolcos *et al.*, 2004; Fastenrath *et al.*, 2014).

So, we showed that two independent depressotypic measures, one representing a neurobiological marker and the other representing a cognitive marker, are associated, not only in individuals with depression, but in individuals with a wide range of (multimorbid) psychiatric disorders. We did not find this association for negative endorsement bias. The negative endorsement bias score reflects to which extent negative words were considered to be self-descriptive and thus

indirectly measures the presence of negative cognitive schemas and is perhaps related explicit self-esteem/self-conceptualisation. So, the amygdala's sensitivity for negative information may be considered a marker for the preferential recall of negative information, but not of its endorsement.

We found no relationship between the amygdala's sensitivity for negative information and self-referent negative memory bias; not when we divided patients into a group with and without self-referent negative memory bias and assessed differences in bilateral amygdala sensitivity for negative information, nor when we assessed this relationship in a subsample (n = 61) of patients who actually showed this bias. While negative endorsement bias reflects negative cognitive schemas and negative recall bias reflects the enhanced memory for negative information, self-referent negative memory bias is dependent on both, but is also more than simply the addition of these two components. Because the self-referent negative memory bias score is calculated by dividing the number of negative endorsed and subsequently recalled words by the total number of endorsed and subsequently recalled words, it is a fitting index of negative schema-related memory. Previous studies have shown that when new information can latch onto already existing schemas, its encoding is less dependent on the hippocampus (Gilboa & Marlatte, 2017; Van Kesteren *et al.*, 2012) and therefore likely also less dependent on modulation by the amygdala. This could explain why, even though this was not significant, the amygdala's sensitivity for negative information and self-referent negative memory bias were negatively associated.

While the positive association between the amygdala's sensitivity for negative information and negative recall bias fits well within the hypothesis of amygdala modulation of memory (Dolcos *et al.*, 2004), we found no relationship between our two depressotypic markers. It is likely that this relationship is more complex and involves interactions with other (depression-specific or transdiagnostic) vulnerability factors such as genetic predisposition and/or childhood adversity (Dainer-Best *et al.*, 2018b). It is possible that only when there is a genetic predisposition and/or experienced childhood adversity, enhanced amygdala sensitivity for negative information leads to a self-referent negative memory bias. This is in line with Beck's model (Beck & Bredemeier, 2016), which shows that cognitive vulnerability is dependent on the interaction of genetic predisposition and childhood trauma, which can both influence the level of amygdala activation in response to negative stimuli (Munafò *et al.*, 2008; Van Harmelen *et al.*, 2013). The interplay between amygdala activation, genetic predisposition, and childhood

trauma on self-referent negative memory bias in naturalistic psychiatric samples requires more investigation.

Part of our study was to elaborate on the line of work that Dainer-Best and colleagues (2018a) have started by dissecting the commonly used self-referent negative memory bias score in order to investigate its components. Our study contributes to this growing knowledge by showing that the memory component of self-referent negative memory bias is differently associated with the amygdala's sensitivity for negative information than the endorsement component. The next step would be to investigate these different components in a large sample of healthy individuals and individuals with (multimorbid) psychiatric disorders on the clinical, behavioural, and brain level.

This study has certain strengths and limitations. One of the strengths is the use of a sample that represents the high level of multimorbidity in the psychiatric population (Kessler *et al.*, 2005) and is well-diagnosed. Such samples are critical for the investigation of shared mechanisms in psychopathology (Insel, 2014). Another strength is that we used robust and frequently used tasks to measure the amygdala's sensitivity for negative information and self-referent negative memory bias, which contributes to the uniformity in methodology and comparability of research findings between studies. A limitation of our study is that we only measured the amygdala's sensitivity for negative information by comparing negative emotional faces to shapes. This means that we do not know whether or how increased or decreased amygdala sensitivity for positive emotional stimuli relates to self-referent negative memory bias and its components.

However, we found that heightened amygdala sensitivity for negative information was associated with a better recall of negative information, independent of its self-referent status and only in psychiatric patients, not in healthy control participants. This confirms that the two components of the self-referent encoding task capture intrinsically different concepts, which is something to be considered in future studies. Thus, we conclude that the amygdala's sensitivity for negative information can be considered a neural marker of negative *memory* bias, but not of self-referent memory bias per se, in a naturalistic psychiatric patient sample.

Supplementary methods

Amygdala reactivity

Differences between patients and control participants in left and right amygdala sensitivity for negative information were assessed using ANCOVAs with gender, age, education level, and antidepressant use as covariates. To gain more insight in amygdala reactivity during each block, we also extracted the amygdala activation parameter estimates from each Faces and Shapes block separately. We did this both for the total patient group (n = 125) and the subsample of patients (n = 61) in which we performed the analyses that assessed the relationship between the amygdala's sensitivity for negative information and self-referent negative memory bias.

Self-referent negative memory bias, negative endorsement bias, and negative recall bias

ANCOVAs with gender, age, education level, antidepressant use, and – in the case of self-referent negative memory bias and negative recall bias – SRET version (i.e. with or without the three-minute time restriction during the recall phase) were used to test differences between patients and control participants in self-referent negative memory bias, negative endorsement bias, and negative recall bias.

Supplementary results

Amygdala reactivity

Both patients and control participants showed significant ($p_{FWE} < .001$) left and right amygdala activation in response to the negative emotional faces condition in comparison to the shapes condition (Faces > Shapes), **Figure S1**. Patients and control participants did not differ significantly in amygdala activation, $F(1,196) = 2.833$, $p = .094$, $\eta^2 = .014$. **Figure S2** and **Figure S3** show left and right amygdala activation during each Faces and Shapes block separately for the total patient group and the subgroup of patients with a self-referent negative memory bias.

Self-referent negative memory bias, negative endorsement bias, and negative recall bias

Patients had significantly more self-referent negative memory bias, $F(1,192) = 17.593$, $p < .001$, $\eta^2 = .084$, negative endorsement bias, $F(1,195) = 42.511$, $p < .001$, $\eta^2 = .179$, and negative recall bias, $F(1,193) = 7.388$, $p = .007$, $\eta^2 = .037$.

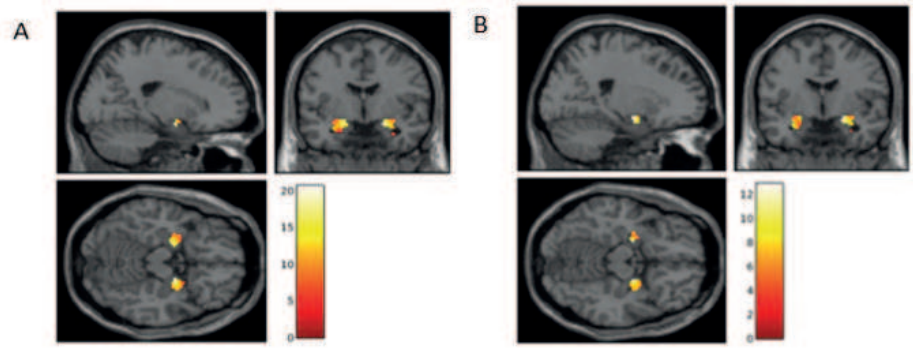

Figure S1. Statistical parametric map of the masked bilateral amygdala activation for the contrast Faces > Shapes with a threshold of $p_{FWE} < .05$ and > 10 contiguous voxels in the total patient group **(A)** and control group **(B)**.

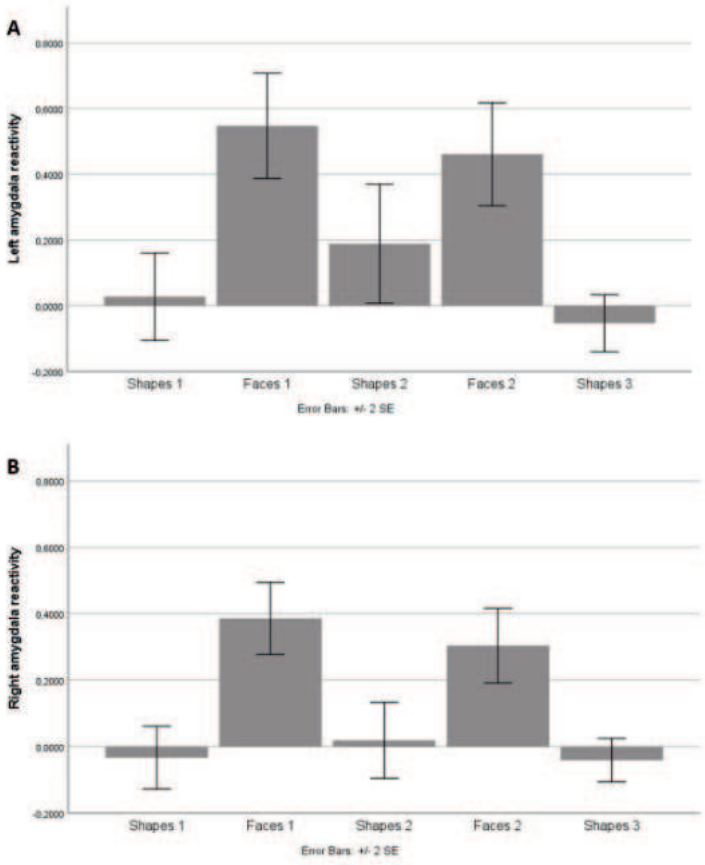

Figure S2. Mean left **(A)** and right **(B)** amygdala activation for each Faces and Shapes block of the emotional faces processing task for the total patient group (n = 125).

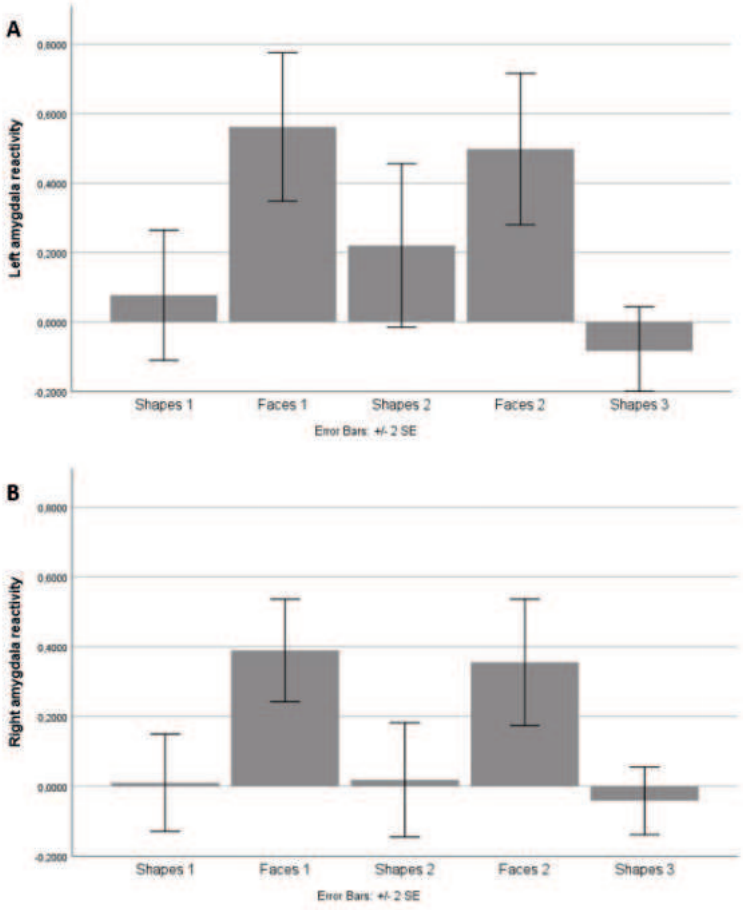

Figure S3. Mean left **(A)** and right **(B)** amygdala activation for each Faces and Shapes block of the emotional faces processing task for the subsample of patients (n = 61) with a self-referent negative memory bias score of greater than zero.

4

Measuring self-referent memory bias as marker for depression: overview, new insights, and recommendations

Duyser, F.A., Van Eijndhoven, P.F., Collard, R.M., Vassena, E., Koekkoek, B., Tendolkar, I., Vrijsen, J.N., (2024). Measuring self-referent memory bias as marker for depression: overview, new insights, and recommendations. *Journal of Psychopathology and Behavioural Assessment,* 47, https://doi.org/10.1007/s10862-024-10190-9

Abstract

Purpose. Negative self-referent memory bias (the preferential memory for negative self-referent information) is a well-known symptom of depression and a risk factor for its development, maintenance, and recurrence. Evidence shows its potential as an add-on tool in clinical practice. However, it is unclear which self-referent memory bias measure(s) could be clinically relevant. Here, as a first step, we investigate which measures best differentiate current depression status and track depressive symptom severity most closely.

Methods. The total sample (N = 956) from three (naturalistic) psychiatric cohorts with matched controls was divided into a current depression, remitted depression, and non-disordered control group. Self-referent memory bias task measures were calculated and the drift diffusion model (DDM) was applied to assess underlying components of the cognitive self-referent decision making process. Measures were compared between groups and linear regression models applied to assess their association with depressive symptom severity.

Results and conclusion. The number of negative endorsed words differentiated best between depression status while a combination of the number of positive endorsed words, self-referent negative memory bias, and positive drift rate was most strongly associated with depressive symptom severity. Our results give direction to the clinical implementation of this task. Its value in assessing, monitoring, and predicting depressive state and trait in clinical settings requires further investigation.

Introduction

Negative self-referent memory bias refers to the better and more frequent memory for self-referent negatively valenced information compared to neutral or positive information. It is a well-known aspect of and risk factor for depression (Gotlib & Joormann, 2010; Beck & Bredemeier, 2016; Marchetti *et al.*, 2018; LeMoult & Gotlib, 2019) that extends beyond current depressive episodes (Joormann & Aditte, 2015; Everaert *et al.*, 2022). This makes it a characteristic of both state and trait depression and a valuable depression marker or predictor. Interestingly, it may be considered a potential cognitive marker for depressive symptoms across the psychopathological spectrum (Duyser *et al.*, 2020). As well as a predictor for diverse psychiatric problems (Fleurkens *et al.*, 2025).

Self-referent memory bias is generally assessed with a computer task where positive and negative words are presented and participants have to indicate how well those words describe them. During this endorsement phase the material is encoded and during the recall phase that follows, participants are asked to retrieve this information. This brief and easy to implement task delivers a large number of possible outcome measures. While this illustrates the flexibility of the task, it also complicates the compatibility of findings and potential translation to clinical practice as there is currently no standard or consensus in research about which outcome measures are used.

For example, the number or proportion of positive and/or negative words endorsed as self-referent is frequently used as a measure of depressotypic self-schema, because negative words like 'worthless' activate the negative dysfunctional believes depressed individuals often have about themselves (Dozois & Dobson, 2001; Moulds *et al.*, 2007; Romero *et al.*, 2014). The number or proportion of positive and/or negative words recalled is used to measure affective memory bias without the self-referent aspect (Vrijsen *et al.*, 2015; Hakamata *et al.*, 2022). However, most common is to calculate a self-referent memory bias index by combining information from the endorsement and recall phases, which can be done in different ways. The number of positive or negative endorsed and subsequently recalled words can be divided by the total number of endorsed words (Goldstein *et al.*, 2015; Allison *et al.*, 2021), which has the advantage that it controls for individual differences in endorsement rates. To correct for differences in recall rates, a division by the total number of recalled words is also possible. Or, to calculate an index of self-referent memory bias, the number of positive or negative endorsed and recalled words can be divided by the total number of endorsed and recalled words (Bradley & Mathews, 1983; Gotlib *et al.*, 2004).

The reaction times (RTs) during the endorsement phase can also be an insightful outcome measure to infer information about the decision-making process. RTs are currently mostly ignored as a source of clinically relevant information while they could be easily implemented in e-health tools. The faster endorsement of negative words as self-referent has been proposed as a characteristic of depression (McDonald & Kuiper, 1985), although the findings have been inconsistent (Bradley & Mathews, 1983; Dozois & Dobson, 2001; Gotlib *et al.*, 2004). Extensively studied in psychology, the dynamics of decision making can be examined with the drift diffusion model (DDM; Ratcliff & Rouder, 1998). The DDM decomposes task responses, reaction times (RTs), and their distribution into distinct components of decision making and information processing. These can be used to draw conclusions about the cognitive processes underlying self-referent decision making. The DDM parameters are therefore considered more implicit, mechanistic measures in comparison to the measures indicating how many positive or negative words were considered self-referent. The model and its parameters, including a schematic representation, are further explained in the Methods section.

One specific DDM parameter, the drift rate, reflects the rate of information accumulation towards one of the decision options. In case of a self-referent memory bias task, it indicates how quickly and easily someone decides to endorse or not endorse a word as self-referent. It has therefore been proposed as a proxy for self-schema activation (Dainer-Best *et al.*, 2018; Allison *et al.*, 2021; Parker & Adleman, 2021). Drift rate has excellent convergent validity with endorsement (Disner *et al.*, 2017). It has been shown that the number of words endorsed as self-referent and negative drift rate were most strongly associated with subclinical depressive symptom severity in healthy samples (Dainer-Best *et al.*, 2018). In remitted depressed individuals, drift rate has also been associated with negative attention bias (Nagrodzki *et al.*, 2023). Importantly, as drift rate incorporates information about the speed of the decision process, it may be a more sensitive and implicit measure compared to the relatively explicit measure of the number of positive or negative words endorsed as self-referent. Despite this converging evidence, it is still unknown if different DDM parameters can also distinguish current depression status or how they are related to depressive symptom severity in clinical samples.

There is growing evidence for self-referent memory bias as an important depression marker. In addition, within-subject changes in self-referent memory bias might be an early marker for (pharmacological) treatment effects (Harmer *et al.*, 2009; Harmer *et al.*, 2017; Terpstra *et al.*, 2023) and thereby a predictor of the course of depression and depressive symptom severity. For example, stronger negative self-referent

memory bias in individuals with remitted depression predicted the onset of new depressive episodes within the next three years (LeMoult *et al.*, 2017). Relatedly, in depressed individuals, stronger positive self-referent memory bias was associated with greater symptomatic improvement nearly nine months later (Johnson *et al.*, 2007). Recently a study in a large naturalistic psychiatric sample showed that more negative memory bias predicted more psychiatric problems three and four years later, even when baseline psychiatric problems and depression were controlled for (Fleurkens *et al.*, 2025). Combining this evidence with the need for more objective, mechanism-based diagnostic strategies to complement the current subjective self-report diagnostic tools in psychiatry (Rosenberg, 2006; Insel *et al.*, 2010), now seems the time to push for a translation of these research insights into clinical practice. For example, the self-referent memory bias task could function as an easy add-on diagnostic tool to assess depression (vulnerability) or monitor and predict depression symptom severity. It could also help target interventions such as Cognitive Bias Modification, where negative memory biases are modified with the goal to alleviate depressive symptoms (Arditte *et al.*, 2018; Vrijsen *et al.*, 2018b).

With the current study, we aim to contribute to this future implementation of self-referent memory bias into healthcare, especially as add-on diagnostic tool. This requires an understanding of the different possible outcome measures and how they relate to depression diagnosis and symptoms. We therefore set out to investigate 1) how well the different self-referent memory bias outcome measures differentiate between current depression status (i.e., current depression, remitted depression, and no depression) and, 2) how strongly these outcome measures are associated with depressive symptom severity. Because psychiatric multimorbidity is more the rule than the exception (Kessler *et al.*, 2005; Plana-Ripoll *et al.*, 2020; Ten Have *et al.*, 2023) and research findings from naturalistic psychiatric samples are more useful for clinical reality, we used a large, accumulated dataset of N = 956, including two naturalistic cohorts with different types of psychiatric multimorbidity and non-disordered controls. We thereby aim to increasing the generalisability of the findings.

Materials and methods

Participants

This study uses data from 956 participants that were originally collected as part of three cohorts: two naturalistic psychiatric cohorts called 'MIND-Set' (n = 402; Van Eijndhoven *et al.*, 2021) and 'MATCH' (n = 143; Koekkoek *et al.*, 2016) from which we included the individuals with current and remitted depression, and

a cohort of individuals with remitted depression named 'Info in Genes' (*n* = 411; Vrijsen *et al.*, 2014). We also included the healthy controls from MIND-Set and Info in Genes (MATCH did not include healthy controls). The data were pooled and participants were divided into three groups: a current depression group (CD), a remitted depression group (RD), and a control group of individuals without current or past depression or other psychiatric diagnoses (no depression; ND). Due to the naturalistic nature of the MIND-Set and MATCH cohorts, one or more current comorbid psychiatric diagnoses were possible (see **Table 1)**. A more detailed description and overview of each cohort can be found in the supplementary methods and **Table S1**, but specific information regarding e.g., the number of depressive episodes or onset was not available.

Diagnoses were determined by trained clinicians using validated and reliable guided diagnostic interviews that are frequently used in Dutch clinical practice. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First *et al.*, 2002; Lobbestael *et al.*, 2011) was used to diagnose depression and anxiety in the MIND-Set and Info in Genes cohorts. The Measurements in the Additions for Triage and Evaluation and Criminality (MATE-Crimi for DSM-IV; Schippers *et al.*, 2011), the Diagnostic Interview for Adult ADHD (DIVA for DSM-IV; Kooij, 2010, Ramos-Quiroga *et al.*, 2019), and the Dutch Interview for Diagnosing Autism Spectrum Disorders (NIDA for DSM-V; Vuijk, 2016, Vuijk *et al.*, 2022) were used in the MIND-Set cohort to diagnose substance use disorder, ADHD, and ASD, respectively. The Mini International Neuropsychiatric Interview Plus (MINI Plus; Sheehan *et al.*, 1997; Lecruibier *et al.*, 1997) was used for diagnosing the MATCH cohort.

Table 1. Demographic information and current comorbid psychiatric diagnoses of the total sample and the depression subgroups (CD = current depression, RD = remitted depression, ND = no depression, i.e., non-disordered controls). SUD = substance abuse disorder, ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder. The group comparisons column shows the results of one-way ANOVA and chi-square tests comparing between CD, RD and ND.

	Total	**CD**	**RD**	**ND**	**Group comparison**
n	956	236	534	186	
From MIND-Set	402	173	125	104	
From MATCH	143	63	80	-	
From Info in Genes	411	-	329	82	
Age (mean, SD)	42.5 (13.6)	40.4 (13.9)	43.9 (13.0)	40.8 (14.3)	$F(2,928) = 6.949$, $p < .001$
Gender (% female)	59.8	55.5	61.6	60.2	$X^2(2) = 2.550$, $p = .279$
Education level[a]					$X^2(2) = 86.425$, $p < .001$
Low (%)	18.1	31.4	16.8	4.9	
Middle (%)	31.0	36.	31.9	21.1	
High (%)	50.9	31.8	51.3	74.1	
Comorbid anxiety (%)	19.4	40.7	16.7	-	
Comorbid SUD (%)	10.9	26.3	7.9	-	
Comorbid ADHD (%)	10.8	16.9	11.8	-	
Comorbid ASD (%)	8.5	14.0	9.0	-	

[a] Education level is the highest education someone finished with a diploma and is calculated conform Stronks *et al.* (2013).

Self-referent encoding task

Task description

In each cohort, self-referent memory bias was measured with an implicit learning computer task (Derry & Kuiper, 1981; Dobson & Shaw, 1987) consisting of three parts: 1) an endorsement phase, 2) a distraction task, i.e., Raven matrices (Raven, 1958) or the symbol substitution task (Royer, 1971), and 3) a recall phase, see **Figure 1**. During the endorsement phase, participants had to indicate on a five-point scale (in the MIND-Set study) or with 'yes' or 'no' (in the MATCH study) if each word described them. In the Info in Genes study, participants were asked to vividly imagine themselves in a scene with each word and then had to indicate on a five-point scale how well they were able to do so. Words yielding a 'yes' response or a score of 4 or 5 on the five-point scale were considered to be endorsed as self-referent. These are small implementation differences that still allow comparison between outcome measures. Positive and negative words had the same average length and the level of Dutch was similar for all words.

After the two-minute non-verbal distraction task, the recall phase immediately started. Participants were given three minutes to type in all the words they remembered from the endorsement phase. Guessing was encouraged and typographical errors were allowed as long as the intended word could unambiguously be recognised (e.g., "healthy" and "haelthy" were both considered correctly recalled). To account for primacy and recency effects, the first two and last two words were not used in the calculation of the outcomes that included the recall phase (following e.g., Gerritsen *et al.*, 2011; Van Oostrom *et al.*, 2012; Vrijsen *et al.*, 2017).

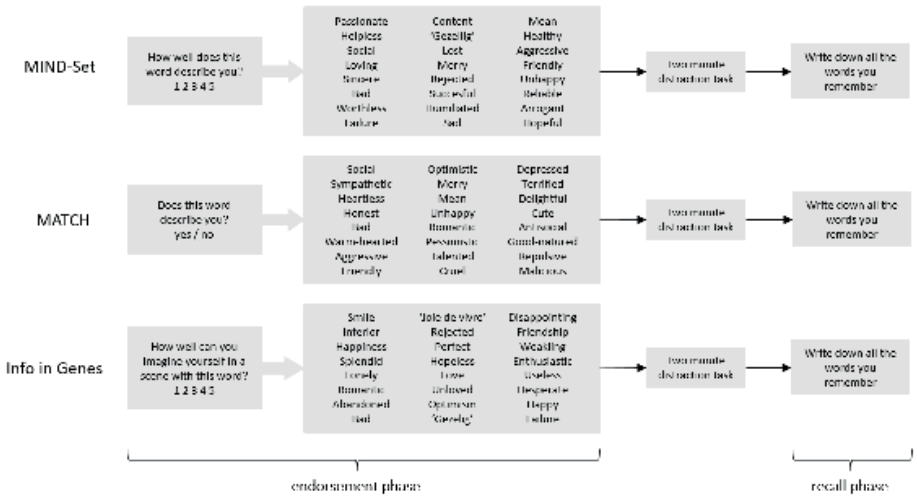

Figure 1. Schematic representation of the Self-Referent Encoding Task across the different cohorts. During the self-referent endorsement phase, participants had to indicate for each word *if* (MATCH) or *how well* (MIND-Set) the word described them or they had to indicate how well they were able to vividly imagine themselves in a scene with that word (Info in Genes). The words were presented in Dutch, but English translations are provided here. 'Gezellig' is a typically Dutch word that cannot be translated into English, but is closest to 'cosy'.

Task outcomes

For this study, we calculated and compared a broad selection of outcome measures from the self-referent memory bias task based on those used in literature, described in the Introduction. They were divided into outcome measures using data from the endorsement phase only (i.e., the number or proportion of positive or negative words endorsed as self-referential), the recall phase only (i.e., the number or proportion of positive or negative words recalled), or both phases (i.e., self-referent memory bias scores), see **Table 2**.

Additionally, when a self-referent memory bias task has non-binary answer options, such as the five-point scales used in the MIND-Set and Info in Genes cohorts (**Figure 1**), different cut-offs for when words are endorsed as self-referential can be (and are) used. Responses of 4 and 5 generally count as endorsed, but responses of 2 and higher have also been used to indicate endorsement (Stalmeier *et al.*, 2021). For completeness and to explore different cut-offs, we also calculated more liberal measures where responses of 2 or higher were considered as endorsed as well as stricter measures where only a 5 counted as endorsed, see supplementary **Table S2**.

Depression symptom severity

Depression symptom severity data were available from the MIND-Set and Info in Genes cohorts. The Inventory of Depressive Symptomatology – Self Rating questionnaire (IDS-SR; Rush *et al.*, 1996) and the Beck Depression Inventory (BDI-II; Beck *et al.*, 1996) were used, respectively. Total scores were transformed into z-scores in order to conduct analyses across cohorts.

Table 2. The name, description, and range of the different self-referent memory bias task outcome measures.

	Variable	Description	Range
Endorsement phase	Positive words endorsed	The number of positive words that were endorsed (rated 4 or 5)	0 – 12
	Negative words endorsed	The number of negative words that were endorsed (rated 4 or 5)	0 – 12
	Negative endorsement score[a]	The number of negative words endorsed divided by the total number of words endorsed	0 – 1
Recall phase	Positive words recalled	The number of positive recalled words	0 – 10[b]
	Negative words recalled	The number of negative recalled words	0 – 10[b]
	Negative recall score[a]	The number of negative words recalled divided by the total number of words recalled	0 – 1
Self-referent negative memory bias	Self-referent negative memory bias variation 1[a]	The number of negative words endorsed and recalled divided by the total number of words endorsed and recalled	0 – 1
	Self-referent negative memory bias variation 2	The number of negative words endorsed and recalled divided by the total number of words endorsed	0 – 1
	Self-referent negative memory bias variation 3	The number of negative words endorsed and recalled divided by the total number of words recalled	0 – 1

[a] The positive and negative scores are complementary with a maximum of 1, so a negative score of 0.33 automatically results in a positive score of 0.66. We therefore only included the negative scores. [b] The first two and last two words were excluded in order to prevent primacy and recency effects, resulting in a range of 0 – 10 rather than 0 – 12.

Drift diffusion model parameters

The drift diffusion model (DDM) is a commonly used computational model that breaks down the dynamics of decision making into different parameters (Ratcliff & Rouder, 1998). It uses task responses, reaction times (RTs), and RT distributions as input and delivers several distinct parameters (listed below) that capture the cognitive process of information processing and decision making. The DDM is increasingly often applied to the self-referent memory bias task to provide a more mechanistic measure of self-referent decision making as opposed to the rather explicit measure of the number of positive or negative words endorsed as self-referent. **Figure 2** schematically illustrates the DDM and its parameters.

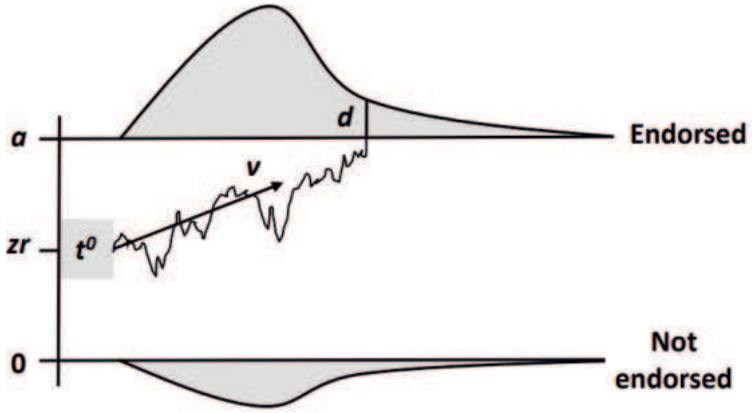

Figure 2. A schematic representation of the drift diffusion model. The decision process starts at the relative starting point (*zr*) after which evidence is accumulated at a certain drift rate (*v*) until one of the decision boundaries (endorsing or not endorsing a word as self-referential) is reached. The threshold separation (*a*) is the distance between the decision boundaries, the response time constant (*t0*) is the time spent on all non-decisional processes, and (*d*) is the difference in how fast the response was executed.

Beginning at the relative starting point (*zr*), evidence is accumulated until one of the two decision boundaries, in this case endorsing or not endorsing a word as self-referent, is met. The relative starting point represents an initial bias towards one decision over the other. The drift rate (*v*) reflects how quickly and strongly a decision is made, and therefore how easy it is to endorse a word as self-referent or not. It is considered a proxy of self-schema activation (Dainer-Best *et al.*, 2018; Disner *et al.*, 2017). The threshold separation (*a*) is the distance between the two boundaries and indicates the amount of evidence that is required before making a decision. The response time constant (*t0*) is the time used for all non-decisional processes like response execution, and the response time difference (*d*) is the difference in how fast the response was executed. The relative starting point (*zr*) and drift rate (*v*) were computed for each valence (positive and negative) separately, because negative and positive bias represent related but distinct clinically-relevant outcomes (Everaert *et al.*, 2022).

All parameters were computed with fast-dm (Voss & Voss, 2007) using the words, responses (endorsed or not endorsed as self-referential), RTs (time between start of response window and entering response), and valences as input. Following Voss *et al.* (2004), RTs below 300 ms and above three times the interquartile range were discarded. Since the mean RTs of the first two presented words were significantly higher

than all other words, most likely due to participants familiarising themselves with the task, they were also discarded, resulting in a total of 22 trials (11 of each valence). The parameters were transformed to z-scores to conduct analyses across cohorts.

Data analyses

Data were analysed using IBM SPSS Statistics version 27 and RStudio 1.1463. We conducted our analyses in several subsamples because some outcome measures were not available for the full sample. Supplementary **Table S1** provides an overview of each subsample.

For the question 'how well do the different self-referent memory bias task outcome measures differentiate depression status?', the whole dataset (N = 956) was used. Differences in outcome measures between depression status were assessed with ACOVAs using gender, age, education level, and cohort as covariates. Post-hoc Tukey tests were performed in case of a significant group comparison. The same analyses were performed on a set of more exploratory outcome measures that could only be calculated on the data from the MIND-Set and Info in Genes cohorts (n = 811).

For the next question, 'how well do the DDM parameters differentiate depression status?', differences in DDM parameters were assessed with ACOVAs also using gender, age, education level, and cohort as covariates. Post-hoc Tukey tests were performed again when the group comparisons were significant. A subsample of 629 participants was used for these analyses. The fast-dm programme required at least 10 trials of each valence. Because some trials were discarded and there were 11 usable trials of each valence to start with, the parameters could be computed for 630 participants. One participant was excluded because of poor model fit (p < .05).

The question 'how are the different self-referent memory bias task outcome measures related to depression symptom severity?' was assessed the same subsample of 811 participants from the MIND-Set and Info in Genes cohorts as the first question. This was because depression symptom severity was not assessed in the MATCH cohort. Linear regression models including gender, age, education level, and current depression status as covariates were used to assess the relationship between each self-referent memory bias task outcome measure and depression symptom severity.

For the fourth question, 'how do the different DDM parameters relate to depressive symptom severity?', we used a subsample of 545 participants. These were the

participants from the subsample of 629 participants from the second question, excluding those from the MATCH cohort because no depression symptom severity data were available from that cohort. We assessed the relationships between the DDM parameters and depression symptom severity with linear regression models that included gender, age, education level, and current depression status.

Finally, in order to draw conclusions about which outcome measure or combination of measures is best able to distinguish between depression status and/or has the best predictive value for depression symptom severity, we ran a multivariate ANCOVA and a hierarchical linear regression analysis with the outcomes from the previous analyses that showed the largest explained variance. Age, gender, education level, and study were again also added to the model. The hierarchical linear regression model also included depression status. Code was not used and the used datasets are not public, but can be requested via the authors of their respective (method) papers (Vrijsen *et al.*, 2014; Koekkoek *et al.,* 2016; Van Eijndhoven *et al.*, 2021). The study and analyses were not preregistered.

Results

How well do different self-referent memory bias task outcome measures differentiate current depression status?

The results from the group- and pairwise comparisons are presented in the first two columns of **Table 3** as well as visually in **Figure 3**. The current depression, remitted depression, and healthy control group differed significantly on all outcome measures. The pairwise comparisons showed that all three outcome measures from the endorsement phase differed significantly between all groups. The number of negative endorsed words explained most variance (i.e., large effect size $\eta^2 = .237$).

Not all pairwise group comparisons were significant for the three recall phase outcome measures. The number of positive recalled words and the negative recall score were able to distinguish current and remitted depressed individuals from healthy controls. This seems to indicate that not necessarily a preferential recall of negative information, but rather decreased recall of positive information appears to be related to depression (vulnerability). The three groups did not differ significantly in the total number of recalled words, $F(2,917) = .010$, $p = .990$, $\eta^2 < .001$ meaning that differences in recall or self-referent memory bias were not due to differences in general memory performance.

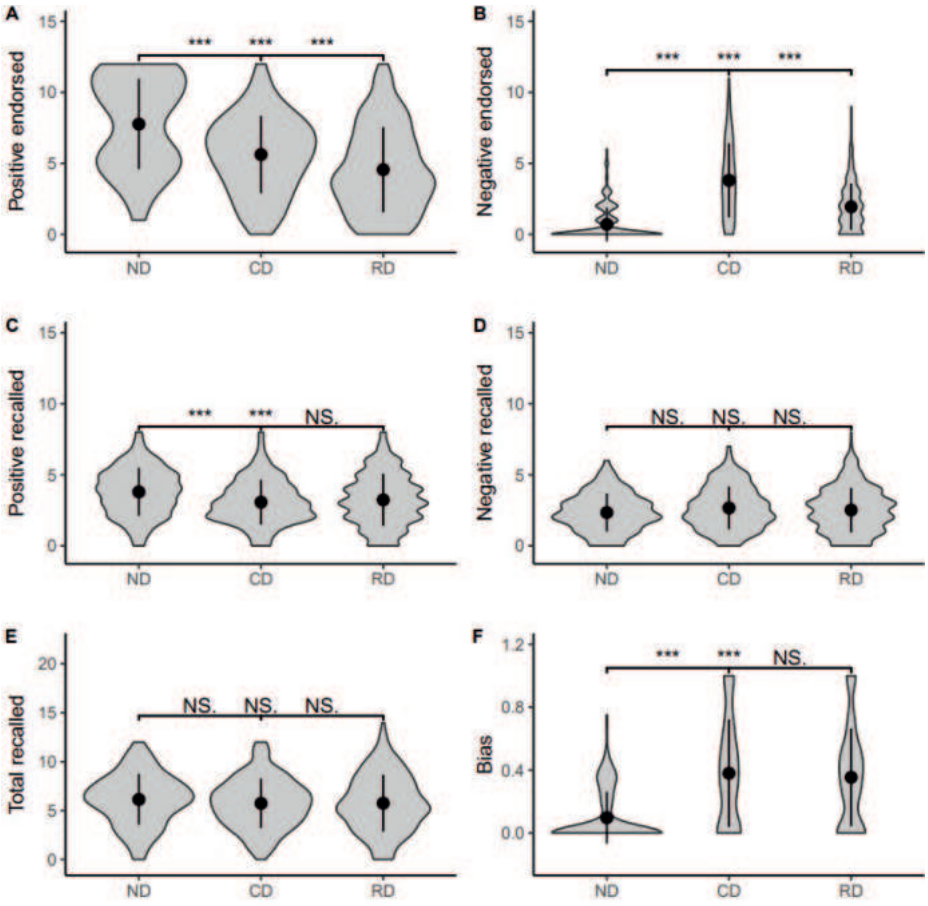

Figure 3. The mean, standard deviation, minimum and maximum values, and probability density of the raw data points of the different self-referent encoding task outcome measures, including comparisons of the never depressed healthy controls (ND), currently depressed (CD), and remitted depressed (RD) groups. *** = $p < .001$, NS. = non-significant.

Table 3. The group comparisons column shows the results from the ANCOVAs testing for differences in self-referent memory bias task outcome measures (see Table 2 for their descriptions) between the never-depressed healthy controls (ND), current depressed (CD), and remitted depressed (RD) individuals. Gender, age, education level, and cohort (MIND-Set, MATCH, or Info in Genes) were included as covariates. The pairwise comparisons column shows the results of the post-hoc Tukey tests. These analyses were performed in the total sample ($N = 956$). The third to sixth columns show the results from the linear regression analyses testing the associations with depression symptom severity which included gender, age, education level, and current depression status as covariates in the models. These analyses were performed in a subsample of the MIND-Set and Info in Genes cohorts ($n = 811$).

	Group comparisons			**Pairwise comparisons**			**Linear regression**			
	F	***p***	η^2	**ND/CD**	**ND/RD**	**CD/RD**	R^2	***β***	***t***	***p***
Positive endorsed	78.427	< .001	.146	< .001	< .001	< .001	.383	-.470	-15.638	< .001
Negative endorsed	142.070	< .001	.237	< .001	< .001	< .001	.223	.215	5.962	< .001
Negative endorsement score	101.817	< .001	.185	< .001	< .001	< .001	.332	.429	12.962	< .001
Positive recalled	4.874	.008	.011	< .001	< .001	.466	.209	-.162	-4.729	< .001
Negative recalled	5.343	.005	.012	.073	.350	.428	.188	-0.43	-1.262	.207
Negative recall score	12.090	< .001	.026	< .001	< .001	.287	.183	0.80	2.407	.016
Self-referent negative memory bias 1	60.255	< .001	.125	< .001	< .001	.544	.254	.273	7.755	< .001
Self-referent negative memory bias 2	20.859	< .001	.044	.524	< . 001	< .001	.205	.144	4.320	< .001
Self-referent negative memory bias 3	23.161	< .001	.049	< .001	< .001	.005	.193	.137	3.875	< .001

The three variations of negative self-referent memory bias (**Table 2**) each appear to have their own strength. The most commonly used first variation (i.e., the number of endorsed and recalled negative words divided by the total number of endorsed and recalled words) explained most variance, as shown by the medium-to-large effect size ($\eta^2 = .125$). It only distinguished current and remitted depressed individuals from healthy controls, indicating that it could represent a depression trait measure. The second and third variations (i.e., the number of endorsed and recalled negative words divided by the total number of endorsed or recalled words) had small effect sizes, but were able to differentiate between current and remitted depression and remitted depression and healthy controls (variation 2) or between all three groups (variation 3). Since these three variations perform differently in differentiating depression status, the choice depends on the intended (specificity) of the use. However, two potential pitfalls associated with these measures should be mentioned.

First, as shown by for example **Figure 3F**, the majority of the never-depressed healthy controls and more than a third of the currently and remitted depressed individuals either had a negative self-referent memory bias index of zero or the score could not be calculated at all. This was due to a low number of negative endorsed and subsequently recalled words. This zero-inflatedness (i.e., an overly large proportion of zeroes) in especially the never-depressed healthy controls means that there is (too) low variability in healthy samples. Still, as shown, this index remains useful to distinguish individuals without depression or other psychiatric diagnoses from remitted and currently depressed individuals.

Second, interestingly, none of the groups had an absolute mean negative self-referent memory bias index. Given the relative nature of the index (i.e., a negative self-referent memory bias index of .33 automatically means a positive self-referent memory bias index of .67), only scores higher than .50 indicate a relative negative bias. However, none of the mean self-referent memory bias scores exceeded this. This indicates that a lack of memory processing of positive self-referent information could be a characteristic of depression (vulnerability) instead of an increased memory processing of negative self-referent information, which is in line with an extensive and recent meta-analysis by Everaert and colleagues (2022).

How well do the DDM parameters differentiate current depression status?

Every DDM parameter except the difference in response execution (*d*) and the response time constant (t_0) differed significantly between the three groups, **Table 4**.

This indicates that depression state is related to the self-referent decision-making process itself and not the non-decision-making components of the task such as how long it took to press the buttons to answer. All effect sizes were small-to-medium and the positive drift rate ($v_{positive}$) explained most variance. Post-hoc pairwise comparisons showed that the parameters were able to distinguish currently and remitted depressed individuals from never-depressed healthy controls.

Partial correlation analyses controlling for gender, age, education level, and cohort, showed moderate significant correlations between the positive drift rate and the number of positive endorsed words, r = .308, p, < .001, as well as between the negative drift rate ($v_{negative}$) and the number of negative endorsed words, r = .285, p < .001. The DDM uses the number of positive and negative endorsed words as direct input to compute the drift rates. However, these correlations indicate that drift rate captures a process distinct from endorsement. Rather than relatively explicitly measuring how positive and negative someone thinks about themself, i.e., by actively endorsing positive and negative self-descriptive words, drift rate may implicitly capture the underlying positive and negative self-schemas (Dainer-Best *et al.*, 2018; Disner *et al.*, 2017). There were no significant partial correlations between the number of positive recalled words and the positive drift rate, r = .012, p = .779, or the number of negative recalled words and the negative drift rate, r = .073, p = .096.

Table 4. The group comparisons column shows the results from the ANCOVAs testing for differences in drift diffusion model parameters between the groups with gender, age, education level, and cohort (MIND-Set, MATCH, or Info in Genes) as covariates. The pairwise comparisons column shows the results of the post-hoc Tukey tests for significant group comparisons. These analyses were formed in a subsample of 629. The third to sixth columns present the results from the linear regression analyses testing the associations with depression symptom severity which included gender, age, education level, and current depression status in the models. These analyses were performed in a subsample of 545.

	Group comparisons			**Pairwise comparisons**			**Linear regression**			
	F	***p***	***η²***	**NC/CD**	**ND/RD**	**CD/RD**	***R²***	***β***	***t***	***p***
$v_{positive}$	16.383	< .001	.052	< .001	< .001	.561	.296	-.188	-4.944	< .001
$v_{negative}$	10.406	< .001	.034	< .001	< .001	.200	.278	.129	3.377	.001
$zr_{positive}$	8.547	< .001	.028	.001	< .001	.926	.271	-.097	-2.526	.012
$zr_{negative}$	6.475	.002	.021	.001	.019	.259	.267	.070	1.835	.067
a	4.886	.008	.016	.017	.034	.695	.267	.067	1.755	.080
d	.037	.963	< .001	-	-	-	.263	.032	.850	.396
t_0	1.636	.196	.005	-	-	-	.262	.007	.190	.849

How are the different self-referent memory bias task outcome measures related to depression symptom severity?

As is evident from **Table 3**, all outcome measures from the endorsement phase and the negative self-referent memory bias indices were significantly associated with depression symptom severity. Because depression status was included as covariate in these regression models, the associations existed independent of current depression status. Interestingly, we showed before that the number of negative endorsed words most strongly differentiated the three diagnostic groups, whereas most variance in depression symptom severity was explained by the number of positive endorsed words. From the recall phase, both the number of positive recalled words and the negative recall score were significantly associated with depression symptom severity, while the number of negative recalled words was not.

How do the different DDM parameters relate to depression symptom severity?

The positive and negative drift rate and the positive relative starting point ($zr_{positive}$) were significantly associated with depression symptom severity, independent of depression status. The positive drift rate explained most variance ($R^2 = .296$), which is in line with the results presented above and matches the finding of Dainer-Best and colleagues (2018).

The optimal (combination of) outcome measure(s) to differentiate depression status and possibly predict depression symptom severity

As a final step and to accommodate outcome measure selection within the clinical setting, we examined which outcome measure(s) is/are best suitable to distinguish between depression status. The measures with the highest explained variance in their own category (i.e., the endorsement phase, the bias indices, and the DDM) were selected. This resulted in the 'classic' outcome measures, i.e., the number of negative endorsed words and the negative self-referent memory bias index (variation 1). We tested whether the positive drift rate had any additional value. MANCOVAs with combinations of these three outcome measures were performed with gender, age, education level, and cohort (MIND-Set, MATCH, and Info in Genes) as covariates. The N = 629 subsample from the DDM analyses was used.

In **Table 5**, the models are ranked by their explained variance. The model only including the number of negative endorsed words explained the highest variance in differences between depression status, with a large effect size, and the bias index or DDM parameter did not have additional value. The number of negative endorsed

words therefore seems the most promising outcome measure to investigate further in a clinical setting.

Table 5. Results from the MANCOVAs testing for differences in depression status (no depression, i.e., healthy controls, current depression, or remitted depression) including gender, age, education level, and cohort (MIND-Set, MATCH, and Info in Genes) as covariates. These analyses were performed in a subsample of 629.

	Λ	F	p	η^2
Negative endorsed	-	77.039	< .001	.205
Negative endorsed + negative self-referent memory bias + $v_{positive}$	.725	32.098	< .001	.149
Negative endorsed + negative self-referent memory bias	.750	42.702	< .001	.134
Negative endorsed + $v_{positive}$	.761	43.700	< .001	.128
Negative self-referent memory bias	-	36.844	< .001	.118
Negative self-referent memory bias + $v_{positive}$	.853	22.914	< .001	.077
$v_{positive}$	-	16.383	< .001	.052

To test which (combination of) outcome measure(s) was most strongly associated with depression symptom severity, we performed a hierarchical linear regression model using the measures that showed the largest explained variance in the previous analyses from the same three categories (endorsement phase, bias index, and DDM). These were the number of positive endorsed words, the negative self-referent memory bias index (variation 1), and the positive drift rate. Gender, age, education level, and depression status were included as covariates. The N = 545 subsample from the DDM analyses, excluding the MATCH cohort (due to no depression symptom severity measure) was used.

The model including all three measures explained most variance, $F(7,466) = 36.873$, $p < .001$, $R^2 = .356$. The change statistics showed that every additional measure contributed to the model significantly: $F_{change}(1,467) = 14.344$, $p < .001$, $R^2_{change} = .020$ for the bias index and $F_{change}(1,466) = 10.192$, $p = .002$, $R^2_{change} = .014$ for the positive drift rate. Adding the number of positive recalled words to ensure that all outcome measure categories from the tasks are included, increased the explained variance further, $F(8,465) = 33.203$, $p < .001$, $R^2 = .364$, which was a significant change, $F_{change}(1,465) = 5.192$, $p = .023$, $R^2_{change} = .007$. Even though some of these measures use similar input (e.g., the number of positive endorsed words and the positive drift rate or the number of positive recalled words and the bias index), there was no multicollinearity (VIF < 1.9 for all). When using the self-referent encoding task to

index depression symptom severity, combining the information from all outcome measure categories seems most informative and would be worth investigating further in clinical practice.

Discussion

We set out to investigate 1) how well different commonly used self-referent memory bias outcome measures differentiate current depression status (i.e., currently depressed and remitted depressed individuals, and never-depressed healthy controls) and, 2) how strongly these outcome measures are associated with depression symptom severity. We further tested which (combination of) outcome measure(s) best distinguished between depression status and had the largest statistically predictive value for depression symptom severity. Our findings, further discussed below, give direction to the clinical implementation of self-referent memory bias. We also discuss its possible roles in assessing, monitoring, and predicting depressive state and trait, but these require further investigation in clinical, longitudinal studies.

We found that the number of negative endorsed words was best able to differentiate all three depression groups while the number of positive endorsed words showed the strongest (negative) association with depressive symptom severity. When combining the best outcome measures from three categories (i.e., the endorsement phase only, self-referent memory bias index, and the DDM), the number of negative endorsed words remained the single best measure to distinguish between depression status. A combination of the number of positive endorsed words, the negative self-referent memory bias index, and the positive drift rate showed the strongest association with depressive symptom severity (i.e., explained most variance). Selecting the optimal (combination of) outcome measure(s) thus depends on the aim and sample, i.e., measuring state and/or trait depression.

When the aim is to differentiate currently depressed individuals, individuals with remitted depression, and never-depressed healthy controls, self-referent processing was most useful, specifically the number of negative endorsed words. This is in line with a wealth of research showing that depressed individuals are more likely to endorse negative words as self-referent compared to non-depressed individuals (i.a., Dobson & Shaw, 1987; Gotlib *et al.*, 2004; Everaert *et al.*, 2022). The variations of the self-referent memory bias index differed in their ability to differentiate

between depression status and had varying effect sizes. As we described earlier, the choice for one over the other depends on the sample and intended goal. A relevant issue for all indices was the low number of negative endorsed and recalled words. Although we based the selection of 12 words of each valence on previous work, more recent studies, especially those also applying the DDM, use a minimum of 24 words of each valence (Hsu *et al.*, 2020; Beevers *et al.*, 2023; Castagna *et al.*, 2023; Terpstra *et al.*, 2023). We recommend carefully considering the number of words when setting up a self-referent memory bias task; a shorter task might be more practical, while a longer task is more suitable when applying the DDM. While the positive and negative drift rate and relative starting point were able to differentiate (remitted) depressed individuals from never-depressed healthy controls, they did not have additional value on top of the number of negative endorsed words. This simple task holds promise to be used as an add-on diagnostic tool in clinical settings to assess current depression and depression trait in a more objective way than self-report questionnaires. This more objective measure is also useful in situations where individuals have difficulty to adequately voice or recognize their symptoms in diagnostic interviews or on self-report questionnaires.

When the aim is to monitor or predict depressive symptom severity, for example during pharmacological or cognitive interventions, a broader set of outcome measures, i.e., the number of positive endorsed words, the negative self-referent memory bias index, and the positive drift rate, showed most promise to be investigated further in clinical settings with a longitudinal study set-up. Interesting is that while depression (vulnerability) is often associated with more negativity across different domains (e.g., attention, interpretation, memory), we here found that less positivity was most strongly related to depressive symptom severity. This is in line with the broader literature on depression and positive and negative affect. While depression and anxiety are both characterised by high negative affect, the lack of positive affect is uniquely related to depression. This is seen in symptoms like anhedonia (the reduced motivation or ability to experience pleasure) and reflected by less positive expectations about the future (Beck *et al.*, 2006; Miranda *et al.*, 2008). Depressed individuals are also less capable in using positive memories to improve negative mood (Joormann & Siemer, 2004; Joormann et al., 2007; Silton *et al.*, 2020). In addition, positivity has a protective effect; being able to use positive emotional words to describe a sad memory predicted improved depressive symptom severity six months later and was also related to a shorter depression recovery time (Brockmeyer *et al.*, 2015). Positivity also works as a buffer to protect individuals from the impact of stress and other negative experiences (Riskind *et al.*, 2013; Speer & Delgado, 2017; Egan *et al.*, 2024), which is only the case for

depression and not for anxiety. Self-referent positive information processing could therefore be a valuable clinical marker to assess and monitor changes in depression symptom severity. In addition, self-referent positive information processing makes a promising intervention target. Specifically, there is growing evidence that therapies augmenting the ability to focus on positive appraisal and positive memories, such as cognitive bias modification (CBM), can indeed function as add-on treatment or prevention tool (Ardette *et al.*, 2017; Becker *et al.*, 2015; Bovy *et al.*, 2022; Dalgleish & Werner-Seidler, 2014; Vrijsen *et al.*), although there are also concerns about CBM's effectiveness (Cristea *et al.*, 2018; Fodor *et al.*, 2020) and further research is necessary.

There are some considerations to be made related to the feasibility of using self-referent memory bias in clinical practice. Our findings match and expand upon previous work (Dainer-Best *et al.*, 2018; Hitchcock *et al.*, 2023). The positive and negative drift rates ($v_{positive}$ and $v_{negative}$) and the positive relative starting point ($zr_{positive}$) were related to depressive symptom severity and able to differentiate current depression status. The positive drift rate was the only DDM parameter included in the optimal combination of outcome measures for the association with depressive symptom severity. It is important to recognise that while the 'classic' outcome measures from the self-referent encoding task are easy to calculate (**Table 2**), extracting the DDM parameters requires a separate computer programme with particularly formatted input, making it less user-friendly and implementable. Easy to use clinical add-on tools for electronic health monitoring and prediction, utilising computational modelling and artificial intelligence, are one of the goals for the near future to enhance personalised mental health care. In the meantime, one should evaluate whether the time and effort to calculate the DDM parameters is worth the relatively low additional value in statistically predicting symptom severity.

Relatedly, although theoretically and conceptually the endorsement measures and the DDM parameters are expected to tap into underlying dysfunctional memory schemas, these operationalisations are not directly representing a memory test, unlike the self-referent memory bias indices, which also includes recall. Both from a theoretical stance (e.g., Beck's generic cognitive model; Beck & Bredemeier, 2016) and based on empirical data showing that self-referent memory bias is predictive of depression status and symptom severity (Johnson *et al.*, 2007; LeMoult *et al.*, 2017), the combination of self-referent endorsement and recall in the parameter holds promise for clinical application. Our findings, as well as other recent findings (e.g., Fleurkens *et al.*, 2025) further support this.

This study has certain strengths and limitations. A strength is the large, accumulated dataset of a remitted depressed individuals and two naturalistic psychiatric patient samples, reflecting diverse clinical reality where psychiatric multimorbidity is common (Kessler *et al.*, 2005; Plana-Ripoll *et al.*, 2020; Ten Have *et al.*, 2023). Diagnoses were determined using validated diagnostic interviews by trained clinicians and information about comorbid anxiety, substance use disorder, ADHD, and ASD was available, although details are missing. Other strengths are the use of a large number and variety of self-referent memory bias task outcome measures and the application of the DDM, which use to represent self-referent processing has seen a rise in popularity recently as it provides a more objective, mechanistic measure of self-referent decision making during the endorsement of positive and negative words. A limitation is that the binary DDM was applied to multialternative decision-making processes in the MIND-Set and Info in Genes versions of the self-referent memory bias task by categorising the responses into endorsed versus not endorsed as self-referent. However, the DDM model fit as applied with fast-dm was good (all $p > .05$ except one participant who was excluded) and the results are in line with previous findings, indicating that the DDM could be successfully applied to different versions of the self-referent memory bias task. Mathematically, multialternative DDMs have been developed (Roxin, 2019), but accessible tools will first have to be created before such new models can be practically applied. In the meantime, it seems that the DDM provides additional useful clinical information on the mechanisms underlying emotional processing (Nagrodzki *et al.*, 2023). Another important limitation is that due to the cross-sectional study design of the available datasets, we were only able to investigate how the different outcome measures differentiated depression status and how they were associated with depressive symptom severity. We were not able to, for example, look at which outcome measure had the best predictive value for depression relapse or symptom improvement. This requires further research in similar large, naturalistic psychiatric samples.

Supplementary methods

See **Table S1** for an overview of the demographic information and comorbid psychiatric diagnoses for each cohort and its subgroups. Below, each cohort is described in more detail.

MIND-Set

MIND-Set (Measuring Integrated Novel Dimensions in neurodevelopmental and stress-related mental disorders; Van Eijndhoven *et al.*, 2021) was a naturalistic psychiatric cohort study from the Department of Psychiatry of the Radboud University Medical Centre and the Donders Institute for Brain, Cognition, and Behaviour in Nijmegen, The Netherlands that aimed to gain a better understanding of unique and shared mechanisms in stress-related and neurodevelopmental psychiatric disorders by studying them on different biological, neurocognitive, and behavioural levels. Adult patients at the outpatient clinic were eligible to participate if they were diagnosed with depression and/or anxiety and/or substance use disorder (SUD) and/or attention-deficit/hyperactivity disorder (ADHD) and/or autism spectrum disorder (ASD) by trained clinicians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First *et al.*, 2002; Lobbestael *et al.*, 2011), the Measurements in the Additions for Triage and Evaluation and Criminality (MATE-Crimi; Schippers *et al.*, 2011), the Diagnostic Interview for Adult ADHD (DIVA; Kooij, 2010; Ramos-Quiroga *et al.*, 2019), and the Dutch Interview for Diagnosing Autism Spectrum Disorders (NIDA; Vuijk, 2016; Vuijk *et al.*, 2022). Exclusion criteria were: a current psychosis, sensorimotor handicaps, inadequate command of the Dutch language, a full-scale IQ estimate of below 70, and not being able to give informed consent. In addition to the patient group (n = 298), a healthy control group (n = 104) was recruited through advertisements and the absence of any present and past psychiatric disorders was assessed through a telephonic screening interview using the same diagnostic instruments as for the patients. They received a monetary compensation for their participation.

Info in Genes

The Info in Genes cohort study aimed to relate different cognitive biases to genetic susceptibility to depression, and was initiated and conducted by the Department of Psychiatry of the Radboud University Medical Centre and HSK, a private regional mental health care organisation. Adults with remitted depression, as diagnosed by trained professionals using the SCID-I for DSM-IV were eligible to participate. Exclusion criteria were: a current depressive episode, current or lifetime bipolar disorder, current psychotic symptoms, alcohol or substance use abuse within

the past six months, deafness, blindness, neurological disorders, sensorimotor handicaps, and intellectual disability. In addition to the 329 individuals with remitted depression, 82 healthy controls were recruited via advertisements and subsequently interviewed (again using the SCID-IV) to confirm the absence of a current or remitted depression. They received a gift card as compensation for their participation.

MATCH

MATCH (Koekkoek *et al.*, 2016) was another naturalistic psychiatric cohort study, initiated by the Social Psychiatry and Mental Health Nursing Research Group at the HAN University of Applied Sciences. Adult patients with one or more of the following psychiatric diagnoses were eligible to participate: depression, anxiety, SUD, ADHD, and manic, eating, and somatoform disorders. Trained professionals used the Mini International Neuropsychiatric Interview Plus (MINI Plus; Sheehan *et al.*, 1997; Lecruibier *et al.*, 1997) to confirm the diagnoses. Patients with a psychotic, bipolar-I, or cognitive disorder as main diagnosis were excluded due to potentially not being able to perform the tasks. Patients (n = 143) were rewarded with a gift card for their participation.

Table S1. Demographic information and comorbid psychiatric diagnoses for each of the three cohorts and their subgroups (CD = current depression, RD = remitted depression, ND = no depression, i.e., healthy controls). SUD = substance abuse disorder, ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder. DDM = drift diffusion model. Group comparisons show the results of one-way ANOVAs and chi-square tests.

MIND-Set cohort					
	Total	**CD**	**RD**	**ND**	**Group comparison**
n	402	173	125	104	
Age (mean, SD)	39.7 (14.7)	41.5 (14.8)	37.9 (12.7)	39.1 (16.3)	$F(2374) = 447.05$, $p = .126$
Gender (% female)	50.5	50.9	46.4	54.8	$X^2(2) = 1.62$, p = .444
Education level					$X^2(4) = 13.54$, p = .009
Low (%)	13.9	19.1	12.8	6.7	
Middle (%)	37.3	37.6	41.6	31.7	
High (%)	40.8	43.4	45.6	61.5	
Comorbid anxiety (%)	24.9	30.1	38.4	-	
Comorbid SUD (%)	19.2	29.5	20.8	-	
Comorbid ADHD (%)	23.9	22.0	46.4	-	
Comorbid ASD (%)	20.1	19.1	38.4	-	
MATCH cohort					
	Total	**CD**	**RD**	**ND**	**Group comparisons**
n	143	63	80	-	
Age (mean, SD)	37.4 (10.9)	37.9 (11.0)	36.9 (11.0)	-	$F(1,142) = .31$, $p = .581$
Gender (% female)	68.5	68.8	68.3	-	$X^2(1) = .01$, $p = .949$
Education level					$X^2(2) = 2.44$, $p = .295$
Low (%)	18.2	23.8	13.8	-	
Middle (%)	43.4	41.3	45.0	-	
High (%)	38.5	34.9	41.3	-	
Comorbid anxiety (%)	59.4	69.8	51.3	-	
Comorbid SUD (%)	18.9	17.5	20.0	-	
Comorbid ADHD (%)	4.9	3.2	6.3	-	
Comorbid ASD (%)	-	-	-	-	

Table S1. Continued

Info in Genes cohort					
	Total	**CD**	**RD**	**ND**	**Group comparisons**
n	411	-	329	82	
Age (mean, SD)	46.8 (12.0)	-	47.8 (12.0)	42.9 (11.1)	$F(1,409) = 1533.22$, $p = .001$
Gender (% female)	65.9	-	65.7	67.1	$X^2(1) = .06$, $p = .808$
Education level[a]					$X^2(2) = 18.07$, $p < .001$
Low (%)	6.7	-	8.0	2.5	
Middle (%)	22.2	-	25.8	7.4	
High (%)	71.0	-	66.2	90.1	
Comorbid anxiety (%)	-	-	-	-	
Comorbid SUD (%)	-	-	-	-	
Comorbid ADHD (%)	-	-	-	-	
Comorbid ASD (%)	-	-	-	-	
Subsample with depression symptom severity data (*n* = 811)					
	Total	**CD**	**RD**	**ND**	**Group comparisons**
Age (mean, SD)	43.4 (13.8)	41.5 (14.8)	45.2 (13.0)	40.8 (14.3)	$F(2,781) = 8.61$, $p < .001$
Gender (% female)	58.2	50.9	60.2	60.2	$X^2(2) = 4.86$, $p = .088$
Education level[a]	21.3	19.1	27.7	7.6	$X^2(4) = 95.35$, $p < .001$
Low (%)	54.4	37.6	59.5	57.6	
Middle (%)	24.4	43.4	12.8	34.8	
High (%)					
Comorbid anxiety (%)	12	30	11	-	
Comorbid SUD (%)	9	30	6	-	
Comorbid ADHD (%)	12	21	13	-	
Comorbid ASD (%)	10	18	11	-	
Subsample for DDM (*n* = 629)					
	Total	**CD**	**RD**	**ND**	**Group comparisons**
Age (mean, SD)	43.4 (13.8)	41.5 (14.8)	45.2 (13.0)	40.8 (14.3)	$F(2,781) = 8.61$, $p < .001$
Gender (% female)	58.2	50.9	60.2	60.2	$X^2(2) = 4.86$, $p = .088$
Education level					$X^2(4) = 95.35$, $p < .001$
Low (%)	21.3	19.1	27.7	7.6	
Middle (%)	54.4	37.6	59.5	57.6	
High (%)	24.4	43.4	12.8	34.8	
Comorbid anxiety (%)	12	30	11	-	
Comorbid SUD (%)	9	30	6	-	
Comorbid ADHD (%)	12	21	13	-	
Comorbid ASD (%)	10	18	11	-	

Supplementary results

How well do the different self-referent memory bias task outcome measures differentiate between depression status?

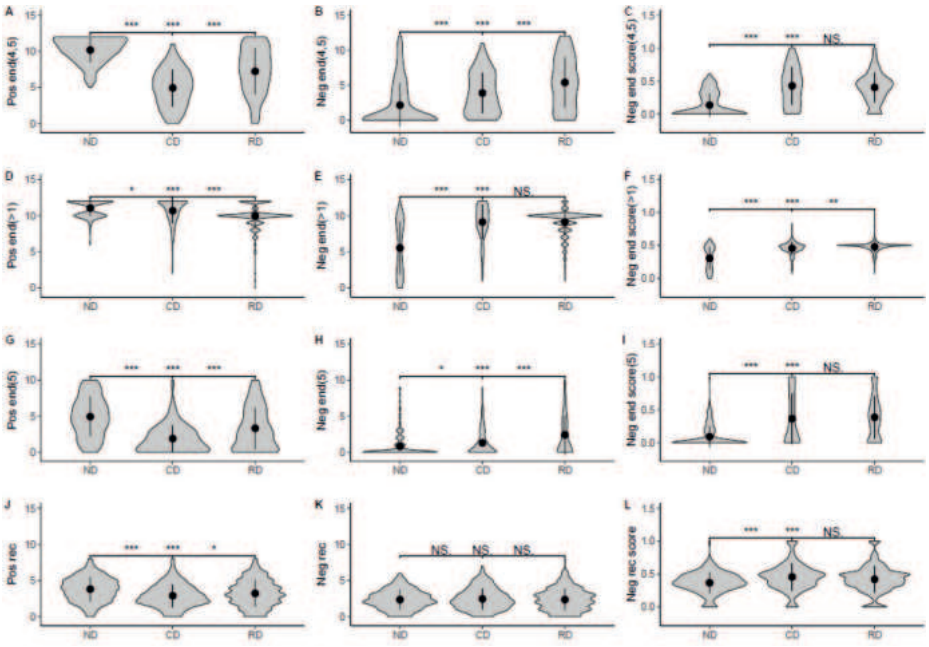

Figure S1. The mean, standard deviation, minimum and maximum values, and probability density of the raw data points of the different self-referent encoding task outcomes from the endorsement and recall phases, including pairwise comparisons of the never depressed healthy conrols (ND), currently depressed (CD), and remitted depressed (RD) groups in the MIND-Set and Info in Genes subsample. See Table S2 for a description of each outcome. Pos = positive, Neg = negative, end = endorsed, rec = recalled. *** = $p < .001$, ** = $p < .01$, * = $p < .05$, NS. = non-significant.

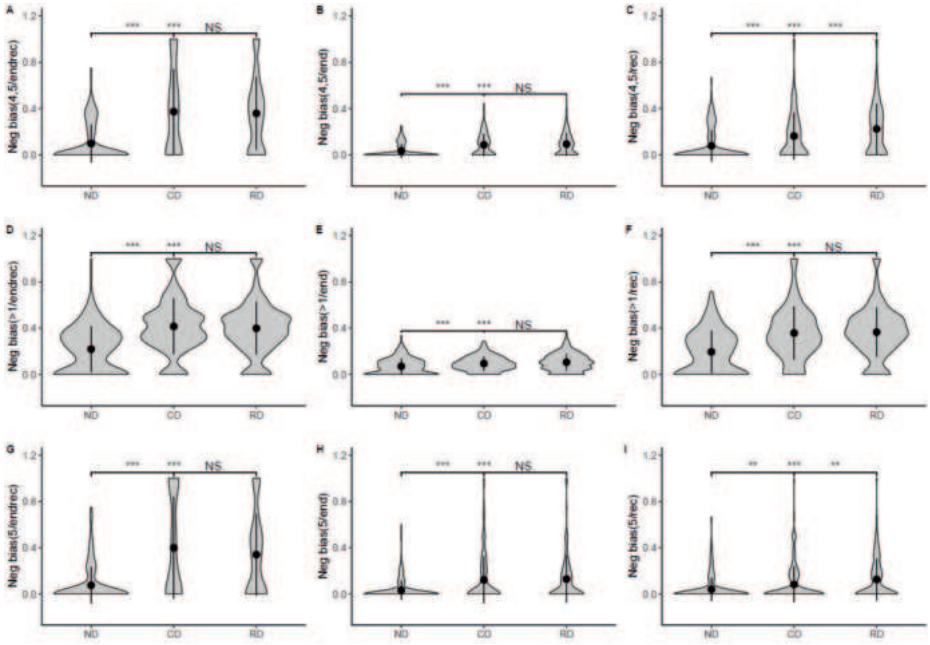

Figure S2. The mean, standard deviation, minimum and maximum values, and probability density of the raw data points of the different self-referent negative memory bias scores, including pairwise comparisons of the never depressed healthy controls (ND), currently depressed (CD), and remitted depressed (RD) groups in the MIND-Set and Info in Genes subsample. See Table S2 for a description of each outcome. Pos = positive, Neg = negative, end = endorsed, rec = recalled. *** = $p < .001$, ** = $p < .01$, * = $p < .05$, NS. = non-significant.

Table S2. Partial correlations (controlling for age, gender, and education level) between the main self-referent memory bias task outcomes and the mood/cognition and anxiety/arousal factors of the IDS-SR (MIND-Set cohort) and the cognitive, affective, and somatic factors of the BDI (Info in Genes cohort).

	IDS-SR Mood / Cognition	**IDS-SR Anxiety / Arousal**	**BDI Cognitive**	**BDI Affective**	**BDI Somatic**
Positive endorsed	r = -.67, p < .001	r = -.58, p < .001	r = -.27, p < .001	r = -.24, p < .001	r = -.24, p < .001
Negative endorsed	r = .68, p < .001	r = .57, p < .001	r = .16, p = .002	r = .13, p = .014	r = .09, p = .103
Positive recalled	r = -.17, p = .002	r = -.21, p < .001	r = -.06, p = .264	r = -.06, p = .236	r = -.10, p = .046
Negative recalled	r = -.03, p = .539	r = .02, p = .784	r = .04, p = .430	r = .02, p = .691	r = -.03, p = .550
Negative self-referent memory bias	r = .48, p < .001	r = .42, p < .001	r = .27, p < .001	r = .26, p = .014	r = .19, p < .001
$v_{positiv}$	r = -.30, p < .001	r = -.28, p < .001	r = -.26, p < .001	r = -.23, p < .001	r = -.23, p < .001
$v_{negative}$	r = .33, p < .001	r = .32, p < .001	r = .04, p = .539	r = .09, p = .125	r = .12, p = .044
$zr_{positive}$	r = -.24, p < .001	r = -.20, p = .003	r = -.12, p = .040	r = -.10, p = .091	r = -.08, p = .181
$zr_{negative}$	r = .18, p = .007	r = .13, p = .049	r = .08, p = .163	r = .04, p = .492	r = .03, p = .656

5
General discussion

In this thesis, I set out to investigate self-referent memory bias as a potential transdiagnostic mechanism within the negative valence domain of the RDoC framework. The ultimate goal was to gain insights in whether self-referent memory bias can be a novel transdiagnostic cognitive marker and future intervention and prevention target. This was approached from three different focus points: 1) the (transdiagnostic) presence and strength of self-referent memory bias in a range of mental disorders and the association with their symptom severity (Chapter 2), 2) the relationship between self-referent memory bias and amygdala reactivity (Chapter 3), and 3) the different possible outcome measures of the self-referent memory bias task and their potential future clinical relevance (Chapter 4). In this final chapter, I will summarise and reflect on the findings and discuss the strengths and limitations as well as their (clinical) implications. I will conclude with suggestions for future research.

The transdiagnostic nature of self-referent memory bias

Chapter 2 presents evidence for a stronger negative self-referent memory bias as a transdiagnostic marker for depression-related cognition across different mental disorders with varying levels of psychiatric comorbidity. The stress-related disorders group expectedly showed the strongest negative self-referent memory bias, followed by the comorbid group. Strikingly, the neurodevelopmental disorders group, which only included individuals with an ADHD and/or ASD diagnosis, also had a significantly stronger negative self-referent bias than the non-disordered controls. This stronger negative memory bias was still present when those with a history of depression were excluded from the neurodevelopmental disorders group, although this finding was not significant, likely due to the small sample. This confirms and expands upon previous work finding evidence for stronger negative self-referent memory bias in a sample of different (multimorbid) mental disorders, including ADHD, where the association also remained when depressed individuals were removed from the sample (Vrijsen *et al.*, 2017).

Our results show that less positive self-referent memory bias (also see the section *More negativity of a lack of positivity?*) is a pathological cognitive process that occurs in varying levels of strength across different groups of mental disorders. We also tested the associations between self-referent memory bias and symptom levels of depression, anxiety, ADHD, and ASD. The association with depressive symptom severity across disorder categories puts less positive self-referent memory bias forward as a transdiagnostic marker for depression. Additionally, given its presence across both stress-related and neurodevelopmental disorders, we propose less positive self-referent memory bias as a broader transdiagnostic factor for

psychopathology within the negative valence domain of the RDoC framework. This is in line with a recent meta and network analysis providing evidence for cognitive biases, including memory bias, as transdiagnostic features of psychopathology (Lavigne *et al.*, 2024). This has important clinical implications, which will collectively be discussed in the *Clinical relevance and future directions* section.

More negativity or a lack of positivity?

We found a stronger negative self-referent memory bias in the group of individuals with one or more mental disorders than in the group of non-disordered controls. Specifically, the first group endorsed more negative words and less positive words as self-referent. Interestingly, they still had an overall positive self-referent memory bias if you regard the absolute memory bias score. To recapitulate, a negative self-referent memory bias score of 0.50 means that an equal number of positive and negative words were endorsed as self-referent and subsequently recalled. A negative self-referent memory bias score of 0.75 means that three quarters of the words endorsed as self-referent and subsequently recalled were negative and a quarter was positive. Therefore, only scores larger than 0.50 indicate a true negative bias. This point is clearly illustrated in both Chapter 2, **Figure 1** and Chapter 4, **Figure 3**. When it comes to recall, depressed individuals (in remission) did not recall more negative words, but recalled less positive words compared to the non-disordered controls instead. This lack of positivity, rather than absolute negativity, was also found in a recent large meta-analysis on explicit memory bias in depression (Everaert *et al.*, 2022). More generally, depression has been uniquely related to a lack of positive affect. A reduced experience of pleasure, i.e., anhedonia, is common, for example. Depression is also characterised by having less positive expectations for the future (Beck, 1974; Beck & Haigh, 2014; Beck & Bredemeier, 2016). A lack of positive self-referent memory bias might thus be an important mechanism contributing to the development and maintenance of depression and depressive symptoms. This is also why in the previous section, we concluded that less positive self-referent memory bias (and not a stronger negative self-referent memory bias) could be a transdiagnostic factor for psychopathology within the negative valence domain, where this construct is now completely missing.

We also found that negative self-referent memory bias was virtually zero in non-disordered controls and therefore positive self-referent memory bias almost fully present. This provides more evidence for a lack of positive self-referent memory bias as a marker for clinically relevant psychopathology. This is in line with previous findings in large community samples (without mental disorders) who also showed low or very low recall of negative self-referent words (Dainer-Best *et al.*, 2018a; Adler

& Pansky, 2020). While a lack of positive (self-referent) memory might be considered a psychopathological risk factor, a better memory for positive information seems to have a protective effect. Recalling positive memories is related to a dampened cortisol stress response during an acute stressor task and reduced negative affect (Speer & Delgado, 2017). Recalling positive memories also predicts reduced vulnerability to depression in adolescents at risk for depression due to early life stress (Dahl Askelund *et al.*, 2019). Positive self-schemas play an important role in this process: preserving a positive view of the self is considered a protective mechanism that is fundamental to maintaining wellbeing (Sedikides *et al.*, 2015; LeMoult & Gotlib, 2019; Vanderlind *et al.*, 2020). The lack or loss of positive (self-referent) memory can therefore be an interesting intervention target for relieving depressive symptoms or even preventing them in vulnerable individuals. This also further discussed in the *Clinical relevance and future directions* section.

Amygdala reactivity as neural correlate of negative memory bias

The amygdala plays an important role in the encoding and retrieval of emotional memories due to its modulating role on the hippocampus (Dolcos *et al.*, 2004; McGaugh, 2004; Fastenrath *et al.*, 2014). While this is a fundamental neurobiological process, amygdala reactivity can become dysregulated in mental disorders like depression and anxiety. In depression, an overly active amygdala response to negative information leads to better and more frequent encoding and retrieval of this negative information (Hamilton & Gotlib, 2008; Hamilton *et al.*, 2012; Beesdo *et al.*, 2009; Yang *et al.*, 2010). This fuels persistent negative thoughts and memories, which can in turn contribute to the development and maintenance of depressive symptoms. In Chapter 3, we found an association between left amygdala reactivity to negative emotional information and negative memory bias (without the explicit self-referent aspect) in individuals with diverse mental disorders, but not in non-disordered controls. This matches the current literature and expands it to a wider range of mental disorders and their comorbidities, providing more insight into the neurobiological underpinnings of memory bias.

We also tested whether there would be an association between amygdala reactivity to negative emotional information and negative endorsement bias (i.e., the explicit self-referent aspect only) and negative self-referent memory bias (both aspects combined), which we did not find. A possible explanation for this is that the intention of the emotional faces processing task is to elicit an amygdala response, which it has proven to do in varied (clinical) samples (Hariri *et al.*, 2002; Tessitore *et al.*, 2005; Stein *et al.*, 2007; Beesdo *et al.*, 2009; Peluso *et al.*, 2009; Yang *et al.*, 2010; Geissberger *et al.*, 2020), but that self-referent processing is not explicitly targeted

in this task. It is therefore understandable that there was no association with the two bias measures that reflect self-referent processing. Although amygdala reactivity is part of the neural pathway that underlies self-referent processing and the activation of self-schemas, higher and intermediate order areas like the anterior cingulate cortex and medial prefrontal cortex are also involved. A hyperactive circuit involving these three structures is believed to facilitate and maintain the negative self-referent beliefs of someone with depression (Disner *et al.*, 2011), but these are not captured in a straightforward amygdala reactivity task. Further research is needed to understand the neurobiological mechanisms underlying positive and negative self-referent memory bias.

Digging deeper: the roles of self-referent processing and memory

The work in this thesis has a strong focus on depression, given that self-referent memory bias is one of its more common characteristics. The findings indeed show that self-referent memory bias is associated with depression and its symptom severity. This association is mostly driven by the self-referent processing of negative information (i.e., the endorsement phase of the SRET). Previous research has shown that only self-referent processing of negative information is relevant for depressive symptoms and that the memory aspect has little additional value (Dainer-Best *et al.*, 2018a). One might wonder whether this self-referent processing of negative information is a near one-to-one translation of assessing depressive symptoms with a self-report questionnaire. However, while the depressive symptoms of sadness, guilt, punishment, self-dislike, suicidal thoughts, indecision, and change in sleep are most strongly associated with the endorsement of negative information, they together only explain 34-45% of variance in negative endorsement (Beevers *et al.*, 2019). This shows that other, additional aspects play a crucial role in the process of self-referent processing of negative information. We believe that memory plays an important role. We argue that memory bias is also a transdiagnostic mechanism of depressotypic cognition that is present across a range of mental disorders. The role of memory bias has explicitly been put forward in Beck and Haigh's generic cognitive model (Beck & Haigh, 2014). So while endorsing positive and negative (depression-specific) words indeed links closely to assessing depressive symptoms and perhaps more broadly, self-esteem, the recall component of the self-referent memory bias score is central to the assessment of the underlying psychopathological mechanism (or intermediate phenotype, see e.g., Vrijsen *et al.*, 2015). By taking this into account, we focus on deeper, underlying mechanisms rather than just the symptom level.

Strengths and limitations

A main strength of this thesis is the use of large naturalistic psychiatric samples and matched non-disordered controls. In all three chapters, the MIND-Set cohort was used; all patients in this cohort were diagnosed by trained professionals using standardised diagnostic instruments and all matched controls underwent the same diagnostic interviews to ensure the absence of any mental disorders. The MIND-Set cohort is known for its representative nature; rather than focusing only on different stress-related disorders or on neurodevelopmental disorders alone, it covers a range of disorders and their comorbidities, which reflects the high multimorbidity found in clinical practice. The sample is also representative in terms of age range, gender, education level, and any somatic comorbidities. Unique cohorts like this are needed to investigate possible shared psychopathological mechanisms that can contribute to restructuring the psychiatric classification system. And when the goal is to investigate mechanisms and tasks that might be of clinical relevance, it is crucial that they are tested in samples similar to those found in clinical reality.

Another strength is the use of validated questionnaires for the different symptom severity levels, and robust, well-known tasks like the SRET and emotional faces processing task to assess self-referent memory bias and amygdala reactivity. Because these tasks are the same or very similar to those used in the existing literature, the findings presented in this thesis build upon and expand the existing knowledge instead of diluting it by adopting different paradigms to investigating the same mechanisms and processes. In addition, the research in this thesis spans different units of analysis: neuropsychological measures are linked to self-report outcomes and neuroimaging results, and computational models are utilised in novel ways. The work presented here contributes to the core RDoC principle; to understand mechanisms at different levels across the psychiatric spectrum with the ultimate aim to find new transdiagnostic treatment targets and preventative interventions.

A possible limitation is the use of relatively few positive and negative words in the SRET; 12 of each valence. A recurrent finding was the low number of words both endorsed as self-referent and recalled. In some instances, this was zero, meaning it was not possible to calculate a self-referent memory bias score, according to the method used by e.g., Bradley & Mathews (1983) and Gotlib and colleagues (2004). The relatively few positive and negative words also meant that the DDM parameters could not be extracted for all participants. This posed methodological challenges. While using a total of 24 words for the SRET remains common practice, other studies applying the DDM to the SRET have often opted for a larger number of words, usually a minimum of 24 per valence (Hsu *et al.*, 2020; Beevers *et al.*, 2019; Castagna

et al., 2023; Hitchcock *et al.*, 2023; Terpstra *et al.*, 2023). A downside of using more words is of course a longer task length, whereas the briefness of this task is one of its strengths. Carefully selecting the optimal number of words suitable for the intended use with or without computational parameters is thus important. Another thing to consider when using the SRET is that it is intended as an implicit learning task; i.e., people are not informed about the recall phase. If the SRET is to be used to assess depressive symptoms at multiple timepoints, this will likely have an effect and should be taken into account. Finally, all studies in this thesis are cross-sectional studies. While we were able to answer our research questions with the available data, we can only speculate about the possible clinical implementations of our findings in terms of predictive value or usefulness in assessing depressive symptoms over time.

Clinical relevance and future directions

In this thesis, we showed that self-referent memory bias can play an important role in approaching psychopathology from a transdiagnostic perspective. In this section, I would like to discuss the clinical relevance of the findings and which further research is needed for the implementation of self-referent memory bias in (clinical) practice. First, we found that left amygdala reactivity can be considered a neural marker of memory bias across different mental disorders. This advances our understanding of the neural processes related to this cognitive process and expands them to other mental disorders as well. Considering the rising healthcare costs and pressure on healthcare workers, an MRI scan as standard part of the psychiatric diagnostic procedure might seem unlikely. However, future research into the usefulness of self-referent memory bias in the selection of the optimal treatment or the prediction of treatment effects could eventually outweigh the limitations. The SRET alone, on the other hand, provides a short and simple computerised assessment procedure. It could even be conducted anywhere via a smartphone since it requires no supervision and includes brief, clear instructions.

If our results are further substantiated and extended to include more evidence for the predictive power of self-referent memory bias on symptoms of psychopathology (Johnson *et al.*, 2007; LeMoult *et al.*, 2017; Weisenburger *et al.*, 2023), the SRET could be a strong candidate add-on tool in clinical practice. It could for example be used in addition to a pre-diagnostic screening questionnaire or as a more objective measure in addition to diagnostic interviews and self-report questionnaires. Furthermore, it might be a useful tool to assess and monitor or even predict (pharmacological) treatment effects. The SRET can thereby serve as a baseline and follow-up measure to assess short-term and longitudinal change in symptoms, although, as mentioned

above, the implicit learning effect will have to be taken into account here. Evidence for this has been accumulating over the years, but clinical implementation still awaits (Harmer *et al.*, 2003; Harmer *et al.*, 2009; Harmer *et al.*, 2017). It might even eventually be useful as an additional marker to predict which form or combination of treatments might be most effective, which requires linking self-referent memory bias to treatment outcomes. In addition, it could be a psychopathological vulnerability marker; a stronger negative self-referent memory bias or less positive self-referent memory bias might indicate a predisposition for the development of more mental disorders and can therefore be seen as an early warning sign.

To implement self-referent memory bias as useful clinical measure, several things related to the performance of the task and the calculation of outcomes require further investigation. The SRET has shown strong test-retest reliability over a one-day, one-week, and two-week period (Dainer-Best *et al.*, 2018a; Weisenburger *et al.*, 2023), but further tests are needed to assess this is a broader sample and over a longer timeframe. There are currently no norm scores yet for the SRET, which is something that large, combined, and shared datasets using Open Science platforms can contribute to. Normative modelling is a framework that also seems highly relevant for these suggested clinical implications. With normative modelling, self-referent memory bias outcomes from clinical and population samples can be mapped onto different symptoms of psychopathology to build a coordinate system that defines how different individuals vary (Marquand *et al.*, 2016; Rutherford *et al.*, 2022), matching the aim of personalised medicine. Finally, the SRET outcome measures now need to be calculated afterwards and might require additional programs or tools, for example to extract the DDM parameters. For optimal usage of this task, an efficient and user-friendly workflow will have to be designed that delivers the requested outcome measures, including their interpretation, directly into the clinical dossier.

An important aim of the RDoC project is to develop new therapy targets or find ways to apply existing therapies and interventions to treat symptoms based on shared underlying mechanisms. Challenges related to the clinical treatment of depression, in terms of non-response and relapse, have led to a focus on the mechanisms that contribute to its development and maintenance such as negative cognitive biases, which includes negative self-referent memory bias. Cognitive bias modification (CBM) is a computerised procedure aimed at modifying negative cognitive biases to relieve depressive symptoms. Compared to interpretation and attention bias modification, the evidence for memory bias modification is still limited, but with some promising results (Hertel & Mathews, 2011; Koster & Hoorelbeke, 2015; Arditte

Hall *et al.*, 2017; Vrijsen *et al.*, 2019; Visser *et al.*, 2020; Bovy *et al.*, 2022; Vrijsen *et al.*, 2024) and is therefore worthy of further exploration as transdiagnostic intervention to reduce depressive symptoms. In this thesis, we also showed that positive self-image and positive memories seem to play an important role in resilience and health. Therapeutic interventions like competitive memory training (COMET), a transdiagnostic imagery training aimed at enhancing self-esteem (Korrelboom *et al.*, 2009) that also reduces co-occurring depressive symptoms, are therefore important tools for those who are more vulnerable for developing or relapsing into depression and other mental disorders. We believe that the results from this thesis, showing the transdiagnostic relevance of self-referent memory bias in psychopathology, contribute both to the basic understanding of this cognitive mechanism and its future clinical implications.

References

Adler, O., & Pansky, A. (2020). A "rosy view" of the past: Positive memory biases. *Cognitive biases in health and disease*, 139-171.

Allan, N.P., Capron, D.W., Raines, A.M., & Schmidt, N.B. (2014). Unique relations among anxiety sensitivity factors and anxiety, depression, and suicidal ideation. *Journal of Anxiety Disorders*, 28, 266-275.

Allison, G.O., Benau, E.M., Asbaghi, S., Pagliacco, D., Stewart, J.G., & Auerbach, R.P. (2021). Neurophysiological markers related to negative self-referential processing differentiate adolescent suicide ideators and attempters. *Biological Psychiatry Global Open Science*, 1, 1, 16-27.

American Psychiatric Association (2022*). Diagnostic and Statistical Manual of Mental Disorders* (5th ed., text rev.). https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787

Arditte Hall, K.A., De Raedt, R., Timpano, K.R., & Joormann, J. (2018). Positive memory enhancement training for individuals with major depressive disorder. *Cognitive Behaviour Therapy*, 47, 2.

Arnold, J.F., Fitzgerald, D.A., Fernandez, G., Rijpkema, M., Rinck, M., Eling, P.A.T.M., Becker, E.S., … & Tendolkar, I. (2011). Rose or black-coloured glasses? Altered neural processing of positive events during memory formation is a trait market of depression. *Journal of Affective Disorders*, 131, 214-223.

Baas, D., Aleman, A., & Kahn, R. S. (2004). Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. *Brain Research Reviews*, 45, 96-103.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum Quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31, 5-17.

Beck, A. T. (1974). The development of depression: a cognitive model. In Friedman, R. J. & Katz, M. M. (Eds.), *The psychology of depression: contemporary theory and research*. Oxford, England: John Wiley & Sons.

Beck, A. T. (1987). Cognitive models of depression. *Journal of Cognitive Psychotherapy*, 1, 5–37.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry*, 165, 969-977.

Beck, A.T., & Bredemeier, K. (2016). A unified model of depression: integrating clinical, cognitive, biological, and evolutionary perspectives. *Clinical Psychological Science*, 4, 596-619.

Beck, A.T., & Haigh, A.P. (2014). Advances in cognitive theory and therapy: The generic cognitive model. *Annual Review of Clinical Psychology*, 10, 1-24.

Beck, A.T., Steer, R.A., & Brown, G. (1996). Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation.

Becker, E.S., Vanderhasselt, M., & Vrijsen, J.N. (2015). Memory training in depression. *Current Opinion in Psychology*, 4, 48-52.

Beesdo, K., Lau, J.Y.F., Guyer, A.E., McClure-Tone, E.B., Monk, C.S., Nelson, E.E., Fromm, S.K., … & Pine, D.S. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry*, 66, 275-285.

Beevers, C.G., Mullarkey, M.C., Dainer-Best, J., Stewart, R.A., Labrada, J., Allen, J.J.B., … & Shumake, J. (2019). Association between negative cognitive bias and depression: a symptom-level approach. *Journal of Abnormal Psychology*, 128, 212-227.

Benau, E.M., Hill, K.E., Atchley, R.A., O'Hare, A.J., Gibson, L.J., Hajcak, G., Ilardi, S.S., & Foti, D. (2019). Increased neural sensitivity to self-relevant stimuli in major depressive disorder. *Psychophysiology*, doi: 10.1111/psyp.13345.

Bovy, L., Ikani, N., van de Kraats, L. N., Dresler, M., Tendolkar, I., & Vrijsen, J. N. (2022). The effects of daily autobiographical memory training on memory bias, mood and stress resilience in dysphoric individuals. *Scientific Reports*, *12*(1), 20873.

Bradley, B., & Mathews, A. (1983). Negative self-schemata in clinical depression. *British Journal of Clinical Psychology*, 22, doi: https://doi.org/10.1111/j.2044-8260.1983.tb00598.x

Bradley, B.P., Mogg, K., & Williams, R. (1995). Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. *Behaviour Research and Therapy*, 33, 755-770.

Bradley, M. M., & Lang, P. J. (1999). *Affective norms for English words (ANEW): Instruction manual and affective ratings*. Technical report C-1, The Center for Research in Psychophysiology, University of Florida.

Brett, M., Anton, J., Valabregue, R., & Poline, J. (2002). Region of interest analysis using an SPM toolbox [Abstract]. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, Sendai, Japan.

Brockmeyer, T., Kulessa, D., Hautzinger, M., Bents, H., & Backenstrass, M. (2015). Mood-incongruent processing during the recall of a sad life event predicts the course and severity of depression. *Journal of Affective Disorders*, 187, 91-96.

Brolsma, S.C.A., Vassena, E., Vrijsen, J.N., Sescousse, G., Collard, R.M., Van Eijndhoven, P.F.P., Schene, A.H., & Cools, R. (2021). Negative learning bias in depression revisited: enhanced neural response to surprising reward across psychiatric disorders. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 6, 280-289.

Burt, D.B., Zembar, M.J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, 117, 285-305.

Castagna, P.J., Waters, A.C., Crowley, M.J. (2023). Computational modelling of self-referential processing reveals domain general associations with adolescent anxiety symptoms. *Research on Child and Adolescent Psychopathology*, 51, 455-468.

Chandrasekhar, T., & Sikich, L. (2015). Challenges in the diagnosis and treatment of depression in autism spectrum disorders across the lifespan. *Dialogues in Clinical Neuroscience*, 17, 219-227.

Chen, J., Short, M., & Kemps, E. (2020). Interpretation bias in social anxiety: A systematic review and meta-analysis. *Journal of Affective Disorders*, 1, 276, 1119-1130.

Clerkin, E.M., Beard, C., Fisher, C.R., & Schofield, C.A. (2015). An attempt to target anxiety sensitivity via cognitive bias modification. *PLoS One*, 10, doi:10.1371/journal.pone.0114578.

Coles, M. E., & Heimberg, R. G. (2002). Memory biases in the anxiety disorders: current status. *Clinical Psychology Review*, 22, 587-627.

Conners, C.K., Erhardt, D., Epstein, J.N., Parker, D.A., Sitarenios, G., & Sparrow, E. (1999). Self-ratings of ADHD symptoms in adults I: factor structure and normative data. *Journal of Attention Disorders*, 3, 141-151.

Cuthbert, B.N., & Insel, T.R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine*, 11, 126.

Dahl Askelund, A., Schweizer, S., Goodyer, I.M., & Van Harmelen, A. (2019). Positive memory specificity is associated with reduced vulnerability to depression. *Nature Human Behaviour*, 3, 265-273.

Dainer-Best, J., Disner, S.G., McGeary, J.E., Hamilton, B.J., & Beevers, C.G. (2018b). Negative self-referential processing is associated with genetic variation in the serotonin transporter-linked polymorphic region (5-HTTLPR): Evidence from two independent studies. *PLoS One, 13,* https://doi.org/10.1371/journal.pone.0198950

Dainer-Best, J., Lee, H.Y., Shumake, J.D., Yeager, D.S., & Beevers, C.G. (2018a). Determining optimal parameters of the self-referent encoding task: A large-scale examination of self-referent cognition and depression. *Psychological Assessment*, 30, 1527-1540.

Dalgleish, T., & Watts, F.N. (1990). Biases of attention and memory in disorders of anxiety and depression. *Clinical Psychology Review*, 10, 589-604.

Dalgleish, T., & Werner-Seidler, A (2014). Disruptions in autobiographical memory processing in depression and the emergence of memory therapeutics. *Trends in Cognitive Sciences*, 18, 11, 596-604.

De Graaf, R., Bijl, R.V., Spijker, J., Beekman, A.T.F., & Vollebergh, W.A.M. (2003). Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders. *Social Psychiatry and Psychiatric Epidemiology*, 38, 1-11.

Deacon, B., & Abramowitz, J. (2006). Anxiety sensitivity and its dimensions across the anxiety disorders. *Journal of Anxiety Disorders*, 20, 837-857.

Del Valle, C.H.C., & Mateos, P.M. (2018). Implicit Mood Congruent Memory Bias in Subclinical Depression. *International Journal of Cognitive Therapy*, 11, 287-298.

Derry, P. A., & Kuiper, N. A. (1981). Schematic processing and self-reference in clinical depression. *Journal of Abnormal Psychology*, 90, 286-297.

Disner, S.G., Beevers, C.G., Haigh, E.A.P., & Beck, A.T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, 12, 467-477.

Disner, S.G., Shumake, J.D., & Beevers, C.G. (2017). Self-referential schemas and attentional bias predict severity and naturalistic course of depression symptoms. *Cognition and Emotion*, 31, 4, doi: https://doi.org/10.1080/02699931.2016.1146123.

Dobson, K. S., & Shaw, B. F. (1987). Specificity and stability of self-referent encoding in clinical depression. *Journal of Abnormal Psychology*, 96, 34-40.

Dolcos, F., LaBar, S.S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron*, 42, 855-863.

Dozois, D.J.A., & Dobson, K.S. (2001). A longitudinal investigation of information processing and cognitive organisation in clinical depression: Stability of schematic interconnectedness. *Journal of Consulting and Clinical Psychology*, 69, 6, 914-925.

Duyser, F.A., Van Eijndhoven, P.F.P., Bergman, M.A., Collard, R.M., Schene, A.H., Tendolkar, I., & Vrijsen, J.N. (2020). Negative memory bias as a transdiagnostic cognitive marker for depression symptom severity. *Journal of Affective Disorders*, 274, 1165-1172.

Egan, L.A., Park, H.R.P., Lam, J., & Gatt, J.M. (2024). Resilience to stress and adversity: a narrative review of the role of positive affect. *Psychology Research and Behavior Management*, 17, 2011-2038.

Everaert, J., Vrijsen, J.N., Martin-Willett, R., Van de Kraats, L., & Joormann, J. (2022). A meta-analytic review of the relationship between explicit memory bias and depression: Depression features an explicit memory bias that persists beyond a depressive episode. *Psychological Bulletin*, 148, 435-463.

Fastenrath, M., Coynel, D., Spalek, K., Milnik, A., Gschwind, L., Roozendaal, B., & De Quervain, D.J.F. (2014). Dynamic modulation of amygdala-hippocampal connectivity by emotional arousal. *Journal of Neuroscience*, 34, 13935-13947.

Fernández, G., & Morris, R.G. (2018). Memory, novelty and prior knowledge. *Trends in Neuroscience*, 41, 654-659.

First, M.B., & Gibbon, M. (2004). The structured clinical interview for DSM-IV axis I disorders (SCID-I) and the structured clinical interview for DSM-IV axis II disorders (SCID-II). In M.J. Hilsenroth & D.L. Segal (Eds.), *Comprehensive handbook of psychological assessment, Vol. 2. Personality assessment* (pp. 134-143). John Wiley & Sons, Inc.

Freeth, M., Ropar, F., Chapman, P., & Mitchell, P. (2010). The eye gaze direction of an observed person can bias perception, memory and attention in adolescents with and without autism spectrum disorder. *Journal of Experimental Child Psychology*, 105, 20-37.

Fu, C.H., Williams, S.C., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., … & Bullmore, E.T. (2004). Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Archives of General Psychiatry,* 61, 877-889.

Gargaro, B.A., Rinehart, N.J., Bradshaw, J.L., Tonge, B.J., & Sheppard, D.M. (2011). Autism and ADHD: how far have we come in the comorbidity debate? *Neuroscience & Biobehavioural Reviews*, 35, 1081-1088.

Geissberger, N., Tik, M., Sladky, R., Woletz, M., Schuler, A., Willinger, D., & Windischberger, C. (2020). Reproducibility of amygdala activation in facial emotion processing at 7T. *NeuroImage*, 211, 116585.

Gerritsen, L., M. Rijpkema, I. Van Oostrom, J. Buitelaar, B. Franke, G. Fernández, I. Tendolkar (2012). Amygdala to hippocampal volume ratio is associated with negative memory bias in healthy subjects. *Psychological Medicine*, 42, 335-343.

Gilboa, A., & Marlatte, H. (2017). Neurobiology of schemas and schema-mediated memory. *Trends in Cognitive Science*, 21, 618-631.

Godlewska, B.R., Norbury, R., Selvaraj, S., Cowen, P.J., & Harmer, C.J. (2012). Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychological Medicine*, 42(12), 2609-2617.

Goldstein, B.L., Hayden, E.P., & Klein, D.N. (2015). Stability of self-referent encoding task performance and associations with change in depressive symptoms from early to middle childhood. *Cognition and Emotion*, 29, 8, doi: https://doi.org/10.1080/02699931.2014.990358.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual Reviews in Clinical Psychology*, 6, 285-312.

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S.L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology*, 113, 386–398.

Gotlib, I.H., & Krasnoperova, E. (1998). Biased information processing as a vulnerability factor for depression. *Behavior Therapy*, 29, 603-617.

Gupta, R., & Kar, B.R. (2012). Attention and memory biases as stable abnormalities among currently depressed and currently remitted individuals with unipolar depression. *Frontiers in Psychiatry*, doi: 10.3389/fpsyt.2012.00099.

Hakamata, Y., Mizukami, S., Izawa, S., Okamura, H., Mihara, K., Marusak, H., Moriguchi, Y., … & Tagaya, H. (2022). Implicit and explicit emotional memory recall in anxiety and depression: Role of basolateral amygdala and cortisol-norepinephrine interaction. *Psychoneuroendocrinology*, 136, doi: https://doi.org/10.1016/j.psyneuen.2021.105598.

Hamilton, J. P., & Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological Psychiatry*, 63, 1155-1162.

Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., & Gotlib, I.H. (2012). Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of baseline activation and neural response data. *The American Journal of Psychiatry*, 169, 693-703.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, … & Weinberger, D.R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, 297, 400-403.

Harkin, B., Snyder, H.R., Gulley, L.D., Schweizer, T.H., Bijttebier, P., Nelis, S., Toh, G., & Vasey, M.W. (2016). Understanding comorbidity among internalizing problems: Integrating latent structural models of psychopathology and risk mechanisms. *Development and Psychopathology*, 28, 987-1012.

Harmer, C.J., Duman, R.S., & Cowen, P.J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry*, 4, 409-418.

Harmer, C.J., Goodwin, G.M., & Cowen, P.J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry*, 195, 102-108.

Harmer, C.J., Hill, S.A., Taylor, M.J., Cowen, P.J., & Goodwin, G.M. (2003). Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *The American Journal of Psychiatry*, 160, 990-992.

Henderson, H. A., Zahka, N. E., Kojkowski, N. M., Inge, A. P., Schwartz, C. B., … Mundy, P. C. (2009). Self-referenced memory, social cognition, and symptom presentation in autism. *The Journal of Child Psychology and Psychiatry*, 50, 853-861.

Hertel, P. T., & Mathews, A. (2011). Cognitive bias modification: past perspectives, current findings, and future applications. *Perspectives on Psychological Science*, 6, 521-536.

Hitchcock, P.F., Britton, W.B., Mehta, K., & Frank, M.J. (2023). Self-judgment dissected: A computational modelling analysis of self-referential processing and its relationship to trait mindfulness facets and depression symptoms. *Cognitive, Affective, & Behavioral Neuroscience*, 23, 171-189.

Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Stahlberg, O., Herbrecht, E., … & Leboyer, M. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry*, 9, doi: 10.1186/1471-244X-9-35.

Hsu, K.J., McNamara, M.E., Shumake, J., Stewart, R.A., Librada, J., Alario, A., Gonzalez, G.D.S., Schnyder, D.M., & Beevers, D.G. (2020). Neurocognitive predictors of self-reported reward responsivity and approach motivation in depression: A data-driven approach. *Depression and Anxiety*, 37, 682-697.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, 167, 7, doi: https://doi.org/10.1176/appi.ajp.2010.09091379.

Insel, T.R. (2014). The NIMH Research Domain Criteria (RDoC) project: precision medicine for psychiatry. *American Journal of Psychiatry*, 171, 395-397.

Johnson, S.L., Joormann, J., & Gotlib, I.H. (2007). Does processing of emotional stimuli predict symptomatic improvement and diagnostic recovery from major depression? *Emotion*, 7, 201-206.

Joormann, J. & Arditte, K.A. (2015). Cognitive aspects of depression. In Gotlib I.H., Hammen, C. (Eds.) *Handbook of depression* (pp. 298-321). New York, NY: Guilford.

Joormann, J., & Stanton, C. H. (2016). Examining emotion regulation in depression: a review and future directions. *Behaviour Research and Therapy*, 86, 35-49.

Joshi, G., Wozniak, J., Petty, C., Martelon, M., Fried, R., Bolfek, A., Kotte, A., … & Biederman, J. (2013). Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *Journal of Autism and Developmental Disorders*, 43, 1314-1325.

Kalenzaga, S., & Jouhaud, V. (2018). The self-reference effect in memory: an implicit way to assess affective self-representations in social anxiety. *Memory*, 26, 894-903.

Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K., & Walters, E.E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, 62, 617-627.

Koekkoek, B., Manders, W., Tendolkar, I., Hutschemaekers, G., & Tiemens, B. (2016). The MATCH cohort study in the Netherlands: Rationale, objectives, methods, and baseline characteristics of patients with (long-term) common mental disorders. *International Journal of Methods in Psychiatric Research*, 26, 1, doi: https://doi.org/10.1002/mpr.1512.

Kooij, J.J.S. (2010). Diagnostic Interview for ADHD in Adults 2.0 (DIVA 2.0). In *Adult ADHD. Diagnostic assessment and treatment*. Amsterdam: Pearson Assessment and Information BC.

Korrelboom, K., Van der Weele, K., Gjaltema, M., & Hoogstraten, C. (2009). Competitive memory training for treating low self-esteem: A pilot study in a routine clinical setting. *The Behavior Therapist*, 32, 3-8.

Koster, E.H.W., & Hoorelbeke, K. (2015). Cognitive bias modification for depression. *Current Opinion in Psychology*, 4, 119-123.

Koster, E.H.W., Combez, G., Verschuere, B., & De Houwer, J. (2006). Attention to threat in anxiety-prone individuals: Mechanisms underlying attentional bias. *Cognitive Therapy and Research*, 30, 635-643.

Lang, T. J., Moulds, M. L., & Holmes, E. A. (2009). Reducing depressive intrusions via a computerizes cognitive bias modification of appraisal task: developing a cognitive vaccine. *Behaviour Research and Therapy*, 47, 139-145.

Lavigne, K.M., Deng, J., Raucher-Chéne, D., Hotte-Meunier, A., Voyer, C., Sarraf, L., Lepage, M., & Sauvé, G. (2024). Transdiagnostic cognitive biases in psychiatric disorders : A systematic review and network meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 129, https://doi.org/10.1016/j.pnpbp.2023.110894

Lecrubier, Y., Sheehan, D.V., Weiller, E., Amorim, P., et al. (1997). The MINI International Neuropsychiatric Interview (M.I.N.I.), a short diagnostic structured interview: Reliability and validity according to the CIDI. European Psychiatry, 12, 224-231.

LeMoult, J., & Gotlib, I.H. (2019). Depression: a cognitive perspective. *Clinical Psychology Review*, 69, 51-66.

LeMoult, J., Kircanski, K., Prasad, G., & Gotlib, I.H. (2017). Negative self-referential processing predicts the recurrence of major depressive episodes. *Clinical Psychological Science*, 5, 174-181.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the structured clinical interview for DSM-IV axis I disorders (SCID-I) and axis II disorders (SCID-II). *Clinical Psychology and Psychotherapy*, 18, 75-79.

MacLeod, C., Grafton, B., & Notebaert, L. (2019). Anxiety-linked attentional bias: Is it reliable? *Annual Review of Clinical Psychology*, 15, 529-554.

Marchetti, I., Everaert, J., Dainer-Best, J., Loeys, T., Beevers, C.G., & Koster, E.H.W. (2018). Specificity and overlap of attention and memory biases in depression. *Journal of Affective Disorders,* 225, 404-412.

Marquand, A.F., Rezek, I., Buitelaar, J., & Beckmann, C.F. (2016). Understanding heterogeneity in clinical cohorts using normative models: beyond case-control studies. *Biological Psychiatry*, 80, 552-561.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, 1, 167-195.

Matt, G.E., Vàzquez, C., Campbell, W.K. (1992). Mood-congruent recall of affectively toned stimuli: a meta-analytic review. *Clinical Psychology Review*, 12, 227-255.

McDonald, M.R., & Kuiper, N.A. (1985). Efficiency and automaticity of self-schema processing in clinical depressives. *Motivation and Emotion*, 9, 171-184.

McGaugh, J.L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience*, 27, 1-28.

Miranda, R., Fontes, M., & Marroquin, B. (2008). Cognitive content-specificity in future expectancies: role of hopelessness and intolerance of uncertainty in depression and GAD symptoms. *Behaviour Research and Therapy*, 46, 1151-1159.

Miskowaik, K.W., & Carvalho, A.F. (2014). 'Hot' cognition in major depressive disorder: a systematic review. *CNS & Neurological Disorders - Drug Targets,* 13, 1787-1803.

Moulds, M.L., Kandris, E., & Williams, A.D. (2007). The impact of rumination on memory for self-referential material. *Memory*, 15, 8, 814-821.

Munafò, M., Brown, S., Hariri, A. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry*, 63, 852-857.

Nagrodzki, J., Passamonti, L., Schweizer, S., Stretton, J., Knights, E., Henson, R., Can, & Wolpe, N. (2023). Behavioural and neuroimaging correlates of attentional biases to angry faces in individuals in remission from depression: a population-derived study. *bioRxiv,* doi: https://doi.org/10.1101/2023.03.13.532400.

Nikendei C., Weisbrod M., Schild S., Bender S., Walther S., Herzog W., … Friederich H. C. (2008). Anorexia nervosa: selective processing of food-related word and pictorial stimuli in recognition and free recall tests. International Journal of Eating Disorders, 41, 439–447.

Orchard, F., & Reynolds, S. (2018). The combined influence of cognitions in adolescent depression: Biases of interpretation, self-evaluation, and memory. *British Journal of Clinical Psychology*, 57, 4, 420-435.

Parker, A.J., & Adleman, N.E. (2021). Current mood influences biases for positive and negative stimuli. *Current Psychology*, doi: https://doi.org/10.1007/s12144-021-01686-8.

Peluso, M.A.M., Glahn, D.C., Matsuo, K., Monkul, E.S., Najt, P., Zamarripa, F., Li, J., … & Soares, J.C. (2009). Amygdala hyperactivation in untreated depressed individuals. *Psychiatry Research: Neuroimaging*, 173, 158-161.

Phelps, E.A., & LeDoux, J.E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behaviour. *Neuron*, 48, 175-187.

Powers, M., Davis, M., Kauffman, B., Baird, S., Zvolensky, M., Marcus, B., … Smits, J.A. (2016). Anxiety sensitivity and smoking variability among treatment seeking smokers. Addictive Disorders & Their Treatment, 15, 136-142.

Ramel, W., Goldin, P.R., Eyler, L.T., Brown, G.G., Gotlib, I.H., & McQuaid, J.R. (2007). Amygdala reactivity and mood-congruent memory in individuals at risk for depressive relapse. *Biological Psychiatry*, 61, 231-239.

Ramos-Quiroga, J.A., Nasillo, V., Richarte, V., Corrales, M., Palma, F., Ibanez, P., Michelsen, M., … & Kooij, J.J.S. (2019). Criteria and concurrent validity of DIVA 2.0: A semi-structured diagnostic interview for adult ADHD. *Journal of Attention Disorders*, 23, 1126-1135.

Ratcliff, R., & Rouder, J.N. (1998). Modeling response times for two-choice decisions. *Psychological Science*, 9, 5, 347-356.

Raven, J.C. (1958). Standard progressive matrices. London: Lewis.

Rijkeboer, M.M., Van den Bergh, H., & Van den Bout, J. (2005). Stability and discriminative power of the Young Schema-Questionnaire in a Dutch clinical versus non-clinical population. *Journal of Behavior Therapy and Experimental Psychiatry*, 36, 2, 129-144.

Riskind, J.H., Kleiman, E.M., & Schafer, K.E. (2013). Undoing effects of positive affect: does it buffer the effects of negative affect in predicting changes in depression? *Journal of Social and Clinical Psychology*, 32, 363-380.

Rodriguez, B.F., Bruce, S.E., Pagano, M.E., Spencer, M.A., Keller, M.B. (2004). Factor structure and stability of the Anxiety Sensitivity Index in a longitudinal study of anxiety disorder patients. *Behaviour Research and Therapy*, 42, 79-91.

Romero, N., Sanchez, A., & Vazquez, C. (2014). Memory biases in remitted depression: The role of negative cognitions at explicit and automatic processing levels. *Journal of Behavior Therapy and Experimental Psychiatry*, 45, 1, 128-135.

Rosenberg, C.E. (2006). Contested boundaries: Psychiatry, disease, and diagnosis. *Perspectives in Biology and Medicine*, 49, 3, 407-424.

Roxin, A. (2019). Drift-diffusion models for multiple-alternative forced-choice decision making. *The Journal of Mathematical Neuroscience*, 9, doi: https://doi.org/10.1186/s13408-019-0073-4

Royer, F. L. (1971). Information processing of visual figures in the digit symbol substitution task. *Journal of Experimental Psychology*, 87, 335-342.

Rush, A.J., Guillion, C.M., Basco, M.R., Jarrett, R.N., & Trivedi, M.H. (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine*, 26, 477-486.

Rutherford, S., Kia, S.M., Wolfers, T., Fraza, C., Zabini, M., Dinga, R., Worker, A., … & Marquand, A.F. (2022). The normative modelling framework for computational psychiatry. *Nature Protocols*, 17, 1711-1734.

Schippers, G.M., Broekman, T.G., & Buchholz, A. (2011). *Manual and protocol*. English Edition: W.M. Cox. Nijmegen: Bèta Boeken.

Sedikides, C., Gaertner, L., & Cai, H. (2015). On the panculturality of self-enhancement and self-protection motivation: the case for the universality of self-esteem. *Advances in Motivation Science*, 2, 185-241.

Sharma, S., Powers, A., Bradley, B., & Ressler, K.J. (2016). Gene × environment determinants of stress- and anxiety-related disorders. *Annual Review of Psychology,* 67, 239-261.

Sheehan, D.V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., … & Dunbar, D.C. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, 12, 5, 232-241.

Siegle, G. J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., & Carter, C.S. (2002). Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry*, 51, 693-707.

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., & Thase, M. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry*, 61, 198-209.

Speer, M.E., & Delgado, M.R. (2017). Reminiscing about positive memories buffers acute stress responses. *Nature Human Behaviour*, 1, 0093.

Stalmeier, T.D.M., Lubbers, J., Cladder-Micus, M.B., Hanssen, I., Huijbers, M.J., Speckens, A.E.M., & Geurts, D.E.M. (2021). Mindfulness based cognitive therapy (MBCT) reduces depression-related self-referential processing in patients with bipolar disorder: An exploratory task-based study. *Cognition and Emotion*, 36, 7, 1255-1272.

Stein, M.B., Simmons, A.N., Feinstein, J.S., & Paulus, M.P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, 164, 318-327.

Stronks, K., Snijder, M.B., Peters, R.J., Prins, M., Schene, A.H., & Zwinderman, A.H. (2013). Unravelling the impact of ethnicity on health in Europe: the HELIUS study. *BMC Public Health*, doi: 10.1186/1471-2458-13-402.

Surguladze, S., Brammer, M.J., Keedwell, P., Giampietro, V., Young, A.W., & Travis, M.J. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry*, 57, 201-209.

Symons, & Johnson (1997). The self-reference effect in memory: A meta-analysis. *Psychological Bulletin*, 121, 371-394.

Terpstra, A.R., Vila-Rodriguez, F., LeMoult, J., Chakrabarty, T., Nair, M., Humaira, A., Gregory, E.C., & Todd, R.M. (2023). Cognitive-affective processed and suicidality in response to repetitive transcranial magnetic stimulation for treatment resistant depression. *Journal of Affective Disorders*, 321, 182-190.

Tessitore, A., Hariri, A.R., Fera, F., Smith, W.G., Das, S., Weinberger, D.R., & Mattay, V.S. (2005). Functional changes in the activity of brain regions underlying emotion processing in the elderly. Psychiatry Research: Neuroimaging, 139, 9-18.

Thapar, A., Cooper, M., Rutter, M. (2017). Neurodevelopmental disorders. *The Lancet Psychiatry*, 4, 339-346.

Van Eijndhoven, P.F.P., Collard, R.M., Vrijsen, J.N., Geurts, D.G.M., Arias-Vasquez, A., Schellekens, A.F.A., van den Munckhof, E., … & Schene, A.H., 2021. Measuring Integrated Novel Dimensions in Neurodevelopmental and Stress-related Mental Disorders (MIND-Set): a cross-sectional comorbidity study from an RDoC perspective. medRxiv, https://www.medrxiv.org/content/10.1101/2021.06.05.21256695v1

Van Harmelen, A.L., van Tol, M.J., Demenescu, L.R., van der Wee, N.J., Veltman, D.J., Aleman, A., … & Elzinga, B.M. (2013). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience*, 8, 362-369.

Van Kesteren, M.T.R., Ruiter, D.J., Fernández, G., & Henson, R.N. (2012). How schema and novelty augment memory function. *Trends in Neursociences*, 35, 211-219.

Van Oostrom, I., Franke, B., Rijpkema, M., Gerritsen, L., Arias-Vásques, A., Fernández, G., & Tendolkar, I. (2012). Interaction between BDNF Val66Met and childhood stressful life events is associated to affective memory bias in men but not women. *Biological Psychology*, 89, 1, 214-219.

Vanderlind, W.M., Millgram, Y., Baskin-Sommers, A.R., Clark, M.S., & Joormann, J. (2020). Understanding positive emotion deficits in depression: From emotion preferences to emotion regulation. *Clinical Psychology Review*, https://doi.org/10.1016/j.cpr.2020.101826

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. Lancet Psychiatry, 3, 171-178.

Visser, D.A., Tendolkar, I., Schene, A.H., Van de Kraats, L., Ruhe, H.G., & Vrijsen, J.N. (2020). A pilot study of smartphone-based memory bias modification and its effect on memory bias and depressive symptoms in an unselected population. *Cognitive Therapy and Research*, 44, 61-72.

Vogel, S., Gerritsen, L., Van Oostrom, I., Arias-Vásquez, A., Rijpkema, M., Joëls, M., … Fernández, G. (2014). Linking genetic variants of the mineralcorticoid receptor and negative memory bias: Interaction with prior life adversity. Psychoneuroendocrinology, 40, 181-190.

Voss, A., & Voss, J. (2007). Fast-dm: A free program for efficient diffusion model analysis. *Behavior Research Methods*, 39, 767-775.

Voss, A., Rothermund, L., & Voss, J. (2004). Interpreting the parameters of the drif-diffusion model: An empirical validation. *Memory & Cognition*, 32, 1206-1220.

Vrijsen, J. N., Van Amen, C. T., Koekkoek, B., Van Oostrom, I., Schene, A. H., & Tendolkar, I. (2017). Childhood trauma and negative memory bias as shared risk factors for psychopathology and comorbidity in a naturalistic psychiatric patient sample. *Brain and Behaviour*, doi: 10.1002/brb3.693.

Vrijsen, J.N., Becker, E.S., Arias-Vásquez, A., Van Dijk, M.K., Speckens, A., & Van Oostrom, I. (2014). What is the contribution of different cognitive biases and stressful childhood events to the presence and number of previous depressive episodes? *Psychiatry Research*, 217, 134-142.

Vrijsen, J.N., Dainer-Best, J., Witcraft, S. M., Papini, S., Hertel, P., Beevers, C.G., … Smits, J.A.J. (2018b). Effect of cognitive bias modification-memory on depressive symptoms and autobiographical memory bias: two independent studies in high ruminating and dysphoric samples. *Cognition and Emotion*, 33, 288-304.

Vrijsen, J.N., Dainer-Best, J., Witcraft, S.M., Papini, S., Hertel, P., Beevers, C.G., Becker, E.S., & Smits, J.A.J. (2019). Effect of cognitive bias modification-memory on depressive symptoms and autobiographical memory bias: two independent studies in high-ruminating and dysphoric samples. *Cognition and Emotion*, 33, 288-304.

Vrijsen, J.N., Tendolkar, I., Arias-Vasquez, A., Franke, B., Schene, A.H., Fernandez, G., & Van Oostrom, I. (2015). Interaction of the 5-HTTLPR and childhood trauma influences memory bias in healthy individuals. *Journal of Affective Disorders*, 186, 83-89.

Vrijsen, J.N., Tendolkar, I., Onnink, M., Hoogman, M., Schene, A.H., Fernández, G., Van Oostrom, I., & Franke, B. (2018a). ADHD symptoms in healthy adults are associated with stressful life events and negative memory bias. *ADHD Attention Deficit and Hyperactivity Disorders*, 10, 151-160.

Vrijsen, J.N., Windbergs, H., Becker, E.S., Scherbaum, N., Müller, B.W., & Tendolkar, I. (2024). A randomized controlled pilot study exploring the additive clinical effect of cognitive bias modification-memory in depressed inpatients. *Cognitive Therapy and Research*, 48, 212-224.

Vuijk, R. (2016). *Nederlands Interview ten behoeven van Diagnostiek Autismespectrumstoornis bij volwassenen (NIDA)*. Rotterdam: Sarr Expertisecentrum Autisme/Dare to Design.

Wager, T. D., Phan, K. L., Liberzon, I., & Taylor, S.F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *NeuroImage*, 19, 513-531.

Watkins, E. (2015). An alternative transdiagnostic mechanistic approach to affective disorders illustrated with research from clinical psychology. *Emotion Review*, 7, 250-255.

Watkins, P.C., Vache, K., Verney, S.P., Muller, S., & Mathews, A. (1996). Unconscious mood-congruent memory bias in depression. *Journal of Abnormal Psychology*, 105, 34-41.

Weisenburger, R.L., Dainer-Best, J., Zisser, M., McNamara, M.E., & Beevers, C.G. (2023). Negative self-referent cognition predicts future depression symptom change: An intensive sampling approach. *Psyarxiv.com*, https://doi.org/10.31234/osf.io/3tn4c

Wiers, R.W., Boelema, S.R., Nikolaou, K., & Gladwin, T.E. (2015). On the development of implicit and control processes in relation to substance use in adolescence. *Current Addiction Reports*, 2, 141-155.

World Health Organization (2021). *International statistical classification of diseases and related health problems* (11th ed.). https://icd.who.int/en

Yang, T.T., Simmons, A.N., Matthews, S.C., Tapert, S.F., Frank, G.K., Max, J.E., Bischoff-Grethe, A., … & Paulus, M.P. (2010). Adolescents with major depression demonstrate increased amygdala activation. *Journal of the American Academy of Child & Adolescent Psychiatry*, 49, 42-51.

Young, J. E. (1990). *Cognitive therapy for personality disorders: a schema-focused approach*. Sarasota: Professional Resource Exchange.

Nederlandse samenvatting

Een depressie is een veelvoorkomende psychiatrische aandoening waar ongeveer een kwart van de mensen in Nederland ooit mee te maken krijgt. Eén van de kenmerken van een depressie is dat informatie op een andere manier verwerkt en onthouden wordt. Niet-depressieve mensen onthouden over het algemeen vaker positieve informatie en dit is een belangrijk beschermingsmechanisme wat bijdraagt aan het mentale welbevinden. Mensen met een depressie onthouden echter minder positieve informatie, maar negatieve informatie juist vaker en beter. Dit is vooral het geval wanneer deze informatie zelf-referent is en dus aansluit bij een negatief zelfbeeld en de negatieve gedachten die iemand al over zichzelf heeft ("Ik kan nooit iets goed doen"). Zij kunnen een compliment van een collega dus zo vergeten, terwijl een kritische opmerking over het werk wat ze afgeleverd hebben lang kan blijven hangen. Dit heet een negatieve geheugenbias en is het onderwerp van dit proefschrift.

Het is al lang bekend dat meer negatieve geheugenbias niet alleen een kenmerk is van een huidige depressieve episode, maar ook een risicofactor is voor het ontwikkelen van een depressie bij mensen die nog nooit een depressie hebben gehad of voor een terugval bij mensen die hersteld zijn van een eerdere depressieve episode. Interessant is dat recenter onderzoek laat zien dat meer negatieve geheugenbias óók een rol lijkt te spelen in andere psychiatrische aandoeningen zoals angststoornissen en ADHD. Dit past goed bij een initiatief in het psychiatrische onderzoeksveld dat al meer dan tien jaar gaande is. Het doel van dit initiatief is om buiten de bestaande hokjes van psychiatrische diagnoses te kijken en naar gedeelde onderliggende mechanismen te zoeken. Die mechanismen kunnen hopelijk een aantal belangrijke vragen beantwoorden. Waaronder: waarom kunnen twee mensen met dezelfde diagnose heel verschillende symptomen ervaren? Waarom zit er zoveel overlap in de symptomen van verschillende psychiatrische aandoeningen? En waarom komt het zo vaak voor dat mensen meerdere psychiatrische aandoeningen hebben (bijvoorbeeld depressie en een angststoornis)? Door op nieuwe manieren naar de onderliggende mechanismen te kijken, kan het diagnose proces verbeterd worden en kunnen er nieuwe en effectievere behandelingen ontwikkeld worden. Heel belangrijk hierbij is dat er onderzoek gedaan wordt in groepen met veel verschillende psychiatrische aandoeningen, waarbij er ook mensen tussen zitten die meerdere psychiatrische aandoeningen tegelijkertijd hebben. Met het MIND-Set project, wat tussen 2016 en 2021 op de Afdeling Psychiatrie van het Radboudumc is uitgevoerd, hebben

wij zo'n unieke groep patiënten op allerlei verschillende niveaus (van gedrag tot hersenstructuur en -functie) kunnen onderzoeken.

In dit proefschrift heb ik data van dit MIND-Set project gebruikt. Ik heb voor het eerst aangetoond dat negatieve geheugenbias een rol speelt in een breed scala aan psychiatrische aandoeningen. Ook heb ik laten zien dat de reactiviteit van de amygdala, een belangrijke hersenstructuur voor de verwerking van emoties, gerelateerd is aan een negatieve geheugenbias. Tot slot heb ik gekeken naar de taak die wordt gebruikt voor het meten van een negatieve geheugenbias en geef ik verschillende aanbevelingen voor hoe deze taak gebruikt zou kunnen worden in de klinische praktijk. De algehele conclusie van al dit onderzoek is dat negatieve geheugenbias een belangrijke gedeelde factor lijkt te zijn voor verschillende psychiatrische aandoeningen en belangrijke klinische implicaties kan hebben in de toekomst. Denk hierbij aan: het voorspellen van de beste behandeling, het meten van het effect van een behandeling, het verlichten van symptomen of zelfs het voorkomen daarvan. Het is hiervoor belangrijk dat er vervolgonderzoek wordt gedaan die negatieve geheugenbias in de praktijk test.

Data management

Ethics and privacy

Chapters 2, 3, and 4 are all based on data from the MIND-Set study (Van Eijndhoven *et al.*, 2021). This is a large cohort study that was initiated by the Department of Psychiatry of the Radboud university medical centre (Radboudumc) in Nijmegen, The Netherlands. The study complied with the Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO), the EU Data Protection Directive (AVG-GDPR), and all institutional regulatory requirements. An accredited medical research ethics committee (METC Oost-Nederland, previously CMO regio Arnhem-Nijmegen) approved the study (NL55618.091.15). MIND-Set was financially supported by the Radboudumc Department of Psychiatry, a grant from the Psychiatry Foundation, and the EU's Horizon 2020 research and innovation programme.

MIND-Set data was collected at the Department of Psychiatry of the Radboudumc and the Donders Centre for Cognitive Neuroimaging (DCCN). All participants received the study information in a timely manner, had the opportunity to ask questions, and gave written informed consent to collect and process their data for these research projects. Participants' privacy was ensured by the use of pseudonymisation. The pseudonymisation key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymisation key was stored separately from the research data. Chapter 4 additionally used existing data from the Info in Genes study (Vrijsen *et al.*, 2014) and MATCH study (Koekkoek *et al.*, 2016). These data were anonymous.

Data collection and storage

The MIND-Set data was obtained during two in-person testing sessions in the testing rooms of the Department of Psychiatry and at the DCCN. CastorEDC, a secure platform that is the standard at the Radboudumc, was used for the case report forms and online surveys. Data collected at the Department of Psychiatry was stored on the secure department server at the time of collection and was later moved to the Digital Research Environment (DRE). This allowed for secure storage where the availability, integrity, and confidentiality of the data is safeguarded. Data collected at the DCCN was stored in a Data Acquisition Collection (di.dccn.DAC_3013061.01_195) in the Radboud Data Repository (RDR) and was later moved to the DRE. As described in the participant information and consent form, data will be stored for 15 years.

Data sharing according to the FAIR principles

Participants did not consent to sharing their data. The data used in these projects are therefore not available in Data Sharing Collections in the RDR. However, the used datasets and scripts are archived in three separate Research Documentation Collections (di.dcmn.RDC_membias_t0000399a_874, di.dcmn.RDC_amygrea_t0000400a_846, and di.dcmn.RDC_sret_t0000401a_245) in the RDR. They will be archived for 15 years.

Curriculum vitae

After completing her secondary education, Fleur started studying Psychobiology at the University of Amsterdam in 2012. During this time, she completed the Honours Programme and went on an Erasmus+-funded exchange semester at the University of Copenhagen. She also did her undergraduate research internship at the Brain & Cognition Department of the University of Amsterdam where she worked on the computational modelling of decision making. In 2015, Fleur started the Cognitive Neuroscience research master at the Radboud University. Inspiring lectures about stress and psychopathology kindled her interest in the neurobiological underpinnings of mental disorders, so she decided to do her graduate research internship at the Radboudumc's Department of Psychiatry. There, the MIND-Set project had just kicked off and she was able to work on the relationship between childhood trauma, amygdala reactivity, and memory bias. She was also actively involved in the project's broader data collection and day-to-day coordination. After obtaining her master's degree in 2017, Fleur continued working for the MIND-Set project as research assistant and study coordinator until the end of 2019. Between November 2018 and December 2021, she worked on her PhD project in which she expanded and delved deeper into the research interests she explored during her internship, but in a much larger cohort and with more varied and advanced methods. During her PhD, she also enthusiastically participated in science communication activities, outreach events, and supervising. Since March 2022, Fleur works as research coordinator and research policy officer at the Donders Centre of Cognitive Neuroimaging.

PhD portfolio

During the PhD, several conferences, courses, and workshops were attended.

Conferences

- Nederlandse Vereniging voor Psychiatrie 2019 (Maastricht) – oral presentation
- British Neuroscience Association 2019 (Birmingham) – poster presentation
- Cognitive Affective Biases 2019 (Krakow) – oral presentation
- Vereniging voor Gedrags- en Cognitieve therapieën 2019 (Veldhoven) – oral presentation
- Cognitive Neuroscience Society 2021 (online) – poster presentation
- Organization for Human Brain Mapping 2021 (online) – oral presentation
- Association for Cognitive Bias Modification 2022 (online) – oral presentation

Courses

- Management voor promovendi, Radboud University, 2019
- Statistical Parametric Mapping, University College London, 2019
- The Art of Presenting Science, Radboud University, 2019
- MATLAB, Coursera, 2020
- Storytelling training, Radboud University, 2020
- The Art of Finishing Up, Radboud University, 2021

Additional activities include supervising research internships, outreach activities, such as representing the MIND-Set project at Radboudumc Open Days, and several talks at meetings and symposiums within the Radboudumc and Radboud University.

List of publications

- **Duyser, F.A.**, Van Eijndhoven, P.F.P., Bergman, M.A., Collard, R.M., Schene, A.H., Tendolkar, I., & Vrijsen, J.N. (2020). Negative memory bias as transdiagnostic cognitive marker for depression symptom severity. *Journal of Affective Disorders,* 10.1016/j.jad.2020.05.156
- Van Oort, J., Kohn, N., Vrijsen, J.N., Collard, R.M., **Duyser, F.A.**, Brolsma, S.C.A., Fernández, G., Schene, A.H., Tendolkar, I., & Van Eijndhoven, P.F.P. (2020). Absence of default mode downregulation in response to a mild psychological stressor marks stress-vulnerability across diverse psychiatric disorders (2020). *Neuroimage Clinical*, 10.1016/j.nicl.2020.102176
- **Duyser, F.A.**, Vrijsen, J.N., Van Oort, J., Collard, R.M., Schene, A.H., Tendolkar, I., & Van Eijndhoven, P.F.P. (2022). Amygdala sensitivity for negative information as a neural marker for negative memory bias across psychiatric diagnoses. *Psychiatry Research: Neuroimaging,* 10.1016/j.pscychresns.2022.111481
- Van Eijndhoven, P.F.P., Collard, R.M., Vrijsen, J.N., Geurts, D.E.M., Arias Vasquez, A., Schellekens, A., Van den Munckhof, E., Brolsma, S.C.A., **Duyser, F.A.**, Bergman, M.A., Van Oort, J., Tendolkar, I., & Schene, A.H. (2022). Measuring integrated novel dimensions in neurodevelopmental and stress-related mental disorders MIND-Set): Protocol for a cross-sectional comorbidity study from a research domain criteria perspective. JMIRx Med, 10.2196/31269
- Van Oort, J., Tendolkar, I., Collard, R., Geurts, D.E.M., Vrijsen, J.N. **Duyser, F.A.**, Kohn, N., Fernandez, G., Schene, A.H., & Van Eijndhoven, P.F.P. (2022). Neural correlates of repetitive negative thinking: Dimensional evidence across the psychopathological continuum. *Frontiers in Psychiatry,* 10.3389/fpsyt.2022.915316
- Mulders, P.C.R., Van Eijndhoven, P.F.P., Van Oort, J., Oldehinkel, M., **Duyser, F.A.**, Kist, J.D., Collard, R.M., Vrijsen, J.N., Van Haak, K., Beckmann, C.F., Tendolkar, I., & Marquand, A.F. (2022). Striatal connectopic maps link to functional domains across psychiatric disorders. *Translational Psychiatry*, 10.1038/s41398-022-02273-6
- Van Oort, J., Llera, A., Kohn, N., Mei, T., Collard, R.M., **Duyser, F.A.**, Vrijsen, J.N., Beckmann, C.F., Schene, A.H., Fernández, G., Tendolkar, I., & Van Eijndhoven, P.F.P. (2023). Brain structure and function link to variation in biobehavioural dimensions across the psychopathological continuum. *eLife,* 10.7554/eLife.85006
- Langenbach, B.P., Grotegerd, D., Mulders, P.C.R., Tendolkar, I., Van Oort, J., **Duyser, F.A.**, Van Eijndhoven, P.F.P., Vrijsen, J.N., Dannlowski, U., Kampmann, Z., & Koelkebeck, K. (2024). Autistic and non-autistic individuals show the same amygdala activity during emotional face processing. *Molecular Autism,* 10.1186/s13229-024-00582-9

- Kist, J.D., Schlüter, L., **Duyser, F.A.**, Mulders, C.R., Vrijsen, J.N., Collard, R.M., Van Eijndhoven, P.F.P., & Tendolkar, I. (2024). How executive control and emotional reactivity influence coping strategies in psychiatric patients during the COVID-19 pandemic. *medRxiv*, https://doi.org/10.1101/2024.01.08.24300980
- **Duyser, F.A.**, Van Eijndhoven, P.F., Collard, R.M., Vassena, E., Koekkoek, B., Tendolkar, I., Vrijsen, J.N. (2024). Measuring self-referent memory bias as marker for depression: overview, new insights, and recommendations. *Journal of Psychopathology and Behavioural Assessment*, 47, https://doi.org/10.1007/s10862-024-10190-9

Acknowledgements

I feel happy and relieved to write this final piece of my thesis now. This PhD journey has been long and quite challenging at times, but I am grateful for everything it has taught me. As with all scientific accomplishments, many different people have directly and indirectly contributed to this work and I want to thank them here.

Allereerst wil ik natuurlijk mijn begeleidingsteam bedanken. Indira, dankzij jouw expertise, kritische blik en vernieuwende ideeën is mijn werk steeds beter geworden. Dankjewel voor al je verhelderende inzichten, het monitoren van mijn PhD traject en het bieden van mooie kansen. Janna, ik ben zo onder de indruk van jou. Heel erg bedankt voor je intensieve begeleiding, de interessante discussies, je luisterend oor en je steun op vele vlakken. Ik heb erg fijn met je samengewerkt. Philip, ik waardeer het ontzettend dat je altijd tijd voor mij maakte in je drukke agenda, zelfs op je vrije dagen. Dankjewel voor al je hulp, geduld, goede suggesties en scherpe inzichten. Ik heb nog steeds veel aan je tips voor tijdsmanagement. En Rose, je bent pas wat later bij mijn PhD project betrokken geraakt, maar je zat natuurlijk al in de kern van het MIND-Set team. Je feedback en inzichten vanuit de klinische praktijk waren altijd zeer welkom, dankjewel. En uiteraard wil ik Aart hier noemen. Vooral in het begin van mijn PhD traject heb ik veel van hem geleerd over het belang van doelen stellen, samenwerken en breed geïnteresseerd blijven. MIND-Set is een fantastisch project en ik ben blij dat ik er onderdeel van mocht zijn.

Over the years, so many different people have put effort in the recruitment and screening of participants, worked on the data collection, advised me on data pre-processing and analysis, and asked me interesting questions during lab meetings and presentations. I want to thank everyone at the Department of Psychiatry and at the DCCN who have helped me along the way with my projects and/or contributed to the MIND-Set study as a whole. Een aantal mensen wil ik in het bijzonder noemen. Annemiek, Sophie en Jasper, bedankt dat ik zo veel van jullie mocht leren! Eva en Femke, bedankt voor jullie bijdrage aan de dataverzameling, de projectcoördinatie en natuurlijk alle gezelligheid. Joosje, ik vind het jammer dat we maar kort samen op kantoor konden werken. Ik vond je energie en creativiteit altijd erg inspirerend. Eliana, thank you for your great ideas and critical insights on a topic that was still relatively new to me. Paul, bedankt voor je hulp tijdens de vele uren scannen. En Livia, dankjewel voor het altijd super snel aanleveren van de juiste datasets en het beantwoorden van al mijn data-gerelateerde vragen. Ik wil natuurlijk ook alle deelnemers aan de MIND-Set studie bedanken voor hun tijd

en voor de interessante gesprekken over hun motivatie om deel te nemen aan wetenschappelijk onderzoek.

Het was best een uitdaging om mijn PhD af te ronden naast mijn nieuwe baan bij het DCCN. Sharon, zonder jouw flexibiliteit en betrokkenheid was het niet gelukt, ik ben je heel dankbaar. Ik wil ook al mijn lieve (oud-)collega's op het DCCN bedanken voor het warme welkom, jullie interesse, motiverende woorden, gezelligheid en dat ik af en toe ook even lekker mocht klagen. It is exciting to still be surrounded by amazing neuroscience every day, both at the DCCN and within the broader DI community. I am glad that I can support and contribute to it in a different role now.

My dear family and friends across the world have always cheered me on and celebrated milestones with me. Heidi, I so appreciate your calm presence, down-to-earth outlook, and being able to talk to you about anything. Okishi, you always manage to motivate me to get things done. Thank you for sharing this journey with me. Maerose, Marnie, and Natsuko, thank you for all those moments of joy and for taking my mind off work. Papa, ik vind het lief dat je altijd laat weten hoe trots je op me bent; dat is een grote motivatie geweest om door te zetten. Dankjewel voor je interesse, gezellige lunches en goede gesprekken. Mama, je weet precies wat ik nodig heb en kan me zo goed opvrolijken met een lief berichtje, mooie planten of een dagje weg. Dankjewel voor al je wijze woorden en dat ik altijd bij je terecht kan. Esmée, je bent altijd zo lief voor me. Ik vind het fijn om samen te zijn en leuke dingen te doen en ben blij dat we over van alles kunnen kletsen. And finally, William, thank you for always being by my side and supporting me in everything I do. I could not have done it without your endless patience, love, comfort, emotional and practical support, and genius problem-solving skills. I love our life together and I'm looking forward to all our future adventures!

Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 600 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher

education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit:

http://www.ru.nl/donders/graduate-school/phd

DONDERS INSTITUTE

Radboud University

Radboudumc