Transdiagnostic assessment of mental disorders using the Research Domain Criteria (RDoC) approach: relationship to disease severity

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List of Abbreviations

AD	=	Anxiety Disorder(s)
AG	=	Agoraphobia
APA	=	American Psychiatric Association
BD	=	Bipolar Disorder
CFA	=	Confirmatory Factor Analysis
CS	=	Cognitive Systems
DSM-5	=	Diagnostic and Statistical Manual of Mental Disorders
FIML	=	Full Information Maximum Likelihood
fMRI	=	functional Magnetic Resonance Imaging
FZPE	=	German Research Network for Mental Disorders
GAD	=	Generalized Anxiety Disorder
GHDx	=	Global Health Data Exchange
GLMM	=	Generalized Linear Mixed Models
HPA	=	Hypothalamic-Pituitary-Adrenal
ICD-10	=	International Classification of Diseases
JBI	=	Joanna Briggs Institute
LM	=	Linear Regression Model
MDD	=	Major Depressive Disorder
NA	=	Negative Affect
NIMH	=	National Institute for Mental Health
NVS	=	Negative Valence Systems
PA	=	Positive Affect
PD	=	Panic Disorder
PD-CAN	=	Phenotypic Diagnostic Domain Assessment Network Germany
PDD	=	Persistent Depressive Disorder
PH	=	Physiological Hyperarousal
PRISMA-ScR	=	Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Scoping Reviews
PVS	=	Positive Valence Systems
RDoC	=	Research Domain Criteria
SAD	=	Social Anxiety/Phobia
SP	=	Systems of Social Process
SPD	=	Specific Phobia
VIF	=	Variance Inflation Factor
WHO	=	World Health Organization

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Abstract

Traditionally, mental disorders have been identified based on specific symptoms and standardized diagnostic systems such as the DSM-5 and ICD-10. However, these symptom-based definitions may only partially represent neurobiological and behavioral research findings, which could impede the development of targeted treatments. A transdiagnostic approach to mental health research, such as the Research Domain Criteria (RDoC) approach, maps resilience and broader aspects of mental health to associated components. By investigating mental disorders in a transnosological way, we can better understand disease patterns and their distinguishing and common factors, leading to more precise prevention and treatment options.

Therefore, this dissertation focuses on (1) the latent domain structure of the RDoC approach in a transnosological sample including healthy controls, (2) its domain associations to disease severity in patients with anxiety and depressive disorders, and (3) an overview of the scientific results found regarding Positive (PVS) and Negative Valence Systems (NVS) associated with mood and anxiety disorders.

The following main results were found: First, the latent RDoC domain structure for PVS and NVS, Cognitive Systems (CS), and Social Processes (SP) could be validated using self-report and behavioral measures in a transnosological sample. Second, we found transdiagnostic and disease-specific associations between those four domains and disease severity in patients with depressive and anxiety disorders. Third, the scoping review showed a sizable amount of RDoC research conducted on PVS and NVS in mood and anxiety disorders, with research gaps for both domains and specific conditions.

In conclusion, the research presented in this dissertation highlights the potential of the transnosological RDoC framework approach in improving our understanding of mental disorders. By exploring the latent RDoC structure and associations with disease severity and disease-specific and transnosological associations for anxiety and depressive disorders, this research provides valuable insights into the full spectrum of psychological functioning. Additionally, this dissertation highlights the need for further research in this area, identifying both RDoC indicators and research gaps. Overall, this dissertation represents an important contribution to the ongoing efforts to improve our understanding and the treatment of mental disorders, particularly within the commonly comorbid disease spectrum of mood and anxiety disorders.

Zusammenfassung (Abstract in the German language)

Traditionell werden psychische Störungen auf der Grundlage spezifischer Symptome und standardisierter Diagnosesysteme wie DSM-5 und ICD-10 diagnostiziert. Diese symptombasierten Definitionen entsprechen jedoch nur teilweise den Erkenntnissen der neurobiologischen und Verhaltensforschung, was die Entwicklung gezielter Behandlungen behindern kann. Ein transdiagnostischer Ansatz zur Erforschung psychischer Gesundheit, wie z. B. der Research Domain Criteria (RDoC) Ansatz, ordnet umfassendere Aspekte psychischer Gesundheit, wie z. B. Resilienz, den entsprechenden Komponenten zu. Durch die Untersuchung psychischer Störungen aus einer transnosologischen Perspektive können wir Krankheitsbilder und ihre gemeinsamen und unterscheidenden Faktoren besser verstehen, was zu präziseren Präventions- und Behandlungsmöglichkeiten führt.

Daher konzentriert sich diese Dissertation auf (1) die latente Domänenstruktur des RDoC-Ansatzes in einer transnosologischen Stichprobe einschließlich gesunder Kontrollen, (2) die domänenspezifischen Assoziationen zur Krankheitsschwere bei Patienten mit Angst- und depressiven Störungen und (3) einen Überblick über die wissenschaftlichen Ergebnisse zu Positiven (PVS) und Negativen Valenzsystemen (NVS), die mit Affektiven Störungen assoziiert sind.

Die folgenden Hauptergebnisse wurden gefunden: Erstens konnte die latente RDoC-Domänenstruktur für PVS und NVS, Kognitive Systeme (CS) und Soziale Prozesse (SP) anhand von Selbstberichten und Verhaltensmessungen in einer transnosologischen Stichprobe validiert werden. Zweitens fanden wir transdiagnostische und krankheitsspezifische Assoziationen zwischen diesen vier Domänen und der Krankheitsschwere bei Patienten mit Angst- und depressiven Störungen. Drittens zeigte die durchgeführte Übersichtsarbeit eine beträchtliche Menge an RDoC-Forschung zu PVS und NVS bei affektiven Störungen, mit Forschungslücken für beide Domänen und spezifische Bedingungen.

Zusammenfassend lässt sich sagen, dass die in dieser Dissertation vorgestellten Forschungsergebnisse das Potenzial des transnosologischen RDoC-Konzepts zur Verbesserung unseres Verständnisses psychischer Störungen unterstreichen. Durch die Untersuchung der latenten RDoC-Struktur und der Assoziationen mit dem Krankheitsschweregrad sowie der krankheitsspezifischen und transnosologischen Assoziationen für Angst- und depressive Störungen liefert diese Forschungsarbeit wertvolle Einblicke in das gesamte Spektrum psychischer Funktionsweisen. Darüber hinaus zeigt diese Dissertation den Bedarf an weiterer Forschung in diesem Bereich auf, indem sie sowohl RDoC-Indikatoren als auch Forschungslücken identifiziert. Insgesamt stellt diese Dissertation einen wichtigen Beitrag zu den laufenden Bemühungen um ein besseres Verständnis und eine bessere Behandlung psychischer Störungen dar, insbesondere innerhalb des häufig komorbiden Krankheitsspektrums der affektiven Störungen.

List of papers

This thesis is based on the following original papers:

Paper 1

Bernd R. Förstner, Mira Tschorn, Nicolas Reinoso-Schiller, Lea Mascarell Maričić, Erik Röcher, Janos L. Kalman, Sanna Stroth, Annalina V. Mayer, Kristina Schwarz, Anna Kaiser, Andrea Pfennig, André Manook, Marcus Ising, Ingmar Heinig, Andre Pittig, Andreas Heinz, Klaus Mathiak, Thomas G. Schulze, Frank Schneider, Inge Kamp-Becker, Andreas Meyer-Lindenberg, Frank Padberg, Tobias Banaschewski, Michael Bauer, Rainer Rupprecht, Hans-Ulrich Wittchen, Michael A. Rapp (2022). Mapping Research Domain Criteria using a transdiagnostic mini-RDoC assessment in mental disorders: a confirmatory factor analysis. *European Archives of Psychiatry and Clinical Neuroscience*. Advanced online publication. https://doi.org/10.1007/s00406-022-01440-6

Paper 2

Bernd R. Förstner, Sarah Jane Böttger, Alexander Moldavski, Malek Bajbouj, Andrea Pfennig, André Manook, Marcus Ising, Andre Pittig, Ingmar Heinig, Andreas Heinz, Klaus Mathiak, Thomas G. Schulze, Frank Schneider, Inge Kamp-Becker, Andreas Meyer-Lindenberg, Frank Padberg, Tobias Banaschewski, Michael Bauer, Rainer Rupprecht, Hans-Ulrich Wittchen, Michael A. Rapp, & Mira Tschorn (2023). The associations of positive and negative valence systems, cognitive systems and social processes on disease severity in anxiety and depressive disorders. *Frontiers in Psychiatry*. Currently Under Review.

Paper 3

Sarah Jane Böttger, Bernd R. Förstner, Laura Szalek, Kristin Koller-Schlaud, Michael A. Rapp, Mira Tschorn (2023). Mood and Anxiety Disorders Within the Research Domain Criteria Framework of Positive and Negative Valence Systems: A Scoping Review. *Frontiers in Clinical Neuroscience*. Accepted for Publication.

"The secret of change is to focus all of your energy, not on fighting the old, but on building the new."

Socrates

1. Introduction

Traditionally, mental disorders have been conceptualized as conditions identified by the presence, degree, and number of specific symptoms, the level of distress/impairment or dysfunction experienced by the individual, and other symptom-based criteria (Aftab & Ryznar, 2021; Klosterkötter, 2016). This approach has resulted in the development of standardized diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association (APA), 2013) and the International Classification of Diseases (ICD-10) (World Health Organization (WHO), 2015), which offer several benefits such as providing a standardized language and criteria for mental health professionals to use in diagnosis. In addition, this standardization level helps ensure that diagnoses are consistent across clinicians and settings, which is essential for reliable and valid research findings and reliable tests of treatment interventions. On the other hand, current neurobiological and behavioral research findings are inadequately represented in many symptom-based definitions, which may lead to an underrepresentation of transdiagnostic research on etiology and pathophysiology and ultimately impede the development of new and more targeted treatment options (Cuthbert & Insel, 2013).

Beyond a symptom-based phenomenological psychopathological view of the mental health spectrum, one may conceptualize key functions that enable individuals to maintain optimal psychological well-being. Some of these concepts are being introduced for conceptual purposes in the following.

Self-regulation is defined as an individual's ability to manage their internal experiences and external behaviors effectively (Gross, 2015). *Emotion regulation* involves managing and regulating one's emotions, including recognizing and labeling emotions and using strategies to cope with difficult emotions (Gross, 1998; Hu et al., 2014). Another key function is the ability to focus and sustain *attention*, as well as to shift attention in an adaptive fashion (Fan & Posner, 2004). *Cognitive flexibility* means the ability to shift one's thinking and adapt to new situations, including being able to see multiple perspectives and consider alternative solutions (Kashdan & Rottenberg, 2010). *Stress management* is the ability to cope with stressors and challenges healthily and adaptively, including relaxation techniques, problem-solving skills, and social support (Lazarus & Folkman, 1984; National Institute of Mental Health [NIMH], 2023). Finally, *social cognition* and relational connection refer to the ability to establish, build and maintain healthy relationships with others (Adolphs, 2009; Bowlby, 1982).

These core functions contribute partly to the overarching concept of resilience, describing the ability of individuals to adapt and recover from adversity, trauma, or significant life stressors. Resilience involves a complex interplay between biological, psychological, and social factors. It is not a fixed characteristic but rather a dynamic process that can be improved and strengthened over time (Luthar, Cicchetti, & Becker, 2000; Southwick & Charney, 2012).

The lack of integration of current neurobiological and behavioral research findings, together with the utility of a dimensional approach that maps resilience and broader aspects of mental health and also considers associated components, have led to the integration of a transdiagnostic approach into the National Institutes for Mental Health (NIMH) (Insel, 2014) Research Domain Criteria (RDoC) approach, which originated from the basis of endophenotypes of mental disorders (Insel & Cuthbert, 2009).

This dissertation focuses on (1) the latent domain structure of this dimensional research approach using RDoC in a transnosological sample including healthy controls and (2) its domain associations to disease severity in patients with anxiety and depressive disorders and (3) gives an overview of the scientific results found regarding positive and negative valence systems associated with mood and anxiety disorders. Why is it important to study transnosological aspects of mental disorders in that way?

First and foremost, mental disorders affect a significant number of people worldwide, with one in every eight individuals living with a mental disorder (WHO, 2023). These disorders can impact an individual's thinking, emotional regulation, or behavior, resulting in distress or impairment in critical areas of functioning. Anxiety and depressive disorders are the most common, and the COVID-19 pandemic has increased the number of people experiencing these disorders (WHO, 2022). Effective prevention and treatment options exist. However, most people cannot access them (Moitra et al., 2022). Moreover, individuals with mental disorders also face stigma, discrimination, and human rights violations (WHO, 2021).

Therefore, there is a need to further investigate mental disorders in a transnosological way better to understand disease patterns and their distinguishing and common factors. This could result in more precise prevention and treatment options in the long run (Insel, 2014).

One step in this process is to further validate the pervasive phenotypes of mental health and disorders postulated by the RDoC approach. We proposed that this can be achieved by using existing and well-established measures in the form of self-report and behavioral assessments that may already map these core domains of psychological functioning in a transnosological way. Existing research has focused primarily on the validation of the two domains Positive (PVS) (Khazanov, Ruscio, & Forbes, 2019; Light, Moran, Zahn-Waxler, & Davidson, 2019; Olino, McMakin, & Forbes, 2018; Tsanas et al., 2017) and Negative Valence Systems (NVS) (Lee et al., 2017; Paulus et al., 2017; Watson, Stanton, &

Clark, 2017). Validation of the other domains, such as Cognitive Systems (CS) and Social Processes (SP), has received scant attention so far (Sanislow et al., 2010; Schretlen et al., 2013; Uljarević et al., 2020). At this point, whether we could use established assessments to map latent domains from the RDoC matrix arose and resulted in the investigation in Paper 1.

Second, demonstrating how these latent constructs are associated with diagnosis-specific symptom burden in a complex disease spectrum such as emotional disorders, where heterogeneity and comorbidity is involved, may help infer differences and thus could be helpful in delineating mechanisms within these disorders. Specifically, mood and anxiety disorders may serve as prime examples of such an approach.

Mood and anxiety disorders are a group of mental health conditions with a complex phenomenology characterized by mood, affect, and emotional regulation disturbances. They include major depressive disorder (MDD), dysthymia/persistent depressive disorder (PDD), bipolar disorder I and II (BD), and anxiety disorders such as panic disorder (PD), generalized anxiety disorder (GAD), mixed anxiety and depressive disorder and phobic anxiety disorders such as agoraphobia (AG), social anxiety/phobia (SAD) and specific phobia (SPD). According to the WHO (2017), mood and anxiety disorders are among the major contributors to the global disease burden. They affected approximately 8.3% of the total global population in 2019 (Global Health Data Exchange (GHDx), 2019).

A German study by Jacobi et al. (2014) found that mood disorders are highly prevalent and often comorbid with other mental health conditions. For example, depression frequently co-occurs with anxiety, substance use, and personality disorders. Additionally, research has reported a substantial overlap in phenomenology and neurobiological mechanisms among mood and anxiety disorders (Kendler, Heath, Martin, & Eaves, 1987; Kendler, Neale, Kessler, Heath, & Eaves, 1992; Watson, 2005). These findings suggest that the boundaries between these disorders may not be as clear-cut as previously proposed and open up a new field of research to examine similarities and differences from an RDoC perspective.

The lack of specificity in diagnostic categories may present challenges for the treatment of mood and anxiety disorders. For instance, medications and psychotherapies that are effective for one mood or anxiety disorder may not be as effective for another. Therefore, refining treatments to ultimately improve treatment responses in these mental disorders would require a more precise understanding of the neurobiological and phenotypic specificity of each disorder. Such an approach may help guide the development of more targeted and effective interventions for individuals with mood and anxiety disorders.

A first step in this direction would be to aid in a better understanding of disease-specific as well as transdiagnostic differences while reducing the complexity within the individual disease spectrum.

Specifically, anxiety and depressive disorder share a common set of dysfunctions (Brown, Chorpita, & Barlow, 1998; Clark & Watson, 1991), which has stimulated transdiagnostic research on both disorder spectra (e.g., Wei & Roodenrys, 2021). Therefore, in Paper 2, we investigated the relationships and differences between the two disorders using the transnosological RDoC domains and their associations with diagnosis-specific symptom burden.

Third, another major issue with symptom-based diagnostic categories, in this case, mood and anxiety disorders, is the problem of heterogeneity. For example, two individuals receiving the same diagnosis may have very different underlying causes or presentations of symptoms. Specifically, two individuals diagnosed with depression may have different experiences of the disorder, and their underlying biological and psychological mechanisms may be vastly different. When the neurobiological mechanisms responsible for a particular disorder display substantial heterogeneity across patients who exhibit minimal or no symptom overlap, it presents a challenge to develop universally effective treatments (Cuthbert, 2014). Therefore, it seems essential to supplement diagnostic categories with transdiagnostic approaches to refine our understanding of mental disorders.

Summarizing all the problems of heterogeneity, comorbidity, and the lack of transnosological and dimensional research that considers the full range of psychological functioning using all available units of analysis (f.e. genes, molecules, circuitry), there was a need for a new research approach that sparked the RDoC framework in 2010 (Insel et al., 2010). As more than a decade of RDoC-specific research has been conducted using this new approach, there is also a need to collect all the findings in an appropriate systematic way. In recent years, this has mostly been done through systematic reviews and meta-analyses (e.g., Fettes, Schulze, & Downar, 2017; Janiri et al., 2020) from the perspective of only one diagnostic category or one RDoC domain. From our point of view, mood and anxiety disorders as a research spectrum were the ideal setting for a scoping review to provide an overview of the RDoC research conducted on this topic according to the new guidelines of the approach. With this review in Paper 3, we aimed to consolidate diagnosis-specific and transdiagnostic knowledge about these mental disorders and identify research gaps to spark future research strategies.

2. Theoretical Background

2.1 Research Domain Criteria Framework (Insel et al., 2010)

The Research Domain Criteria (RDoC) framework (see Figure 1) is a research approach developed by the NIMH in 2009 to investigate mental disorders in a transdiagnostic approach. The primary goal of this framework is to develop new research approaches that can help improve the diagnosis, prevention, intervention, and treatment of mental disorders. Therefore, the RDoC approach is not intended to replace current diagnostic systems, such as the DSM-5 or ICD-10, but rather to represent an alternative approach to understanding the nature of mental health and disorder.

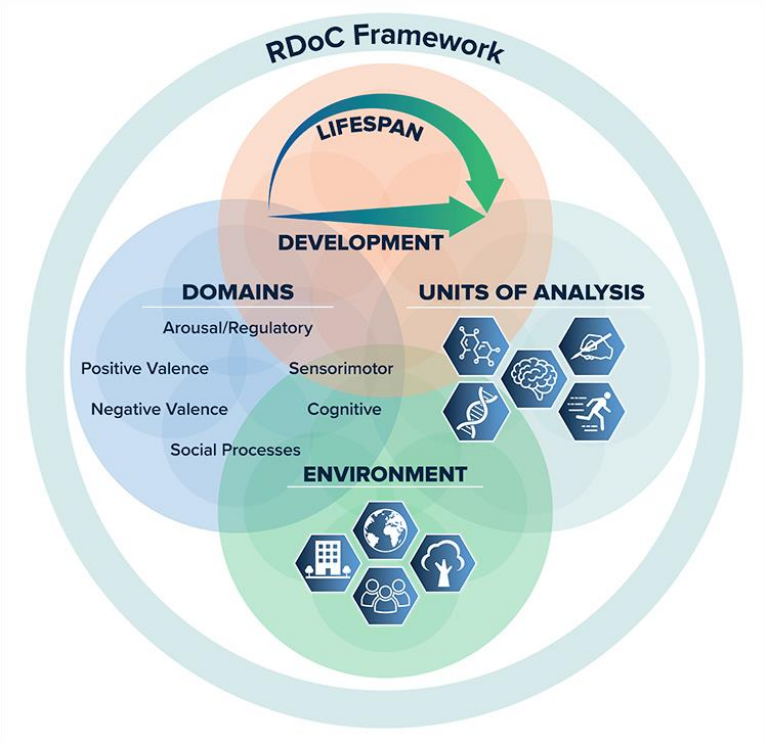

Figure 1. The Research Domain Criteria Framework[1]

The RDoC framework is centered around six functional domains that examine mental health and psychopathology in the context of basic human neuro-behavioral functioning. These domains consist of three to six psychological and biological dimensions or constructs explored across the entire spectrum of functioning, from normal to abnormal. In order to map these domains and constructs, eight different units of analysis are also being considered, including genes, molecules, circuits, physiology, behavior, self-report, and paradigms. In addition, techniques like (functional) neuroimaging and animal models are utilized to investigate units of analysis such as circuits (e.g., emotion-modulated startle, event-related potentials with established source localization).

[1] Image source: NIMH website; used with the kind permission of the NIMH; retrieved March 10, 2023

Another essential part of this framework is assessing the development of these components across the lifespan, as these aspects change and mature during childhood/adolescence and later in life. Various environmental factors are also incorporated within the framework, including the physical environment, cultural components, and social determinants of health.

The framework encourages researchers to integrate multiple classes of variables to develop a comprehensive understanding of the construct(s) under study and was developed through a series of workshops to identify initial concepts for investigation. However, this framework is not a complete or fixed compendium of RDoC-related topics. Rather, as new scientific advances are made, it is intended to evolve and grow. An evident illustration can be observed in the development process of the six domains within the RDoC framework. The first workshop was held in 2010 (NIMH, 2010) on working memory. This was followed by workshops on Negative Valence Systems (NIMH, 2011b), Positive Valence Systems (NIMH, 2011c), Cognitive Systems (NIMH, 2011a) and later Systems for Social Processes (NIMH, 2012b), Arousal and Regulatory Systems (NIMH, 2012a), and the newest domain Sensorimotor Systems (NIMH, 2018). There were also readjustments on already developed domains and constructs throughout this period, such as the latest update on the analysis unit genes in May 2017 (NIMH, 2017).

In summary, the main goal of RDoC is to provide data on basic biological and cognitive processes related to mental health and disorder that can then be used to develop mental health screening tools, revise diagnostic systems, and inform prevention and treatment interventions. The knowledge gained through research based on the RDoC framework is hoped to lead to better outcomes for people with mental disorders ultimately.

2.2 The RDoC Matrix

The RDoC bio-behavioral domains and constructs of mental functions, their units of analysis, and their respective elements are structured within a matrix. Because the overarching framework is designed to encourage researchers to take a more holistic and interdisciplinary view of mental disorders and to focus on identifying the underlying mechanisms that contribute to these disorders, the RDoC matrix is intended to be a flexible and dynamic structure, which will be continuously updated, expanded, and refined based on the latest research findings.

Currently, the RDoC matrix is structured into six comprehensive functional domains (latent dimensional constructs), each representing an underlying pattern.

1. Positive Valence Systems (PVS) (NIMH, 2011c; Walter, Daniels, & Wellan, 2021): This domain includes processes related to responses to positive experiences, such as reward and motivation. In addition to constructs related to reward and motivation, this domain also includes constructs related to the ability to experience pleasure, as well as an individual's ability to anticipate reward. Research within this domain aims to identify the underlying neural and psychological mechanisms that contribute to positive experiences and the development of interventions to enhance positive experiences. Within this domain, the construct of *Reward Responsiveness* encompasses the subconstructs of *Reward Anticipation*, *Initial Response to Reward*, and *Reward Satiation*. These subconstructs reflect different aspects of how individuals respond to rewards, including their expectations, immediate reactions, and changes in motivation over time.

   Another key construct is *Reward Learning*, which includes the subconstructs of *Probabilistic and Reinforcement Learning* and *Reward Prediction Error* and *Habit-PVS*. These subconstructs reflect different ways in which individuals learn about rewards, including their ability to associate specific outcomes with particular actions and their ability to adjust their expectations based on feedback.

Construct/Subconstruct		Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Reward Responsiveness	Reward Anticipation								Monetary Incentive Task
	Initial Response to Reward		CREB		Anterior insula		Taste reactivity	PANAS (state version)	Simple Guessing Task
	Reward Satiation								Fixed-Ratio Satiation Schedule
Reward Learning	Probabilistic and Reinforcement Learning								Pavlovian Conditioning
	Reward Prediction Error		Dopamine		Amygdala	Cortical slow waves	Goal tracking	Affective forecasting	Rutledge Passive Lottery Task
	Habit - PVS		Acetylcholine	Dopaminergic neurons	dorsal striatum		Compulsive behaviors	Aberrant behaviors checklist	Habit Learning Task
Reward Valuation	Reward (probability)								Probability Choice Task
	Delay								Delay discounting
	Effort		Adenosine		Basolateral amygdala			Drive subscale of the Behavioral Activation Scale	EEfRT task

Figure 2. RDoC Matrix – Positive Valance Systems[2]

[2] RDoC Matrix for PVS filled with examples of the individual units of analysis. Source NIMH website; retrieved March 10, 2023

Finally, the construct of *Reward Valuation* encompasses the subconstructs of *Reward (Probability)*, *Delay,* and *Effort*. These subconstructs reflect different aspects of how individuals value rewards, including the likelihood of receiving a reward, the amount of time they must wait for it, and the level of effort required to obtain it. Collectively, these constructs and subconstructs provide a comprehensive structure for understanding the complex processes involved in reward processing and decision-making.

2. Negative Valence Systems (NVS) (Korn & Wolf, 2021; NIMH, 2011b): This domain predominantly includes processes related to responses to aversive experiences, such as fear and anxiety. In addition, this domain also includes constructs related to other negative emotions, such as frustration and loss. Research within this domain aims to identify the neural and psychological processes that contribute to the development and maintenance of negative emotions, as well as potential interventions to regulate these emotions. The domain constructs are:

   Acute threat, also known as fear, refers to the immediate response to a perceived threat or danger. *Potential threat*, also known as anxiety, is anticipating a future threat or danger. *Sustained threat* involves a persistent sense of danger or harm that persists over time. The construct of *Loss* refers to the experience of losing something valuable, whether it be a person, a pet, a possession, a job, or something else. It is often accompanied by feelings of sadness, grief, and even despair. Finally, *Frustrative Nonreward* refers to the feeling of disappointment or frustration that arises when one's efforts do not lead to a desired outcome.

3. Cognitive Systems (CS) (Kubera, Hirjak, Wolf, & Wolf, 2021; NIMH, 2011a): Over the last few decades, and even dating back to the last century, this field has become increasingly complex due to extensive research. The domain constructs are:

   Attention refers to the capacity to concentrate on specific elements of the surroundings and disregard others, which is a fundamental aspect of psychological functioning; also necessary for efficient information processing and helps us to filter out distractions.

   Perception refers to the process by which sensory information is organized and interpreted and involves the subconstructs of visual perception, auditory perception, and other sensory modalities, such as olfactory and somatosensory perception.

   Declarative memory is a type of long-term memory that enables the conscious recollection of facts and events and therefore is critical for learning and everyday functioning.

Language is a complex cognitive system that involves the use of symbols and rules to communicate with others. Processes of thinking, learning, and social interaction rely on language as a critical tool.

Cognitive control refers to the ability to regulate one's thoughts, emotions, and behavior to achieve specific goals. This involves the subconstructs of goal selection, updating, representation, maintenance, response selection, inhibition/suppression, and performance monitoring.

Working memory is a system for temporarily storing and manipulating information in the mind and is essential for tasks such as problem-solving and decision-making, with subconstructs of active maintenance, flexible updating, limited capacity, and interference control.

Research within this domain aims to identify the neural and psychological mechanisms underlying cognitive processes, enhancing our understanding of cognitive functioning in daily life.

4. Systems for Social Processes (SP) (NIMH, 2012b; Praus, Bilek, Holz, & Braun, 2021): *Social Process*es are an essential aspect of human behavior that includes various constructs and sub-constructs. One of the primary constructs of Social Processes is *Affiliation and Attachment*, which refers to the need for social connection and belongingness. Another significant construct is *Social Communication*, which includes various subconstructs such as *Reception of Facial Communication*, *Production of Facial Communication*, *Reception of Non-Facial Communication*, and *Production of Non-Facial Communication*. These subconstructs are crucial in facilitating effective communication and interpersonal interactions.

   Furthermore, *Perception and Understanding of Self* is another essential construct that involves two subconstructs: *Agency* and *Self-Knowledge*. *Agency* refers to the sense of control and ownership over one's actions and decisions, while *Self-Knowledge* relates to the understanding of one's traits, abilities, and limitations. Similarly, *Perception and Understanding of Others* is another crucial construct that involves various subconstructs, such as *Animacy Perception*, *Action Perception*, and *Understanding of Mental States*. For example, *Animacy Perception* refers to the ability to perceive others as living beings with their own intentions and desires. *Action Perception* refers to understanding others' actions and movements while *Understanding Mental States* involves inferring and interpreting others' thoughts, feelings, and beliefs. Overall, the study of *Social Processes*, their constructs, and subconstructs can help us understand how humans interact with each other and how we form meaningful relationships in society.

Since data for the following two domains were unavailable for this thesis, they are only summarized.

5. Arousal/Regulatory Systems (Feld & Feige, 2021; NIMH, 2012a): The construct of *Arousal* refers to the state of physiological and psychological activation in the body, which can vary from low to high levels. This construct is linked to the arousal system, which is responsible for maintaining the optimal level of alertness and responsiveness. *Circadian Rhythms*, on the other hand, refer to the natural 24-hour cycles that regulate various physiological processes in the body, like f.e. hormone secretion or body temperature. The circadian system helps us adapt to the environment's daily changes and maintain a healthy sleep-wake cycle (*Sleep-Wakefulness*). In summary, our body's *Arousal and Regulatory Systems* play a crucial role in regulating different constructs essential for our physical and mental health. Therefore, understanding these systems can help us to make lifestyle choices that promote optimal health and physical as well as psychological well-being.

6. Sensorimotor Systems (Hirjak, Fritze, Northoff, Kubera, & Wolf, 2021; NIMH, 2018): The domain of *Sensorimotor Systems* encompasses various constructs and subconstructs crucial to understanding how our bodies interact with the environment around us. A critical construct within this domain is *Motor Actions*, which can be further broken down into subconstructs such as *Action Planning and Selection*, *Sensorimotor Dynamics*, *Initiation*, *Execution*, and *Inhibition and Termination*. Another construct within this domain is *Agency and Ownership*, which refers to our subjective sense of control over our actions and the objects we interact with. This construct is closely related to the concept of *Habit*, which refers to the automatic and unconscious sensorimotor patterns that we develop through repeated practice. Finally, there are also *Innate Motor Patterns* that are present from birth and are essential for survival and development. These patterns include grasping and sucking, which play a fundamental role in our early interactions with the world around us. Understanding these various constructs and subconstructs is critical for comprehending the complex interplay between our bodies and the environment and for developing effective interventions for individuals with sensorimotor impairments.

2.3 The Tripartite Model of Anxiety and Depression (Clark & Watson, 1991)

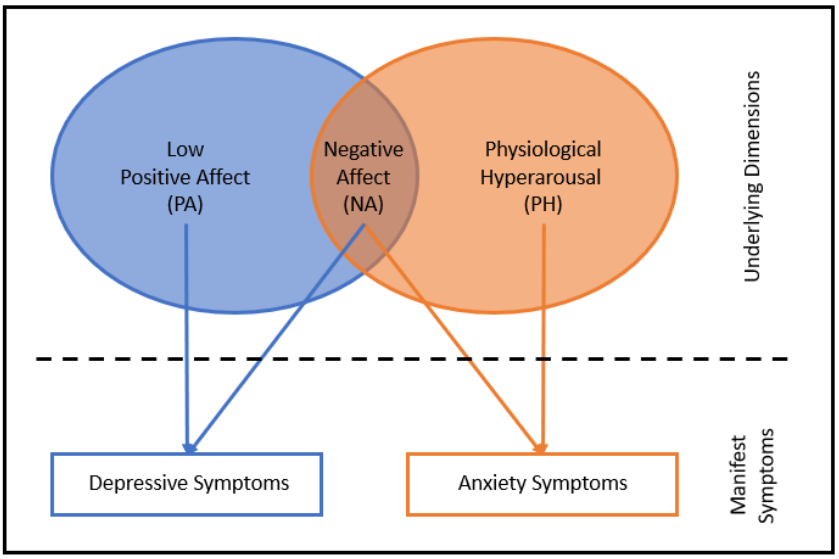

Figure 3: Tripartite Model of Anxiety and Depression (Clark & Watson, 1991)

The Tripartite Model of Anxiety and Depression (Boschen, 2009; Clark & Watson, 1991) is a widely accepted theoretical framework that explains the overlap and distinctions between these two common mental health conditions. According to this model, anxiety and depressive disorders share a common underlying factor called negative affect (NA; originally: general distress). This factor stands for "…the extent to which an individual feels upset or unpleasantly engaged, rather than peaceful" (Anderson & Hope, 2008, p.277), referring to the experience of negative emotions such as sadness, fear, and anger.

However, the model also proposes that both disorders have distinct factors contributing to their unique symptoms. Specifically, anxiety disorders are characterized by an additional factor called *Physiological Hyperarousal* (PH), which refers to heightened activity in the sympathetic nervous system as a response to (acute) threat (Gencoz, Gencoz, & Joiner, 2000) characterized by physiological symptoms such as rapid heartbeat, shortness of breath, sweating or others.

In contrast, depressive disorders are characterized by low levels of *Positive Affect* (PA) or anhedonia, which refers to the inability to experience pleasure or joy in former enjoyable or rewarding activities (Clark & Watson, 1991). This means that individuals with depressive disorders experience high levels of anhedonic symptoms, such as reduced motivation, lack of enjoyment in activities, and decreased social engagement.

The Tripartite Model has been supported by a significant body of research, including studies that have found that anxiety and depression often co-occur and that individuals with both conditions tend to have higher levels of negative affect than those with only one condition (Gaylord-Harden, Elmore,

Campbell, & Wethington, 2011; P. C. Kendall, Kortlander, Chansky, & Brady, 1992; Mineka, Watson, & Clark, 1998).

To further distinguish between both disorder spectra, the following chapters explore the phenomenology of both disorders and show links to RDoC associations.

2.4 Phenomenology of Depressive Disorders

The phenomenology of depressive disorders is complex and multifaceted, with alterations in brain structure and function, genetic and environmental risk factors, and a wide range of symptoms that can affect daily functioning. This spectrum of disorders may be characterized by a persistent low mood, reduced interest in activities, and other symptoms such as changes in appetite, sleep disturbances, and feelings of worthlessness. The manifestations of depressive disorders can vary widely, ranging from mild symptoms that resolve quickly to severe and persistent symptoms that can lead to significant impairment in daily functioning (APA, 2013).

Depressive disorders have been associated with changes in brain structure and function, including alterations in the activity of specific neurotransmitters, such as serotonin, dopamine, and norepinephrine. Neuroimaging studies have revealed that individuals with depression exhibit reduced activity in the prefrontal cortex, which is involved in decision-making, planning, and emotional regulation, and increased activity in the amygdala, which is associated with the processing of emotions such as fear and anxiety (Fava & Kendler, 2000).

Regarding the RDoC domains, PVS has been extensively studied in individuals with depressive disorders. Research has shown that individuals with depression have a reduced ability to experience pleasure or positive affect, known as anhedonia (Snaith, 1993). Anhedonia is considered a core symptom of depression and therefore is a key diagnostic criterion in the DSM-5 (APA, 2013). There are several theories about the underlying mechanisms of anhedonia in depression. One theory suggests that depression is associated with a disruption of the brain's reward system, which is responsible for the experience of pleasure (Pizzagalli, 2014). This disruption can lead to reduced motivation to engage in pleasurable activities and a decreased ability to experience pleasure.

Another theory suggests that anhedonia in depression is related to a negative cognitive bias, where individuals with depression tend to interpret positive experiences and events in a negative way (Gotlib & Joormann, 2010). Such bias may lead to a reduced ability to experience pleasure, as individuals with depression may not fully appreciate or recognize positive experiences.

The presence of anhedonia symptoms has also been linked to a reduced ability to respond to positively valenced and rewarding stimuli (Barch, Pagliaccio, & Luking, 2016; Baskin-Sommers & Foti, 2015; Dillon

et al., 2014; Hägele et al., 2015), as well as a decrease in activity within neural circuits associated with processing such stimuli (Groenewold, Opmeer, Jonge, Aleman, & Costafreda, 2013; Nusslock & Alloy, 2017; Treadway & Zald, 2011). Concerning NVS, depressive disorders have been linked to a tendency to perceive and attend more strongly to stimuli with negative valence and to negative stimuli associated with threat. Several studies have reported similar findings (Groenewold et al., 2013; Hamilton et al., 2012; Jaworska, Yang, Knott, & MacQueen, 2015; Stuhrmann, Suslow, & Dannlowski, 2011).

As for the cognitive systems domain, deficits in attention, memory, and executive functioning are well established (Ferreri, Lapp, & Peretti, 2011; Rock, Roiser, Riedel, & Blackwell, 2014). As noted above, cognitive impairment is a major factor in depressive disorders, is not limited to the acute phase of the disorder and may persist after the resolution of depressive symptoms. In addition, cognitive impairment can be present in individuals with subthreshold depressive symptoms or those who have recovered from a major depressive episode (Rock et al., 2014). Heterogenous evidence exists for depressive disorders specific circuitry alterations compared to anxiety disorder circuits, which impedes generating a disease-specific pattern (Sindermann et al., 2021; Wei & Roodenrys, 2021). This is also due to the scarcity of transdiagnostic research in this domain (Williams, 2017).

Regarding depressive disorders , a noticeable indication and component of the disease is the deterioration of social functioning. A study (Kupferberg, Bicks, & Hasler, 2016) has compiled that all SP sub-constructs are compromised in individuals with depression, leading to social anhedonia, heightened sensitivity to social rejection, avoidance of competition, and increased altruistic punishment regarding affiliation and attachment sub-constructs. Additionally, depression results in reduced capacity for emotion recognition, diminished cooperativeness in social communication, and ultimately, impaired empathy or theory-of-mind deficits concerning social perception.

2.5 Phenomenology of Anxiety Disorders

The phenomenology of anxiety disorders can be complex and multifaceted, as it involves both cognitive and physiological components, and its spectrum is very heterogeneous. For example, individuals with anxiety disorders often experience a persistent sense of threat or danger, even in situations where there is no actual threat present. This sense of threat can lead to hypervigilance, increased startle responses, and an overactive sympathetic nervous system, resulting in physical symptoms such as sweating, trembling, and increased heart rate. Additionally, individuals with anxiety disorders often experience cognitive distortions, such as catastrophic thinking or overgeneralization, which can exacerbate feelings of anxiety and lead to avoidance behaviors (Craske & Stein, 2016).

Regarding the RDoC domains, there is a scarcity of research on PVS functioning in patients with anxiety disorders, given that they are primarily characterized by excessive fear or worry, which refers more to NVS. However, there may also be hedonic aspects to these conditions. For example, research has shown that individuals with anxiety disorders may experience a reduced ability to experience pleasure or positive affect, similar to individuals with depression (Taylor, Hoffman, & Khan, 2022). This reduced hedonic experience may be related to the cognitive and physiological symptoms of anxiety disorders, such as excessive worry, hypervigilance, and physiological arousal, which can interfere with the ability to experience pleasure and enjoy activities.

Furthermore, individuals with anxiety disorders may also experience anhedonic symptoms as a result of avoidance behaviors, which can limit exposure to positive experiences and reinforce negative affect. For example, individuals with social anxiety may avoid social situations, which can limit opportunities for positive social interactions and lead to reduced experiences of pleasure (Morrison & Heimberg, 2013). In addition, some types of anxiety disorders, such as panic disorder, may be associated with physiological symptoms, such as respiratory symptoms and heart palpitations (Nardi, Freire, & Zin, 2009), that can be unpleasant and interfere with hedonic experiences. In summary, existing studies mainly focus on specific disorder types such as SAD (e.g., Kashdan, 2007; Kashdan et al., 2013; Taylor, Bomyea, & Amir, 2010) and show that individuals have reduced positive experiences, which leads to using experiential avoidance as a coping mechanism.

As for NVS, anxiety disorders have been shown to present with an inclination toward negative information processing, known as negativity bias, towards stimuli with negative emotional connotations (e.g., Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013; Shin & Liberzon, 2010). In addition, anxiety disorders are also characterized by changes in the activity of specific brain structures associated with the response to stimuli that elicit threat-related emotions (e.g., (Etkin & Wager, 2007; Killgore et al., 2014).

Regarding CS, cognitive deficits in attention, memory, and executive functioning exist (Ferreri et al., 2011; Rock et al., 2014).

Anxiety disorders have been associated with certain subconstructs of SP, such as attachment, which may contribute to social anxiety (Fang, Hoge, Heinrichs, & Hofmann, 2014). However, the overall impact of SP on anxiety disorders is not yet fully understood, as SP encompasses a wide range of constructs, and anxiety disorders are highly heterogeneous in their presentation. Nonetheless, the role of SP in specific anxiety disorder types, such as SAD, has been extensively studied due to the close connection between its symptoms and dysfunction in automatic association with social cues (Glashouwer, Vroling, Jong, Lange, & Keijser, 2013).

3. Research Questions

This thesis aims to examine a part of the latent structure of the RDoC-Matrix as well as the associations to disease severity in patients with anxiety and depressive disorders. Furthermore, it aims to give an overview of RDoC research on PVS and NVS in mood and anxiety disorders conducted in the past decade.

The following broad research questions arose from the main aim of the dissertation and will be discussed further:

1. Can a latent structure of four RDoC domains be validated with items or scales from well-established self-report and behavioral measures in a transnosological sample?

In the RDoC literature, we find that the two domains of PVS and NVS have already been well documented both individually (Lee et al., 2017; Olino et al., 2018; Tsanas et al., 2017) and in combination (Paulus et al., 2017), unlike the latent constructs of CS and SP, where only the individual (sub)constructs within these domains have been studied transnosologically in adults so far (e.g., (Sanislow et al., 2010; Schretlen et al., 2013). There has even been the development of a specific PVS assessment scale (Khazanov et al., 2019) and a review of existing self-reports to use for the assessment of NVS (Watson et al., 2017). Summarizing, while there has been more than one piece of evidence for the latent structure of the RDoC matrix in recent years, with priority given to PVS and NVS, no validation studies have yet been conducted for CS and SP as latent constructs based on behavioral and self-report measures in adults. However, there is evidence for individual sub-constructs within both domains. For example, Uljarević et al. (2020) found a latent structure for SP in children with an autism spectrum disorder. Our study aimed to examine all four latent RDoC domains simultaneously for the first time using behavioral and self-report measures in adults in a transnosological approach.

H1: The latent structure of these four RDoC domains can be validated by the a priori selected variables/scales of the mini-RDoC dataset.

H1a: The latent Positive Valence Systems (PVS) domain can be validated by self-report measures of Reward Responsiveness, Reward Valuation, and Reward Learning.

H1b: The latent Negative Valence Systems (NVS) domain can be validated by self-report measures of Potential Threat (Anxiety), Frustrative nonreward, Loss, and Sustained Threat.

H1c: The latent Cognitive Systems (CS) domain can be validated by self-report and behavioral measures of Language, Attention, Cognitive Control, and Working memory.

H1d: The latent Social Processes (SP) domain can be validated by self-report measures of Affiliation and Attachment, and Perception and understanding of self.

2. What are the associations between the four latent domains Positive (PVS) and Negative Valence Systems (NVS), Cognitive Systems (CS) and Social Processes (SP), and disease-specific symptom burden in patients with anxiety and depressive disorders?

To our knowledge, no attempt has yet been made to show transnosological associations of latent construct RDoC domains with disorder burden in patients with depressive and anxiety disorders. Instead, research has mostly focused on those domains that are specifically associated with current diagnostic categories. For example, there are numerous findings on PVS in patients with mood disorders (Baskin-Sommers & Foti, 2015; Groenewold et al., 2013; Nusslock & Alloy, 2017) and NVS in patients with anxiety disorders (e.g., Bar-Haim et al., 2007; Etkin & Wager, 2007; Klumpp et al., 2013).

Recently, interest in transdiagnostic research approaches has increased (e.g., Fusar-Poli et al., 2019). Researchers have sought to identify transdiagnostic and disorder-specific psychopathological endophenotypes, including abnormal threat processing in NVS in patients with anxiety and depressive disorders (MacNamara, Klumpp, Kennedy, Langenecker, & Phan, 2017; Williams, 2017), attentional biases to negative stimuli in anxiety and depressive disorders (Goldstein & Klein, 2014; Hasler, Drevets, Manji, & Charney, 2004; Williams, 2016), and dysfunctional reward functioning in PVS in depressive disorders, which is phenomenologically characterized by anhedonia (Hasler et al., 2004; Webb et al., 2016; Williams, 2017). Concerning domain-level PVS, low levels of global positive emotion have been identified as risk factors for depressive disorders, SAD, and GAD (Kendall et al., 2015; Khazanov & Ruscio, 2016).

Regarding the Tripartite Model of Anxiety and Depression by Clark & Watson (1991) and the associations of the distinguishing constructs of low *Positive Affect* (PA), which resembles anhedonia and can therefore be associated with PVS, *Physiological Hyperarousal* (PH), which can be associated to the RDoC construct of *Acute Threat* of the NVS domain (e.g., Yilmaz Balban et al., 2021)) and the common factor *Negative Affectivity* (NA) which can also be assigned to NVS, we expect an anhedonia driven disease-specific association for PVS. However, since NA, as the common factor of the Tripartite Model, integrates into NVS, this may dilute the disease-specific effects of this domain.

This leads to the assumption that there are both disease-specific as well as transnosological associations between the RDoC domains and disorder-specific disease burden. Against this background, we hypothesized as follows:

H2: All four domains have a transdiagnostic relationship with disease severity.

H3: Positive Valence Systems (PVS), Cognitive Systems (CS), and Social Processes (SP) also show a disease-specific relationship with disease severity.

H4: Positive Valence Systems (PVS), Cognitive Systems (CS), and Social Processes (SP) are negatively associated with disease severity, while Negative Valence Systems (NVS) would be positively related to disease severity.

3. What is the current scope of published RDOC-specific research regarding the Positive (PVS) and Negative Valence Systems (NVS) in patients with mood and anxiety disorder symptoms?

Since its beginning in 2009, the body of literature on the RDoC framework has grown steadily as the framework's complexity has also grown. Now, after more than a decade of research on this approach, it is a good vantage point to gather results found on specific parts of the RDoC framework to be able to discuss its status, research gaps, and future directions.

For the reasons already stated in the introduction, such as heterogeneity of syndromes, comorbidities, and impact on mental health worldwide, as well as a lack of RDoC reviews (Carcone & Ruocco, 2017), it seemed natural to look at RDoC-related research findings on mood and anxiety disorders. Against this background integrating the Tripartite Model (Clark & Watson, 1991), the two domains, PVS and NVS, are of particular interest because, on the one hand, PVS and its subconstructs are connected to the reward system and thus have a strong relation to anhedonia in depression (NIMH, 2011c). On the other hand, NVS is mostly related to processes in response to aversive situations and, for this reason, is strongly connected to anxiety (NIMH, 2011c). In addition, however, it is precisely in the construction of NVS that the link between the two domains is evident through the constructs *Loss* and *Frustrative Nonreward* and, at the disease level, thus, the link between mood and anxiety disorders. Therefore, exploring the similarities and differences by bringing together the information collected thus far on mood and anxiety disorders, especially on other units of analysis than self-report, was particularly intriguing, given the progress made in RDoC research on these disorders. We hypothesized:

H5: Conducting a scoping review from the RDoC perspective would enhance our comprehension of the varied diagnostic categories of mood and anxiety disorders. This, in turn, would augment our fundamental knowledge of the resemblances and disparities within this range of mental disorders.

The present dissertation is publication oriented. Therefore, the following chapters describe the specific methods used to address these questions and the results of these investigations.

4. Summary of related papers

4.1 Paper 1

Bernd R. Förstner, Mira Tschorn, Nicolas Reinoso-Schiller, Lea Mascarell Maričić, Erik Röcher, Janos L. Kalman, Sanna Stroth, Annalina V. Mayer, Kristina Schwarz, Anna Kaiser, Andrea Pfennig, André Manook, Marcus Ising, Ingmar Heinig, Andre Pittig, Andreas Heinz, Klaus Mathiak, Thomas G. Schulze, Frank Schneider, Inge Kamp-Becker, Andreas Meyer-Lindenberg, Frank Padberg, Tobias Banaschewski, Michael Bauer, Rainer Rupprecht, Hans-Ulrich Wittchen, Michael A. Rapp (2022). Mapping Research Domain Criteria using a transdiagnostic mini-RDoC assessment in mental disorders: a confirmatory factor analysis. European Archives of Psychiatry and Clinical Neuroscience. Advanced online publication. https://doi.org/10.1007/s00406-022-01440-6

Theoretical Background

The RDoC framework by the NIMH aims to improve classification systems and treatment approaches for mental disorders by incorporating biological, physiological, and behavioral knowledge. It offers a transnosological approach that also aims to understand mental health and disorder on a broader spectrum, seeking to overcome existing problems of symptom-based heterogeneity, comorbidity, and research limitations induced by diagnostic categories. There is some evidence for the validation of RDoC domains as latent constructs. Recent studies have explored or confirmed the multifactorial structure of the PVS domain (Khazanov et al., 2019; Light et al., 2019; Olino et al., 2018) and validated subconstructs assessing the latent structure of mood symptoms that further support the PVS construct (Tsanas et al., 2017) using self-report measures. Evidence suggests that the PVS and NVS domains should be treated independently rather than as opposing sides of the same dimension (Paulus et al., 2017). While more exploratory work is needed to develop valid instruments to measure the NVS domain (Watson et al., 2017), a higher-order NVS with a multifactorial internal structure has been found in children with internalizing disorder symptoms (Lee et al., 2017). The CS domain has not yet been validated using an explicit RDoC framework for self-report or behavioral measures, but its subconstructs have strong neurobiological support (Sanislow et al., 2010; Schretlen et al., 2013). Finally, recent research on the SP domain has shown promising results in capturing dimensional constructs with an existing self-report measure in children with normative development and autism spectrum disorder (Uljarević et al., 2020). Overall, while there is partial validation of the RDoC framework, more research is needed to fully validate the latent core domains.

The purpose of the current study was to provide initial insight into latent constructs of PVS, NVS, CS, and SP and their relationships using pre-existing self-report and behavioral measures in a transnosological mixed population spanning the DSM-5/ICD-10 disorder criteria categories. In addition, we aimed to further our understanding of the characteristics of these latent variables and their intercorrelations.

Hypothesis

We hypothesized that the variables chosen from the mini-RDoC Dataset could validate the latent four-domain structure.

Methods

A transnosological adult sample of 1,912 participants (primary diagnoses: 42.1% anxiety/fear-related, 18.2% depressive, 7.9% schizophrenia spectrum, 7.5% bipolar, 3.4% autism spectrum, 2.2 % from other disorders, 18.4% healthy controls, and rest with no diagnosis specified) was recruited in studies within the German research network for mental disorders (FZPE) (Bauer et al., 2016) in related consortia (PROTECT-AD, ESCAlife, ASD-Net, BipoLife, OptiMD, GCBS, APIC, ESPRIT) for the Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany (PD-CAN). Participants were all examined with a Mini-RDoC-Assessment, including well-established behavioral and self-report measures incorporated in a shell model to fit the existing requirements of the individual studies. These Assessments included parts of the BSI-53, PANAS, BIS/BAS, WHO-DAS, TMT A/B, DSST, and other assessments that were excluded later on in the process. The Mini-RDoC battery was built in a group consent process which also a priori determined and assigned the respective RDoC domains inside the assessment set. After careful data integration and handling of missing data (36,7%; leading to the exclusion of N= 481), data were analyzed with confirmatory factor analysis (CFA) in R (version 4.0.2) and the lavaan package (version 0.6.6.) with full information maximum likelihood (FIML) treating missingness, to depict the underlying latent RDoC domain structure. Latent factors underwent standardization. As changes to the original model had to be made, several model comparisons were carried out to show goodness of fit of the final model. Since the Shapiro-Wilk Test showed that none of the variables had a normal distribution, we used matching transformation methods.

Results

In the first model, all indicators had significant factor loadings ranging from -.76 to .49 for PVS, -.53 to .85 for NVS, -.79 to .71 for CS, and -.92 to .54 for SP. Even though its model fit was superior to a one-

factor/independent factor model solution, the overall model fit was poor (CFI = .77; TLI = .75). After eliminating indicators with R^2<.20, reexamining items and using theoretically driven modification indices adjustments, the updated four-factor model including the core domains PVS and NVS, CS, and SP showed a good fit (CFI - .93; TLI = .92) across this transnosological sample. This final model also showed a significantly better fit compared to a one-factor solution ($\chi2(6) = 1656.3$, p<.001) or a model with independent factors ($\chi2(6) = 2327.8$, p<.001). Participants who had higher positive affectivity tended to have better social (β = .891, p<.001) and cognitive skills (β = .221, p<.001) and less negative affect (β = -.757, p<.001). On the other hand, those with higher negative affectivity showed lower social (β = -.818, p<.001) and cognitive skills (β = -.232, p<.001). Furthermore, the results suggested that better cognitive skills were associated with better social skills (β = .175, p<.001).

Conclusion

In summary, this study provides an initial understanding of the underlying latent structure and correlations between four key RDoC domains in a sample that cuts across diagnostic categories based on symptomatology. Furthermore, we highlight the potential of using established self-report and behavioral measures to capture the latent structure formed by the RDoC matrix. This approach could facilitate further investigations into the connections between the RDoC domains of PVS, NVS, CS, and SP and outcome measures such as disease severity. By doing so, we may gain a better understanding of the specific effects of these domains across different mental disorders, which could inform the development of personalized treatment strategies.

4.2 Paper 2

Bernd R. Förstner, Sarah Jane Böttger, Alexander Moldavski, Malek Bajbouj, Andrea Pfennig, André Manook, Marcus Ising, Andre Pittig, Ingmar Heinig, Andreas Heinz, Klaus Mathiak, Thomas G. Schulze, Frank Schneider, Inge Kamp-Becker, Andreas Meyer-Lindenberg, Frank Padberg, Tobias Banaschewski, Michael Bauer, Rainer Rupprecht, Hans-Ulrich Wittchen, Michael A. Rapp, & Mira Tschorn (2023). The associations of positive and negative valence systems, cognitive systems, and social processes on disease severity in anxiety and depressive disorders. Frontiers in Psychiatry. Currently Under Review.

Theoretical Background

Limited research has investigated PVS functioning in anxiety disorders, with most studies focusing on specific anxiety disorders such as SAD and GAD (Kashdan, 2007; Kashdan et al., 2013; Taylor et al., 2010). However, PVS-related processing has been extensively studied in mood disorders (e.g., Barch et al., 2016; Baskin-Sommers & Foti, 2015; Dillon et al., 2014; Hägele et al., 2015). Overall, existing literature suggests that there are disease-specific and distinct profiles of reward processing in both types of disorders.

Behavioral, physiological, and neuronal data provide substantial evidence of comparable processing related to the NVS in depressive and anxiety disorder. Both disorders display a negativity bias towards negative stimuli (Bar-Haim et al., 2007; Klumpp et al., 2013; Shin & Liberzon, 2010), accompanied by altered brain activity in response to threat-related stimuli (Etkin & Wager, 2007; Killgore et al., 2014).

Cognitive impairments in attention, memory, and executive function are widely recognized in both anxiety and depressive disorder (Ferreri et al., 2011; Rock et al., 2014). Nonetheless, identifying disease-specific neural circuitry is difficult due to a shortage of transdiagnostic and multimodal research (Williams, 2017) and due to the presence of conflicting evidence regarding disorder-specific circuit changes (Sindermann et al., 2021; Wei & Roodenrys, 2021).

Although subconstructs of SP, such as attachment, may be linked to social anxiety (Fang et al., 2014; Glashouwer et al., 2013), the general impact of SP on anxiety disorders is uncertain due to the wide range of SP subconstructs combined with the diverse patterns of anxiety disorders. In depressive disorder, impairment of social functioning is a prominent feature and part of the disease's structure (Kupferberg et al., 2016).

In recent years, there has been increasing interest in transdiagnostic research approaches (e.g., (Fusar-Poli et al., 2019). Studies have sought to provide evidence for psychopathological endophenotypes of abnormal threat processing in anxiety and depressive disorders (MacNamara et al., 2017; Williams, 2017), as well as impaired reward functioning in depressive disorders characterized by anhedonia

(Hasler et al., 2004; Webb et al., 2016; Williams, 2017). In addition, low levels of global positive emotion have been identified as risk factors for several disorders, including depressive disorders, SAD, and GAD (Kendall et al., 2015; Khazanov & Ruscio, 2016).

The study aimed to investigate how PVS, NVS, CS, and SP relate to disease severity in psychiatric disorders using a transdiagnostic and dimensional approach. This research aims to enhance our understanding of the disease spectrum's underlying mechanisms and identify disease-specific and transdiagnostic indicators of disease severity in anxiety and depressive disorders.

Hypotheses

We hypothesized that PVS, CS, and SP would exhibit a negative association with disease severity. In contrast, NVS would demonstrate a positive correlation with disease severity. Additionally, we hypothesized that PVS, CS, and SP would display a disease-specific relationship with disease severity. At the same time, all four domains would also have a general transdiagnostic association with disease severity.

Methods

This was an observational cross-sectional study that evaluated the four core domains of the RDoC matrix (PVS, NVS, CS, SP) within the German research network for mental disorders (FZPE) (Bauer et al., 2016) in continuation of previous work by Foerstner et al. (2022). Participants were recruited from clinical and observational studies, and a minimal RDoC test battery was used to evaluate the domains at baseline. A total of 859 patients with a main diagnosis of major depression or an anxiety disorder were selected for analysis. Expert clinicians determined diagnoses according to the ICD-10 and/or DSM-4 criteria. Patients with anxiety disorders were generally younger and had more comorbidities, while a higher percentage of individuals with major depression were found to be utilizing psychotropic medication. No significant differences were observed between the two groups in terms of gender, education, and other sociodemographic variables.

The study utilized individual patient factor scores from a previously conducted four-factor CFA to represent the four RDoC domains. The standardized factor scores were estimated using a linear regression method. To simplify interpretation, factor scores were recoded positively so that higher scores indicate higher expressions of the assessed domain. Further details regarding the factor score composition are available in this article's supplementary material, and further details on the sample are in the articles´ tables.

Disease severity was evaluated using self-report scales, observer ratings, or global rating scales specific to each disease. To allow for a transdiagnostic analysis, all severity values were z-standardized based on normative data from adult clinical samples that met specific criteria.

Linear models (LM) were used in this analysis to examine the relationship between the type of diagnosis, PVS, NVS, CS, and SP factor scores, and disease severity z-score. To control for multicollinearity, domain-specific models were used. Although the variables were not normally distributed, their deviations were acceptable due to the large sample size. Grouped box plots and Cook's distance were used to identify outliers. No data points were removed. Levene's test indicated equal variances for SP but not for disease severity, PVS, NVS, and CS. When heteroscedasticity was present, a suitable heteroskedasticity-consistent covariance estimation method was used. The analyses were conducted in R version 4.2.2 with RStudio 2022.07.2 Build 576.

Results

We used LM in four steps to analyze the data. The first model (m0) included only the main diagnosis and disease severity (R^2 = .19). The anxiety disorder group had higher disease severity scores than the major depression group. In the second model (m1), we added all four RDoC domain factor scores as independent covariates, revealing significant effects of main diagnosis (β = -.42; p < .001), PVS (β = -.37; p < .001), NVS (β = .30; p < .001), and SP (β = .18; p < .05) on disease severity (R^2 = .41). We calculated variance inflation factors (VIF) for m1 to control for multicollinearity. PVS and SP exceeded the cut-off (VIF > 10). In the third model (m2), we added the four interactions of the domains with primary diagnosis to m1, which showed additional diagnosis-specific effects. Again, we found significant main effects for main diagnosis, PVS, and NVS (R^2 = .42). In the last fourth step, we analyzed domain-specific models (m3-6) with main diagnosis, separate domain covariates, and their associated interaction as predictors. We found significant main effects for diagnosis (range: β = -.51 to -.38) and the respective domain (PVS: β = -.35, p < .001; NVS: β = .39, p < .001; CS: β = -.12, p > .001; SP: β = -.32, p < .001) as well as a significant domain by disease interactions for PVS (β = -.15, p < .001), NVS (β = .09, p < .01) and SP (β = -.16, p < .001) in these models.

Due to the heteroskedasticity of the models, we conducted robust model analyses (m0-m6). Results showed no changes in most models except for m2 and m4. In m2, the main effect of SP became significant (t = 2.53, p = .012), and in m4, the interaction of main diagnosis and NVS changed from a significant effect to a trend-level effect (t = 1,81, p = .071). Controlling for age and present comorbidities did not affect the results. However, age was found to significantly predict disease severity in the CS single domain model (m5).

Conclusion

In summary, our findings highlight a robust link between symptom burden in individuals with anxiety and major depressive disorder and latent RDoC indicators, specifically PVS, NVS, CS, and SP, in a transdiagnostic manner. Moreover, our results suggest a disease-specific correlation between PVS, NVS, and SP. Further research is needed to elucidate the relationship between these indicators and disease severity to inform tailored therapeutic interventions in the future (Pasion, Martins, & Barbosa, 2019).

4.3 Paper 3

Sarah Jane Böttger, Bernd R. Förstner, Laura Szalek, Kristin Koller-Schlaud, Michael A. Rapp, Mira Tschorn (2023). Mood and Anxiety Disorders Within the Research Domain Criteria Framework of Positive and Negative Valence Systems: A Scoping Review. Frontiers in Clinical Neuroscience. Accepted for Publication.

Theoretical Background

As more studies embrace the RDoC approach and concepts, there remains a need for more extensive evaluations of published research on PVS and NVS in anxiety and mood disorders that align with the RDoC framework. These two constructs play an important role in the identification of commonalities and differences in this disorder spectrum. Considering the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991) and its constructs, references to the RDoC domains PVS and NVS can be drawn. Despite the growing number of studies utilizing RDoC-based methodologies and constructs, a thorough review of the state of research on PVS and NVS is still lacking (Carcone & Ruocco, 2017). Respectively, this scoping review aimed to identify and synthesize existing literature on the relationship between positive and negative valence systems and mood and anxiety disorders in adults.

Hypothesis

We hypothesized that performing a scoping review on mood and anxiety disorders within the RDoC domains PVS and NVS could provide an overview of past research and help identify research gaps.

Methods

The review was conducted following the Joanna Briggs Institute (JBI) recommendations (Arksey & O'Malley, 2005) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). The objectives, inclusion criteria, and methods for this scoping review were pre-specified and documented in our protocol prior to conducting the review.

Eligibility criteria included research with outcome measures (regarding all possible units of analysis: i.e., genes, molecules, cells, circuits, physiology, behavior, self-repot, paradigms) related to PVS and NVS in the RDoC framework, human studies of adult participants, individuals experiencing symptoms of mood and anxiety disorders, and all types of empirical research published in peer-reviewed journal papers with an available full text.

The search was conducted on five electronic databases (PubMed, PsychInfo, PsychArticles, PSYNDEX, and Web of Science) and included keywords related to positive and negative valence, affect, and emotion. Four research team members independently screened and selected relevant articles for inclusion, and data were extracted with a focus on disorder, domain and constructs assessed, units of analysis, main aim, key findings, and general information. Citavi, Covidence, and Excel were used in the screening process. We used a two-step screening process, first screening titles and abstracts and then screening the full text. A consensus process resolved disagreements between reviewers.

For eligible articles, we extracted data on the disorder, domain, constructs, units of analysis, main aim, key findings, and general information such as author, publication year, country/language, and study design. Risk of bias was not assessed following scoping review guidelines (Tricco et al., 2018), and the included studies had heterogeneous extracted information. Therefore, we grouped sources by RDoC domain and study design and mapped information to disorder type, seven units of analysis, and RDoC constructs. Empirical elements were listed, and key findings were also reported.

Results

A total of 231 abstracts were initially identified for this scoping review, of which 43 met the inclusion criteria. Psychological constructs were typically analyzed across different units of analysis, and most publications used multiple measures. While review articles focused on molecular, genetic, and physiological aspects, primary articles primarily used self-report, behavioral, and, less frequently, physiological measures.

Seventeen publications were identified regarding PVS, including ten primary articles and seven review articles. Most primary articles included self-report measures and at least one additional unit of analysis, such as physiology or behavior. However, only one publication included the molecules unit. No published primary research investigating PVS-related genes or cells in mood and anxiety disorders was found that was oriented toward the RDoC framework. Also, none of the articles focused exclusively on patients with anxiety disorders, and only one review included anxiety disorders. Therefore, only one research finding per construct will be highlighted below concerning the three PVS constructs.

Reward responsiveness: Impaired hedonic experience, which is a marker of impaired reward responsiveness, is particularly relevant in patients with major depressive disorder (Barch et al., 2016; Nakonezny et al., 2015; Nusslock & Alloy, 2017; Trøstheim et al., 2020) and has been found to be a unidimensional factor (Nakonezny et al., 2015) that is responsive to exercise treatment (Toups et al., 2017).

Reward learning: Depression-related hedonic impairments may trigger deficits in other PVS mechanisms like anticipation, learning, effort, and action selection, and the observed deficits are linked to changes in the signaling of dopamine and/or opioids in the striatum (Barch et al., 2016; Nusslock & Alloy, 2017).

Reward valuation: Nusslock et al. (2015) and Nusslock & Alloy (2017) suggest that reduced approach motivation linked with reward valuation could be associated with unipolar depression, while amplified approach motivation could be associated with bipolar disorder. Both mechanisms are associated with unique neuronal correlates.

In addition to the results found regarding the reward system, the development of a specific PVS scale (Khazanov et al., 2019), the implementation of an exploratory factor analysis (Olino et al., 2018), and the evidence for a PVS-based intervention (George S. Alexopoulos et al., 2015; George S. Alexopoulos et al., 2016) as well as the (non-)invasive treatment by brain stimulation (Fettes et al., 2017) should be highlighted.

For NVS, we found seventeen publications (eight primary articles, nine reviews) exploring its role in mood and anxiety disorders. Most primary articles (except one) used self-report measures along with additional analysis methods. No research was found on molecular or cellular levels except for one twin study (Ellingson, Richmond-Rakerd, Statham, Martin, & Slutske, 2016). Reviews mainly used physiological measures combined with other analysis methods, while only one integrated cellular research on depressive disorders (Ross, Foster, & Ionescu, 2017). Among the articles, 24% focused on patients with depressive disorders, 24% on patients with anxiety disorders, and 47% on multiple patient groups. Patients with bipolar disorder (BD) were underrepresented in both types of articles. NVS subconstructs were studied across diagnostic categories, mostly using multiple analysis methods. Acute, potential, and sustained threat received the most attention, while frustrative nonreward received the least, with only one primary article investigating its relation to depressive symptoms (Cochran et al., 2020).

Acute Threat: acute threat, imaging studies revealed shared neural dysfunctions in threat processing in patients diagnosed with anxiety and depression (MacNamara et al., 2017).

Sustained threat: Prolonged exposure to traumatic experiences and chronic stress has been associated with changes in the expression of proteins, neurocircuitry, physiology, and behavior. This evidence suggests that there are specific effects on the activation of the amygdala and reactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, both of which play a critical role in the development of mood and anxiety disorders (Ross et al., 2017; Sambuco, Bradley, Herring, Hillbrandt, & Lang, 2020).

Loss: Two literature reviews on the NVS subconstruct loss have addressed the impact of rumination on patients with depressive and bipolar disorder and proposed potential methods to investigate

depressive symptomatology within the RDoC framework (Silveira, Érico de M Jr & Kauer-Sant'Anna, 2015; Woody & Gibb, 2015).

In general, the research findings indicate the existence of transdiagnostic as well as disorder-specific dysfunctions in NVS domains across different units of analysis in patients with mood and anxiety disorders.

We found nine publications on PVS and NVS in mood and anxiety disorders using the RDoC framework, including five primary and four review articles. Most articles included more than one patient group, and only one focused on depressive disorders. None of the articles focused solely on anxiety disorders. Self-report measures were used in primary articles, while review articles focused on circuits, physiology, and behavior. One review article looked at molecules. Two articles could not be assigned to a specific RDoC construct. Overall, the articles covered a broad range of PVS- and NVS-related constructs.

Studies examining across domains have produced varying results. While one study did not find a cross-modal latent structure (Peng et al., 2021), two others identified independent "meta"-dimensions and four latent and transnosological factors (Förstner et al., 2022; Paulus et al., 2017). Associations with symptom scores have also been identified with PV symptoms linked to higher impairment and more inflammatory markers, while NV symptoms were linked to younger age and more frequent comorbid symptoms (Medeiros et al., 2020). In perinatal women, potential threat was suggested as a transdiagnostic feature of anxiety and depression, while reward valuation was suggested to be a symptom-specific feature of depression (Wenzel, Eisenlohr-Moul, Nagelli, Bernabé, & Maki, 2022). Individuals with major depressive or bipolar disorder may show differences in processing positive stimuli compared to healthy controls, with NVS circuitry being more pronounced (Langenecker, Jacobs, & Passarotti, 2014). Transdiagnostic neuronal disease mechanisms have been identified, but RDoC domains did not contribute differentially (Janiri et al., 2020). Abnormal glutamate activity has also been linked to NVS and PVS in mood and anxiety disorders (Terbeck, Akkus, Chesterman, & Hasler, 2015).

Conclusion

This scoping review revealed that researchers have extensively investigated mood and anxiety disorders using various analytical units within the RDoC framework. The results emphasize the crucial involvement of particular cortical frontal brain structures and subcortical limbic structures in the compromised emotional processing observed in these disorders. Additionally, the findings indicate a scarcity of research (on NVS) in bipolar disorders and PVS in anxiety disorders, primarily relying on self-report studies and observational research. Finally, the study emphasized the necessity for future research to focus on developing more RDoC-consistent innovations targeting neuroscience-driven constructs.

5. General Discussion and Conclusion

The upcoming chapter will provide a summary of the significant outcomes of the conducted studies and their integration into the current knowledge. In addition, the strengths and weaknesses of the studies will be highlighted, and possible future research directions and clinical implications will be delineated.

5.1 Main Findings

This thesis investigated the transdiagnostic assessment of mental disorders and their association with disease severity. In Paper 1, we validated the transdiagnostic assessment of core RDoC domains using established psychological measures. As a result, we identified a latent four-domain structure that spans across known nosologies. In Paper 2, we investigated the associations between these latent constructs and disease-specific symptom burden in patients with anxiety and depressive disorders. Results from this study showed transdiagnostic as well as disease-specific associations of the latent RDoC domains and symptom burden in these patients. Finally, paper 3 provided an overview of RDoC research on PVS and NVS in patients with mood and anxiety disorders from the last decade and identified research gaps.

Transdiagnostic Assessment of Mental Disorders

Regarding our contribution to transdiagnostic research approaches and the related question of whether it is possible to map the latent dimensional RDoC constructs with existing self-report and behavioral assessment instruments, we confirmed the assumed matrix for four core domains in Paper 1. Accordingly, we were able to confirm our hypothesis H1 in this regard. Summarizing the results, the four-factor model showed good fit and transnosological validity, with the core domains including PVS, NVS, CS, and SP. For PVS, hedonic and anhedonic aspects of *Reward Responsiveness* and *Habituation* were confirmed, while items reflecting *Reward Valuation* and *Responsiveness* were excluded due to poor fit. *Anhedonia* was a valid indicator of PVS and was therefore reconfigured from its former position associated to NVS. For NVS, potential threat indicators were also valid, while *Hostility* was more closely related to SP and, therefore, also reassigned. Behavioral measurements for *Attention*, *Cognitive Control*, and *Working Memory* confirmed a higher-level CS domain. The self-report measures for cognitive control failed to contribute to the model. SP was best represented by the a priori set variables, including *Social Hedonia*, *Ability to maintain Friendships*, *Interpersonal Sensitivity*, and *Paranoid Ideation*. Regarding the latent matrix structure, a strong connection was found between PVS, NVS, and SP, with smaller but meaningful factor loadings for CS. Regarding H1a to H1d, we could

conclude that they are partially supported, as indicated by the remaining variables after item reduction and the change in the assignment of two variables based on theoretical underpinnings.

In summary, the findings in Paper 1 suggest that a subset of self-report and behavioral measures included in the Mini-RDoC battery successfully resemble aspects of the examined latent factor structure. Identifying this shared underlying factor structure among various mental disorders examined in this investigation, as predicted by the RDoC framework, also provides an opportunity to enhance the definition of the latent (sub)constructs and their interrelationships. This also adds significant value to RDoC research in general by providing a first look at the existing latent matrix structure.

Disease-specific and Transdiagnostic RDoC Associations

Paper 2 aimed to understand the underlying RDoC mechanisms in anxiety and depressive disorders by examining the associations of the four core domains, validated in Paper 1, with disease severity across this diagnostic spectrum. The results confirmed the transdiagnostic relationship of PVS, NVS, CS, and SP on disease severity, as hypothesized in H2. Regarding H3, this hypothesis could also be confirmed for PVS and SP with the addition that we could also show a disease-specific relationship between NVS and symptom burden. This finding for NVS is also interesting concerning the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991), based on which we assumed that disease-specific effects might be diluted for NVS. We now have evidence that this may not be the case. The association of NVS with depressive symptom burden is even stronger than for anxiety symptoms, whereas patients with anxiety disorders in our sample reported a higher symptom burden overall. For CS, we were unable to show this putative association, perhaps due to the lack of information on specific CS subconstructs involved as distinguishing constructs, while using a single cognitive factor score solution. Finally, the predicted associations in H4 could also be confirmed. These associations also confirm the assumptions of the Tripartite Model of Anxiety and Depression.

Review Key Findings and the Tripartite Model (Clark & Watson, 1991)

Based on the scoping review's findings, it is evident that a vast amount of research has been conducted on the role of positive and negative valence in mood and anxiety disorders, specifically utilizing genetic, molecular, neuronal, physiological, behavioral, and self-report measures. Concerning the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991), three selected key findings will be discussed in the following:

Several investigations have reported distinct modifications in startle responses, serving as an index of acute Threat, particularly the NVS domain in diagnostic-specific contexts (Boecker & Pauli, 2019;

Vaidyanathan, Nelson, & Patrick, 2012), thereby distinguishing between depressive and anxiety disorders.

Furthermore, this particular NVS subconstruct has demonstrated transdiagnostic patterns, as demonstrated in an fMRI environment (MacNamara et al., 2017). These findings suggest that RDoC NVS constructs, such as acute threat, could be an additional marker of distinction for anxiety disorders, comparable to the physiological hyperarousal within the Tripartite Model. This evidence on transdiagnostic as well as diagnosis-specific threat processing could also have a possible link to the attentional bias found in patients with anxiety disorders (f.e., Bar-Haim et al., 2007). However, the specific integration into the Tripartite Model is unresolved and therefore provides an opportunity for future research.

Impaired hedonic experience, which is a marker of impaired reward responsiveness, has been shown to be a relevant PVS-related construct, specifically in patients with major depressive disorder (Barch et al., 2016; Nakonezny et al., 2015; Nusslock & Alloy, 2017; Trøstheim et al., 2020). This suggests that hedonic experience may be a valuable marker for distinguishing depression from other mood and anxiety disorders, which aligns with Tripartite Model assumptions.

Reduced effort and drive, as well as reduced reward responsiveness, have been linked to depressive symptoms (Nusslock et al., 2015; Nusslock & Alloy, 2017; Swope et al., 2020). However, reward responsiveness may serve as a proximal marker for acute affective symptoms (f.e., anhedonia) rather than being a trait or stable marker of patients with mood disorders (Langenecker et al., 2014). This suggests that the relationship between reward processing and depressive symptoms may be complex and could be further investigated through future research.

Moreover, the review revealed a scarcity of research on frustrative nonreward (NVS) in general, as well as the lack of primary articles on NVS research focused on bipolar disorder and PVS research focused on anxiety disorders. However, the review highlights the increasing number of publications originating from outside the US, indicating a growing acceptance of the dimensional research approach.

Finally, the review identified one treatment, the Engage therapy, which has been developed to enhance symptoms connected to the positive valence domain targeting neural mechanisms underlying disordered emotional processing in mood and anxiety disorders (Alexopoulos & Arean, 2014). This finding underscores the feasibility of developing treatments that target specific neural mechanisms underlying emotional processing in order to improve the efficacy of treatment for mood and anxiety disorders.

5.2 Strengths and Limitations

In general, evaluating mental disorders through the transdiagnostic RDoC framework approach is a highly intricate process, owing to the heterogeneity of known mental disorders and the complex nature of the RDoC framework, which exceeds the scope of this work. Nevertheless, this dissertation offers a new perspective by investigating the latent RDoC structure across various disorders and its relationship with disease severity in patients with anxiety and depressive disorders. However, a more comprehensive investigation would necessitate detailed research at the (sub-)construct level within the RDoC framework and integration of various disease patterns.

The use of well-established psychological assessments to evaluate the constructs of the RDoC matrix is a significant strength of Paper 1. This approach allows for the analysis of data using a standardized framework, making it easier to compare findings across mental disorders. This also provides an opportunity for post hoc RDoC analysis in samples with integratable RDoC measures, which can further strengthen our knowledge about psychological functioning in mental health.

Another strength also lies in providing a first glimpse of the latent structure of the RDoC domains in a large transnosological sample. This allows for an initial exploration of the relationship between different domains and their interactions across various mental disorders. This can provide a foundation for future research to further build upon and explore the underlying dimensional structure of mental health and disorders through the RDoC framework.

The second paper's strength is in demonstrating the disease-specific and transdiagnostic associations of the latent constructs to symptom burden in patients with anxiety and depressive disorders. Specifically, the finding of a stronger NVS effect on depressive than anxiety symptoms highlights the opportunities offered by transnosological research approaches such as RDOC. This also helps in identifying possible underlying disease mechanisms that could be targeted with personalized interventions.

The third paper's strength lies in providing a brief summary of RDoC-related publications on PVS and NVS, which regarding the Tripartite Model, the key domains in identifying the commonalities and differences of the mood and anxiety disorders spectrum. This review can serve as a valuable resource for researchers and clinicians interested in these domains/disorders and provide an overview of the current state of RDoC knowledge in these areas. In addition, by summarizing relevant research, this paper can help guide future studies by pointing out research gaps and providing information on possible starting points for new treatment approaches, ultimately advancing our understanding of these mental disorders and improving treatments in terms of precision medicine.

As for Limitations, Paper 1 included over- or under-representation of some diagnostic categories, the use of variable reduction and modification indices for the analysis, the focus on behavioral and self-

report units, and the need for further validation of the self-report measurements within the RDoC framework.

Paper 2 has limitations due to incomplete information on comorbidities and some main diagnoses resulting in limited subgroup data sets. The cross-sectional design prevents causal conclusions about the relationship of PVS, NVS, CS, and SP functioning with disease severity in patients with anxiety and depressive disorders. The use of LM models may have a limited understanding of domain-specific relations and generalized linear mixed models (GLMM) or other more sophisticated methods could be considered for further investigations. Although outliers, heteroskedasticity, and multicollinearity were addressed, the results should be interpreted within the context of these specific conditions. The associational structure between PVS, NVS, and SP also needs further investigation, especially in light of multicollinearity and changes in significance with robust testing.

The scoping review in Paper 3 has certain limitations, as it was not designed to provide a comprehensive overview of all research related to PVS and NVS in mood and anxiety disorders. Instead, the focus was mainly on the PVS and NVS domain level. Consequently, it is possible that some relevant publications may have been excluded since specific PVS and NVS constructs or subconstructs were not searched using keywords. Another limitation was excluding studies that did not clearly assign their research to specific RDoC constructs. This exclusion criterion is subjective and may have led to the exclusion of some RDoC-related results. Additionally, the review mapped articles from before 2017 to the revised PVS structure released by the NIMH in 2017, which could have resulted in different mapping than intended by the authors. Lastly, since there was no systematic review, there was no quality assessment of the included studies, a limitation inherent in a scoping review.

5.3 Theoretical Implications and Future Directions

This thesis demonstrates the potential of using the RDoC framework and its latent structure to improve our understanding of mental health functioning. This approach can identify disease-specific and transnosological constructs using various units of analysis, leading to more precise treatment options in the future (Pasion et al., 2019). Additionally, this thesis shows that the investigation of the coherent disease spectrum of anxiety and depressive disorders should not only consider symptom-related domains like PVS and NVS, but also extend to domains of mental functions such as SP and the other domains not covered by this thesis.

Furthermore, our transdiagnostic approach yielded the following results: Transdiagnostic latent constructs were validated, which could help to increase our understanding of the etiology of mental disorders and help further distinguish diagnosis-specific as well as transdiagnostic self-report and behavioral markers of mental health functioning. We could also show that even though the RDoC domains are distinct constructs, they have a transnosological overlap. This also increased our

knowledge on the concept and diagnostic problem of comorbidity in diagnostic categories. Future RDoC-driven phenotypes may reveal differences and therefore help to refine treatment strategies and individualized precision treatment.

We could also show that for the specific disorder spectrum of depressive and anxiety disorders with a high comorbidity rate, the RDoC domains have diagnosis-specific relations to disease severity, which could help to further differentiate building on the Tripartite Model of Anxiety and Depression.

Furthermore, the literature review on RDoC domain level revealed an increasing number of RDoC-specific publications but also identified research gaps that could foster future research to further differentiate diagnoses in the spectrum of mood and anxiety disorders.

Regarding future research a promising direction is to examine the (sub)constructs of RDoC domains in relation to disease severity. This might include identifying specific aspects of functioning that are most strongly associated with the severity of mental disorders. For example, within the NVS domain, it might be helpful to investigate which subconstructs, such as fear, anxiety, or frustrative nonreward, are associated with which symptomatology as well as their level of association regarding specific diagnostic symptoms. This information could help to develop more targeted interventions and inform individual treatment options.

Another promising direction for future research is to develop more precise and adequate self-report assessments designed to capture the RDoC domains and subconstructs (Khazanov et al., 2019). This would involve developing assessment tools that are more sensitive and specific to the dimensions of functioning being measured. Developing more precise self-report measures could help clinicians and researchers better understand the specific dimensions of functioning most relevant to particular mental disorders.

Finally, using larger samples and new research approaches, such as supervised and unsupervised machine learning algorithms, could help further advance research in the RDoC framework. These algorithms can analyze large amounts of data identifying patterns/clusters that may not be immediately apparent through traditional statistical methods. This could be particularly useful for identifying functioning patterns across different mental disorders or disorder subtypes. Additionally, larger samples would provide more power to detect meaningful associations and enable more complex analysis methods to help uncover specific dimensions of functioning and transnosological features of mental disorders.

5.4 Conclusion

In Conclusion, there is already more than a decade of research exploring the transnosological RDoC framework approach to help cut through known diagnostic barriers by trying to solve problems of heterogeneity and comorbidity and to understand the full spectrum of psychological functioning. This dissertation not only opened up a first look at the latent RDoC structure but also explored disease-specific and transnosological associations for two common mental disorders with a high comorbidity rate and gathered the body of RDoC-specific literature on this disease spectrum.

Paper 1 gave a first impression of the latent RDoC structure and thus enabled the exploration of the associations to disease severity. Consequently, Paper 2 explored these associations for anxiety and depressive disorders giving insight into possible distinguishing and common factors. Followed by a scoping review of the body of RDoC research gathered during the last decade in Paper 3, identifying further indicators and research gaps.

This dissertation, therefore, is one step towards a better understanding of latent constructs of RDoC functioning in a transnosological population in general, as well as in distinguishing within the commonly comorbid disease spectrum of mood and anxiety disorders.

"What lies behind us and what lies before us are tiny matters compared to what lies within us."

Ralph Waldo Emerson

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Appendix

Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit selbstständig und ohne Zuhilfenahme anderer als der angegebenen Quellen und Hilfsmittel angefertigt habe. Die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen sind als solche kenntlich gemacht. Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

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Mapping Research domain criteria using a transdiagnostic Mini-RDoC assessment in mental disorders – a confirmatory factor analysis

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Conflicts of Interests

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[9] Frank Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and has received speaker's honoraria from Mag&More GmbH and the neuroCare Group. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, and Mag&More GmbH and Brainsway Inc., Jerusalem, Israel.

[10] Dr. Banaschewski served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Medice and Takeda. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships.

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[12] Dr. Rupprecht served as advisor for SAGE Inc. and GABA Therapeutics.

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Availability of Data All original data are on record and accessible to inspection, but are not available publicly based on local and national data protection regulations.

Code availability Available from the authors upon request.

Author`s contributions All authors contributed to the study conception, design and data collection. Material preparation and analysis were performed by Mira Tschorn and Bernd R. Förstner. The first draft of the manuscript was written by Bernd R. Förstner, Michael Rapp and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Abstract

Objective: This study aimed to build on the relationship of well-established self-report and behavioral assessments to the latent constructs positive (PVS) and negative valence systems (NVS), cognitive systems (CS), and social processes (SP) of the Research Domain Criteria (RDoC) framework in a large transnosological population which cuts across DSM/ICD-10 disorder criteria categories.

Methods: 1,431 participants (42.1% suffering from anxiety/fear-related, 18.2% from depressive, 7.9% from schizophrenia spectrum, 7.5% from bipolar, 3.4% from autism spectrum, 2.2 % from other disorders, 18.4% healthy controls, and 0.2% with no diagnosis specified) recruited in studies within the German research network for mental disorders for the Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany (PD-CAN) were examined with a Mini-RDoC-Assessment including behavioral and self-report measures. The respective data was analyzed with confirmatory factor analysis (CFA) to delineate the underlying latent RDoC-structure.

Results: A revised four-factor model reflecting the core domains positive and negative valence systems as well as cognitive systems and social processes showed a good fit across this sample and showed significantly better fit compared to a one factor solution. The connections between the domains PVS, NVS and SP could be substantiated, indicating a universal latent structure spanning across known nosological entities.

Conclusions: This study is the first to give an impression on the latent structure and intercorrelations between four core Research Domain Criteria in a transnosological sample. We emphasize the possibility of using already existing and well validated self-report and behavioral measurements to capture aspects of the latent structure informed by the RDoC matrix.

Keywords: Diagnosis and Classification, Research Domain Criteria, PD-CAN, confirmatory factor analysis CFA, RDoC, transdiagnostic

Introduction

Since its launch in 2010, the Research Domain Criteria (RDoC) framework by the National Institute of Mental Health (NIMH) [1] gained traction, in an effort to transgress established symptom based diagnostic systems (Diagnostic and Statistical Manual of Mental Disorders [DSM] [2] / International classification of diseases [ICD] [3]), implementing new categories representing fundamental principles underlying these taxonomies [4]. This transnosological approach aims to understand the full spectrum of mental health and illness through incorporating biological, physiological and behavioral knowledge, while it seeks to overcome existing problems of symptom based heterogeneity, comorbidity and research limitations induced by diagnostic categories [5–7].

The RDoC approach represents a framework based on behavioral dimensions and neurobiological measures with the final goal of improving classification systems for mental diseases and treatment approaches [1, 8]. This goal arose from a fundamental critique on the DSM-5 and its lack of validity, which is caused by symptom-based diagnosis that do not categorize by etiology and fail to match mechanisms or markers identified in biological psychiatry [9]. These shortcomings have been linked to low response and remission rates in psychopharmacology, furthermore to potential harming of patients with needless treatments and diagnoses [10, 11].

The RDoC matrix [6] offers a systematic overview of currently six core domains forming basic dimensions of human functioning: positive (PVS) [12] and negative valence systems (NVS) [13], cognitive systems (CS) [14], social processes (SP) [15], arousal and regulatory systems (ARS) [16] and sensorimotor systems (SMS) [17]. For each domain a hierarchical system of constructs and subconstructs is defined to cover specific facets of this domain. Each (sub-)construct has eight “units of analysis” representing methodological aspects to integrate the following levels of information covering Genes, Molecules, Cells, Circuits, Physiology, Behavior, Self-report and Paradigms. In this current study only four domains are being investigated since ARS and SMS were subsequently added to the matrix after data collection started. The domains, (sub-)constructs and units of analysis investigated in the current work, are described in detail in the methods section.

Little work has been done to validate these RDoC defined core domains using the units self-report and behavioral investigation, while the existing literature on this subject shows large variations of methodological approaches and definitions on these functional core domains. Recent studies using self-report measures explored or confirmed the multi-factorial structure of the PVS domain and showed connection to common constructs of personality [18, 19]. In addition, a specific PVS-scale and a subscale for empathy were implemented and validated [18, 20]. In a purely psychometric approach, Tsanas and colleagues (2017) found valid subconstructs assessing the latent structure of mood symptoms that further validate the RDoC construct PVS [21]. Paulus et al. (2017) used an RDoC

framework with self-report and behavioral measures to define the domains NVS and PVS and provided evidence suggesting that both domains should be treated independently and not as two sides of the same coin [22]. Their findings supported the assumption of an independent reward neural circuit [23].

Regarding the NVS domain, a review of self-report measures concluded that more exploratory work needs to be conducted in order to develop valid instruments to measure this domain and its subconstructs [24]. Nonetheless, a confirmatory study in children with internalizing disorder symptoms using self-report measures revealed an „higher order NVS“ with a multifactorial internal structure, supporting the idea of a latent NVS domain in developing children and suggesting an underlying set of biological mechanisms with construct specific elements [25].

Until this date, no validation studies regarding the CS domain exist, that use an explicit RDoC framework for self-report or behavioral measures. However, the sub-constructs integrating the domain have been investigated fairly well and have strong neurobiological support [26]. Furthermore, a latent cognitive multifactorial structure common in subjects diagnosed with schizophrenia, bipolar disorder and healthy adults has been validated which supports the idea of a cognitive multifactorial system congruent to the propositions of the RDoC framework [27]. Recent research on the SP domain showed promising results on capturing dimensional SP constructs with an already existing self-report measure in children with normative development and autism spectrum disorder [28].

In summary, single domains forming the latent structure of the RDoC framework regarding self-report measures have partially been substantiated. Following this research and the current recommendations by the NIMH [29, 30] our study sought to investigate the RDoC framework spanning across four of the core domains for the first time.

Specifically, the goal of the current study was to establish a first look at the latent constructs of PVS, NVS, CS, and SP and their relationship using already existing self-report and behavioral assessments in a transnosological mixed population which cuts across DSM-V/ICD-10 disorder criteria categories. Moreover, we aimed to improve our understanding about the characteristics of these latent variables and their intercorrelations.

Methods

Participants and procedures

Overall, 1,912 participants were recruited for the Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany (PD-CAN) within the German research network for mental disorders [31]. All patients were initially recruited for specific intervention and observation studies of a given disease entity within each of the nine network consortia. Specifically, in this study, we report data from eight research consortia (PROTECT-AD, ESCAlife, ASD-Net, BipoLife, OptiMD, GCBS, APIC, ESPRIT). Since

the main cohort of the AERIAL project focusing on the development of substance use disorders represents a primarily adolescent at risk sample with comparably low prevalence of mental disorders, measuring similar domains using partially different assessment methods, we excluded data from this consortium from the present analyses given the focus on confirmatory factor analysis. Due to the heterogeneity of the studies within the network, each of the projects implemented specific in- and exclusion criteria as well as the Mini-RDoC assessment in toto or partially depending on the individual assessment fit in the respective study (see SI1 or below for details). An overview on the main aims, sampling including in-/exclusion criteria and number of participants included for each specific study is available in supplementary material SI2. All subjects gave additional written informed consent to participate in and contribute their data to the PD-CAN network in an anonymized fashion at the local sites. Data were transmitted from the partner site via secure servers and data carriers, or an anonymized electronic research file implemented in secuTrial® (interActive Systems GmbH, Berlin).

A consented test-battery with 16 psychological tests was administered after recruitment in addition or embedded into the usual testing of each study, with the principal aim to measure behavioral and self-report constructs of the RDoC matrix [1, 4, 6]. The battery comprises a shell model (Figure SI1) with two layers and a core. Baseline implementation of the core variables was obligatory and shell variables were optional depending on their fit to the specific assessment process (f.e. questionnaire processing time) to accommodate the individual study designs. The consent process on the battery was managed through a Delphi process including experts from each of the nine consortia and resulted in a selection of tasks for shell and core assessments in 2014. The consent group also determined and assigned a priori the domains assessed within the RDoC matrix by using the information given by the NIMH and publications on self-report/behavioral measures within the RDOC framework at that time [12–16, 22, 25, 32]. Supplementary Table SI3 shows a detailed description of this battery and the tests. The derived 29 variables/scales included in the model were implemented to assess PVS, NVS, CS und SP as latent factors.

Measurements

Positive and negative valence systems: the Positive and Negative Affect Schedule (PANAS) [33] is a 10-item self-report scale on positive and negative affect. The Behavioral Inhibition and Activation Scale (BIS/BAS) [34] includes 24-items assessing motivation towards goal-motivated or avoidance of aversive outcomes. The BSI-53 (Brief Symptom Inventory) [35] is a self-report psychometric instrument to assess a broad range of psychological problems and symptoms of psychopathology. It consists of 53 items yielding 9 scores for primary symptom dimensions and three global distress indices. Abuse and neglect during childhood and adolescence was measured using the 5-item Childhood Trauma Screener (CTS) [36].

Cognitive systems: The two-tiered TMT A/B [37] is a widely used neuropsychological instrument that measures speed of scanning, visuomotor tracking, divided attention and cognitive flexibility. Also included were two subtests of the Wechsler Adult intelligence Scale (WAIS-IV) [38]. First, Digit-span Forward task (DF) assesses working memory capacity by asking participants to recall an increasing sequence of spoken digits. Second, the Digit Symbol Substitution Test (DSST) measures cognitive processing speed, short term memory, learning ability, visual perception, visuomotor coordination, ability for visual scanning and attention. The short form of the Barratt Impulsiveness Scale (BIS-15) [39] consists of 15 items assessing the behavioral or personality construct of impulsiveness represented in three subscales of non-planning, attentional and motor impulsivity. Lastly, the Multiple-choice Word Test (MWT-B) [40] with 37 items offers an estimate for premorbid cognitive ability.

Social processes: The WHO Disability Assessment Schedule 2.0 (WHO-DAS 2.0) [41] is a 12-item instrument developed by the WHO for assessing health status and disability. Specifically, the single item reflecting social integration was used. Similarly, additional subscales from the BSI-53 [35] assessing social relationships and social anhedonia were used. The Emotion Regulation Questionnaire (ERQ) [42] is a 10-item scale assessing two emotion regulation strategies, cognitive reappraisal and expressive suppression, in relation to SP. In addition, three sociodemographic variables were implemented to include indirect measures of existing social relations, affiliation and attachment. Used subscales and their relation to the RDoC matrix are shown in Table 1.

The structure of data showed heterogeneous missingness (36.68 % throughout the whole raw dataset). To deal with missingness, we applied the following strategy: First, we excluded all participants (*N*=481) lacking all the indicator variables/scales for at least one of the four RDoC from our analyses. Overall missingness was thus reduced by 12.69 %. Missing values within the observed variables (see Table 2) that were considered (a priori) for the factor analysis by the consent group amounted to 11.12 %. Even though the overall missing rate can be considered as typical [43], in a second step, we considered individual items exhibiting missingness in more than 35 % of data. Four specific variables retained missingness at approximately 39 %: BIS/BAS subscales Behavioral Inhibition, BAS-Drive, BAS-Reward Responsiveness and PANAS Positive Affect (see also Table 2). Given that three of the indicators had been selected for PVS, we decided to use three of the six single items from the BSI-53 Obsessive-compulsive scale (focusing on inhibition and habituation as parts of PVS [12]) instead of the whole scale as indicators in order to strengthen the database informing the latent factor PVS. This benefited the full information maximum likelihood method (FIML) [44] used to handle missing data, because more detailed information was available for missing variable estimation. The final sample to evaluate the structure of our four-factor model consisted of *n*=1,431 participants. A descriptive overview on the demographic and diagnostic information of the final sample can be found in Table 3.

Statistics

The underlying latent RDoC factor structure of the PD-CAN assessment was tested using confirmatory factor analysis (CFA) with Maximum likelihood (ML) estimation. Specifically, we fit the confirmatory four-factor model using lavaan version 0.6-6 in R version 4.0.2 with RStudio 1.3.1073 with FIML [44] handling missing data which was considered missing at random (MAR). Latent factors were standardized, i.e., variance was restricted to 1, allowing free estimation of all factor loadings. In addition, the four-factor model was compared to a one-factor solution using the same variables, which sets the correlation between the latent factors to 1 and another model which doesn´t allow covariances between the latent factors treating them as independent.

Given that exploratory data analysis with the Shapiro Wilk Test [45] for multivariate normal distribution revealed that none of the indicator variables were normally distributed. We used natural logarithm (ln) for right skewed variables or Johnson transformation [46] for variables with a high range to adjust the distribution. Variables/scales that were already z-transformed (DSST score) or were dichotomous or categorical (e.g., residential status) did not undergo transformation. To ensure a congruent polarity for SP we reversed the WHO-DAS 2.0 single item 'friendships' since all utilized indicators for SP had negative polarity. Raw scores for all observed variables as well as item-specific missingness are provided in Table 2.

Results

Confirming the primary hypothesis, all indicators showed significant ($p<.001$, except BIS-15 Non-planning Impulsivity scale with $p<.05$) factor loadings on the considered domains with standardized coefficients ranging from -.76 to .49 for PVS, -.53 to .85 for NVS, -.79 to .71 for CS and -.92 to .54 for SP. However, the four-factor model fit (model 1) was poor with a comparative fit index (CFI) of .77, a Tucker-Lewis index (TLI) of .75 and a root mean square error of approximation (RMSEA) of .078 with a 90 % confidence interval (CI) (.076 -.081). However, compared to a single factor solution (model 2: $\chi2(6)$ 1158.1, <.001) or a solution assuming the four factors as independent (model 3: $\chi2(6)$ 2571.2, $p<.001$), fit was significantly better. For more information on all analyzed CFA-models see supplementary table SI5 for details.

To address poor fit, we examined the amount of variance explained by each variable/scale using R-Squared estimates for each indicator. Twelve indicators explained less than 20 % of the variance in the respective domain and were excluded from further analyses (see Table 4).

In addition, using modification indices (mi) as a starting point, we reconfigured the model for two indicators. Modification indices reflect a test for covariance across the four factors (RDoC) under study

in CFA when covariances are fixed a priori. Specifically, we defined that all variables with a mi > 200, that showed larger covariance of an indicator to another factorial domain were changed to the other domain. In a first step, we relocated the BSI53 Anhedonia item (mi = 270.30) to PVS (instead of NVS). This change was informed by research that suggests anhedonia to be strongly associated with general approach behavior [19], a decrease in positive affect [47] and the reward system as a core component of PVS [48, 49]. In a second step, the BSI53 Hostility subscale (mi = 203.40) was moved to indicate SP since examining the scale items revealed proximity to interpersonal hostility and significant distance to frustrative nonreward to which it was assigned a priori. Subsequently, all modification indices ranged below 200.

Finally, we re-examined the scales on item level that were removed for low R-squares earlier to test for an increased shared variance in the latent structure altered based on modification indices. To maximize explained variance, we formed mean scores based on these items. Shared variance significantly improved when we combined items from the BIS/BAS Drive and Reward Responsiveness subscales. Additionally, we also restricted items in the PANAS Positive Affect subscale to reflect hedonic items, items from the BSI Obsessive-Compulsive subscale to items reflecting habituation, and items from the BIS Behavioral Inhibition subscale to reflect anxiety and threat more closely. All changes can be found in Table SI4.

Applying these changes created a significantly improved model fit CFI of .93, TLI of .92. and RMSEA of .077 with 90 % CI (.072 - .082). The overall fit as estimated with the CFI now indicated good fit [50]. This full four factor model (model 4) again fitted the data significantly better than a single factor solution (model 5: $\chi2(6) = 1656.3$, $p<.001$) or the solution with four independent factors (model 6: $\chi2(6) = 2327.8$, $p<.001$).

Regarding the relationship between the indicators and their latent factors, highly significant factor loadings suggest that participants with higher scores in PVS tended to have more hedonic affect ($\beta = .545$, $p<.001$), better habituation ($\beta = .810$ $p<.001$) and less anhedonia ($\beta = -.758$, $p<.001$).

Participants with high scores in NVS tended to have higher levels of general ($\beta = .909$, $p<.001$) and phobic anxiety ($\beta = .812$, $p<.001$), more somatization ($\beta = .746$, $p<.001$), and more anxiety-based behavioral inhibition ($\beta = .491$, $p< .001$).

As expected, participants with higher cognitive abilities exhibited better premorbid intelligence ($\beta = .688$, $p<.001$), better cognitive speed processing ($\beta = -.796$, $p<.001$) and executive functioning ($\beta = -.796$, $p<.001$).

Higher scores in the SP domain aligned with better skills in keeping friendships (β = .532, p<.001) and less paranoid ideation (β = -.787, p<.001), less social anhedonia (β = -.756, p<.001), as well as less interpersonal sensitivity (β = -.909, p<.001) and hostility (β = -.764, p<.001).

There were also significant relations between the four latent factors in that participants with positive affectivity had higher social (β = .891, p<.001) and cognitive skills (β = .221, p<.001) and less negative affect or aversion against events, objects, and situations (β = -.757, p<.001). At the same time, participants with high levels of negative affect exhibited decreased cognitive (β = -.232, p<.001) and social skills (β = -.818, p<.001). Finally, higher cognitive skills were related to better social skills (β = .175, p<.001, see Figure 1 for details).

Figure 1

Factorial loadings of the final model on the four Research Domain Criteria

[insert figure 1 here]

Fig.1 Standardized latent variables: PVS = Positive valence systems; NVS = Negative valence systems; CS = Cognitive systems; SP = Social processes; Manifest variables: BIS/BAS Behavioral Inhibition Anxiety =Anxiety based inhibition aspects of BIS/BAS subscale Behavioral Inhibition ; BSI-53 Anhedonia = BSI-53 single item Anhedonia; BIS-53 Anxiety = BIS-53 subscale Anxiety; BSI-53 Habituation = habituational aspects of BSI-53 single items Obsessive-compulsive ; BSI-53 Hostility = BSI-53 subscale Hostility; BSI-53 Interpersonal Sensitivity = BSI-53 subscale Interpersonal Sensitivity; BSI-53 Phobic Anxiety = BSI-53 subscale Phobic Anxiety; BSI-53 Paranoid Ideas = BSI-53 subscale Paranoid Ideation; BSI-53 Social Anhedonia = BSI-53 single Item Social Anhedonia; BSI-53 Somatization = BSI-53 subscale Somatization; DSST Work Memory = Digit Symbol Substitution Test raw score; PANAS Hedonic = Hedonic aspects of PANAS subscale Positive Affect; TMT-A Time Attention = Trail Making Test – Version A completion time; TMT-B Time Cognitive Control = Trail Making Test – Version B completion time; WHO-DAS Friendships = WHO-DAS 2.0 Single item Friendships reversed

Discussion

The present study used CFA to delineate four core domains of the RDoC framework using behavioral and self-report assessments in a heterogeneous sample of patients suffering from mental disorders and controls. Following the implementation of a short and efficient Mini-RDoC-Assessment approach for this task in multiple studies from within the German Research Network for mental disorders, it was expected to identify latent constructs shared by multiple disorders that may eventually generate a better understanding of the transnosological structure formed by the RDoC framework.

The four-factor model reflecting the core domains PVS and NVS as well as CS and SP showed good fit across a sample of clinical and nonclinical participants spanning across major mental disorder diagnoses supporting the potential transnosological validity of the RDoC framework as implemented

using behavioral assessments only. Compared to a one factor solution and a version treating all factors as independent, it also showed significantly better fit.

Specifically, regarding PVS, hedonic (PANAS) and anhedonic aspects of reward responsiveness as well as habituation (BSI-53) connected with reward learning as part of this domain could be confirmed. However, items reflecting reward valuation and reward responsiveness had to be excluded because of high levels of error variance indicating poor fit with the overall construct of PVS. At the same time, anhedonia showed to be a valid indicator of the dimension forming PVS as compared to NVS. These results correspond to previous findings for this construct [24].

For NVS, especially potential threat indicators (BSI-53, BIS/BAS) remained valid within the overall factorial structure. Interestingly, hostility shared more variance with SP than with NVS as a measure for frustrative nonreward.

For CS, behavioral measurements for attention (TMT-A), cognitive control (TMT-B) and working memory (DSST) confirm these constructs as informative for this latent factor. Presumably because of measurement invariance, the self-report measures for subconstructs of cognitive control failed to contribute to the model.

As for SP, this domain could be best represented by the a priori set variables. Despite the observation that almost half of the measures had high levels of error variance (sociodemographic and emotion regulation) and in result had to be removed as indicators from the model (see [22] for similar results), the final model represents a clear representation of SP including social hedonia (BSI-53), the ability to maintain friendships (WHO-DAS), as well as interpersonal sensitivity and paranoid ideation (BSI-53).

Across domains, a strong connection between the domains PVS, NVS and SP could be substantiated, indicating a universal latent structure spanning across known nosological entities. CS showed smaller but meaningful correlations with the other domains, suggesting that the associations of cognitive abilities with key aspects of affectivity and SP are small and may be moderated by specific disease mechanisms in e.g. schizophrenia [51], autism spectrum disorders [52, 53] and affective disorders [54].

Concerning all removed subconstructs and their measurements, further research needs to be conducted examining existing self-report measures and their allocation inside the RDoC framework as well as to conceptualize new comprehensive measurement tools improving valid measurement of its dimensional latent structure for better adoption in clinical assessment and research.

Finally, our findings suggest that the Mini-RDoC test battery, specifically subsets of the self-report questionnaires BSI-53, PANAS, BIS/BAS, WHO-DAS and TMT A/B and DSST as cognitive tests, successfully resemble aspects of the four core domains measured. Revealing a latent factor structure

common to all mental disorders included in this study, as anticipated by the RDoC framework, and gives space for a definition improvement on the latent (sub-)constructs and their relations in-between.

Several limitations need to be addressed considering our findings from this study. The implementation of the Mini-RDoC assessment as a core assessment inside the German research network for mental disorders enabled us to build a considerable amount of data providing a transnosological view cutting across known disorder-based categories. However, some diagnostic categories were over- or underrepresented. Thus, while findings are generalizable throughout a large variety of mental diseases future research could validate our findings using a more balanced distribution.

The initial poor model-fit and the need to use variable reduction and modification indices to guide and reshape our a priori assumptions introduced a bias resulting in reduction of robustness and generalizability of our final model. However, we used these methods very carefully and gave detailed information on the changes made. We would like to point out that all changes applied refer to a theoretical basis in our procedures and that model fit was superior to other factor solutions. Nevertheless, future research should replicate our findings to confirm the formed latent structure. Though this procedure may have been a little exploratory, the significantly better fit in comparison to the one factor solution, supports the assumption of a four factor latent structure.

In contrast to the basic assumption of the RDoC approach that latent variables would become apparent across units of analyses (i.e., considering molecules, cells, physiology, circuits, behavior, and self-report) within domains, our approach is mainly symptom-oriented and focuses on the behavioral and self-report units. Therefore, our study did not evaluate cross-unit validity of the RDoC but investigated latent variables within the self-report unit.

Furthermore, our findings on the assignment changes implicated by modification indices and the removal of several constructs due to high error variance should be re-examined and cross-validated in further, preferentially larger, datasets.

Also, there is some ambiguity with respect to the self-report measurements within the RDoC framework [24], suggesting that more research on embedding already validated and reliable self-report measures into the RDoC framework needs to be done, as well as validating new measurements for specific domains that emerged after our initial consensus on the used measurements (e.g., the sensorimotor domain [17]) and their integration with other units of analysis as suggested by f.e. MacNamara and Phan (2016) [55].

To conclude, this study gives a first impression on the latent structure and intercorrelations between four core Research Domain Criteria in a transnosological sample cutting across symptom-based diagnostics. We emphasize the possibility of using already existing and well validated self-report and

behavioral measurements to capture aspects of the latent structure formed by the RDoC matrix. This will enable future research connecting the RDoC matrix and its core domains PVS, NVS, CS and SP to outcome measures like disease severity to better characterize domain-specific effects across mental disorders, which may help inform the development of stratified treatment strategies.

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Tables

Table 1

A priori allocation of the PD-CAN assessment to RDoC

Measured RDoC and constructs	Instrument	
Positive valence systems (PVS)		
Reward responsiveness	PANAS	Subscale Positive Affect
Reward responsiveness	BIS/BAS	Subscale Reward Responsiveness
Reward valuation	BIS/BAS	Subscale Drive
Reward learning	BSI-53	Single items Obsessive-Compulsive
Negative valence systems (NVS)		
Potential threat (anxiety)	BIS/BAS	Subscale Behavioral Inhibition
Potential threat (anxiety)	BSI-53	Subscale Anxiety
Potential threat (anxiety)	BSI-53	Subscale Phobic Anxiety
Potential threat (anxiety)	BSI-53	Subscale Somatization
Frustrative nonreward	BSI-53	Subscale Hostility
Loss	BSI-53	Single item Anhedonia
Sustained threat	CTS	Sumscore Childhood Trauma
Cognitive systems (CS)		
Language	MWT-B	Raw score Multiple-Choice Word Test – Version B
Attention	TMT-A	Raw score Trail Making Test – Version A
Cognitive control	TMT-B	Raw score Trail Making Test – Version B
Cognitive control	BIS-15	Subscale Attentional Impulsivity
Cognitive control	BIS-15	Subscale Non-planning Impulsivity
Working memory	DF	Sumscore Digit span forward
Working memory	DSST	Raw score Digit Symbol Substitution Test
Social processes (SP)		
Affiliation and attachment	Demography	Single item graduation
Affiliation and attachment	Demography	Single item occupation
Affiliation and attachment	Demography	Single item residential status
Affiliation and attachment	WHO-DAS 2.0	Single item Friendships reversed
Affiliation and attachment	BSI-53	Subscale Interpersonal Sensitivity
Affiliation and attachment	BSI-53	Single item Social Anhedonia
Perception and understanding of self	BSI-53	Subscale Paranoid Ideation
Perception and understanding of self	ERQ	Subscale Reappraisal
Perception and understanding of self	ERQ	Subscale Suppression

Note. BIS-15 = Barratt Impulsiveness Scale - Short Form; BIS/BAS = Behavioral Inhibition System/ Behavioral Activation System Scale; BSI-53 = Brief Symptom Checklist; CTS = Childhood Trauma Screener; DF = Digit span forward; DSST = Digit Symbol Substitution Test; ERQ = Emotion Regulation Questionnaire; PANAS = Positive and Negative Affect Scale; WHO-DAS 2.0 = WHO Disability Assessment Schedule 2.0.

Table 2

Descriptive Statistics of Observed Variables (untransformed)

Variable	Instrument	*Mean*	*SD*	Min	Max	*Mdn*	IQR	% Missing
Subscale Positive Affect (PVS)	PANAS	16.39	7.56	0.00	42.00	16.00	10.00	38.50
Subscale Reward Responsiveness (PVS)	BIS/BAS	10.27	2.53	4.00	20.00	10.00	3.00	39.20
Subscale Drive (PVS)	BIS/BAS	8.94	2.42	4.00	16.00	9.00	4.00	39.20
Single item (15) Obsessive-Compulsive (PVS)	BSI-53	1.38	1.20	0.00	4.00	1.00	2.00	0.63
Single item (26) Obsessive-Compulsive (PVS)	BSI-53	0.48	0.88	0.00	4.00	0.00	1.00	0.35
Single item (27) Obsessive-Compulsive (PVS)	BSI-53	1.16	1.13	0.00	4.00	1.00	2.00	0.28
Subscale Behavioral Inhibition (NVS)	BIS/BAS	12.02	3.63	7.00	26.00	12.00	6.00	39.20
Subscale Anxiety (NVS)	BSI-53	0.87	0.76	0.00	3.83	0.67	1.13	0.35
Subscale Phobic Anxiety (NVS)	BSI-53	0.73	0.85	0.00	4.00	0.40	1.20	0.35
Subscale Somatization (NVS)	BSI-53	0.60	0.62	0.00	3.57	0.43	0.71	0.35
Subscale Hostility (NVS)	BSI-53	0.56	0.60	0.00	3.40	0.40	0.60	0.35
Single item Anhedonia (NVS)	BSI-53	0.93	1.17	0.00	4.00	1.00	1.00	0.42
Sumscore Childhood Trauma (NVS)	CTS	2.91	3.30	0.00	19.00	2.00	4.00	1.05
Raw score MWT-B (CS)	MWT-B	27.85	5.17	0.00	37.00	28.00	6.00	11.11
Raw score TMT-A (CS)	TMT-A	28.17	11.96	10.00	114.00	25.19	12.61	18.24
Raw Score TMT-B (CS)	TMT-B	61.88	27.99	15.33	282.00	55.00	26.24	16.00
Subscale Attentional Impulsivity (CS)	BIS-15	5.34	2.88	0.00	14.00	5.00	4.00	12.86
Subscale Non-planning Impulsivity (CS)	BIS-15	6.32	3.13	0.00	15.00	6.00	4.00	12.86

Variable	Instrument	*Mean*	*SD*	**M**in	**M**ax	*Mdn*	**IQR**	% Missing
Sumscore DF (CS)	DF	8.33	2.35	2.00	16.00	8.00	3.00	17.12
Raw score DSST (CS)	DSST	-0.33	1.07	-4.91	4.26	-0.34	1.35	8.18
Single item graduation (SP)		5.67	1.67	0.00	8.00	7.00	3.00	0.49
Single item occupation (SP)		0.64	0.48	0.00	1.00	1.00	1.00	2.94
Single item residential status (SP)		0.61	0.49	0.00	1.00			0.42
Single item Friendships (r) (SP)	WHO-DAS 2.0	2.90	1.16	0.00	4.00	3.00	2.00	29.63
Subscale Interpersonal Sensitivity (SP)	BSI-53	0.98	0.97	0.00	4.00	0.75	1.25	0.28
Single item Social Anhedonia (SP)	BSI-53	0.90	1.13	0.00	4.00	1.00	1.00	0.28
Subscale Paranoid Ideation (SP)	BSI-53	0.67	0.74	0.00	4.00	0.40	1.00	0.42
Subscale Reappraisal (SP)	ERQ	24.34	7.36	3.00	42.00			15.72
Subscale Suppression (SP)	ERQ	15.56	5.07	2.00	28.00			15.72

Note. *SD* = Standard deviation; *Mdn* = Median; IQR = Interquartile range; (r) = reversed; PVS = Positive valence systems; NVS = Negative valence systems; CS = Cognitive systems; SP = Social processes; BIS-15 = Barratt Impulsiveness Scale - Short Form; BIS/BAS = Behavioral Inhibition System/Behavioral Activation System Scale; BSI-53 = Brief Symptom Checklist; CTS = Childhood Trauma Screener; DF = Digit span forward; DSST = Digit Symbol Substitution Test; ERQ = Emotion Regulation Questionnaire; PANAS = Positive and Negative Affect Scale; TMT-A/B = Trail Making Test A/B; WHO-DAS 2.0 = WHO Disability Assessment Schedule 2.0; all variables were plausibility checked: scores were in range of respective assessment.

Table 3

Total sample characteristics and consortia sample details

Variable	Total sample	PROTECT-AD	ESCAlife	ASD-NET	BipoLife	Opti-MD	GCBS	APIC	ESPRIT
Subjects, used in analysis, *n*	1,431	600	25	23	99	171	40	89	384
					Demographic characteristics				
Age, y									
MD ± *SD*	34.6 ± 12.5	33.0 ± 11.2	27.6 ± 7.5	26.4 ± 5.1	35.4 ± 12.5	43.2 ± 15.3	37.4 ± 14.5	35.7 ± 11.8	33.8 ± 11.7
Range	15-78	15-68	18-43	19-38	18-69	18-78	20-64	18-61	18-65
Missing data, %	0.3	-	-	-	-	1.2	-	-	-
Gender, %									
Female	50.2	55.3	24.0	-	54.5	51.4	47.5	39.3	49.0
Male	49.8	44.7	76.0	100.0	45.5	48.3	52.5	60.7	51.0
Marital status, %									
Single	34.6	38.8	52.0	78.3	66.7	46.2	67.5	66.3	-
Married/partnership	30.7	53.0	36.0	21.7	18.2	35.7	22.5	22.5	-
Separated	4.3	1.3	8.0	-	6.1	7.6	-	2.2	-
Divorced	5.2	6.5	4.0	-	8.1	9.9	7.5	7.9	-
Widowed	0.3	0.3	-	-	-	0.6	2.5	-	-
Missing data	27.0	-	-	-	1.0	-	-	1.1	100.0
Migration, %									
Yes	26.1	25.8	32.0	8.7	33.3	15.2	45.0	44.9	24.2
No	70.9	73.8	68.0	91.3	66.7	33.9	55.0	53.9	75.0
Missing data	3.0	0.3	-	-	-	22.8	-	1.2	0.8
Graduation [a], y									
MD ± *SD*	11.7 ± 1.5	11.6 ± 1.5	11.1 ± 1.5	12.4 ± 1.0	12.1 ± 1.4	11.8 ± 1.6	11.8 ± 1.7	11.2 ± 1.7	12.0 ± 1.4
Missing data, %	9.1	2.3	8.0	-	2.0	8.2	5.0	6.7	1.3

Variable	Total sample	PROTECT-AD	ESCAlife	ASD-NET	BipoLife	Opti-MD	GCBS	APIC	ESPRIT
Occupation, %									
Unemployed	35.0	30.8	32.0	43.5	53.5	33.9	50.0	53.9	31.0
Employed	62.1	69.2	68.0	56.5	46.5	43.3	50.0	44.9	68.5
Missing data	2.9	-	-	-	-	22.8	-	1.1	0.5
Net income, €, %									
Up to 500	7.5	-	20.0	34.8	29.3	15.2	17.5	37.1	-
500-1,000	7.3	-	36.0	43.5	20.2	16.4	27.5	31.3	-
1,000-2,000	8.4	-	28.0	8.7	33.3	26.3	30.0	23.6	-
2,000-3,000	2.2	-	12.0	-	9.1	7.0	15.0	2.2	-
3,000-4,000	1.0	-	-	-	3.0	5.3	5.0	2.2	-
Over 4,000	1.1	-	4.0	4.3	4.0	1.2	2.5	-	-
Missing data	72.3	100.0	-	8.7	1.0	25.1	2.5	4.5	100.0
Municipality size classes, *n*, %									
Up to 5,000	8.2	11.3	44.0	4.3	6.1	18.1	0.9	-	-
Up to 20,000	7.0	9.2	8.0	8.7	16.2	12.3	3.5	-	-
Up to 50,000	5.0	6.3	12.0	4.3	11.1	7.6	5.2	-	-
Up to 100,000	8.2	17.3	4.0	4.3	6.1	2.9	27.0	-	-
Up to 500,000	11.9	16.3	32.0	60.9	21.2	17.0	-	-	-
Over 500.000	23.5	38.2	-	17.4	39.4	20.5	63.5	-	-
Missing data	36.2	1.3	-	-	-	21.5	-	100.0	100.0
					Clinical characteristics				
Primary diagnosis, %									
AD	42.1	100.0	-	-	2.0	-	-	-	-
MDD	18.1	-	4.0	-	25.3	83.0	100.0	9.0	11.2
SZ	7.9	-	-	-	-	0.6	-	71.9	12.5
BD	7.8	-	-	-	60.6	5.8	-	-	10.7

Variable	Total sample	PROTECT-AD	ESCAlife	ASD-NET	BipoLife	Opti-MD	GCBS	APIC	ESPRIT
ASD	3.4	-	-	52.2	-	-	-	-	9.6
PD	0.1	-	-	-	2.0	-	-	-	-
ADHD	1.7	-	96.0	-	-	-	-	-	-
SUD	0.3	-	-	-	4.0	-	-	-	-
PTSD/AjD	0.1	-	-	-	-	0.6	-	-	-
HC	18.4	-	-	47.8	5.1	9.4	-	19.1	55.7
Missing data	0.2	-	-	-	1.0	0.6	-	-	0.3
Comorbidity, %									
Yes	45.2	87.8	36.0	4.3	15.2	17.0	5.0	1.1	16.4
No or not collected	54.8	12.2	64.0	95.7	84.8	83.0	95.0	98.9	83.6
Psychotropic drugs, %									
Yes	51.2	49.0	-	-	76.8	85.4	100.0	57.3	32.6
No	45.4	51.0	100.0	100.0	22.2	4.1	-	9.0	67.4
Missing data	3.4	-	-	-	1.0	10.5	-	33.7	-

Note. *M* = Mean; *SD* = Standard deviation. **Disorder**: AD = Anxiety disorders; ADHD = Attention deficit hyperactivity disorders; AjD = Adjustment disorders; ASD = Autism spectrum disorders; BD = Bipolar spectrum disorders (Type I/II); MDD = (Major) Depressive disorders; PD = Personality disorders; PDD = Persistent depressive disorders (dysthymia, cyclothymia); PTSD = Posttraumatic stress disorders; SUD = Substance use disorders; SZ = Schizophrenia spectrum disorders.

[a] **Graduation**: 9 years = Certificate of Secondary Education [Hauptschulabschluss]; 10 years = General Certificate of Secondary Education [Realschulabschluss] or Polytechnic degree [Abschluss der allgemeinbildenden Polytechnischen Oberschule der ehemaligen DDR]; 12 years = Technical-diploma [Fachabitur, Fachhochschulreife, Fachgebundene Hochschulreife]; 13 years = University-entrance diploma = [Abitur, Allgemeine Hochschulreife]; missing data = still in school, other types of school (e.g., school for handicapped children), school dropout or missing data.

Table 4

Dropped Indicators with low R-Square

RDoC	Instrument	Variable	Estimate
PVS	BIS/BAS	Subscale Reward Responsiveness	.074
PVS	BIS/BAS	Subscale Drive	.121
NVS	CTS	Sumscore Childhood Trauma	.088
CS	MWT-B	Raw score MWT-B	.119
CS	BIS-15	Subscale Attentional Impulsivity	.005
CS	BIS-15	Subscale Non-planning Impulsivity	.055
CS	DF	Sumscore DF	.114
SP	Sociodemographic	Single item graduation	.013
SP	Sociodemographic	Single item occupation	.022
SP	Sociodemographic	Single item residential status	.009
SP	ERQ	Subscale Reappraisal	.083
SP	ERQ	Subscale Suppression	.041

Note. Cut-off ($r^2 < .20$). RDoC = Research Domain Criteria; PVS = Positive valence systems; NVS = Negative valence systems; CS = Cognitive systems; SP = Social processes; BIS-15 = Barratt Impulsiveness Scale - Short Form; BIS/BAS = Behavioral Inhibition System/Behavioral Activation System Scale; CTS = Childhood Trauma Screener; DF = Digit span forward; ERQ = Emotion Regulation Questionnaire; MWT-B = Multiple-Choice Word Test - Version B.

Figure 1: *Factorial loadings of the final model on the four Research Domain Criteria*

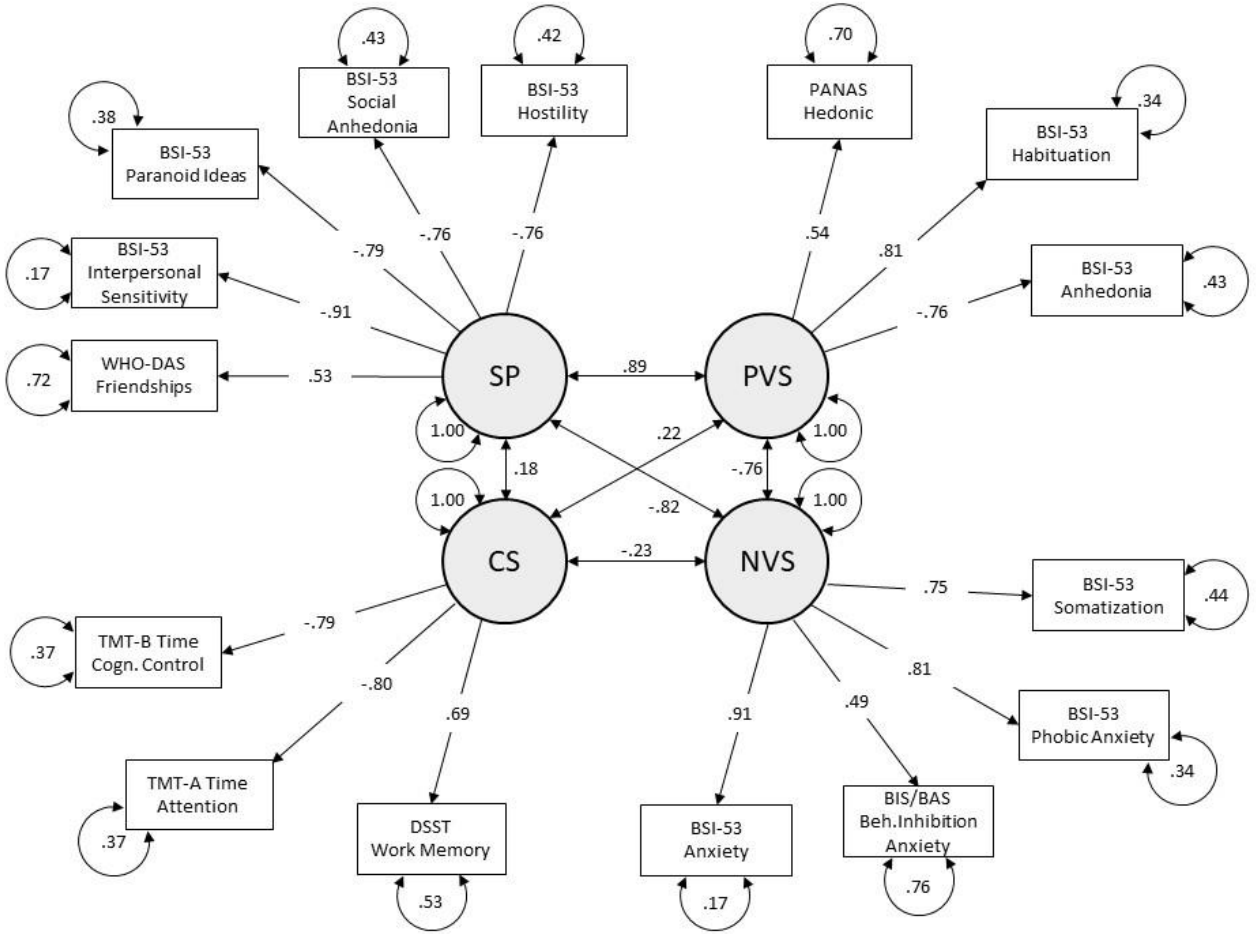
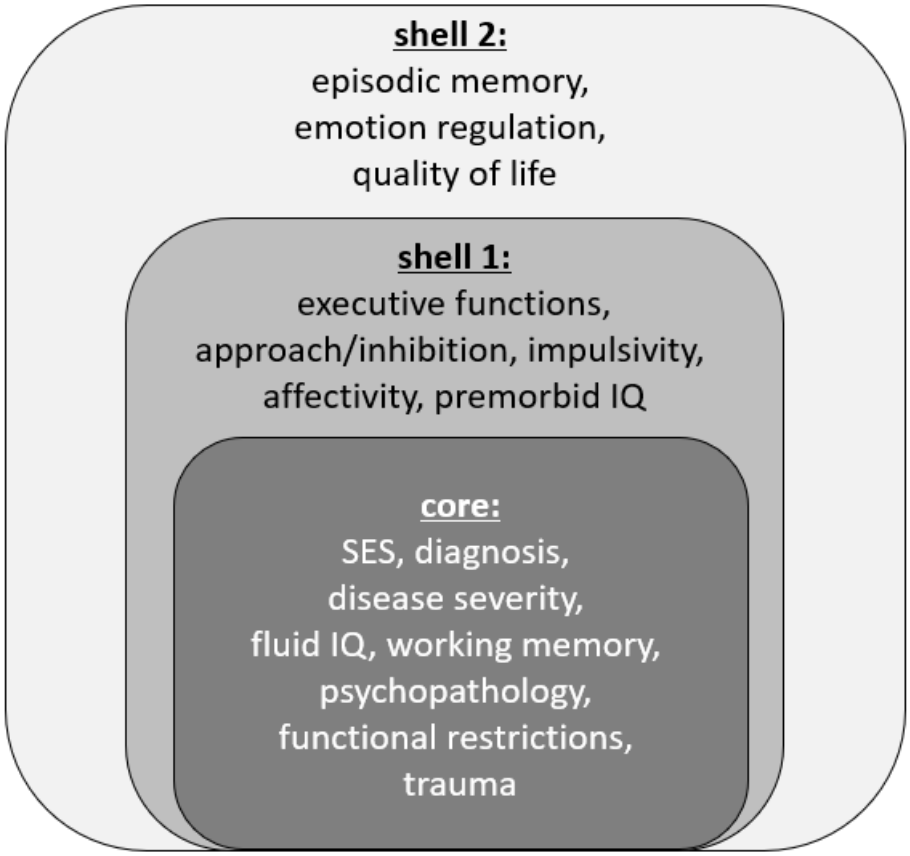


Fig.1 Standardized latent variables: PVS = Positive valence systems; NVS = Negative valence systems; CS = Cognitive systems; SP = Social processes; Manifest variables: BIS/BAS Behavioral Inhibition Anxiety =Anxiety based inhibition aspects of BIS/BAS subscale Behavioral Inhibition ; BSI-53 Anhedonia = BSI-53 single item Anhedonia; BIS-53 Anxiety = BIS-53 subscale Anxiety; BSI-53 Habituation = habituational aspects of BSI-53 single items Obsessive-compulsive ; BSI-53 Hostility = BSI-53 subscale Hostility; BSI-53 Interpersonal Sensitivity = BSI-53 subscale Interpersonal Sensitivity; BSI-53 Phobic Anxiety = BSI-53 subscale Phobic Anxiety; BSI-53 Paranoid Ideas = BSI-53 subscale Paranoid Ideation; BSI-53 Social Anhedonia = BSI-53 single Item Social Anhedonia; BSI-53 Somatization = BSI-53 subscale Somatization; DSST Work Memory = Digit Symbol Substitution Test raw score; PANAS Hedonic = Hedonic aspects of PANAS subscale Positive Affect; TMT-A Time Attention = Trail Making Test – Version A completion time; TMT-B Time Cognitive Control = Trail Making Test – Version B completion time; WHO-DAS Friendships = WHO-DAS 2.0 Single item Friendships reversed

Figure SI1

Shell model of assembled Mini-RDoC assessment



Note. Core had to be implemented inside the assessment process of the study; shells were optional depending on their fit to the specific assessment process of the respective study.

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Table SI2

Data contributions and Characteristics of the German Research Network of Mental Disorders

Consortium, coordination[a]	Partici-pants	Main aim	Inclusion criteria	Exclusion criteria
PROTECT-AD, H.-U. Wittchen, TU Dresden	*N*=600; data used: *N*=600	Optimized extinction: intensified cognitive-behavioral therapy of AD with and without comorbidity	- 15-70 years; ♂, ♀ - current primary AD (DSM-V) - severity at baseline HAM-A>18 and CGI>3 - able to attend on his/her own or accompanied by significant other - language competence	- general medical contraindications - acute suicidality - any DSM-IV/V psychotic/primary mood disorders (BD I, recurrent or chronic MDD) - mono-symptomatic specific phobia - current substance use dependence - concomitant psychological/psychiatric treatment
ESCALIFE, ESCAlate, T. Banaschewski, Central Institute of Mental Health (CIMH) Mannheim	*N*=25; data used: *N*=25	Evidence-based, gradual care of ADHD over the life span	- 16-45years; ♂, ♀ - ADHD diagnosis (DSM-V)	- severe heart disease - epilepsy - IQ<80 - psychiatric disorders - medication (psychotropic or ADHD): need of a 4-week wash-out period before participation in the study - insufficient language skills - current alcohol or drug dependence - pregnancy or breast feeding - common comorbidities (e.g., conduct disorder, PD (except ASPD); AD or mild to moderate MDD and SUD in remission did not lead to exclusion
ASD-NET, I. Kamp-Becker, Philipps University Marburg	*N*=23; data used: *N*=23	ASD over the life span: more effective care through valid diagnoses and a better understanding of etiology	- 19-40 years; ♂ - infantile autism - Asperger's syndrome - atypical autism (ICD-10) - native language german	- BMI≤18 or ≥30 - IQ<70 - investigational product contraindication (e.g., cardiac arrhythmia) - screening results: HR>120 bpm, SBP>180 mmHg, DPD>100 mmHg - medication intake affecting the central nervous system (e.g., opiate, psychotropic drugs) - past neurological and endocrinological diseases - acute suicidality

				- psychiatric disorders - psychotherapeutic treatment - first or second degree relative with ASD - MRI-contraindications - regular consumption of drugs, alcohol, nicotine - AQ-Interview ≥ 32 points
BipoLife, M. Bauer, University Hospital Dresden	*N*=99; data used: *N*=99	Improving the detection and treatment of BD	**Dresden**: - 15-35 years; ♂, ♀ Risk group I: - consultation of an early recognition center - presence of at least one risk factors for BD: family history, affective symptomatology/ depressive syndrome, hypomanic/ mood swings, disturbances of circadian rhythm/sleep, other clinical hints Risk group II: - in- or outpatients with a depressive syndrome (in the context of MDD, dysthymic disorder, cyclothymic disorder, minor depressive disorder, recurrent brief depressive disorder, adjustment disorder with depressed mood, depressive disorder not otherwise specified)	**Dresden**: - primary diagnosis: BD, SZ, SZA, AD, OCD or SUD - limited ability to comprehend the study - implied expressed negative declaration of intent to participate in the study by a minor - acute suicidality
			Tübingen: - 18-55 years; ♂, ♀ - current primary BD-I or BD-II (DSM-V) - current on psychiatric treatment with adequate medication - at least 4 weeks of remission - mood disorder (QIDS-C≤10, YMRS≤12)	**Tübingen:** - IQ<85 - schizophrenic or other psychotic disorder (eg., ASPD, SZ, SZA or any psychotic disorder); psychotic features within an affective episode are not an exclusion criteria - acute suicidality - substance abuse

			Munich[b]: Project A2: - 18-55 years; ♂, ♀ - current BD-I or BD-II (DSM-V) - current on psychiatric treatment - appropriate medication according S3-guideline - stable remission (at least 4 weeks) - regarding to the affective episode: clinically relevant limits of external (clinician) rating: (QIDS-C≤10, YMRS≤12) - at least one affective episode in the last 2 years Project B3: - ≥18 years; ♂, ♀ - previous or current lithium treatment for a period > 1 year - overall > 4 episodes	**Munich**[b]: - acute suicidality - schizophrenic or other psychotic disorder (DSM-V); Project A2: psychotic characteristics during affective episodes are no criterion for exclusion - IQ <85 Project A2: - lack of willingness of prescribed medication intake (normally long-term medication) - receiving current or previous (< 6 months) ambulant standard psychotherapy - SZA, ASPD, or BPD (DSM-V) - SUD (DSM-V, except nicotine) during the last 6 months (earlier SUD and actual stable remissions for over 6 months are allowed) - SUD (DSM-V) endangering study participation Project B3: - clear organic or substance induced cause of the psychiatric disorder
OptiMD, R. Rupprecht, University of Regensburg	*N*=360; data used: *N*=171	New strategies for the optimized treatment of depression	- ≥18 years; ♂, ♀ **Regensburg, Munich, Heidelberg**: - inpatients with depressive syndrome (HAM-D-21 ≥ 14): first depressive episode, recurrent MDD, BD (current depressive episode), SZA, mixed AD and MDD - caucasian origin **Berlin**: - current primary MDD (ICD-10) during hospital stay	**Regensburg, Munich, Heidelberg**: - severe neurological or internal accompanying illness (e.g., dementia, morbus cushing) - depressive episode secondary to a somatic/neurological disease or substance abuse/dependence - pregnancy or breast-feeding **Berlin**: - control group: current ICD-10 psychiatric disorder

GCBS, F. Padberg, University of Munich	*N*=115; data used: *N*=40	Brain stimulation for mental disorders	**Munich**: - 18-65 years; ♂, ♀ - MDD (DSM-V), current depressive episode of less than 5 years duration - HAM-D-21≥15 at screening visit - medications: patient did not respond to at least one antidepressant treatment in the current episode; patient is taking a SSRI of adequate dose and ≥ 4 weeks in the current episode **Berlin**: - 20-65 years; ♂, ♀ - MDD (DSM-V), current depressive episode less than 5 years duration - medications: no psychotropic medication (≥4 weeks) or current stable medication (≥ 4 weeks) with SSRIs	**Munich**: - any relevant instable medical condition - high degree of therapy resistance: >4 sufficient treatment attempts in the current episode - any other relevant psychiatric axis-I- and/or axis-II-disorder - electroconvulsive therapy treatment in the present episode - history of clinical transcranial direct current stimulation treatment (except single experimental sessions) - treatment with deep brain stimulation or vagus nerve stimulation and/or any other intracranial implants - acute suicidality - investigators, site personnel directly affiliated with this study, and their immediate families - pregnancy **Berlin**: - medication: more than four failed attempts in current episode; other psychotropic medications - outpatient treatment (behavioral therapy) for the current episode - electroconvulsive therapy for the current episode - MRI-contraindications - stroke (past 2 years), epileptic seizure or diagnosed epilepsy, dementia, Parkinson's disease, Huntington's chorea, multiple sclerosis, any other neurological disease, which leads to intracranial pressure, brain lesions or higher risk for epileptic seizures - psychotic tendencies in lifetime - BD, AD, PTSD, ED, PD - Substance abuse or dependence in the past 6 months (except nicotine, caffeine)

APIC, F. Schneider, RWTH Aachen, Jülich Aachen Research Alliance (JARA-BRAIN)	*N*=295; data used: *N*=89	Antipsychotic-induced structural and functional brain changes	- 18-65 years; ♂, ♀ - SZ (DSM-V) - legally competent and capable of taking part in the study	- severe physical diseases (e.g., epilepsy, cancer) - missing or incomplete medication history - MRI-contraindications - pregnancy or breast-feeding - persons placed in an institution on the orders of public authorities or courts - dependency or employment relationship with the sponsor or investigator - simultaneous participation in another clinical trial
ESPRIT, A. Meyer-Lindenberg, Central Institute of Mental Health (CIMH) Mannheim	*N*=395; data used: *N*=384	Improving prevention and recovery in schizophrenia through innovative therapies	- 18-65 years; ♂, ♀ - patients: SZ, MDD, BD-I, ASD - control group: no personal or family history of psychiatric disorders	- chronic physical disease - MRI-contraindications - patients: BD-II, SUD, PD - patients with comorbidities were not excluded, if comorbidities 1) evolved as a consequence of, or 2) were markedly less pronounced as the primary disorder

Note. Characteristics of eight consortia of the German Research Network of Mental Disorders. *N* = 1,912 (entry data) and 1,431 (after data preparation, used in analyses). **Consortia**: AERIAL = Early Recognition and Intervention Across the Lifespan; APIC = Antipsychotic induced brain changes; ASD-NET = Autism spectrum disorder - net; ESCAlife = Evidence-based, stepped care of ADHD along the life-span; ESPRIT = Enhancing schizophrenia prevention and recovery through innovative treatments; GCBS = German center for brain stimulation; OptiMD = Optimized treatment of major depression; PROTECT-AD = Providing tools for effective care and treatment of anxiety disorders. **Disorders**: AD = Anxiety disorder; ADHD = Attention deficit hyperactivity disorder; ASD = Autism spectrum disorder; ASPD = Antisocial personality disorder, BD = Bipolar disorder; BPD = Borderline personality disorder; ED = Eating disorder; MDD = Major depression disorder; OCD = Obsessive-compulsive disorder; PD = Personality disorder; PTSD = Posttraumatic stress disorder; SUD = Substance use disorder; SZ = Schizophrenia; SZA = Schizoaffective disorder. **Other**: AQ = Autism-Spectrum Quotient; DPD = Diastolic blood pressure; DSM-V/DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition; CGI = Clinical Global Impression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D-21 = Hamilton Depression Rating Scale, Version 21; HR = Heart rate; ICD-10 = International Classification of Diseases, 10th Revision; MRI = Magnet Resonance Imaging; QIDS-C = Quick Inventory of Depression Symptomatology - Clinician rating; SBP = Systolic blood pressure; SSRI = Selective Serotonin Reuptake Inhibitor; YMRS = Young Mania Rating Scale.

[a] Coordination center for each consortium (for details of all consortia members, see Bauer et al. (20))

[b] Location provided data of two subprojects: Bipolife A2 and Bipolife B3

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Table SI3

Construction of the PD-CAN-Assessment as a shell model

RDoC construct	Units of Analysis	Instrument	Abbreviation
Core			
SES, medication	Anamnesis	Standardized interview	
Diagnosis	Anamnesis	Standardized interviews and checklists [a]	
Fluid intelligence	Behavior	Digit Symbol SubstitutionTest	DSST
Working memory	Behavior	Digit span (forward)	DF
Psychopathology	Self-report	Brief Symptom Inventory	BSI-53
Functional restriction	Self-report	WHO Disability Assessment Schedule 2.0	WHO-DAS 2.0
Childhood Trauma	Self-report	Childhood Trauma Screener	CTS
Shell 1			
Cognitive speed processing	Behavior	Trail Making Test A	TMT-A
Executive functioning	Behavior	Trail Making Test B	TMT-B
Approach	Self-report	Behavioral Approach Scale	BIS/BAS
Inhibition	Self-report	Behavioral Inhibition Scale	BIS/BAS
Impulsivity	Self-report	Barratt Impulsiveness Scale – Short Version	BIS-15
Affect	Self-report	Positive and Negative Affect Schedule	PANAS
Premorbid Intelligence	Behavior	Multiple-Choice Word Test – Version B	MWT-B
Shell 2			
Episodic Memory	Behavior	Verbal Learning and Memory Test	VLMT
Emotion Regulation	Self-report	Emotion Regulation Questionnaire	ERQ
Quality of Life	Self-report	WHO- 5 Well-Being Index	WHO-5

Note. SES = Socioeconomic status; RDoC = Research Domain Criteria

[a] Standardized interviews and checklists: SCID (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]), CIDI (Composite International Diagnostic Interview), IDCL (International Diagnostic Checklists for International Classification of Diseases [ICD-10]), DIPS (Diagnostic Interview for Mental Disorders) or Mini-DIPS.

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Table SI4

Additional changes on scales and items with descriptive statistics

RDoC	Old variable	Items	Transformation	New variable	*Mean*	*SD*
PVS	BIS/BAS subscales Drive and Reward Responsiveness	3, 7, 12, 21	Forming mean score	Scale Goal Attainment	2.90	0.58
PVS	PANAS subscale Positive Affect	active, interested, enthusiastic, determined	Item reduction and forming mean score	Scale Hedonic Affect	1.78	0.82
PVS	BSI-53 single items Obsessive-compulsive	15r, 26r, 27r	Forming mean score	Scale Habituation	2.99	0.86
NVS	BIS/BAS subscale Behavioral Inhibition	2r, 8, 22r, 24	Forming mean score	Scale Anxiety-based Inhibition	3.23	0.59

Note. Variables were transformed with log10 to address normal distribution issue. *SD* = Standard deviation; r = reversed; RDoC = Research Domain Criteria; PVS = Positive valence systems; NVS = Negative valence systems; BIS/BAS = Behavioral Inhibition System/Behavioral Activation System Scale; BSI-53 = Brief Symptom Checklist; PANAS = Positive and Negative Affect Scale.

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Table SI5

Model comparison: Fit indices and X^2-test

Model no.	Model characteristics	CFI	TLI	RMSEA (90% CI)	Comparison	X^2 (df diff), (p)
1	4 factor model with a priori variables (transformed if necessary)	.77	.75	.078 (.076 - .081)		
2	Model 1 with 1 factor only	.69	.67	.090 (.088 - .093)	1 vs. 2	(6) 1158.1 (<.001)
3	Model 1: no covariances allowed between the factors	.59	.56	.104 (.102 - .106)	1 vs. 3	(6) 2571.2 (<.001)
4	4 factor model with reduced/changed variables (transformed if necessary)	.93	.92	.077 (.072 - .082)		
5	Model 4 with 1 factor only	.78	.74	.136 (.131 - .140)	4 vs. 5	(6) 1656.3 (<.001)
6	Model 4 with no covariances allowed between the factors	.71	.66	.154 (.149 - .158)	4 vs. 6	(6) 2327.8 (<.001)

Note. CFI = Comparative Fit Index; CI = Confidence Interval; df diff = degrees of freedom difference; TLI = Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation.

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Manuscript II

This is the most recent version under review of manuscript 2.

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The associations of positive and negative valence systems, cognitive systems and social processes on disease severity in anxiety and depressive disorders

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1 Abstract

Background: Anxiety and depressive disorders share common features of mood dysfunctions. This has stimulated interest in transdiagnostic dimensional research as proposed by the Research domain criteria (RDoC) approach by the National Institute of Mental Health (NIMH) aiming to improve the understanding of underlying disease mechanisms. The purpose of this study was to investigate the processing of RDoC domains in relation to disease severity in order to identify latent disorder-specific as well as transdiagnostic indicators of disease severity in patients with anxiety and depressive disorders.

Methods: Within the German research network for mental disorders, 895 participants (n=476 female, n=602 anxiety disorder, n=257 depressive disorder) were recruited for the Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany (PD-CAN) and included in this cross-sectional study. We performed incremental regression models to investigate the association of four RDoC domains on disease severity in patients with affective disorders: positive (PVS) and negative valance system (NVS), cognitive systems (CS) and social processes (SP).

Results: The results confirmed a transdiagnostic relationship for all four domains, as we found significant main effects on disease severity within domain-specific models (PVS: β=-.35; NVS: β=.39; CS: β=-.12; SP: β=-.32). We also found three significant interaction effects with main diagnosis showing a disease-specific association.

Limitations: The cross-sectional study design prevents causal conclusions. Further limitations include possible outliers and heteroskedasticity in all regression models which we appropriately controlled for.

Conclusion: Our key results show that symptom burden in anxiety and depressive disorders is associated with latent RDoC indicators in transdiagnostic and disease-specific ways.

2 Introduction

Major depressive (MDD), as well as anxiety disorders (AD) may be characterized by altered emotional processes expressed upwards from neural circuitry to clinically relevant variations of symptomatology. On symptom level, MDD and AD share common features of aberrations of mood and emotions. On the one hand, high negative affect is present in both types of disorders, with depressed mood/anhedonia as well as anxious mood associated with both MDD and AD. On the other hand, anxious hyperarousal and persistent fear, anxiety or avoidance of perceived threats are considered general characteristics of AD, whereas low positive affect is relatively specific to MDD and only to certain distress-related types of AD, such as social anxiety disorder (SAD) or generalized anxiety disorder (GAD) (1–3). Furthermore, symptoms of anhedonia, meaning the loss of pleasure or interest in previously rewarding activities, are strongly tied to MDD. There is also an association of cognitive dysfunction for both disorders, while this association is more heterogenous for AD due to its broad disease spectrum (4). Existing literature also shows heterogeneous associations with respect to social processes. For example, the construct of affiliation and attachment has been associated with MDD and SAD, whereas the construct of understanding of self and others has been associated with GAD (5).

Common features in symptomatology and common neurobiological mechanisms in depressive and anxiety disorders can be considered partly responsible for limitations in diagnostic specificity, which is necessary to develop precise treatments (precision medicine) that can improve the stagnant treatment of mental illness.

The Research Domain Criteria (RDoC) approach promoted by the National Institute of Mental Health (NIMH) aims to address these issues and guide research toward a better understanding of mental disorders and their underlying psychological, neural and biological mechanisms, ultimately leading to improved treatments. The RDoC approach views mental disorders as syndromes at multiple levels, also connected to disrupted or dysfunctional brain circuitry (6, 7). To gain a better understanding of the links between disease-specific symptomatology and the underlying neural mechanisms of emotional (dys)function, the latent RDoC domains positive (PVS) and negative valence systems (NVS), cognitive systems (CS) and social processes (SP) were established and proved to be valid research constructs (8–12).

The PVS domain includes mechanisms involved in responses to attractive stimuli, such as responding to reward, as well as learning and valuation of rewards as parts of the reward system. In contrast, the NVS domain comprises responses to aversive stimuli of acute, potential, and sustained threat, loss, or aggression due to frustration. The CS domain comprises of circuits generating attentional processes, perception, memory functioning, language processing and cognitive control. The SP domain contains concepts of affiliation and attachment, social communication, as well as perception and understanding of self and others (13). In our previous research, we identified four distinct domains (PVS, NVS, CS, SP) in a latent structure of four overlapping factors (12).

There is limited research on PVS functioning within the spectrum of anxiety disorders, with most studies focusing on patients with specific anxiety disorders such as SAD and GAD (e.g., 14–16). These studies suggest that individuals with SAD and GAD tend to have reduced positive experiences and use experiential avoidance as a coping mechanism. However, PVS-related processing has been extensively studied in mood disorders. Symptoms of anhedonia in MDD have been associated with blunted reactivity to positively valanced and rewarding stimuli (e.g., 17–20),

as well as hypoactivation of brain circuits linked to those stimuli (e.g., 21–23). In summary, existing literature on both types of disorders highlights disease-specific and therefore distinct profiles of reward processing.

Across units of behavioral, physiological, and neuronal data, there is ample evidence of similar NVS-related processing in MDD and AD: AD has been associated with a negativity bias towards negatively valanced stimuli (e.g., 24–26), and altered activity in brain structures associated with responses to threat-related stimuli (e.g., 27, 28); analogously, MDD has also been associated to a bias towards negatively valanced stimuli (e.g., 21, 29, 30), and threat-related negative stimuli (e.g., 31).

The occurrence of cognitive deficits regarding attention, memory and executive functioning in AD and MDD is well established (4, 32). However, the differentiation of disease-specific neural circuitry is challenging due to the lack of transdiagnostic and multimodal research (33) and because heterogeneous evidence exists for disorder-specific circuit alterations (3, 34).

While subconstructs of SP like attachment could be associated with social anxiety for example (35), the general impact of social processes on AD is unclear due to the broad construct spectrum of SP in combination to the heterogenous disease patterns. Yet, the role of social processes in specific types of AD such as SAD, has been more extensively investigated. This is because its symptomatology is closely linked to social processes, such as dysfunction in automatic association to social cues (36). As for MDD, impairment of social functioning is an evident sign and part of the structure of the disease. (37) summarized that all SP subconstructs are impaired in patients with depression, resulting in social anhedonia, hyper-sensitivity to social rejection, competition avoidance and increased altruistic punishment regarding the affiliation and attachment subconstruct, impaired emotion recognition, diminished cooperativeness regarding social communication and lastly reduced empathy or theory-of-mind deficits regarding social perception.

In recent years, there has been growing interest in transdiagnostic research approaches (e.g. 38). Recent studies aimed to provide evidence for transdiagnostic and disorder-specific psychopathological endophenotypes of NVS-related abnormal threat processing in AD and MDD (33, 39), an attentional bias to negative stimuli in AD and MDD (40–42), as well as PVS-related impaired reward functioning in MDD that is phenomenologically characterized by anhedonia (33, 41, 43). Regarding PVS on the domain level, low levels of positive emotions at a global level have been identified as risk factors for MDD, SAD, and GAD (44, 45).

Using the RDoC approach to investigate transdiagnostic markers of disease severity could help clarify whether mechanisms associated with PVS, NVS, CS and SP contribute to disease severity. Consequently, investigating how individual differences across RDoC domains (PVS, NVS, SP, CS) explain variance in disease severity, could enhance our understanding of possible mechanisms contributing to disease severity. Dimensional assessment of these four domains could help modify classical diagnostic categories and furthermore, it could inform the development of individualized precision treatment for psychiatric disorders (7, 42).

The main aim of this study was to investigate PVS, NVS, CS and SP processing in relation to disease severity implemented into a transdiagnostic and dimensional approach. We thereby aim to improve the understanding of underlying mechanisms of the AD and MDD disease spectrum and shed light on disease-specific as well as transdiagnostic indicators of disease severity. To the best of our knowledge, to date, no study has yet focused on testing RDoC domains as indicators of

disease severity in psychiatric disorders. Therefore, our research focuses on both the relationship between the four RDoC domains and transdiagnostic disease severity, as well as the domains diagnosis-specific effects. We hypothesized that PVS, CS, SP would be negatively associated with disease severity, while NVS would be positively related with disease severity. Second, we predicted that PVS, CS and SP would have a disease-specific relationship with disease severity, while all four domains were expected to also show a general transdiagnostic relationship with disease severity.

3 Methods

Participants

This investigation is an observational cross-sectional study assessing four core domains of the RDoC matrix (PVS, NVS, CS, SP) within the German research network for mental disorders [Forschungszentrum zu psychischen Erkrankungen; FZPE] (46) as outlined by Foerstner et. al.(2022) (12). Study centers throughout the FZPE network recruited participants for clinical and observational studies. A minimal RDoC test battery covering behavioral and self-report units of analysis was incorporated into the existing assessment process at baseline to evaluate the aforementioned RDoC domains. The process of data collection and processing has been previously described in further detail (12). A subsample of patients with a primary diagnosis of major depression (MDD; ICD-10 F 32, F33, F34.1) or an anxiety disorder (AD; ICD-10 F 40, F41) (N = 859) was selected for analysis (see Table 1 and supplementary Tables S1 and S2 for sample characteristics). Diagnoses were determined by expert clinicians in accordance with the 10th Revision of the International Classification of Diseases (ICD-10; World Health Organization [WHO], 47) and/or the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV; American Psychiatric Association [APA], 48). On average, patients with AD were younger than patients with MDD, had a higher number of comorbidities, and were more likely to be married. Regarding comorbidities 54.53% (n=289) of patients with AD had comorbid MDD (diagnostic data from CIDI interview only (49)) and 23.08% (n=12) of patients with MDD had comorbid AD. A greater proportion of patients with MDD were receiving psychotropic medication. There were no further significant differences between AD and MDD patients with respect to gender and sociodemographic variables, including education.

Self-report and behavioral RDoC operationalization

The four RDoC domains PVS, NVS, CS and SP were represented as individual patient factor scores from the four-factor CFA that had been conducted previously. Standardized factor scores were estimated using a linear regression method as reported by (Förstner et al., 2022). For ease of interpretation, factor scores were recoded positively, so that higher scores indicate higher expressions of the assessed domain. Therefore, higher scores in PVS indicate greater hedonic affect, and higher NVS scores indicate higher levels of anxious affect and somatization. Higher CS scores indicate better executive control, attention and working memory and higher SP scores indicate increased social skills, less interpersonal hostility and sensitivity, less paranoid ideas and less social anhedonia. For further details regarding the factor score composition see supplementary Table S3 and (12). Table 2 provides sample details on the domain scores and the outcome variable disease severity, which is described below.

Disease severity assessment

Disease severity was assessed using disease-specific symptom-based self-report scales (4.7%), observer ratings (85.4%) or expert-based global rating scales (9.9%). To serve as a transdiagnostic outcome variable, all disease-specific severity values were z-standardized considering normative data from adult clinical samples. These samples had to meet the following criteria: (1) provide a baseline distribution for the specific disease severity score, (2) as closely as possible represent the reference population (e.g., patients with MDD), and (3) contain a minimum of 500 participants and be representative if possible. Supplementary Table S4 provides detailed information on the normative data that was used for z-transformation.

Statistical methods

Several simple and multiple Linear Models (LM) were used (models 0-6) in this analysis with step-by-step insertion of type of diagnosis (dichotomous variable) as fixed-effect, followed by PVS, NVS, CS and SP factor scores as continuous independent covariates, and followed by PVS by diagnosis, NVS by diagnosis, CS by diagnosis and SP by diagnosis (factor-covariate) interactions, and disease severity z-score as the dependent outcome. To address the overlapping structure identified in the previous CFA (12), we controlled for multicollinearity in the models m1 and m2. Since multicollinearity was present in both models, we decided to perform further analyses on domain-specific models (m3-6) by including diagnosis as fixed effect, the specific domain as an independent covariate, and their respective interaction (f.e. m3: disease severity ~ diagnosis + PVS + PVS by diagnosis).

The Shapiro-Wilks test, which was used to check for normal distribution of variables, indicated that all 5 variables were significantly different from a normal distribution ($p < .001$). Since our sample size largely exceeded the central limit theorem cut-off ($N > 30$), these deviations can be considered acceptable. To identify possible outliers, grouped boxplots were used for independent variables. Furthermore, Cook´s Distance (50) was used to identify influential data points in the analyzed regression models (Di > .85 (51)). No data were removed as no data point exceeded the cut-off in any model. Levene`s test showed that equal variances between groups (AD vs. MDD) could be assumed for SP but not for disease severity ($p < .001$), PVS ($p < .05$), NVS ($p < .01$) and CS ($p < .001$). Breush Pagan tests were used to check for homoscedasticity. When heteroscedasticity was present, a suitable heteroskedasticity-consistent (HC) covariance estimation method (f.e. Zeileis, 2014) was used in addition. All analyses were performed using R version 4.2.2 with RStudio 2022.07.2 Build 576.

4 Results

We performed incremental linear regression models (LM) in four steps starting with a simple LM containing only main diagnosis and disease severity (m0: $R^2 = .19$; $F(1,857) = 198.70$, $p < .001$). Main diagnosis significantly predicted disease severity ($\beta = -.43$; $p < .001$) with higher scores of disease severity in the AD group compared to the MDD group. In the next step (m1), we added all four RDoC domain factor scores as independent covariates to the m0 equation ($R^2 = .41$; $F(5,853) = 116.80$, $p < .001$). M1 revealed significant main effects for main diagnosis ($\beta = -.42$; $p < .001$), PVS ($\beta = -.37$; $p < .001$), NVS ($\beta = .30$; $p < .001$) and SP ($\beta = .18$; $p < .05$). The previous effect of diagnosis remained significant and additionally PVS was negatively associated to disease severity, while NVS and SP were positively associated with disease severity. We found no significant main effect of CS on disease severity. To control for multicollinearity, we calculated variance inflation

factors (VIF) for m1. PVS (VIF= 10.04) and SP (VIF= 10.74) exceeded the cut-off (VIF > 10) indicating a high correlation of those predictors. Compared to m0, m1 showed a significantly better fit ($F(4,853)= 78.38$, $p < .001$) and larger R^2. In a third step (m2), we added the four interactions of the domains with main diagnosis to m1 ($R^2 = .42$; $F(9,849) = 67.01$, $p < .001$) to assess additional diagnosis-specific effects. Here we found significant main effects for main diagnosis ($\beta = -.45$; $p < .001$), PVS ($\beta = -.30$; $p < .01$) and NVS ($\beta = .31$; $p < .001$) while SP was only significant in the robust model ($\beta = .18$; $p = .07$; HC robust: $p < .01$). Other interactions included were not found to be significant. Even though R^2 only increased by .01, model m2 had a significantly better fit ($F(4,849) = 3.231$, $p = .05$) than model m1. To check for multicollinearity in model m2, we calculated the variance inflation factors (GVIFs) for each predictor. This involved combining the main effect of the predictor with any interactions it has with other predictors in the model. The VIFs for PVS (VIF = 136.68), NVS (VIF = 15.09), and SP (VIF = 193.77) largely exceeded the cut-off. Consequently, we analyzed domain-specific models (m3-6) with main diagnosis, separate domain covariates and their associated interaction as predictors. Table 3 includes the results of models 3-6, which indicate significant domain-by-disease severity interactions for all domains. Figure 1 shows the interaction plots of the fitted values from these separate models for the four domains.

We found significant main effects for diagnosis and the respective domain in all four models (m3-m6). Specifically, PVS was significantly associated with disease severity in both AD and MDD, but the effect was stronger in MDD. A similar picture emerged for NVS and SP. With regard to the CS domain, we found a significant negative association with disease severity as a main effect in m5. A higher score on the CS factor was associated with lower disease severity.

Considering the heteroskedasticity of the models, we performed additional robust model analyses for all models (m0-m6). The results showed no changes in the reported results, except for the following two models: In m2 the main effect of SP at trend level became significant ($t = 2.53$, $p = .012$) and in m4 the interaction of main diagnosis and NVS changed from a significant effect to an effect at trend level ($t = 1,81$, $p = .071$). Furthermore, results did not differ when controlling for age differences and present comorbidities in our analyzed models. In the CS single domain model (m5) age additionally significantly predicted disease severity ($p < .01$).

5 Discussion

The main aim of our study was to examine the relationship between four core RDoC domains and disease severity among AD and MDD. As far as we know, this is the first study investigating these four transdiagnostic indicators on a domain level and their associations with disease severity in a transdiagnostic sample. Our first aim was to explore the relationship of PVS, NVS, CS, SP and disease severity across diagnostic categories. The results confirmed our hypotheses on this transdiagnostic relationship for all four domains, as we found significant main effects for PVS, NVS, CS and SP on disease severity within domain-specific models. For three domains, except CS, this main effect could also be found in the overall model as well. While NVS was positively associated with disease severity in our sample, PVS, CS and SP had a negative association with disease severity. Since we were able to show that some of these effects only occur within domain-specific analysis with similar R^2 values, it stands to reason to assume that for AD and MDD, especially the effects of PVS and NVS play a superior role in this relationship to disease severity within patients with AD and MDD. However, this does not necessarily imply that anxiety predicts

AD and anhedonia predicts depression; specifically, both PVS and NVS predicted diseases severity across disorders, and more so in patients suffering from MDD. Thus, we could show a transdiagnostic predictive value of both domains, which corresponds to our second main aim.

For this second aim, we investigated a disorder-specific interaction between these four domains and disease severity. Our results yielded three significant interaction effects within domain-specific models. Overall, we found a stronger association of PVS, NVS and SP with disease severity in MDD in comparison to AD, despite lower disease severity in patients with MDD compared to patients with AD. Therefore, future research should aim to replicate our findings in a longitudinal design to confirm this association.

In regards to the single RDoC domains starting with PVS, we found that low PVS manifestations, representing low hedonic affect and low habituation, were associated with high symptom burden, which is consistent with previous findings of diminished PVS processing in MDD (e.g., 21, 52) and SAD and GAD (e.g., 14, 45, 53). The finding that disease severity scores were affected by low PVS manifestations most strongly in patients with MDD is also consistent with previous research that suggests PVS-related processing as a marker for MDD (e.g., 40, 42, 54).

Our results regarding NVS are also in line with previous research in AD (e.g., 25–27) and MDD (e.g., 21, 30, 31). This previous research supports our findings of a link between high symptom burden in patients with AD and MDD with high NVS manifestations, representing high levels of anxiety and behavioral inhibition. As NVS-related processing is a common dysfunction in AD and MDD (e.g., 39, 42, 55), our results are further evidence for altered NVS functioning as a transdiagnostic marker for the spectrum of depressive and anxiety disorders.

As mentioned earlier, research on the association of a latent construct CS domain with disease severity is limited. Our results are in line with previous findings on a negative association of cognitive functioning and disease severity in MDD and AD (32, 56, 57). Our findings did not reveal a disease-specific interaction for CS, represented by executive functioning, attention, and working memory, but we did find a main effect of the disorder, indicating a decreased cognitive function in patients with MDD. The lack of a significant interaction, in the presence of known disease-specific evidence for cognitive deficits in episodic memory in patients with MDD and attentional bias in patients with AD, may be due to combining variables of several different cognitive processes into one latent variable, thereby losing crucial variance. This should be closely examined in future research.

Our findings for the SP domain are consistent with previous research that has identified dysfunction in affiliation and attachment in patients with MDD, as well as dysfunction in perception and understanding of self in patients with AD, particularly GAD (5). Additionally, there is evidence of global social functioning deficits in both AD and MDD (37, 58). Previous research on the SP domain that aligned with RDoC has primarily focused on youth or adolescent samples (11, 59). Our study extends previous research on this particular domain to adult populations by identifying disease-specific and transdiagnostic associations of social processes and symptom burden within an adult sample.

As noted, the data of this present study was provided by pooling anonymized data from all FZPE consortia. Incomplete information on comorbidities and some main diagnoses resulted in the limited availability of subgroup data sets. Specifically, the comorbidity overlap in our sample may have diluted symptom specific effects on disease severity. It should be noted, however, that despite

this possible limitation, we found different associations of the domains with the diagnosis-specific symptom burden. Especially for NVS, which has been associated with anxiety, our results present differential associations despite the high comorbidity of AD with MDD in the subsample. Future studies are needed to investigate PVS, NVS, CS and SP dys-/function in specific types of AD and MDD, as well as to consider comorbidities within AD and MDD. As this is a cross-sectional study, the interpretation of our results is limited. Given that the relationship of PVS, NVS, CS and SP functioning with disease severity in AD and MDD unfolds over time, no causal conclusions can be inferred. However, we reliably showed that RDoC domains are associated with disease severity across disorders.

We would also like to point out that the majority of our disease severity ratings was based on self-report. Since the RDoC domains maybe more sensitive to self-reported disease severity future research on differential effects on self-reported versus expert-based ratings of disease severity could be additionally informative. While we used LM models as a statistical method of analysis, this approach may have limited our understanding of the domain-specific relations to the disease severity burden, because we were unable to account for random effects which could have affected the results. More sophisticated models like generalized linear mixed models (GLMM) should be considered for further investigations.

Since domain factor scores were constructed using many BSI-Items and considering the presence of well documented correlations between BSI-53 (SCL-90) and other severity measures f.e. BDI-II (60) this could be considered as another limitation impacting our results. We would like to argue, that even though there is a surplus of BSI-53 items involved in the factor structure, we still measured the latent RDoC domains and not only different types of symptom burden. Model fit of the four-factor model was significantly better in comparison to a one factor model (measuring general psychopathology) and a model with independent factors (12). Additionally, if our results were solely driven by symptom burden, we would expect that the association of NVS to disease-specific AD severity would be stronger than for MDD, which is not the case.

Given the presence of possible outliers, heteroskedasticity, and multicollinearity during our analyses, which we addressed adequately, it is important to interpret our results within the context of these specific conditions. Especially in light of multicollinearity and the change in significance with robust testing in two of the models, the associational structure between PVS, NVS and SP has to be further investigated.

Although it is still at an early stage, there is some indication from our results that a specific RDoC-based treatment may be more effective for patients with MDD. Further investigation is needed to confirm this hypothesis. Nevertheless, there is already some evidence in this direction with an RDoC-based treatment called ENGAGE, which targets f.e. reward processing (PVS) and has shown promising results in improving outcomes for patients with MDD (61). Therefore, further development and implementation of RDoC-based disease-specific treatments could lead to more tailored and effective interventions for all mental disorders. Overall, our findings suggest that a more nuanced transnosological understanding of mental disorders' underlying mechanisms and dimensions is needed to inform the development of more effective treatment.

In Conclusion, our key results demonstrate a strong association between symptom burden in patients with AD and MDD and latent RDoC indicators (PVS, NVS, CS, and SP) in a transdiagnostic way. There is also evidence for a disease-specific association between PVS, NVS

and SP, which requires future research to further understand the association of PVS, NVS and SP with disease severity, hopefully informing specific treatment options in the future (62).

6 Tables

Table 1: Sample characteristics

Variable	Sample			*p*
	Overall (*N* = 859)	**AD** (*n* = 602)	**MDD** (*n* = 257)	
Gender, *N* (%)				.812
Female	476 (55.4)	332 (55.1)	144 (56.0)	
Age, y				
M ± *SD*	35.05 ± 12.83	32.94 ± 11.21	40.02 ± 14.89	**<.001**
Range	15-78	15-68	18-78	
Marital status, *N* (%)				**<.001**
Single	352 (40.0)	235 (39.0)	117 (45.5)	
Married/partnership	379 (44.1)	318 (52.8)	61 (23.7)	
Separated	20 (2.3)	8 (1.3)	12 (4.7)	
Divorced	60 (7.0)	39 (6.5)	21 (8.2)	
Widowed	4 (0.5)	2 (0.3)	2 (0.8)	
Missing	44 (5.1)	-	44 (17.1)	
Graduation, *N* (%)				.939
Still in school	9 (1.1)	3 (0.5)	6 (2.3)	
CSE	75 (8.7)	54 (9.0)	21 (12.1)	
GSCE	220 (25.6)	171 (28.4)	49 (19.1)	
Polytechnic degree	6 (0.7)	3 (0.5)	3 (1.2)	
Technical-diploma	87 (10.1)	72 (12.1)	15 (5.8)	
University-entrance diploma	429 (53.4)	286 (47.5)	143 (55.6)	
Other	2 (0.2)	2 (0.3)	-	
School dropout	18 (2.1)	10 (1.7)	8 (3.1)	
Missings	13(1.5)	-	13 (0.8)	
Occupation, *N* (%)				.350
Employed	533 (62.1)	416 (69.1)	117 (45.5)	
Unemployed	295 (34.3)	186 (30.9)	109 (42.4)	
Missings	31 (3.6)		31 (12.1)	
Clinical characteristics				
Comorbidity, *N* (%)	582 (67.8)	530 (88.0)[a]	52 (20.2)	**<.001**
Psychotropics, *N* (%)	521 (60.7)	296 (49.2)	225 (87.5)	**<.001**

Note. To compare patient groups appropriate analyses were performed. *M* = Mean; *SD* = Standard deviation; y = years. **Disorder**: AD = Anxiety disorders; MDD = Major depressive disorders. **Graduation**: CSE = Certificate of Secondary Education [Hauptschulabschluss]; Polytechnic degree = [Abschluss der allgemeinbildenden Polytechnischen Oberschule der ehemaligen DDR]; GCSE = General Certificate of Secondary Education [Realschulabschluss]; Technical-diploma = [Fachabitur, Fachhochschulreife, Fachgebundene Hochschulreife]; University-entrance diploma = [Abitur, Allgemeine Hochschulreife]. [a] Only indication of comorbid AD

Table 2: Characteristics of domain-factor scores and disease severity

	M	***SD***	**Min**	**Max**	***Mdn***	**IQR**	**AD** (M, SD)	**MDD** (M, SD)	**p**
PVS	-0.29	0.91	-3.31	1.29	-0.14	1.25	-0.23, 0.86	-0.41, 1.01	**< .01**
NVS	0.37	0.90	-1.16	3.61	0.21	1.19	0.46, 0.83	0.15, 1.00	**< .001**
CS	-0.09	0.87	-5.46	2.75	0.05	0.91	-0.07. 0.73	-0.12, 1.13	-
SP	-0.30	0.94	-3.36	1.16	-0.11	1.31	-0.28, 0.91	-0.33, 1.01	-
DS z-score	-0.35	1.16	-3.81	3.34	-0.37	1.14	-0.03, 0.78	-1.12, 1.49	**< .001**

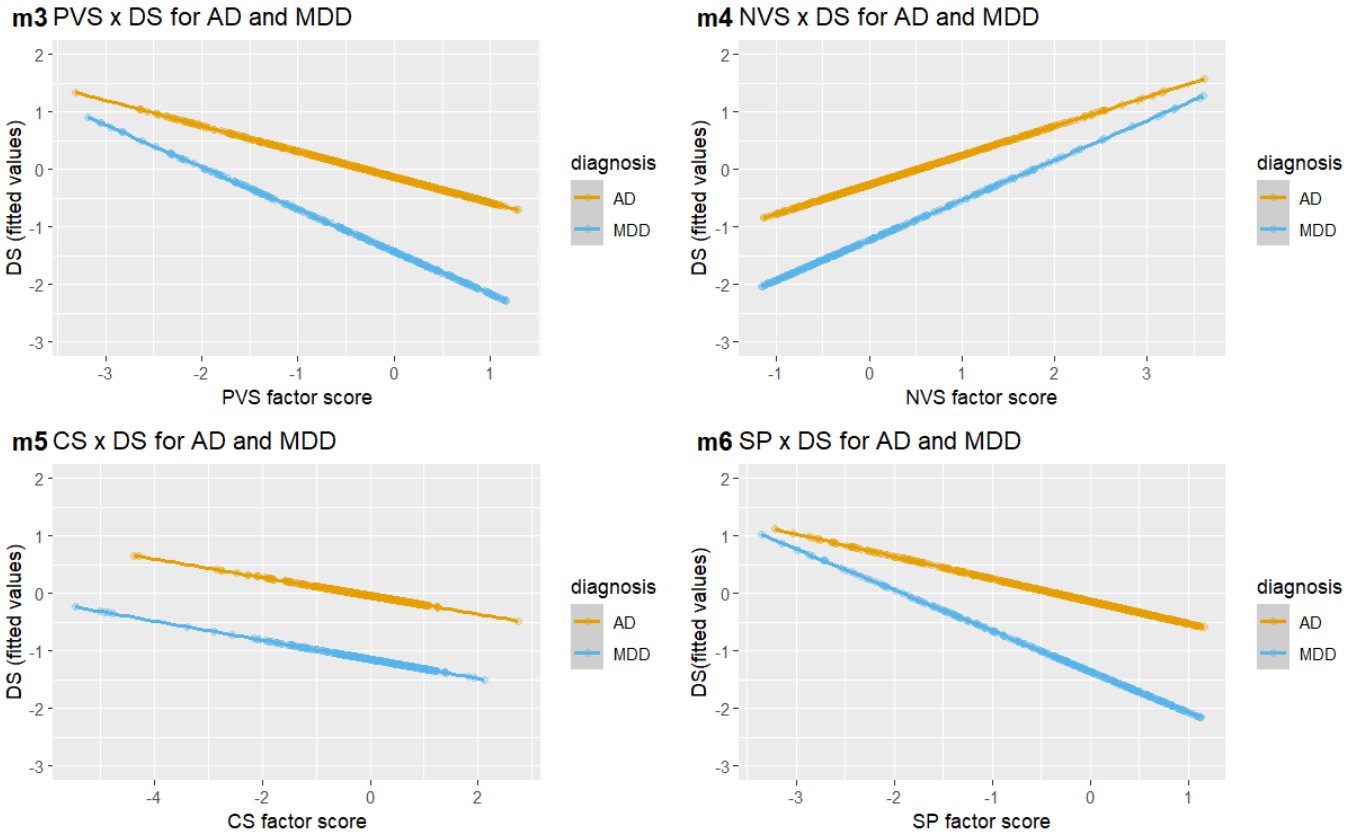
Note. Total N = 859; PVS= Positive valance system factor score, NVS= Negative valence systems factor score, CS= Cognitive systems factor score, SP= Social processes factor score, DS= Disease severity; *M*= Mean; *SD*= Standard deviation; Min = Minimum Score; Max = Maximum score; *Mdn*= Median; IQR= Interquartile range.

Table 3: Results of models 0-6

Model no, equation	main diagnosis β (p)	Domain factor score β (p)	Interaction β (p)	Adj. R^2	AIC	Model F test
m0 DS ~ Dia	-.43 ***	-	-	.19	2515.21	F(1,857)= 198.7 ***
m1 DS ~ Dia + PVS +NVS +CS+ SP	-.42 ***	PVS: -.37 *** NVS: .30 *** CS: -.02 (ns) SP: .18 ***	-	.40	2254.34	F(5,853)= 116.8 ***
m2 DS ~ Dia + PVS + NVS + CS + SP + PVSxDia + NVSxDia + CSxDia + SPxDia	-.45 ***	PVS: -.30 ** NVS: .31 *** CS: -.03 (ns) SP: .18 (.07)[a]	PVSxDia: -.09 (ns) NVSxDia: -.09 (ns) CSxDia: .004 (ns) SPxDia: -.11 (ns)	.41	2249.36	F(9,849)= 67.0 ***
m3 DS ~ Dia + PVS + PVSxDia	-.51 ***	-.35 ***	-.15 ***	.39	2277.51	F(3,855)= 180.2 ***
m4 DS ~ Dia + NVS + NVSxDia	-.38 ***	.39 ***	.09 ** [b]	.39	2275.22	F(3,855)= 181.4 ***
m5 DS ~ Dia + CS + CSxDia	-.44 ***	-.12 ***	-.004 (ns)	.20	2503.26	F(3,855)= 72.67 ***
m6 DS ~ Dia + SP + SPxDia	-.48 ***	-.32 ***	-.16 ***	.37	2303.22	F(3,855)= 166.5 ***

Note. DS= disease severity, Dia= main diagnosis (AD/MDD), PVS= Positive valence systems, NVS = Negative valence systems, CS = Cognitive systems, SP = Social processes; x = by (in interaction terms); ns = not significant, * p < .05, ** p < .01, *** p < .001; [a] with robust HC analysis p < .05; [b] with robust HC analysis p= .07

Figure1: Relationship of RDoC domains with disease severity in AD and MDD



Note. Grouped scatter graph of domain associations (PVS, NVS, CS and SP) with fitted DS scores. Each dot corresponds to an individual score on both variables, the color represents the patient groups (orange: AD; blue: MDD;). RDoC = Research Domain Criteria; AD = Anxiety disorders; MDD = Major depressive disorders; DS = disease severity; PVS= Positive valence systems, NVS = Negative valence systems, CS = Cognitive systems, SP = Social processes

7 Contribution to the field statement

This study is a contribution to the field of RDoC research and sheds light on the trans-nosological associations of four domains - positive and negative valence systems, cognitive systems and social processes - with disease severity in patients with anxiety and depressive disorders. We were able to show that the RDoC domains have a transdiagnostic as well as a disease-specific impact on disease severity. This may improve the understanding of underlying disease mechanisms. Our results may also help to further differentiate between these two mental disorders, which are known to often co-occur.

8 Conflict of Interest:

Frank Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and the International Scientific Advisory Board of Sooma, Helsinki, Finland. He has received speaker's honoraria from Mag&More GmbH, the neuroCare Group, Munich, Germany, and Brainsway Inc. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, Mag&More GmbH and Brainsway Inc.

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All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9 Author Contributions:

All authors designed the study and wrote the protocol. Authors Foerstner, Boettger, and Tschorn managed the literature searches and analyses. Authors Foerstner, Tschorn, Boettger and Rapp undertook the statistical analysis, and author Foerstner wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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11 List of non-standard abbreviations

AD: Anxiety Disorders

MDD: (Major) Depressive Disorder

SAD: Social Anxiety Disorder

GAD: Generalized Anxiety Disorder

PD-CAN: Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany

FZPE: German research network for mental disorders [Forschungszentrum zu psychischen Erkrankungen]

PVS: Positive Valence Systems

NVS: Negative Valence Systems

CS: Cognitive Systems

SP: Social Processes

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665

Table S1: *Sampling and eligibility criteria of the FZPE subsample*

Consortium: coordination center (PI, location), *N* **Inclusion criteria**	**Exclusion criteria**
PROTECT-AD (Providing tools for effective care and treatment of anxiety disorders): Wittchen, TU Dresden, *N*=600	
Current primary diagnosis: agoraphobia with or without panic disorder, social phobia, multiple specific (isolated) phobias, panic disorder (CIDI); outpatient status; age: 15–70 years; HAM-A >18; CGI> 3; written informed consent; ability to attend sessions and language competence	(1) any current DSM-V psychotic or substance use disorder (except nicotine); concomitant psychological or psychiatric treatment (psychopharmacological medication was allowed, if dosing was stable (for at least 3 months) and the medication was considered appropriate by the monitoring study clinician); acute suicidality; general medical contraindications; mono-symptomatic specific phobia.
ESCAlife (Evidence-based, stepped care of ADHD along the lifespan), ESCAlate: Banaschewski, CIMH Mannheim; *N*=1	
ADHD (DSM-V); 16-45 y., m/f	(1) psychiatric disorders; current alcohol or drug dependence; common comorbidities (e.g., CD, PD excl. ASPD); no exclusion if AD, mild to moderate MDD, or SUD in remission; severe heart disease; epilepsy; (2) psychotropics or ADHD medication: ≥4-week wash-out period prior study participation; (3) IQ<80; insufficient language skills; pregnancy or breast-feeding
BipoLife (Improving the detection and treatment of BD): Bauer, University Hospital, TU Dresden, *N*=27	
Dresden: 15-35 y., m/f; Risk group I: consultation of an early detection center; the presence of ≥1 risk factors for BD [a]; Risk group II: in- or outpatients with a depressive syndrome (MDD, PDD, mDD, RBD, AjD with depressed mood, unspecified)	Dresden: (1) primary diagnosis of BD, SZ, SZA, AD, OCD, or SUD; acute suicidality; (3) limited ability to comprehend the study; implied expressed negative declaration of intent to participate in the study by a minor
OptiMD (Novel strategies for the optimized treatment of major depression): Rupprecht, University of Regensburg, *N*=140	
Regensburg, Munich, Heidelberg: inpatients with depressive syndrome (HAM-D-21≥14; first depressive episode, recurrent MDD, BD current depressive episode, SZA, mixed AD, and MDD); ≥18 y., m/f; Caucasian origin	Regensburg, Munich, Heidelberg: (1) organic (somatic/neurological) or substance-induced cause of depressive episode; severe organic disease; (3) pregnancy or breast-feeding
Berlin: current primary MDD (ICD-10) during hospital stay; ≥18 y., m/f	Berlin: (1) CG: current psychiatric disorder (ICD-10)
GCBS (German center for brain stimulation for psychiatric disorders): Padberg, University Hospital, LMU Munich, *N*=40	
Munich: MDD (DSM-V; HAM-D-21≥15); current depressive episode ≤5 y. duration; in current episode no responding to ≥1 antidepressant treatment, and ≥4 weeks SSRI-intake of adequate dose; 18-65 y., m/f	Munich: (1) any other relevant psychiatric DSM-V axis-I- and/or axis-II-disorder, or unstable medical condition; acute suicidality; high degree of therapy resistance (>4 treatment attempts in the current episode); ECT in the current episode; treatment with tDCS (no single experimental sessions), DBS, or VNS; any intracranial implants; (3) investigators, site personnel directly affiliated with this study, and their immediate families; pregnancy
Berlin: MDD (DSM-V), current depressive episode ≤5 y. duration; no psychotropics (≥4 weeks) or stable SSRI-intake (≥ 4 weeks); 20-65 y., m/f	Berlin: (1) BD, AD, PTSD, ED, PD; psychotic tendencies in a lifetime; substance abuse or dependence in the past 6 months (except nicotine, caffeine); stroke (past 2 y.), epileptic seizure or diagnosed epilepsy, dementia, Parkinson's disease, Huntington's chorea, multiple sclerosis, any other neurological disease, which leads to intracranial pressure, brain lesions or higher risk for epileptic seizures; behavioral therapy or ECT in the current episode; (2) ≥4 failed medication attempts in the current episode; other psychotropic medications; (3) MRI-contraindications

Consortium: coordination center (PI, location), *N* **Inclusion criteria**	**Exclusion criteria**
APIC (Antipsychotic-induced structural and functional brain changes): Schneider, RWTH Aachen University, JARA-BRAIN, *N*=8	
SZ (DSM-V); 18-65 y., m/f; legally competent and capable of taking part in the study	(1) severe organic disease; (2) missing or incomplete medication history; (3) MRI-contraindications; pregnancy or breast-feeding; when placed in an institution by order of public authorities or courts; dependency or employment relationship with the sponsor or investigator; concurrent clinical trial participation
ESPRIT (Enhancing schizophrenia prevention and recovery through innovative treatments): Meyer-Lindenberg, CIMH Mannheim, *N*=43	
SZ, MDD, BD-I, ASD; CG: no history of psychiatric disorders; 18-65 y., m/f	(1) BD-II, SUD, PD; no exclusion if comorbidities evolved as a consequence of, or were markedly less pronounced as the primary disorder; chronic physical disease; (3) MRI-contraindications

Note. *N* = 1,912 (entry data), *N* = 1,431 (after data preparation), *N* = 859 (AD/MDD subsample, used in analyses). If applicable, exclusion criteria are listed according to three categories: (1) diagnoses, treatments, (2) medications, (3) other. **Consortia**: CIMH = Central Institute of Mental Health, Mannheim; JARA-BRAIN = Jülich Aachen Research Alliance; LMU Munich = Ludwig-Maximilians-Universität München; PI = Principal investigator; RWTH= Rheinisch-Westfälische Technische Hochschule, Aachen; TU Dresden= Technische Universität Dresden. **Disorder**: AD = Anxiety disorder; ADHD = Attention deficit hyperactivity disorder; AjD = Adjustment disorder; ASD = Autism spectrum disorder; ASPD = Antisocial personality disorder; BD (-I/-II) = Bipolar disorder (Type I/II); BPD = Borderline personality disorder; CD = Conduct disorder; ED = Eating disorder; MDD = Major depressive disorder; mDD = Minor depressive disorder; OCD = Obsessive-compulsive disorder; PD = Personality disorder; PDD = Persistent depressive disorder (dysthymia, cyclothymia); PTSD = Posttraumatic stress disorder; RBD = Recurrent brief depressive disorder; SPD = Specific phobic disorder; SUD = Substance use disorder; SZ = Schizophrenia; SZA = Schizoaffective disorder. **Instrument/Manual**: DSM-V/DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition (APA, 1994, 2000, 2013); CIDI = Composite International Diagnostic Interview (Robins, 1988); CGI = Clinical Global Impression Scale (Guy, 1976); HAM-A = Hamilton Anxiety Rating Scale (Hamilton, 1969; Maier et al., 1988); HAM-D-21 = Hamilton Depression Rating Scale, Version 21 (Hamilton, 1960, 1967); ICD-10 = International Classification of Diseases, 10th Revision (WHO, 2015); QIDS-C = Quick Inventory of Depression Symptomatology - Clinician rating (Rush et al., 2003); YMRS = Young Mania Rating Scale (Young et al., 1978). **Other**: DBS = Deep brain stimulation; CG = Control group; ECT = Electroconvulsive therapy**;** IQ = Intelligence quotient; m/f = male and female; MRI = Magnetic resonance imaging; SSRI = Selective serotonin reuptake inhibitor; tDCS = Transcranial direct current stimulation; VNS = Vagus nerve stimulation; y. = year(s).

[a] Listed risk factors for BD: family history, affective symptomatology/depressive syndrome, hypomanic/mood swings, disturbances of circadian rhythm/sleep, or other

Table S2: *Diagnostic information of the subsample patient groups*

Diagnosis	**ICD-10 code**	***N***	***DS instrument***
Major depressive disorder (MDD)		**257**	
MDD, single episode	F32	8	BDI-II, HAM-D21
MDD, single episode, mild	F32.0	1	HDRS-21
MDD, single episode, moderate	F32.1	27	BDI-II, CGI, HAM-D21
MDD, single episode, severe without psychotic symptoms	F32.2	42	
MDD, single episode, severe with psychotic symptoms	F32.3	3	
Other depressive episodes	F32.8	1	
MDD, single episode, unspecified	F32.9	1	
MDD, single episode or recurrent, unspecified	F32/33	1	
MDD, recurrent, current episode unspecified	F33	20	
MDD, recurrent, current episode mild	F33.0	6	
MDD, recurrent, current episode moderate	F33.1	40	
MDD, recurrent, current episode severe without psychotic symptoms	F33.2	98	
MDD, recurrent, current episode severe with psychotic symptoms	F33.3	6	
MDD, recurrent, currently in remission	F33.4	2	
PDD, dysthymia	F34.1	1	
Anxiety disorders (AD)		**602**	HAM-A, GAF
AD, Agoraphobia without panic disorder	F40.0	30	HAM-A
AD, Agoraphobia with panic disorder	F40.01	280	HAM-A
AD, Social phobia	F40.1	182	HAM-A, GAF
AD, multiple Specific (isolated) phobias	F40.2	48	HAM-A
Panic disorder	F41.0	62	HAM-A, GAF

Note. AD = Anxiety disorder; MDD = Major depressive disorder; PDD = Persistent depressive disorder.

Table S3: *Construct-level indicators and factor loadings of the domain-level PVS, NVS, CS and SP factors*

RDoC factor, construct	**Indicator**	**Self-report/ behave. Assess.**	**Item(s)**	***β***
PVS				
Reward responsiveness	Anhedonia	BSI-53 item [d]	18	-.76
Reward responsiveness	Hedonic affect	PANAS items [c]	1, 3, 4, 17	.55
Reward learning	Habituation	BSI-53 items [b]	15r, 26r, 27r	.81
NVS				
Potential threat	Anxiety	BSI-53 subscale	1, 12, 19, 38, 45, 49	.91
Potential threat	Phobic anxiety	BSI-53 subscale	8, 28, 31, 43, 47	.81
Potential threat	Somatization	BSI-53 subscale	2, 7, 23, 29, 30, 33, 37	.75
Potential threat	Anxiety-based BIS	BIS/BAS items [a]	2r, 8, 22r, 24	.49
CS				
Attention	Raw score Trail Making Test – Version A	TMT A	Time raw score	-.80
Cognitive control	Trail Making Test – Version B	TMT B	Time raw score	-.79
Working memory	Digit Symbol Substitution Test	DSST	Raw test score	.69
SP				
Perception and understanding of others	Hostility	BSI-53 subscale	6, 13, 40, 41, 46	-.76
Affiliation and attachment	Social Anhedonia	BSI-53	14	-.76
Affiliation and attachment	Interpersonal sensitivity	BSI-53 subscale	20, 21, 22, 42	-.91
Affiliation and attachment	Friendships	WHO-DAS-20	11r	.53
Perception and understanding of self	Paranoid ideation	BSI-53 subscale	4, 10, 24, 48, 51	-.79

Note. Indicators and factor loadings of PVS, NVS, CS and SP factors, which resulted from a CFA on the latent RDoC structure using behavioral and self-report assessments in a transdiagnostic sample. General CFA model fit was evaluated using the following fit indices: CFI = .93, TLI = .92, RMSEA = .077. All factor loadings were highly significant ($p < .001$). **RDoC**: PVS = Positive valence systems; NVS = Negative valence systems; CS = Cognitive systems; SP = Systems of social processes; RDoC = Research Domain Criteria. **CFA**: *β* = Factor loadings; CFI = Comparative Fit Index; r= Reversed items; RMSEA = Root Mean Square Error of Approximation; TLI = Tucker-Lewis Index. **Instrument**: BIS/BAS = Behavioral Inhibition System, Behavior Activation System Scales (Strobel et al., 2001); BSI-53 = Brief Symptom Inventory-53 (Franke, 2000); PANAS = Positive and Negative Affect Schedule (Breyer & Bluemke, 2016); WHO-DAS-20 = ; TMT A/B = Trail making Test A/B; DSST = Digit Symbol substitution Test.

[a] Selected items from the BIS subscale forming a mean score of anxiety-based BIS
[b] Selected items from the BSI-53 obsessive-compulsive subscale forming a mean score of habituation
[c] Selected items from the PANAS positive affect subscale forming a mean score of hedonic affect
[d] Selected single item from the BSI-53 using the raw value to measure anhedonia

Table S4: *Normative z-transformation of disease severity scores*

Test	Range [a]	Group	Reference population			Source	No. used in sample (N=859)
			Sample	*N*	*M* ± *SD*		n, (%)
Disease-specific self-report scales							**AD: 0 (0%); MDD: 40 (100%)** [b]
BDI-II	0-63	MDD	MDD and PDD outpatients	4,019	30.8 ± 10.52	Schulte-van Maaren et al., 2013	40 (4.7)
Disease-specific observer ratings							**AD: 600 (81.7); MDD: 134 (18.3)** [b]
MADRS	0-60	MDD	MDD and PDD outpatients	4,627	23.44 ± 7.75	Schulte-van Maaren et al., 2013	6 (0.7)
HAM-A	0-56	AD	GAD outpatients	688	24.6 ± 7.0	Allgulander et al., 2007	600 (69.8)
HAM-D-21	0-66	MDD	MDD and BD inpatients	768	25.9 ± 6.80	Hennings et al., 2009	117 (13.6)
IDS-C-30	0-84	MDD	MDD outpatients	544	37.7 ± 13.80	Rush et al., 2006	11 (1.3)
Expert-based global rating scales							**AD: 2 (2.3); MDD: 83 (97.7)** [b]
CGI-S	1-7	MDD	MDD patients	6,895	4.5 ± 0.8	Leucht et al., 2013	82 (9.6)
GAF	1-100	AD	SAD outpatients	644	49.9 ± 9.3	Kelly et al., 2013	2 (0.2)
GAF	1-100	MDD	MDD and PDD outpatients	1,489	57.3 ± 6.8	van Noorden et al., 2012	1 (0.1)

Note. The individual disease severity scores were converted into z-values by means and standard deviations of normative data from adult clinical samples. *M* = Mean; *SD* = Standard deviation. **Disorder**: AD = Anxiety disorder; BD = Bipolar disorder; GAD = General anxiety disorder; MDD = Major depressive disorder; PDD = Persistent depressive disorder (dysthymia). **Instrument**: BDI-II = Beck Depression Inventory-II (Beck and Steer, 1987); CGI-S = Clinical Global Impressions Scale - Severity of Illness (Guy, 1976); GAF = Global Assessment of Functioning Scale (Aas, 2010; APA, 1994; Rey et al., 1995); HAM-A = Hamilton Anxiety Scale (Hamilton, 1969; Maier et al., 1988); HAM-D-21 = Hamilton Rating Scale for Depression (Hamilton, 1960, 1967); IDS-C-30 = 30-Item Inventory of Depressive Symptomatology - Clinician Rating (Rush et al., 1996); MADRS = Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); YMRS = Young Mania Rating Scale (Young et al., 1978).

[a] Higher test scores indicate higher levels of disease severity, except for GAF scores ranging from 100 (extremely high functioning) to 1 (severely impaired), these scores were reversed.

[b] Percentage of the respective Ratings

Manuscript III

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“Mood and Anxiety Disorders Within the Research Domain Criteria Framework of Positive and Negative Valence Systems: A Scoping Review”

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Abstract

Introduction While a growing body of research is adopting Research Domain Criteria (RDoC)-related methods and constructs, there is still a lack of comprehensive reviews on the state of published research on Positive Valence Systems (PVS) and Negative Valence Systems (NVS) in mood and anxiety disorders consistent with the RDoC framework.

Methods Five electronic databases were searched to identify peer-reviewed publications covering research of "positive valence" and "negative valence" as well as "valence", "affect", and "emotion" for individuals with symptoms of mood and anxiety disorders. Data was extracted with a focus on disorder, domain, (sub-)constructs, units of analysis, key results, and study design. Findings are presented along four sections, distinguishing between primary articles and reviews each for PVS, NVS, and cross-domain PVS and NVS.

Results A total of 231 abstracts were identified, and 43 met the inclusion criteria for this scoping review. Seventeen publications addressed research on PVS, 17 on NVS, and nine covered cross-domain research on PVS and NVS. Psychological constructs were typically examined across different units of analysis, with the majority of publications incorporating two or more measures. Molecular, genetic, and physiological aspects were mainly investigated via review articles, primary articles focused on self-report, behavioral, and, to a lesser extent, physiological measures.

Conclusions This present scoping review shows that mood and anxiety disorders were actively studied using a range of genetic, molecular, neuronal, physiological, behavioral, and self-reported measures within the RDoC PVS and NVS. Results highlight the essential role of specific cortical frontal brain structures and of subcortical limbic structures in impaired emotional processing in mood and anxiety disorders. Findings also indicate overall limited research on NVS in bipolar disorders and PVS in anxiety disorders, a majority of self-report studies, and predominantly observational studies. Future research is needed to develop more RDoC-consistent advancements and intervention studies targeting neuroscience-driven PVS and NVS constructs.

Word count: 303

1 Introduction

Mood and anxiety disorders are highly prevalent and comorbid (Jacobi et al., 2014; World Health Organization [WHO], 2017) with mood disorders including major depression (MDD), dysthymia, bipolar disorder I and II (BD). Anxiety disorders (AD) comprise panic disorder (PD), agoraphobia (AG), generalized anxiety disorder (GAD), social anxiety/phobia (SAD), and specific phobia (SPD) and together with depressive disorders are amongst the major contributors of global disease burden (WHO, 2017), with mood and anxiety disorders affecting approximately 8.3% of the total global population in 2019 (Global Health Data Exchange [GHDx], 2020). Regarding the various diagnostic categories within mood and anxiety disorders , research has reported a substantial overlap in phenomenology and neurobiological mechanisms (Kendler et al., 1992; Watson, 2005). Especially for these disorders there are challenges to the neurobiological phenotypic and diagnostic specificity that would be essential to refine treatments to ultimately improve treatment response in mental illness (Insel et al., 2010).

The United States (US) National Institute of Mental Health (NIMH) initiated the Research Domain Criteria (RDoC) project in 2010 to address the above mentioned issue of limited specificity and to offer a new framework to investigate mental disorders. The RDoC initiative had been developed to guide research on mental disorders with reference to disrupted brain and behavioral mechanisms, in contrast to "classifying nontaxonic [sic], multidimensional phenomena […] as mental disorders" (Clark et al., 2017, p. 94; NIMH, 2008; Cuthbert and Insel, 2010, 2013). Providing a dynamic guiding framework for research, the idea of the dimensional approach of RDoC has been to understand mental illness in all its complexity, therefore studying the full range of human functioning from normal to abnormal with respect to basic circuit-based behavioral dimensions, organized into major systems of emotion, cognition, motivation, and social behavior (Cuthbert and Insel, 2013; Clark et al., 2017; NIMH, 2023a). The NIMH's hope is that the RDoC framework will help to generate research that enables an improved characterization within this multidimensionality (Clark et al., 2017). The RDoC framework is conceptualized as a matrix currently grouped into six basic domains of functioning: Positive Valence Systems (PVS), Negative Valence Systems (NVS), Cognitive Systems (CS), Social Processes (SP), Arousal and Regulatory Systems (ARS), and Sensorimotor Systems (SmS) (Insel et al., 2010; NIMH, 2023a, 2023b). These domains can be investigated using the following units of analysis: genes, molecules, cells, circuits, physiology, behavior, and self-report. The six domains are divided into constructs of which some are again divided into subconstructs. Within the RDoC framework there is great flexibility regarding the use of measures within each domain and regarding the units of analysis to allow for the investigation of all constructs that are relevant to improve knowledge about the etiology of mental diseases (Cuthbert, 2014; Clark et al., 2017).

The two domains of PVS and NVS and their corresponding constructs and subconstructs are particularly relevant to mood and anxiety disorders, as these systems are also represented in the Tripartite Model of Anxiety and Depression (Clark and Watson, 1991). Specifically, the model posits that NVS is predominant in anxiety disorders, and for PVS, alterations in hedonia may be more specific to mood disorders, while depressed mood has been shown to be present in both mood and anxiety disorders. The PVS domain encompasses systems that are "responsible for responses to positive motivational situations or contexts" (NIMH, 2023b). The PVS domain is currently grouped into the constructs reward responsiveness, reward learning, and reward valuation. Subconstructs within these constructs are reward anticipation, initial response to reward and reward satiation for reward responsiveness, probabilistic and reinforcement learning, reward prediction error and habit for reward learning, reward probability, delay and effort for reward valuation. The NVS domain covers systems that are "primarily responsible for responses to aversive situations or contexts" (NIMH, 2023b). The NVS domain currently encompasses the constructs acute threat (fear), potential threat (anxiety),

sustained threat, loss, and frustrative nonreward. These constructs are not further divided into subconstructs.

While there has been a growing body of research adopting RDoC-related methods and constructs since its launch in 2010, there is a lack of comprehensive reviews providing an overview of published empirical research consistent with the RDoC framework (Carcone and Ruocco, 2017) and its dimensional and transnosological view on specific symptoms prevalent in existing diagnostic categories. Therefore, by changing the perspective from a focus on disease categories to broader RDoC domains, our goal was to bring together the existing research from this period into one review, which specifically focuses on overlapping constructs that are associated to comorbid and overlapping symptoms. Specifically, the purpose of this study was to conduct a scoping literature review to systematically summarize research investigating PVS and NVS constructs in mood and anxiety disorder symptoms as an approach towards the RDoC system. The following research question was formulated: What is the state of published research investigating the role of PVS and NVS with respect to mood and anxiety disorder symptoms using the RDoC framework? We hypothesized that this scoping review would add insight into the heterogenic diagnostic category of mood and anxiety disorders from the RDoC perspective and therefore enrich our basic understanding of the similarities and differences within this disease spectrum.

2 Methods

2.1 Review Approach

The present scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) specific recommendations for conducting scoping reviews (Arksey and O'Malley, 2005) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018; see checklist in Supplementary Material A). The objectives, inclusion criteria, and methods for this scoping review had been specified in advance and had been documented in our protocol (see Supplementary Material B).

2.2 Eligibility Criteria

Articles were included if the following inclusion criteria were met: (1) research with outcome measures of positive or negative valence with reference to the RDoC PVS and NVS framework, (2) research on all RDoC units of analysis, which are genetic, molecular, cellular, circuitry, physiological, behavioral and self-report assessments. (3) human studies of adult (18 years and older) participants, (4) individuals with symptoms of mood (depression, bipolar) or anxiety (anxiety or phobic) disorders, (5) all types of empirical research (6), published in peer-reviewed journal papers, and (7) with full texts available. There were no language restrictions.

2.3 Information Sources and Search

We systematically searched the five electronic databases PubMed, PsychInfo, PsychArticles, PSYNDEX, and Web of Science first on April 26, 2021 and again on January 21, 2023. The search was conducted at domain level of PVS (keywords “positive valence”) and NVS (“negative valence”) and using the search terms "valence," "affect," and "emotion". Our intention was to provide a more comprehensive coverage of search results, as authors in the initial RDoC publications referred to "positive affect", "negative affect", "positive emotionality" (Sanislow et al., 2010, p. 634) or "negative emotionality" (Insel et al., 2010, p. 749) when discussing potential areas of research that might have links to psychopathological mechanisms. The final search strategy for PsychInfo is presented in Table 1. For detailed search strategies for all sources, see Supplementary Material C.

2.4 Selection of Sources of Evidence

To identify relevant articles, a total of four members of our research team rated the articles independently, with two raters at each screening stage. We exported the search results into Citavi (version 6.14.4) and Covidence software. Both software programs detected and removed duplicates. Citavi was used to organize the extracted publications, while Covidence was used for the management of the search results, study selection, and data extraction. The study selection was carried out in two stages. First, we screened titles and abstracts of all articles against the eligibility criteria. Screening of titles and abstracts was performed with Covidence, alongside with double-checking references in Citavi and Microsoft Excel (version Microsoft 365) to ensure high quality of our review. In a second step, we examined full texts for all articles that were potentially relevant to our research objective. Disagreements between raters at each step were resolved by consensus after reviewing the full text.

2.5 Data Charting and Synthesis of Results

If an article was eligible for inclusion in this study, we extracted data with focus on disorder, domain and constructs assessed, units of analysis, main aim, key findings, and general information including first author, year of appearance, origin (country/language), and study design. In line with scoping review guidelines, risk of bias assessment was not carried out (Tricco et al., 2018). The included studies were heterogeneous in terms of the outlined extracted information. We grouped sources by type of domain and study design and mapped information from the articles to the type of disorder, the seven units of analysis, and RDoC constructs. In addition, we listed relevant empirical elements and reported the key findings of the publication (see Tables 3-8). As a relevant number of articles were cross-domain oriented and this approach may shed light on differential effects of PVS and NVS on mood and anxiety disorder symptoms, we grouped those findings in a cross-domain section.

3 Results

3.1 Selection of Sources of Evidence

After duplicates were removed, we identified a total of 231 citations from searches of the five electronic databases. Based on title and abstract, 142 publications were excluded, with 89 full text papers to be assessed for eligibility. Of these, 46 were excluded. The remaining 43 studies were considered eligible for this scoping literature review (for reference lists of all papers searched, see Supplementary Material D). The flow diagram is shown in Figure 1.

3.2 Characteristics of Sources of Evidence

The characteristics of the 43 included studies are presented in Table 2. The majority of studies were conducted in the US (n = 33, 75 %), three studies in Germany, two in Canada, and one study each in Australia, Brazil, Norway, the Netherlands, and the United Kingdom (UK). All articles were written in English. In this final scoping review, we identified 23 primary studies and 20 reviews addressing PVS and NVS in patients suffering from mood and anxiety disorders published between 2014 and 2023. Most of the papers included in this review reported results from self-report questionnaires and interviews (59%; 22 primary articles, 4 reviews), half used physiological measures (50%; 8 primary articles, 14 reviews), and 19 included behavioral indicators (43%; 10 primary articles, 9 reviews). Circuitry played a role in about a third of the reviewed publications (32%; 5 primary articles, 12 reviews). Not as strongly represented were cellular (7%; 3 reviews), molecular (11%; 1 primary article, 4 reviews), and genetic (11%; 1 primary article, 4 reviews) components. Findings are presented separately for PVS, NVS, and cross-domain studies (Table 3-8).

3.3 Positive Valence Systems

We identified 17 publications (10 primary articles, 7 review articles) addressing research on PVS in mood and anxiety disorders guided by the RDoC framework. All primary and two of the review articles included self-report measures (71%). The majority of these articles combined self-reports with at least one additional unit of analysis, most commonly physiology or behavior. Only two publications included the cellular unit (12%, 2 reviews). In this scoping review, we did not identify any published primary research focusing on PVS-related genes or cells in mood and anxiety disorders that was oriented towards the RDoC framework. Review articles focusing on the RDoC framework and investigating PVS in mood and anxiety disorders mostly reviewed research investigating the circuit unit of analysis (35%, 1 primary article, 5 reviews). A total of 12 articles exclusively focused on patients suffering from depressive disorders or symptoms (71%; 8 primary articles, 4 reviews). While none focused exclusively on patients with AD, five articles included more than one patient group (29%; 2 primary articles, 3 reviews).

Impaired hedonic experience as a marker of impaired reward responsiveness has proven to be a relevant PVS-related construct specifically in patients with MDD (Nakonezny et al., 2015; Barch et al., 2016; Nusslock and Alloy, 2017; Trøstheim et al., 2020). Hedonic experience has been confirmed to be a unidimensional factor (Nakonezny et al., 2015) that has been found to be a responsive target of exercise treatment (Toups et al., 2017). Literature suggests that depression-related hedonic impairments trigger deficits in other PVS mechanisms like anticipation, learning, effort, and action selection and that these impairments are associated with alterations in striatal dopamine and/or opioid signaling (Barch et al., 2016; Nusslock and Alloy, 2017). Orbitofrontal cortico-striatal circuits (OFC-striatal circuits) were found to be associated with reward valuation and dysfunctions were found in patients with MDD. Furthermore, this review found that abnormal activation in these circuits was modifiable through (non-)invasive brain stimulation techniques (Fettes et al., 2017). One study (Alexopoulos et al., 2015; Alexopoulos et al., 2016) focused on an RDoC-oriented neuroscience-driven psychotherapeutic intervention. In this study, reward-exposure served as an RDoC-based intervention in late life depression. This approach proved efficacious in eliciting changes in behavioral activation that in turn led to improvement of depressive symptoms during treatment and follow-up (Alexopoulos et al., 2015; Alexopoulos et al., 2016). Familial risk of depression and aberrant reward processing has been shown to have significant impact on individuals' reward processing which increases over the course of puberty (Nusslock and Alloy, 2017; Ethridge et al., 2021). Furthermore, aberrant reward sensitivity on a neural and behavioral level was associated with risk for depression (Baskin-Sommers and Foti, 2015). Furthermore, aberrant reward processing was linked to molecular alterations in the dopamine system and an increased vulnerability to late-life depression (Taylor et al., 2022). Depressive symptoms could be linked to increased reward valuation and reduced effort (drive) as well as reduced reward responsiveness (Nusslock et al., 2015; Nusslock and Alloy, 2017; Swope et al., 2020). However, regarding behavioral and circuit-related reward responsiveness, Langenecker et al. (2022) found no differences between patients with remitted mood disorders and healthy controls. According to the authors, these results therefore suggest that reward responsiveness may serve as a proximal marker for acute affective symptoms rather than being a trait or stable marker of patients with mood disorders. Regarding the RDoC construct reward valuation, motivation, and energy as constructs matchable to effort and drive were suggested to be more clinically relevant compared to anhedonia/hedonic experience (Toups et al., 2017). Furthermore, decreased approach motivation (as part of reward valuation) could be related to unipolar depression, whereas increased approach motivation could be related to bipolar disorder with both mechanisms showing distinct neuronal correlates (Nusslock et al., 2015; Nusslock and Alloy, 2017). PVS functioning as measured by the newly developed Positive Valence Systems Scale (PVSS-21), was more strongly linked to symptoms of depression compared to symptoms of anxiety, was able to distinguish between depressed versus

non-depressed individuals, and predicted severity of anhedonia (Khazanov et al., 2020). Using an exploratory factor analysis (EFA) approach, several PVS factors were identified as significantly related to depressive symptoms (Olino et al., 2018). Notably, positive emotions showed the strongest negative association with depressive symptoms among all identified factors. High-frequency heart rate variability as a marker of disturbances in positive emotional functioning has been shown to exhibit greater intra-individual variation in patients with bipolar disorder compared to patients with MDD or healthy controls (Gruber et al., 2015).

3.4 Negative Valence Systems

We identified 17 publications (8 primary articles, 9 reviews) investigating the role of NVS in mood and anxiety disorders within the RDoC framework. With one exception, all primary articles employed self-report measures (53%, 7 primary articles, 2 reviews), regularly in conjunction with one or more additional units of analysis. We did not find any primary research examining MDD and AD on a molecular or cellular level, and only one paper that accounted for genetic influences by incorporating twin data. Reviews were mainly centered around physiological measures (71%, 4 primary articles, 8 reviews) that were often combined with behavioral tasks (47%, 3 primary articles, 5 reviews), neuroimaging (41%, 3 primary articles, 4 reviews), or genomic aspects (29%, 1 primary article, 4 reviews). Only one review also integrated research on the cellular correlates of MDD. Four out of 17 articles exclusively focused on patients diagnosed with MDD (24%), four on patients with AD (24%), and eight articles included more than one group of patients (47%). There were no primary articles and only one review pertaining to NVS in BD patients (5%). All NVS subconstructs were studied across diagnostic categories and generally assessed using multiple units of analysis. Acute, potential, and sustained threat received the most empirical attention, with many review articles examining all of them together. Frustrative nonreward received the least empirical attention with only one primary article investigating the construct in relation to depressive symptoms.

For the NVS subconstruct acute threat, an fMRI study of patients with symptoms of depression and anxiety revealed transdiagnostic patterns of altered threat processing in the bilateral insula, the cingulate and the dorsolateral prefrontal cortex (MacNamara et al., 2017). Self-reported stress reactivity as a measure of potential threat was found to modulate risk for comorbid expressions of MDD and alcohol use disorders (AUD) via genetic and environmental factors (Ellingson et al., 2016). Sustained threat in the form of trauma and chronic stress was linked to alterations in protein expression, neurocircuitry, physiology, and behavior, with evidence suggesting specific modulations of amygdala activation and Hypothalamic–Pituitary–Adrenal axis (HPA-axis) reactivity, highlighting the role of this subconstruct in the development of mood as well as anxiety disorders (Ross et al., 2017; Sambuco et al., 2020). ERP studies showed that while individuals with internalizing psychopathologies exhibited certain transdiagnostic abnormalities in threat processing (Klumpp and Shankman, 2018), depressive and anxious disorders were marked by diagnosis-specific modulations in startle response (Vaidyanathan et al., 2012; Boecker and Pauli, 2019) that predicted the severity and the extent of psychopathology (Lang et al., 2016; Lang et al., 2018). Some of these abnormalities have been traced back to disorder-specific genetic alterations within the serotonergic system and the HPA-axis (Hamm et al., 2016). Two review articles regarding the NVS subconstruct loss discussed the role of rumination in MDD and BD patients and outlined potential approaches for the further study of depressive symptomatology within the RDoC framework (Silveira, E. and Kauer-Sant'Anna, 2015; Woody and Gibb, 2015). As a behavioral component of loss, self-reported anhedonia was found to predict symptom severity for a broad range of psychiatric disorders, with particularly strong associations existing between anhedonia and depression (Guineau et al., 2022). A single article focused on frustrative nonreward in conjunction with loss and potential threat, establishing these constructs as transdiagnostic features implicated in the development and change of depressive symptoms over the

course of pregnancy and postpartum in a factor analysis of self-report questionnaire data (Cochran et al., 2020). Examining sustained threat and loss, a review of genetic influences on attentional bias showed that MDD and AD patients were characterized by disorder-specific alterations in attentional bias for affectively salient stimuli, and that the development of these differences was a consequence of environmental factors interacting with genes related to HPA-axis reactivity. Overall, research suggests the existence of transdiagnostic as well as disorder-specific dysfunctions in NVS domains across different units of analysis in MDD, AD, and BD patients.

3.5 Cross-domain Positive and Negative Valence Systems

We identified nine publications (5 primary articles, 4 review articles) covering cross-domain research on PVS and NVS in mood and anxiety disorders in accordance with the RDoC framework. All primary articles but none of the reviews reported results from self-report questionnaires or interviews (50%). Behavioral measures also mainly played a role in primary research (40%, 3 primary articles, 1 review) while review articles again put more emphasis on circuitry (40%, 1 primary article, 3 review articles) and physiology (30%, 1 primary article, 2 reviews). Two articles also reported findings on the molecular level (20%, 1 primary article, 1 review). We did not identify relevant cross-domain research regarding genetic and cellular correlates of PVS and NVS functioning. Cross-domain articles reported mainly on samples including more than one patient group (89%; 4 primary articles, 4 reviews). One primary article exclusively focused on patients suffering from depressive disorders (11%). None of the identified articles focused exclusively on patients with AD. Finally, two out of nine articles could not be allocated to a specific RDoC (sub-)construct. Hence, we reported the results on the domain level. All other cross-domain articles focused on the broad spectrum of PVS- and NVS (sub-)constructs.

With regards to factorial analytic studies, one article investigating the multimodal factorial structure underlying a broad test battery comprised of self-report, behavioral, and neuroimaging assessments to capture PVS and NVS functioning in patients with mood and anxiety disorder symptoms failed to identify a cross-modal latent structure and attributed this to challenges in the RDoC approach (Peng et al., 2021). However, Paulus et al. (2017) reported finding two independent "meta"-dimensions of PVS and NVS using a factorial analytic approach on self-report and behavioral data. Likewise focusing on self-report and behavioral units, Förstner et al. (2022) found a structure of four latent and transnosological factors (PVS, NVS, CS, SP) using a confirmatory factor analysis (CFA) approach, although these factors were not cross-modal. Differential associations between PV and NV symptom scores and clinical impairment, antidepressant response, and inflammation-related immunomarkers were revealed in a sample of MDD patients by Medeiros et al. (2020). Specifically, PV symptoms were linked to higher cognitive and physical impairment, showed associations to a greater number of inflammatory markers, and were more responsive to treatment with antidepressants, while NV symptoms were linked to younger age and a higher rate of comorbid anxiety symptoms. Wenzel et al. (2022) investigated self-reported PVS and NVS functioning in perinatal women: Trait- and state-like NVS functioning (potential threat) as well as state-like PVS functioning (reward valuation) were linked to worse depressive symptoms, while trait- and state-like NVS functioning (potential threat) were also linked to higher anxiety scores . Therefore, Wenzel et al. suggested potential threat as a transdiagnostic feature of perinatal anxiety and depression, whereas reward valuation was suggested to be a disease- or symptom-specific feature of perinatal depression. Compared to healthy controls, individuals with MDD or BD showed no preferential processing of positive stimuli (PVS circuit), while NVS circuitry was more pronounced (Langenecker et al., 2014). PVS mechanisms may be more often investigated in BD and underutilized in MDD (Langenecker et al., 2014). In a meta-analysis of 226 fMRI studies, Janiri et al. (2020) identified transdiagnostic neural phenotypes characteristic of patients with mood, anxiety, and posttraumatic stress disorders: In particular, the authors describe clusters of hypoactivation in the inferior prefrontal cortex, the inferior parietal lobule, and the putamen as well as

clusters of hyperactivation in the left amygdala/parahippocampal gyrus, the left thalamus, and the dorsal anterior cingulate cortex, supporting the hypothesis of transdiagnostic neuronal disease mechanisms. However, RDoC domains did not contribute differentially to these clusters, which points to the clusters being domain-independent. Regarding PVS- and NVS-circuits, transdiagnostic patterns of disrupted activity were identified in the ventrolateral, ventromedial and dorsomedial prefrontal cortex, the amygdala, and thalamo-cortical networks by McTeague et al. (2020) for MDD and AD, while they also found evidence for disease-specific aberrant activation for AD, BD, and MDD. One review investigating the molecular basis of PVS and NVS in mood and anxiety disorders identified abnormal glutamate activity related to PVS and NVS (Terbeck et al., 2015).

4 Discussion

4.1 Summary of Evidence

Our scoping review aimed to explore the recent research activity on the RDoC PVS and NVS in mood and anxiety disorders. We identified 44 publications that investigated positive and negative valence in mood and anxiety disorders, utilizing various measures from a range of genetic, molecular, neuronal, physiological, behavioral, and self-report approaches. Primary articles chiefly employed self-report questionnaires and interviews, often in conjunction with behavioral data. Reviews frequently included results from the molecules, circuitry, and physiology units of analysis. The structural and functional imaging literature included in this review highlighted the essential role of specific cortical frontal brain structures and of certain subcortical limbic structures, such as the amygdala and the hippocampus, in impaired emotional processing among patients with mood and anxiety disorders. Both reward- and threat-related processing were investigated in terms of genetic and molecular aspects, underlying circuitry, physiological responses, observed behavior, and self-reported symptoms, with many articles examining relationships between multiple units of analysis. Transdiagnostic as well as diagnosis-specific anomalies could be demonstrated -inter alia- on the levels of protein expression, concentration of hormones and immunomarkers, neural activity in brain areas associated with salience and reward, HPA-axis activation, behavioral indicators like attentional bias and startle response, and self-reported reward and threat sensitivity. However, identifying cross-modal constructs to characterize PVS and NVS functioning has proven challenging, an issue that is exemplified by a number of factor analytic studies reporting a lack of coherence in latent structure between tasks and measurement levels. We identified one intervention study testing the effectiveness of Engage therapy, an approach to improve symptoms connected to the positive valence domain by targeting the neural mechanisms underlying disordered emotional processing in late-life depression.

Both depressive and anxiety disorders were actively studied in the context of NVS, with a particular emphasis on the subconstructs of acute, potential, and sustained threat for anxious symptoms and loss for depressive symptoms. As we only identified one review investigating NVS in bipolar disorders, our scoping review highlights the lack of primary articles on NVS research focused on BD. Additionally, the review underscores the scarcity of research on frustrative nonreward in general, a gap initially identified by Carcone and Ruocco (2017). However, these research gaps could also be due to limitations in the search strategy employed, i.e., not explicitly searching for frustrative nonreward. There was limited research on the psychopathology of anxiety disorders within the PVS. Findings were largely connected to anxiety-related NVS constructs that cut across different AD, revealing a distinction between fear- or phobic-based disorders from non-phobic anxiety disorders. While mood disorders were widely studied in regards to both PVS and NVS, the number of publications exploring the psychopathology of BD was considerably smaller than those for MDD.

In relation to the Tripartite Model of Anxiety and Depression proposed by Clark and Watson (1991), we focus on three selected key findings. Observed diagnosis-specific modulations in startle responses, as a marker of acute threat (NVS), enable to distinguish between depressive and anxiety disorders (Vaidyanathan et al., 2012; Boecker and Pauli, 2019), while this subconstruct also showed transdiagnostic patterns in an fMRI setting (MacNamara et al., 2017). These results show that RDoC subconstructs such as acute threat can be an additional marker distinctive of AD, as is physiological hyperarousal in the Tripartite Model. Impaired hedonic experience, indicative of impaired reward responsiveness (PVS), has been identified as a useful marker (Nakonezny et al., 2015; Barch et al., 2016; Nusslock and Alloy, 2017; Trøstheim et al., 2020) for distinguishing depressive symptoms from other mood and anxiety disorder symptoms, which is consistent with Tripartite Model assumptions. The relationship between reward processing and depressive symptoms in the context of PVS (Nusslock et al., 2015; Nusslock and Alloy, 2017; Swope et al., 2020) may be complex and requires further investigation in future research, as reward responsiveness may serve as a more proximal marker for acute affective symptoms such as anhedonia rather than being a stable trait marker of patients with mood disorders (Langenecker et al., 2022).

The findings in our review align with the work of Carcone and Ruocco (2017), who stated that RDoC-related publications typically investigate a single construct using multiple units of analysis, examine relationships between constructs and/or elements, or apply a transdiagnostic approach to measure them. More recent reviews of RDoC research tend to adopt a diagnosis-focused approach. For instance, Wei and Roodenrys (2021) focused on anxiety-related research, and Tschida and Yerys (2021) pursued a combined domain and diagnosis approach to explore PVS in autism spectrum disorder. In comparison, in our review we pursued a more transnosological approach. The number of articles originating from outside the US has increased. This increasing number originating from outside the US suggests that the scientific community is increasingly embracing the dimensional research approach by integrating it into their research efforts in recent years (Carcone and Ruocco, 2017).

4.2 Limitations

This scoping review has some limitations. This review was not intended to provide a comprehensive overview of all research on PVS and NVS in mood and anxiety disorders. Rather, our search strategy was focused specifically on PVS and NVS domain level. Therefore, we did not conduct keyword searches for specific PVS and NVS constructs or subconstructs, which may have resulted in the exclusion of relevant publications. Another limitation lies in the exclusion of studies that did not provide a clear assignment of their research to specific RDoC constructs (e.g., BIS/BAS). This exclusion criterion is not completely objectifiable and therefore the current review we may have excluded single RDoC-related results. Of note, the present review included RDoC related articles that specifically focused on PVS and NVS on the domain level. The aim of this review was not to synthesize the entire literature on symptoms or constructs related to transdiagnostic or RDoC associated domains. Specifically, we focused on articles explicitly investigating PVS and NVS domains but did not search for all articles that for example investigated fear in mood and anxiety disorders. Therefore, the present review does not cover all transdiagnostic issues related to mood and anxiety disorder symptoms (e.g., Sindermann et al., 2021; van Tol et al., 2021) but reflects research from the last decade conceptualizing PVS and NVS on the domain level only. Given our primary aim was to conduct a scoping review of articles with a direct mention of the RDoC approach, we did not systematically include primary articles included in reviews or meta-analyses presented here, but extracted relevant RDoC information from these articles. Be it in relation to individual articles within the listed reviews/meta-analyses or be it of results or conclusions of the authors of these reviews/meta-analyses. While this approach may have hampered the generalizability and precision of our findings with respect to all available data, we would argue that we could therefore better present the current state of research with regard to RDoC research

efforts, which is also in line with our main aim, with value-added information from reviews/meta-analyses that are themselves RDoC-related but whose primary articles would not have been selected based on our eligibility criteria. A further limitation arises from the NIMH's update of the PVS domain. We mapped articles from before 2017 to the revised PVS structure released by the NIMH in 2017. As a result, it is possible that some articles may have been mapped to the PVS domain differently than originally intended by the authors. An additional limitation may arise from the incorporation of heterogenous research studies. However, given the nature of this review we could not address heterogeneity on a quantitative level. Lastly, as no systematic review was conducted, there was no quality assessment of the included studies, which is an inherent limitation of a scoping review.

4.3 Conclusions

The RDoC initiative was proposed as a translational framework for psychopathology research with the goal of addressing issues related to symptom-based diagnostic categories by shifting emphasis to dimensions of human functioning defined by observable behavior as well as neurobiological indicators (Cuthbert, 2020). This scoping review shows that overall, mood and anxiety disorders are actively studied in the context of PVS and NVS within the RDoC framework. In line with the integrative approach of the RDoC initiative, psychological constructs related to mood and anxiety disorders were typically examined across different units of analysis, with the majority of publications incorporating two or more measures to capture multiple facets of dysregulated functioning. While molecular, genetic, and physiological aspects were mainly investigated via review articles analyzing large bodies of research through the lens of the RDoC framework, current primary articles focused on self-report, behavioral, and—to a lesser extent—physiological measures as well.

It is clear that the RDoC initiative is influencing the direction of research into diagnosis-specific as well as transdiagnostic features of mood and anxiety disorders. This trend is particularly evident in the US, although our review suggests that the RDoC framework is increasingly being adopted in other countries as well. A major challenge for future research will be the translation of RDoC-guided findings into clinical practice (Pacheco et al., 2022). In this regard, the present scoping review emphasizes the potential of further research into depressive and anxious symptomatology conducted within the RDoC framework to potentially catalyze the development of neuroscience-driven interventions that target PVS and NVS functioning in alignment with current advancements in precision medicine approaches to diagnosis, treatment, and prevention of mood and anxiety disorders.

5 List of non-standard abbreviations

AD: Anxiety disorder

BD: Bipolar disorder

MDD: Major depressive disorder

NIMH: National Institute of Mental Health

NV: Negative valence

NVS: Negative Valence Systems

PD-CAN: Phenotypic, Diagnostic and Clinical Domain Assessment Network Germany

PV: Positive valence

PVS: Positive Valence Systems

RDoC: Research Domain Criteria

6 Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

7 Author Contributions

SJB, BF, MR and MT contributed to the conception and design of the study. MT, MR, and KKS mentored the research project. SJB prepared the review, ran the database searches, organized the studies, created the tables and figure, and wrote the first draft of the manuscript. SJB, BF, LS and MT performed all steps of the review: screening, eligibility, data extraction and synthesis of search results into the tables. All authors substantially contributed to manuscript revision, read, and approved the submitted version.

8 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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10 Tables

Table 1: PsychInfo Search Strategy

Search component	Search terms
Search 1	
S1	AB (“depression” or “depressive disorder*” or “depressive symptom*” or “major depressive disorder”) OR AB “affective disorder*” OR AB “mood disorder*” OR AB (“bipolar disorder*” or “bipolar” i or “bipolar ii” or “manic depression” or “bipolar affective disorder*” or “bipolar depression”) OR AB (“mania” or “manic” or “manic episode”) OR AB (“anxiety disorder*” or “anxiety”) OR AB (“phobia” or “phobic disorder*”) OR AB (“panic disorder*”)
S2	AB “rdoc” OR AB “research domain criteria”
S3	AB “positive valence” OR AB “negative valence”
S4	S1 AND S2 AND S3
Search 2	
S5	AB “valence” OR AB “affect*” OR AB “emotion*”
S6	S2 AND S3 AND S5
Conjunction of Search 1 and 2	
S7	S4 OR S6

AB = Abstract; rdoc = Research Domain Criteria.

Table 2 Characteristics of sources included.

First author, year	Origin [a]	Design	Disorder [b]	RDoC domain(s)	RDoC construct(s)	RDoC units of analysis
Alexopoulos, 2015	US	Proof of concept study	MDD	PVS	Reward learning, reward valuation	Behavior, self-report
Alexopoulos, 2016	US	Cohort study	MDD	PVS	Reward learning, reward valuation	Behavior, self-report
Barch, 2016	US	Literature review	MDD	PVS	Initial responsiveness to reward, reward anticipation or expectancy, incentive or reinforcement learning, effort valuation, action selection	Circuits, behavior
Baskin-Sommers, 2015	US	Literature review	MDD	PVS	Reward processing: initial responsiveness to reward, reward valuation (approach motivation), reward learning (habit)	Cells, circuits, physiology
Boecker, 2019	Germany	Literature review	MDD, AD	NVS	Threat processing: acute (fear), potential (anxiety), sustained threat	Physiology
Cochran, 2020	US	Cohort study	MDD, AD	NVS	Potential threat (anxiety), loss, frustrative nonreward	Self-report
Ellingson, 2016	Australia	Cohort study	MDD	NVS	Potential threat (anxiety)	Genes, self-report
Ethridge, 2021	Canada	Case control study	MDD	PVS	PVS functioning	Physiology, self-report
Fettes, 2017	Canada	Literature review	MDD	PVS	Reward learning, reward valuation (reappraisal)	Circuits, physiology
Förstner, 2022	Germany	Cohort study	MDD, BD, AD	PVS, NVS	Reward responsiveness, Reward learning, potential threat (anxiety)	Behavior, self-report
Gibb, 2016	US	Literature review	MDD, AD	NVS	Sustained threat, loss	Genes, circuits, physiology, behavior
Gruber, 2015	US	Case control study	MDD, BD	PVS	Positive affectivity, reward responsiveness (initial response to reward)	Physiology, self-report
Guineau, 2022	Netherlands	Cohort study	MDD, AD	NVS	Loss (anhedonia)	Self-report
Gunzler, 2020	US	Cohort study	MDD	NVS	Loss (anhedonia, guilt, self-harm)	Self-report
Hamm, 2016	Germany	Literature review	AD	NVS	Threat processing: acute (fear), potential (anxiety), sustained threat	Genes, physiology, behavior
Janiri, 2020	US	Meta-analysis	MDD, BD, AD	PVS, NVS	Reward responsiveness, reward valuation, acute threat (fear), potential threat (anxiety), frustrative nonreward	Circuits, physiology
Khazanov, 2020	US	Validation study	MDD	PVS	Reward processing (anticipation, responsiveness, learning, valuation, satiation, anhedonia)	Self-report
Klumpp, 2018	US	Literature review	MDD, AD	NVS	Threat processing: acute (fear), potential (anxiety), sustained threat	Physiology

First author, year	Origin [a]	Design	Disorder [b]	RDoC domain(s)	RDoC construct(s)	RDoC units of analysis
Lang, 2016	US	Cohort study	MDD, AD	NVS	Acute threat (fear)	Circuits, physiology, behavior, self-report
Lang, 2018	US	Cohort study	MDD, AD	NVS	Acute threat (fear)	Physiology, self-report
Langenecker, 2014	US	Literature review	MDD, BD	PVS, NVS	Reward, loss (rumination)	Circuits, physiology, behavior
Langenecker, 2022	US	Cohort study	MDD, BD	PVS	Reward responsiveness	Circuits, physiology, behavior, self-report
MacNamara, 2017	US	Case control study	MDD, AD	NVS	Threat processing	Circuits, physiology, behavior
McTeague, 2020	US	Meta-analysis	MDD, BD, AD	PVS, NVS	PVS and NVS functioning (emotional processing)	Circuits
Medeiros, 2020	US	RCT study	MDD	PVS, NVS	Reward responsiveness, reward learning, reward valuation; acute threat (fear), potential threat (anxiety), sustained threat, loss, frustrative nonreward	Molecules, self-report
Nakonezny, 2015	US	Validity study	MDD	PVS	Anhedonia (reward responsiveness)	Self-report
Nusslock, 2015	US	Literature review	MDD, BD, AD	PVS	Reward valuation (approach motivation)	Physiology
Nusslock, 2017	US	Literature review	MDD, BD	PVS	Reward processing, reward valuation (approach motivation), anhedonia	Circuits, behavior
Olino, 2018	US	Cohort study	MDD [b]	PVS	Anhedonia, reward sensitivity, positive emotionality (reward responsiveness, reward valuation)	Self-report
Paulus, 2017	US	Cohort study	MDD, AD	PVS, NVS	PVS and NVS functioning	Behavior, self-report
Peng, 2021	US	Cohort study	MDD, AD	PVS, NVS	PVS and NVS functioning	Circuits, physiology, behavior, self-report
Ross, 2017	US	Literature review	MDD	NVS	Sustained threat (chronic stress)	Molecules, cells, circuits, physiology, behavior
Sambuco, 2020	US	Cohort study	MDD, AD	NVS	Sustained threat	Circuits, physiology, behavior, self-report
Savage, 2017	US	Literature review	AD	NVS	Acute threat (fear), potential threat (distress), sustained threat	Genes, molecules, circuits, physiology, behavior
Silveira, 2015	Brazil	Systematic review	BD	NVS	Loss (rumination)	Self-report
Swope, 2020	US	Cohort study	MDD [c]	PVS	Reward responsiveness, reward learning, reward valuation	Self-report
Taylor, 2022	US	Literature review	MDD	PVS	PVS functioning	Cells, circuits, physiology, behavior, self-report
Terbeck, 2015	UK	Literature review	MDD, AD	PVS, NVS	PVS and NVS functioning	Molecules
Toups, 2017	US	Cohort study	MDD	PVS	PV symptoms	Behavior, self-report

First author, year	Origin [a]	Design	Disorder [b]	RDoC domain(s)	RDoC construct(s)	RDoC units of analysis
Trøstheim, 2020	Norway	Meta-analysis	MDD, BD	PVS	Anhedonia (reward learning, reward valuation)	Self-report
Vaidyanathan, 2012	US	Literature review	MDD, AD	NVS	Threat processing: acute (fear), potential (anxiety), sustained threat	Physiology
Wenzel, 2022	US	Cohort study	MDD, AD	PVS, NVS	Reward valuation, potential threat (anxiety)	Self-report
Woody, 2015	US	Literature review	MDD	NVS	Loss (rumination)	Genes, molecules, circuits, physiology, behavior, self-report

Included sources and characteristics in alphabetical order. RDoC terms: NVS = Negative Valence Systems; PV = Positive valence; PVS = Positive Valence Systems. **Origin:** UK = United Kingdom; US = United States. **Disorder:** AD = Anxiety Disorder; BD = Bipolar Disorder; MDD = Major Depression Disorder. **Study design**: RCT = Randomized Controlled Trial.

[a] All articles were written and published in English.

[b] For clarity, the specific diagnostic subtypes are listed in Tables 3 to 8.

[c] Depressive symptoms in other mental disorder or healthy population.

Table 3 Positive Valence Systems (PVS) primary articles.

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis							PVS				Elements/paradigms [a]	Key findings
				Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward responsiveness	Reward learning	Reward valuation		
Ethridge, 2021	x							x		x	x				Elements: SCID-5-CV, MINI Kid, PDS, UCLA LSI, EEG recording of reward-related neural responses during doors task. Aim: examine influence of pubertal development on familial transmission of PVS functioning in mother-daughter dyads with and without maternal history of depression	Association between mothers' and daughters' reward processing was moderated by daughters' pubertal development with dyads becoming more similar at more advanced stages of puberty; maternal history of depression was linked to reduced reward response at more advanced stages of puberty → relationship between familial psychopathology risk and PVS functioning may change over the course of adolescent development
Alexopoulos, 2015	x								x	x			x	x	Elements: SCID-R, WHODAS, HAM-D, MMSE, HVLT, NEO; Engage therapy. Constructs: reward exposure (reward learning, reward valuation); barriers of reward exposure (negativity bias (loss), apathy (arousal), and emotional dysregulation (cognitive control)). Aim: proof of concept study of the efficacy of Engage as a streamlined RDoC psychotherapy	Psychotherapy using neurobiological constructs to identify and use behavioral strategies to promote engagement in meaningful, rewarding activities, thereby increasing reward exposure → preliminary evidence suggests that Engage as the first RDoC-based neuroscience-driven psychotherapeutic intervention constitutes an efficacious approach to the treatment of late-life depression
Alexopoulos, 2016	x								x	x			x	x	Elements: Engage therapy (9-week treatment for late-life depression); training of reward exposure (engagement in meaningful, rewarding activities); SCID-R, WHODAS, HAM-D, BADS (measurement points at baseline, and after 6, 9 (end of treatment), and 36 weeks), MMSE, Stroop CWIT, response inhibition test, DRS-IP, HVLT-R. Constructs: reward learning, reward valuation	Changes in behavioral activation (BA) led to improvement of late-life MDD symptoms during Engage treatment and follow-up: both BA and late-life MDD symptoms significantly changed; at each observation period, change in BA and time predicted MDD severity

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis							PVS				Elements/paradigms [a]	Key findings
				Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward responsiveness	Reward learning	Reward valuation		
Toups, 2017	x								x	x	x				Elements: 12-week treatment with Exercise Augmentation for Depression (TREAD) study; SHAPS, MEI, QIDS. Domain level: PV symptoms	SHAPS and MEI scores sign. improved with exercise; MEI score change was a significant moderator and mediator of exercise in MDD → PV symptoms improve with exercise treatment for depression; PV symptoms: motivation and energy more clinically relevant than anhedonia
Nakonezny, 2015	x									x		x			Element: SHAPS; HAM-D17; IDS-C 30; IDS-SR 30; QIDS-C-16; QIDS-SR-30; QLES-Q. Subconstruct: anhedonia (hedonic ↔ anhedonic)	PCA confirmed a unidimensional (hedonic experience) factor structure and the SHAPS as a reliable and valid instrument (pos. associations to psychometric scales) to examine hedonic experience (PV) in MDD outpatients
Olino, 2018	x [b]									x	x	x		x	Elements: PAS; SAS; FCPS; SHAPS; TEPS; PANAS (PA only); BIS/BAS; CES-D (PA only); MPQ-BF (PE only), BFI; PROMIS-Dep. Constructs: anhedonia, reward sensitivity, and positive emotionality (PE)	Associations between latent factors (sociability, PE, assertiveness, pleasure seeking, BA) and self-reported depressive symptoms: (1) EFA solution: all factors negatively associated (PE strongest); (2) Bifactor solution: only two specific and the general factor negatively associated (again, PE strongest) → results help to understand the contribution of the PVS to depressive psychopathology
Swope, 2020	x [b]									x		x	x	x	Elements: ACI; BAARS-IV (ADHD); DASS-21 depression subscale; VHS; SBI anticipating subscale, TEPS-ANT; BIS/BAS drive subscale; SBI savoring the moment subscale, DPES; RPA positive rumination subscale. Aim: situate Sluggish Cognitive Tempo (SCT) within RDoC framework by investigating relationship with PVS components	SCT within RDoC PVS components: SCT was associated with increased reward valuation and expectancy but reduced willingness to work for rewarding experiences; no unique relationship between SCT and initial/sustained reward response; depressive symptoms linked to increased reward valuation and reduced expectancy, willingness to work, initial and sustained reward response → both SCT and depressive symptoms found to be uniquely related to PVS while controlling for demographic factors and co-occurring psychopathology

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward responsiveness	Reward learning	Reward valuation	Elements/paradigms [a]	Key findings
	Units of Analysis										**PVS**					
Khazanov, 2020	x									x		x	x	x	Element: PVSS-21. (Sub-)constructs: reward processing (anticipation, responsiveness, learning, valuation, satiation, anhedonia)	PVSS-21 showed strong internal consistency, retest reliability, and factorial validity; it showed a stronger correlation with reward sensitivity than punishment sensitivity, PA than NA, and depression than anxiety; PVSS-21 scores distinguished depressed from non-depressed and predicted anhedonia severity, even after adjusting for depression; PVSS-21 has potential in improving our understanding of reward-related abnormalities in depression and other disorders
Gruber, 2015	x	x						x		x	x	x			Elements: ambulatory psycho-physiological measurement (six-day consecutive period): HRV-HF (mean level, intra-individual variability, sympathetic activity, somatic movement → positive emotional disturbances), cardiovascular arousal (HR), sympathetic nervous system activity (skin temperature), GSM; mDES (state/trait PA). Constructs: positive affectivity (state PA, trait PA); reward responsiveness (initial response to reward)	Consistent with the HRV-HF instability hypothesis: BD exhibited higher HRV-HF instability compared to both MDD and CG (due to subsyndromal remitted manic symptoms); results support models of PVS disturbances and underlying psychophysiological mechanisms
Langenecker, 2022	x	x					x	x	x	x		x			Disorder: MDD, BD, Mood disorder not otherwise specified, HC. Elements: resting-state fMRI, parametric Go/NoGo test, monetary incentive delay task. (Sub-)constructs: reward responsiveness, inhibitory control. Aim: identify potential disease connectome edges as biomarkers of risk for mood disorder recurrence in participants with currently remitted MDD/BD and HC	No behavioral performance differences between mood disorder patients and HC in reward responsiveness and inhibitory control; differences in reward responsiveness reflected as differences in negative edges in the ventral attention/salience and emotion network; no overlap in edges related to diagnostic group membership and reward responsiveness connectomic profiles → no evidence of disrupted reward responsiveness in remitted mood disorders → role of reward responsiveness as a proximal marker of acute MDD/BD symptoms

RDoC terms: NA = Negative Affect; NV = Negative Valence; PA = Positive Affect(ivity); PV = Positive Valence; PE = Positive Emotion; PVS = Positive Valence Systems; RDoC = Research Domain Criteria. **Disorder**: ADHD = Attention Deficit Hyperactivity Disorder; BD = Bipolar Disorder; MDD = Major Depression Disorder; SZ= Schizophrenia. **Physiology**: EEG =

Electroencephalography; fMRI = functional Magnetic Resonance Imaging; HR = Heart Rate; HRV-HF = High-frequency Heart Rate Variability; GSM = Gross Somatic Movement; PET = Positron Emission Tomography. **Behavior**: BA = Behavioral Activation; SCT = Sluggish Cognitive Tempo; Stroop CWIT = Stroop Color Word Interference Test; TREAD = Treatment with Exercise Augmentation for Depression. **Self-report/interview**: BADS = Behavioral Activation for Depression Scale; BAARS-IV = Barkley Adult ADHD Rating Scale-IV; BFI = Big Five Inventory; BIS/BAS = Behavioral Inhibition and Behavioral Activation Scales; CES-D = Center for Epidemiologic Studies Depression Scale; DASS-21 = Depression Anxiety Stress Scales-21; mDES = modified Differential Emotions Scale; DPES = Dispositional Positive Emotion Scale; DRS-IP = Dementia Rating Scale, Initiation/Perseveration Scale; FCPS = Fawcett–Clark Pleasure Scale; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; HVLT = Hopkins Verbal Learning Test; IDS-C/SR = Inventory of Depressive Symptomatology - Clinician rated/Self-rated; MEI = Motivation and Energy Inventory; MINI Kid = Mini-International Neuropsychiatric Interview for Children and Adolescents; MMSE = Mini-Mental State Examination; MPQ-BF = Multidimensional Personality Questionnaire - Brief Form; PANAS = Positive and Negative Affect Scale; PANSS = Positive and Negative Syndrome Scale; PAS = Physical Anhedonia Scale; PDS = Pubertal Development Scale; PROMIS-Dep = Patient-Reported Outcomes Measurement Information System - Depression; PVSS-21 = Positive Valence Systems Scale; QIDS-C/SR = Quick Inventory of Depression Symptomatology - Clinician rated/Self-rated; QLES-Q = Quality of Life, Enjoyment, and Satisfaction Questionnaire; RPA = Response to Positive Affect Scale; SAS = Social Anhedonia Scale; SBI = Savoring Beliefs Inventory; SCID-5-CV = Structured Clinical Interview for DSM–5 Disorders Clinician Version; SCID-R = Structured Clinical Interview for DSM-IV; SHAPS = Snaith–Hamilton Pleasure Scale; TEPS = Temporal Experience of Pleasure Scale; TEPS-ANT = Temporal Experience of Pleasure Scale Anticipatory Subscale; UCLA LSI = University of California, Los Angeles Life Stress Interview; VHS = Valuing Happiness Scale; WHODAS = World Health Organization Disability Assessment Schedule; YMRS = Young Mania Rating Scale. **Methods**: CG = Control Group; EFA = Exploratory Factor Analysis; HC = Healthy Controls; PCA = Principal Component Analysis.

[a] We added specific disorder codes if this provides additional information.

[b] Depressive symptoms in other mental disorder or healthy population.

Table 4 Positive Valence Systems (PVS) reviews.

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	Main aim of review [a]	Key findings
	Units of Analysis										PVS					
Taylor, 2022	x					x	x	x	x	x	x				Elements: dopaminergic system, inflammation markers, neuroimaging. Constructs: reward processing, cognitive systems, sensorimotor systems. Aim: develop a model for the relationship between dopaminergic dysfunction and LLD	Age-related reduction in dopamine system signaling contributes to deficits in positive valence systems (reflected in higher effort cost as well as reduced motivation and reward learning) that combine and interact with impairments in cognitive and sensorimotor systems to increase vulnerability to LDD
Baskin-Sommers, 2015	x					x	x	x				x	x	x	Elements: GABA, OFC, ACC, d/rACC, NAc, ventral tegmentum, ventral pallidum, amygdala; EEG, fMRI. Constructs: initial responsiveness to reward (liking), reward valuation (approach motivation, wanting), reward learning (habit formation). Aim: overview of preclinical, electro-physiological, and neuroimaging literature on reward processing from a transdiagnostic, multidimensional perspective	Individual differences in reward sensitivity associated with risk for substance abuse and depression: MDD: blunted reactivity to monetary reward in striatum, incl. bilateral putamen, caudate, and NAc; deficit in striatal activation to types of pleasant stimuli; impaired reward learning associated with blunted activity within the NAc, dACC, rACC)
Barch, 2016	x						x		x			x	x	x	Element: circuit-behavioral; ERP and fMRI measures. Constructs: initial responsiveness to reward, reward anticipation or expectancy, incentive or reinforcement learning, effort valuation, action selection. Aim: review of impairments in motivational and hedonic constructs in individuals with psychosis vs. with depressive pathology	Differences of reward-related and hedonic deficits associated with psychosis vs. depression; (anhedonic) MDD: hedonic impairments → these deficits may trigger other impairments (anticipation, learning, effort, action selection); hedonic impairments associated with alterations in dopamine and/or opioid signaling in the striatum (relatively intact hedonic processing in psychosis, but impaired reward learning and action selection)
Fettes, 2017	x						x	x					x	x	Elements: structural and functional neuroimaging (VBM, fMRI, PET), neurostimulatory techniques (DBS, ECT, rTMS, tDCS). Constructs: reward-guided learning, reward valuation (reappraisal). Aim: review role of disturbances in	OFC-striatal circuits play a key role in reward valuation, affect regulation, and decision-making; dysfunction in these circuits is associated with OCD, MDD, and SUD symptomatology; abnormal activity in mOFC or lOFC-striatal pathways is

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	Main aim of review [a]	Key findings
															cortico-striatal-thalamic loop circuits of the OFC (mOFC and lOFC) in MDD, OCD, and SUD	amenable to intervention by invasive as well as non-invasive brain stimulation techniques → neurostimulation inventions may have the potential selectively modulate psychiatric symptoms related to OFC dysfunction
Nusslock, 2015	x	x	x					x						x	Element: EEG. Construct: Reward valuation (approach motivation). Aim: relationship between relative left frontal EEG activity and mood and anxiety related symptoms → approach–withdrawal motivational model of frontal EEG asymmetry	Greater relative left frontal EEG activity (increased approach motivation → BD/manic symptoms) and decreased relative left frontal EEG activity (decreased approach motivation or increased withdrawal tendencies → MDD/anhedonia); specific symptom clusters of depression (anhedonia), hypomania/ mania (excessive approach motivation), and anxiety (apprehension vs. anxious arousal)
Nusslock, 2017	x	x					x		x		x		x	x	Element: circuit-behavioral. (Sub-)constructs: reward valuation (approach motivation), anhedonia. Aim: relationship between reward processing and mood-related symptoms	MDD and BD have distinct patters of reward processing and reward-related brain activity; anhedonia in MDD is characterized by reward hyposensitivity and decreased approach motivation; reward hypersensitivity and elevated approach motivation relates to hypo/manic symptoms in BD
Trøstheim, 2020 [Meta-Analysis]	x	x								x				x	Disorder: (current/past/remitted) MDD, BD, HC. Element: SHAPS (assessed at baseline or in a no-treatment condition). Subconstruct: Anhedonia. Aim: generate and compare reference values for anhedonia levels in adults with and without mental illness	Patients scored higher on the SHAPS than HC; MDD higher than all other patient groups (remitted MDD within the healthy range) → anhedonia in MDD affects multiple pleasure domains; less effects for other disorders

RDoC terms: PVS = Positive Valence Systems; RDoC = Research Domain Criteria. **Disorder**: BD = Bipolar Disorder; MDD = Major Depression Disorder; LLD = Late-Life Depression; OCD = Obsessive-compulsive Disorder; SUD = Substance Use Disorder. **Circuit**: ACC = Anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; rACC = rostral anterior cingulate cortex; OFC = Orbitofrontal Cortex; medial Orbitofrontal Cortex; l/mOFC = lateral/medial Orbitofrontal Cortex; NAc = Nucleus Accumbens. **Physiology**: DBS = Deep Brain Stimulation; tDCS = transcranial Direct Current Stimulation; ECT = Electroconvulsive Therapy; EEG = Electroencephalography; ERP = Event-Related Potential; fMRI = functional Magnetic Resonance Imaging; PET = Positron Emission Tomography; rTMS = Repetitive Transcranial Magnetic Stimulation; VBM = Voxel-Based Morphometry. **Self-report/interview**: HAM-D = Hamilton Depression Rating Scale; SHAPS = Snaith–Hamilton Pleasure Scale; WHODAS = World Health Organization Disability Assessment Schedule. **Methods**: HC = Healthy Controls.
[a] We added specific disorder codes if this provides additional information.

Table 5 Negative Valence Systems (NVS) primary articles.

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis: Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	NVS: Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Elements/paradigms [a]	Key findings
Ellingson, 2016	x			x						x		x				Elements: MPQ stress reactivity (SR) and control (CON) subscales; CIDI (AUD section); AUDADIS-IV (modified version for MDD assessment). Aim: examine whether covariation between MDD and AUD can be traced back to phenotypic, genetic, and environmental variance in NE and behavioral control	SR and CON explained 70% of the genetic and 20% of the environmental covariation between MDD and AUD (sample of same-sex DZ and MZ twins), with trait measures of behavioral control accounting for unique covariation between MDD and AUD beyond what was explained by NE → first study to show role of NE and behavioral control as modulators of risk for the co-occurrence of MDD and AUD via genetic and environmental factors
Gunzler, 2020	x									x				x		Element: PHQ-9. Construct: loss (anhedonia, guilt, self-harm). Aim: use FA and qualitative analysis to identify depressive phenotypes by mapping PHQ items along RDoC domains	Four depressive phenotypes: NVS and externalizing (anhedonia, depression), NVS and internalizing (depression, guilt, self-harm), ARS (sleep, fatigue, appetite), and CS and SmS (concentration, psychomotor)
MacNamara, 2017	x		x				x	x	x		x					Disorder: MDD, AD (GAD, SAD). Elements: fMRI; emotional face-matching task during processing of affective scenes and faces (fearful, angry, happy and geometric shapes); bilateral insula, ACC, MCC and dlPFC. Construct: threat processing	Transdiagnostic anxiety and depressive symptomatology marked by activation in paralimbic, cingulate, and lateral prefrontal regions in response to angry; lateral prefrontal activation may be affected differently by symptoms of anxiety and depression; Shared neural dysfunction in threat processing in patients with GAD, SAD, and MDD → varies with symptom severity
Sambuco, 2020	x		x				x	x	x	x			x			Disorder: MDD, AD (SAD, GAD, SPD, PD), HC. Elements: fMRI; rapid serial visual presentation/emotional scene	Emotional reactivity: amygdala and ventral visual cortex (BOLD) activity enhanced when watching emotional arousing scenes; changes during emotional processing predicted self-reported experienced trauma, PTSD-

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Elements/paradigms [a]	Key findings
																processing (IAPS); BDI-II, STAI, IIRS, MASQ, PAS, PDS. Construct: sustained threat (trauma severity). Primary analyses: functional brain activity in the amygdala, inferotemporal, and occipital visual cortex. Additional: BOLD activity association to individual trauma factor	like symptoms and associated functional impairment; highest (lowest) trauma scores ↔ smallest (largest) changes in BOLD; experience of a life-threatening event associated with reduced functional limbic-visual activity. Experienced trauma may be a common underlying factor contributing to the development of psychopathology in patients with various anxiety and mood disorders
Cochran, 2020	x		x							x		x		x	x	Disorders: MDD (MDD, DD-NOS), AD (GAD, PD, SAD). Elements: STAI, HAM-D, HAM-A, EPDS, BDI, PSS, PSQI. Aim: establish transdiagnostic framework for understanding depressive and related symptoms during pregnancy and postpartum. Method: FA (bifactor model)	FA bifactor model with six transdiagnostic factors (loss, potential threat, frustrative nonreward, sleep-wakefulness, somatic, and coping) and general factor showed good fit, but model components needed to vary across perinatal period → overall coherence of factor structures for depressive symptomatology, yet importance of certain symptoms as pathology markers changed between earlier pregnancy and later postpartum → symptoms may need to be viewed in connection with specific life phases within as well as beyond the perinatal context
Guineau, 2022	x		x							x				x		Elements: SCID-IV-RV, MATE, DIVA, NIDA; anhedonia items of the OQ-45-2; IDS-SR; ASI; CAARS-S; AQ-50; Method: graphical Least Absolute Shrinkage and Selection Operator (LASSO) network	Anhedonia severity predicted severity of depressive and (to a lesser extent) anxious, ADHD, and ASD symptoms; reverse influences on anhedonia severity existed but were less pronounced → role of anhedonia as a transdiagnostic feature of psychopathology
Lang, 2016	x		x				x	x	x	x	x					Disorders: MDD, AD (PD, AG, GAD, SAD, SPD, AD-NOS). Paradigm: Emotional imagery. Elements: HR reactivity, skin conductance level, facial EMG, blink-response magnitude during ideographic fear imagery with startle probes; Anxiety Sensitivity Index, BDI-II,	Self-report: PCA resulted in 3 factors negative affectivity/general distress, anxious/hyperarousal and cumulative life stress. Composite index of startle reflex and heart rate reactivity during idiographic fear imagery for each patient was translated into a defensive dimension defined by ranking patients from most defensively reactive to least reactive → paralleled by diminishing reactivity in electrodermal and facial EMG reactions across this defensive dimension. Only PCA factor negative affectivity/general distress

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Elements/paradigms [a]	Key findings
																MASQ subscales, STAI-trait, STAXI-trait, FSS, IIRS, subscales of SRRS, 17-item checklist of early life stressor occurrence	showed association to defensive dimension - as distress levels increased, defensive reactivity decreased. → Each principal diagnosis was represented in every quintile → within-diagnosis heterogeneity regarding defensive reactivity
Lang, 2018	x		x					x		x	x					Disorder: MDD, AD (SPD, SAD, PD, PD/AG, GAD, other AD). Elements: event-related potential (acoustic startle probes), EEG; BDI-II, MASQ subscales, STAI-trait, IIRS, SUDS	Reduced positive amplitude of centro-parietal startle-evoked event-related potential were related to higher scores of depression/anxiety, increased life dysfunction, greater co-morbidity and disease severity and less favorable prognosis → Startle reaction predicted severity and extent of psychopathology

RDoC terms: ARS = Arousal and Regulatory Systems; CS = Cognitive Systems; NE = Negative Emotionality; NVS = Negative Valence Systems; RDoC = Research Domain Criteria; SmS = Sensorimotor Systems. **Disorder:** ADHD = Attention Deficit Hyperactivity Disorder; AD-NOS = Anxiety Disorder Not Otherwise Specified; AG = Agoraphobia; ASD = Autism Spectrum Disorder; AUD = Alcohol Use Disorder; DD-NOS = Depressive Disorder Not Otherwise Specified; GAD = General Anxiety Disorder; MDD = Major Depression Disorder; PD = Panic Disorder; PD/AG = Panic Disorder with Agoraphobia; PTSD = Post-Traumatic Stress Disorder; SAD = Social Anxiety Disorder; SPD = Specific Phobic Disorder. **Genes**: DZ/MZ = Di-/Monozygotic. **Circuit**: ACC = Anterior Cingulate Cortex; BOLD activity = blood-oxygen-level dependent activity; MCC = Midcingulate Cortex; PFC = Prefrontal Cortex; dlPFC = dorsolateral Prefrontal Cortex. **Physiology**: EEG = Electroencephalography; EMG = Electromyography; HR = Heart rate; fMRI = functional Magnet Resonance Imaging. **Behavior**: IAPS = International Affective Picture Systems. **Self-Report/interview**: AQ-50 = Autism Spectrum Quotient; ASI = Anxiety Sensitivity Index; AUDADIS-IV = Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; BDI/BDI-II = Beck Depression Inventory; CAARS-S = Conners' Adult ADHD Rating Scale; CIDI = Composite International Diagnostic Interview; DIVA = Diagnostic Interview for ADHD in adults; EPDS = Edinburgh Postnatal Depression Scale; FSS = Fear Survey Schedule; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology Self-Report; IIRS = Illness Intrusiveness Rating Scale; MASQ = Mood and Anxiety Symptoms Questionnaire; MATE = Structured Interview Measurements in the Addictions for Triage and Evaluation; MPQ = Multidimensional Personality Questionnaire; NIDA = Dutch Interview for Autism Spectrum Disorders in Adults; OQ-45-2 = Outcome Questionnaire; PAS = Panic and Agoraphobia Scale; PDS = Posttraumatic Diagnostic Scale; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburg Sleep Quality Index; PSS = Perceived Stress Scale; SCID-IV-RV = Structured Clinical Interview for DSM-IV Axis I Disorders; SRRS = Social Readjustment Rating Scale; STAI-trait = State-Trait Anxiety Inventory; STAXI-trait = State-Trait Anger Expression Inventory; SUDS = Subjective Units of Distress Scale. **Methods:** FA = Factor analysis; HC = Healthy Controls; LASSO = Least Absolute Shrinkage and Selection Operator; PCA = principal component analysis.

[a] We added specific disorder codes if this provides additional information.

Table 6 Negative Valence Systems (NVS) reviews.

First author, year	Units of Analysis									NVS					Main aim of review [a]	Key findings
	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward		
Woody, 2015	x			x	x		x	x	x	x				x		Elements: Genes: MAOA, COMT, DAT1, 5-HTRs. Molecules: downregulation of GCR; upregulation of CRH, estrogens, androgens, oxytocin, vasopressin, inflammatory molecules. Circuits: sustained amygdala reactivity, decreased dlPFC Recruitment; decreased vmPFC (incl. rostral cingulate), increased insula activation, increased PCC activity, decreased R Parietal; PVN; hippocampus; OFC, habit systems (striatum/ caudate/ accumbens), increased DMN activity; dysregulated reward circuitry). Physiology: ANS, HPA, neuroimmune dysregulation, prolonged psychophysiological reactivity. Behavior: rumination, withdrawal, worry, crying, sadness, loss-relevant recall bias, shame, attentional bias to negative valenced information, guilt, morbid thoughts, psychomotor retardation, anhedonia, increased self-focus, deficits in executive function (e.g., impaired sustained attention), loss of drive (sleep, appetite, libido), amotivation. Self-report: change in attributional style, hopelessness. Aim: depression research with focus on loss (rumination) within RDoC framework	Circuitry: disruption of cortico-limbic circuitry; increased activity in default mode network. Genes: regulating neurotransmission of monoamines. Molecular: e. g., sex hormones. Physiology: pupil dilation. Behavior: heterogenous list of features. Self-report: attributional style; hopelessness → summary: rumination dynamic processes influencing neurodevelopmental progression of MDD; imaging studies mostly focused on current MDD; loss as a RDoC construct; loss in environmental and developmental contexts; research of rumination as an example of RDoC research

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Main aim of review [a]	Key findings
	Units of Analysis										NVS						
Ross, 2017	x				x	x	x	x	x				x			Disorder: (anxious) MDD. Elements: inflammation processes, alterations in protein expression; neurocircuitry alterations (BNST, amygdala); ERN; HPA axis dysfunction; reduced reactivity to passive stimuli, increased activity to aversive stimuli; clinical profiles. Construct: sustained threat (chronic stress)	Anxious MDD: increased risk for treatment-resistance to standard antidepressants, increased morbidity risk; review of the impact of sustained threat (chronic stress: childhood trauma, physical illness) on (anxious) MDD depression through pathological changes to molecules, cells, neurocircuitry, physiology, and behavior
Gibb, 2016	x		x	x			x	x	x				x	x		Elements: dot probe task (RT indices), Posner spatial cueing task, Stroop task, eye-tracking/passive viewing task, ERPs. Constructs: sustained threat, loss (attention bias to specific stimuli for both). Aim: review findings regarding genetic influence on attentional biases in clinical and non-clinical populations (twin and candidate gene studies)	Review of approaches to assessing biased attention to emotional stimuli with links to psychopathology and neural influences: MDD and AD patients exhibit disorder-specific alterations in attentional bias for affectively-salient stimuli; twin and candidate gene studies show robust genetic influence on attentional bias; development of attentional bias is influenced by specific environmental factors that can interact with genes related to HPA axis reactivity
Vaidyanathan, 2012	x		x					x			x	x	x			Disorder: MDD, (phobic/non phobic) AD (SPD, SAD, PD, PD/AG, GAD). Elements: ERN, startle blink reflex. Constructs: threat processing. Aim: physiological measures among disorders entailing salient anxiety or depressive symptomatology	Phobia: normal-range ERN, increased startle to unpleasant stimuli; non-phobic AD: increased ERN, increased startle across all types of emotional stimuli and increased baseline startle; MDD: patterns of response for startle and ERN appear to vary as a function of severity and distinct symptomatology; fear, anxiety and depression are distinguishable (by ERN and startle results) constructs
Klumpp, 2018	x		x					x			x	x	x			Disorder: MDD, AD (PD, SAD, GAD). Elements: ERP, EMG-startle blink; negative processing bias. Construct: threat processing. Aim: How can ERP and startle studies inform the role of chronometry in anxiety and depression	ERP: Individuals with internalizing psychopathologies show transdiagnostic abnormalities in early stages of processing; startle reactivity: fear-based disorders (PD, SAD) can be distinguished from other AD (GAD) and different internalizing phenotypes show different patterns of habituation

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Main aim of review [a]	Key findings
	Units of Analysis										NVS						
Boecker, 2019	x		x					x			x	x	x			Disorder: MDD, AD (PD, PD/AG, SPD, SAD, GAD). Elements: EMG of the musculus orbicularis oculi, affective startle modulation (ASM). Construct: threat processing. Aim: review findings regarding ASM anomalies across psychiatric categories; motivational priming hypothesis	Different psychopathologies were related to specific changes in startle potentiation/attenuation, anomalies in only one motivational system: increased startle potentiation to unpleasant stimuli (AD); general hyporeactivity to affective stimuli (MDD); increased vs. decreased startle responses to disorder-specific stimuli (SPD)
Savage, 2017			x	x	x		x	x	x		x	x	x			Constructs: acute threat (fear), potential threat, sustained threat (distress). Aim: review of genetic epidemiological data (twin studies, heritability) and molecular genetic findings for NVS phenotypic measures	Molecular genetic basis of NVS phenotypes (early stages); a few research (attentional bias, peripheral physiology, or brain-based measures of threat response); most studies with small number of genes selected for putative association to AD; current NVS constructs may be too broad (including constructs with little overlap, e.g., threat vs. loss) for genetic analyses
Hamm, 2016			x	x				x	x		x	x	x			Disorder: AD (PD/AG). Elements: BAT; heart rate, skin conductance, startle blink, MAOA-uVNTR, 5-HTR1A. Construct: threat processing	Panic attacks (strike defense): fear reaction to acute threat with desire to actively avoid or flee when internal threat stimuli are impending, related to genetic modulators within serotonergic system; anxious apprehension (postencounter defense): related to general distress and depressive mood, as to genetic modulations within HPA axis
Silveira, 2015 [systematic review]		x								x				x		Objective: systematic review of rumination in BD; inclusion criteria: studies involving at least one validated scale for the assessment of rumination (reviews were excluded)	Rumination is present in all BD phases; associated with symptoms of depression, anxiety, hypomania; no research on neurobiological findings; independent of mood state; negative impact on cognitive and executive functions (inhibitory control); rumination in response to both PA and NA possible; lack of neurobiological research

RDoC terms: NA = Negative affect; NVS = Negative Valence Systems; PA = Positive affect; RDOC = Research Domain Criteria. **Disorder:** AD = Anxiety Disorder; BD = Bipolar Disorder; GAD = General Anxiety Disorder; MDD = Major Depression Disorder; PD = Panic Disorder; PD/AG = Panic Disorder with Agoraphobia; SAD = Social Anxiety Disorder; SPD = Specific Phobic Disorder. **Genetic:** COMT = Catechol-O-Methyltransferase; DAT-1 = Dopamine Active Transporter-1; 5-HTRs = 5-Hydroxytryptamine Receptors; 5-HTR1A = 5-Hydroxytryptamine Receptor

1A; MAOA = Monoamine Oxidase; MAOA-uVNTR = Monoamine Oxidase A – Upstream Variable Number of Tandem Repeats. **Molecules**: CRH = Corticotropin-releasing hormone GCR = Glucocorticoid receptor. **Circuit**: BNST = Bed Nucleus of the Stria Terminalis; DMN = Default Mode Network; OFC = Orbitofrontal Cortex; PPC = Posterior Cingulate Cortex; dlPFC = dorsolateral Prefrontal Cortex; vmPFC = ventromedial Prefrontal Cortex; PVN = Paraventricular Nucleus. **Physiology**: ANS = Autonomic Nervous System; ASM = Affective Startle Modulation; EMG = Electromyography; ERN = Error-related Negativity; ERP = Event-related Potential; HPA axis = Hypothalamic–Pituitary–Adrenal axis. **Behavior**: BAT = Behavioral Avoidance Task; RT = Reaction Time.

[a] We added specific disorder codes if this provides additional information.

Table 7 Cross-domain primary articles.

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis							PVS				NVS						Elements/paradigms [a]	Key findings
				Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	Domain level	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward		
Medeiros, 2020	x				x					x		x	x	x		x	x	x	x	x	Elements: immunomarkers (CRP, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α), IDS-C30 and QIDS-C16, HAM-D, CAST, WSAS, CPFQ, PDSQ, self-administered comorbidity questionnaire (medical comorbidities)	PV and NV symptom scores in a MDD-sample were linked to different clinical characteristics: (1) PV symptom scores (impaired motivation etc.) positively correlated with female gender, older age, higher impairment, the level of three pro- and one anti-inflammatory immuno-markers; (2) NV symptom scores (anxiety and interpersonal sensitivity) correlated with younger age, anxious comorbidities, symptom load and negatively associated with only one proinflammatory immuno-marker; antidepressants were more effective on PV symptoms than NV symptoms
Peng, 2021	x		x				x	x	x	x	x				x						Elements: MID (reward (e.g., ventral striatum, insula, NAcc), and caudate head) and loss processing (e.g., anterior insula)); fear conditioning fMRI task (vmPFC, dmPFC, sgACC, dACC, left/right anterior insula, ventral hippocampus, and amygdala); HR/SCR while rating emotional pictures and while performing MTPT; OASIS; PHQ-9; PANAS; GAD-7; MASQ; BIS/BAS; SPSRQ; TEPS; AcSEAS. Domain level: PVS functioning, NVS functioning	Group FA could not identify any latent variables that could explain variance across tasks; instead, variance was best explained by individual variables within each task (Post hoc analyses: (1) small effect sizes between latent variables from fMRI and self-report data and (2) some latent variables not directly related to individual PVS/NVS constructs) → lack of cross-modal latent structure suggests challenges in the RDoC approach and highlights the need for more targeted approaches

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis							PVS				NVS						Elements/paradigms [a]	Key findings
				Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	Domain level	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward		
Paulus, 2017	x		x						x	x	x	x	x	x	x							Elements: AAT, MPDT; PANAS, MASQ, TEPS, BIS/BAS, SPSRQ, PID-5, AsSEAS, WHODAS, GAD-7, latent variable analysis (PCA) underlying PVS and NVS processing in terms of symptoms and behavioral units of analysis	PCA resulted in two "meta-components": NVS processing (NV symptoms, negative approach bias, high sustained and selective attention), PVS processing (PV symptoms, positive approach bias, slow selective or sustained attention)
Wenzel, 2022	x		x							x				x			x					Disorder: perinatal MDD, perinatal AD. Elements: BIS/BAS (BIS → potential threat; BAS drive → reward valuation), IUS (potential threat), PHQ-9, GAD-7	Higher trait BIS+IUS (time stable potential threat), higher state BIS (time variant potential threat) and lower state BAS drive (reward valuation) were associated with higher depressive symptom burden. Higher trait BIS+IUS and higher state BIS was associated with higher anxiety symptom burden. Potential threat may be a transdiagnostic feature of perinatal anxiety and depression, reward valuation may be non-transdiagnostic, weaker feature of perinatal depression. Potential threat showed relevance as both a "trait-like" feature (sustained across perinatal period) and a "state-like" feature (within-variability across pregnancy)
Förstner, 2022	x	x	x						x	x	x	x	x		x		x					Elements: TMT A/B, DSST; BSI-53, PANAS, WHO-DAS20	A CFA four-factor latent structure (PVS, NVS, CS, SP) was validated indicating a transnosological latent structure for these domains. It was shown that well established assessments can be used to measure RDoC constructs

RDoC terms: CS = Cognitive Systems; NV = Negative valence; NVS = Negative Valence Systems; PVS = Positive Valence Systems; RDoC = Research Domain Criteria; SP = Social Processes. **Disorder:** AD = Anxiety Disorder; BD = Bipolar Disorder; MDD = Major Depression Disorder; SUD = Substance Use Disorder. **Molecules**: CRP = C-reactive Protein; IFN-γ = Interferon-γ Necrosis Factor; TNF-α = Tumor Necrosis Factor-α; IL = Interleukin. **Circuit**: dACC = dorsal Anterior Cingulate Cortex; pgACC = pregenual Anterior Cingulate Cortex; NAcc = Nucleus Accumbens; dmPFC = dorsomedial Prefrontal Cortex; vmPFC = ventromedial Prefrontal Cortex. **Physiology**: fMRI = functional Magnet Resonance Imaging; HR = Heart Rate; SCR = Skin

Conductance Response. **Behavior**: AAT = Approach Avoidance Task; DSST = Digit Symbol Substitution Test; MPDT = Modified Probe Detection Task; MTPT = Mirror Tracing Persistence Task; TMT-A/B = Trail Making Test-Version A/B. **Self-Report/interview**: AsSEAS = Acceptance, Safety, Escape/Avoidance Scale; BIS/BAS = Behavioral Inhibition and Behavioral Activation Scales; BFNE-S = Brief Fear of Negative Evaluation Scale - Straightforward Items; BSI-53 = Brief Symptom Checklist; CAST = Concise Associated Symptoms Tracking; CPFQ = Cognitive and Physical Functioning Questionnaire; GAD-7 = General Anxiety Disorder; HAM-D = Hamilton Rating Scale for Depression; IDS-C30 = Depressive Symptomatology-Clinician Version; IUS = Intolerance of Uncertainty Scale; MASQ = Mood and Anxiety symptom Questionnaire; MINI = Mini International Neuropsychiatric Interview; OASIS = Overall Anxiety Severity and Impairment Scale; PANAS = Positive and Negative Affect Schedule; PDSQ = Psychiatric Diagnostic Screening Questionnaire; PHQ-9 = Patient Health Questionnaire-9; PID-5 = Personality Inventory for DSM-5-Adult; QIDS-C = Quick Inventory of Depression Symptomatology - Clinician rated; RTQ = Repetitive Thinking Questionnaire; Shipley = Shipley Institute of Living Scale - Vocabulary Test; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; TEPS = Temporal Experience of Pleasure Scale; WHODAS = World Health Organization Disability Assessment Schedule; WSAS = Work and Social Adjustment Scale. **Paradigms**: MID = Monetary Incentive Delay; MTPT = Mirror Tracing Persistence Task. **Methods**: CFA = Confirmatory Factor Analysis; FA = Factor Analysis; PCA = Principal Component Analysis.

[a] We added specific disorder codes if this provides additional information.

Table 8 Cross-domain reviews.

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Units of Analysis: Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	PVS: Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	NVS: Domain level	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Main aim of review [a]	Key findings
Terbeck, 2015	x		x		x						x				x						Elements: mGluR5 (metabotropic glutamate receptor 5). Aim: review of mGluR5 within RDoC (PVS, NVS, SP, ARS)	Evidence for abnormal glutamate activity related to NVS and PVS: antagonistic mGluR5 intervention may have prominent anti-addictive, anti-depressive and anxiolytic effects; initial human clinical PET research: predisposition for psychiatric problems due to abnormal metabotropic glutamate activity
Langenecker, 2014	x	x					x	x	x			x	x	x					x		Elements: PV circuitry (reward), NV circuitry (rumination). Aim: understanding the neurobiology of mood disorders	HC displayed preferential processing of positive stimuli (PV circuit), which resulted in a greater available range of approach behaviors and magnified regulatory capacities for appraisal, reappraisal, and the appropriate selection of alternative responses; MDD and BD: decreased preferential strengths of PV circuit and regulatory capacity, NV circuit and corresponding avoidance behaviors are more pronounced, PVS is over-/under-utilized in BD/MDD
Janiri, 2020 [meta-analysis]	x	x	x				x	x				x	x	x		x	x			x	Elements: task-related fMRI. Aim: neural phenotypes for highly comorbid mood and anxiety disorders; is their clinical overlap reflected at neurobiological level? Detection of transdiagnostic abnormalities in task-related brain activation	Dominant abnormality in mood, anxiety disorders, and PTSD: disruption in salience processing and inhibitory control; three transdiagnostic clusters of hypoactivation (inferior PFC/insula, inferior parietal lobule, putamen) → diagnostic differences only in putamen; three transdiagnostic clusters of hyperactivation (pgACC/dACC, left amygdala/PHC, left thalamus) → no

First author, year	Depressive Disorders	Bipolar Disorders	Anxiety Disorders	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-report	Domain level	Reward Responsiveness	Reward Learning	Reward Valuation	Domain level	Acute Threat (fear)	Potential Threat (anxiety)	Sustained Threat	Loss	Frustrative Nonreward	Main aim of review [a]	Key findings
																						diagnostic differences → RDoC domains/ constructs did not contribute differently to any clusters
McTeague, 2020 [meta-analysis]	x	x	x				x				x									x	Elements: fMRI, PET, SPECT during emotional processing (230 reactivity, 56 emotional/ cognitive, 18 regulation). Aim: a transdiagnostic quantitative meta-analysis of published neuroimaging data to investigate functional disruptions in the neural circuitry responsible for emotional processing across various tasks and psychiatric disorders	(1) Aberrant activation by disorder groupings: aberrant activation in the left amygdala and hippocampus in AD; BD associated with convergence in right amygdala and right vlPFC; MDD revealed no convergent patterns; (2) Hyper-vs. hypoactivation by disorder groupings: AD and MDD displayed overlapping hyperactivation in the left amygdala and the hippocampus; (3) Neurocircuit disruption across major psychiatric disorders in key regions of adaptive emotional reactivity/regulation → these corresponded to "salience" network, ventral striatal/ventromedial prefrontal (reward) network and lateral orbitofrontal (nonreward) network

RDoC terms: ARS = Arousal and Regulatory Systems; NV = Negative valence; NVS = Negative Valence Systems; PV = Positive valence; PVS = Positive Valence Systems; RDoC = Research Domain Criteria; SP = Social Processes. **Disorder:** AD = Anxiety Disorder; BD = Bipolar Disorder; MDD = Major Depression Disorder; PTSD = Post-Traumatic Stress Disorder. **Molecules**: mGluR5 = Metabotropic Glutamate Receptor 5. **Circuit**: dACC = dorsal anterior cingulate cortex; pgACC = pregenual Anterior Cingulate Cortex; PFC = Prefrontal Cortex; vlPFC = ventrolateral Prefrontal Cortex; PHC = Parahippocampal Cortex. **Physiology**: fMRI = functional Magnet Resonance Imaging; PET = Positron Emission Tomography; SPECT = Single Photon Emission Computed Tomography. **Methods**: HC = Healthy Controls.

[a] We added specific disorder codes if this provides additional information.

11 Figure

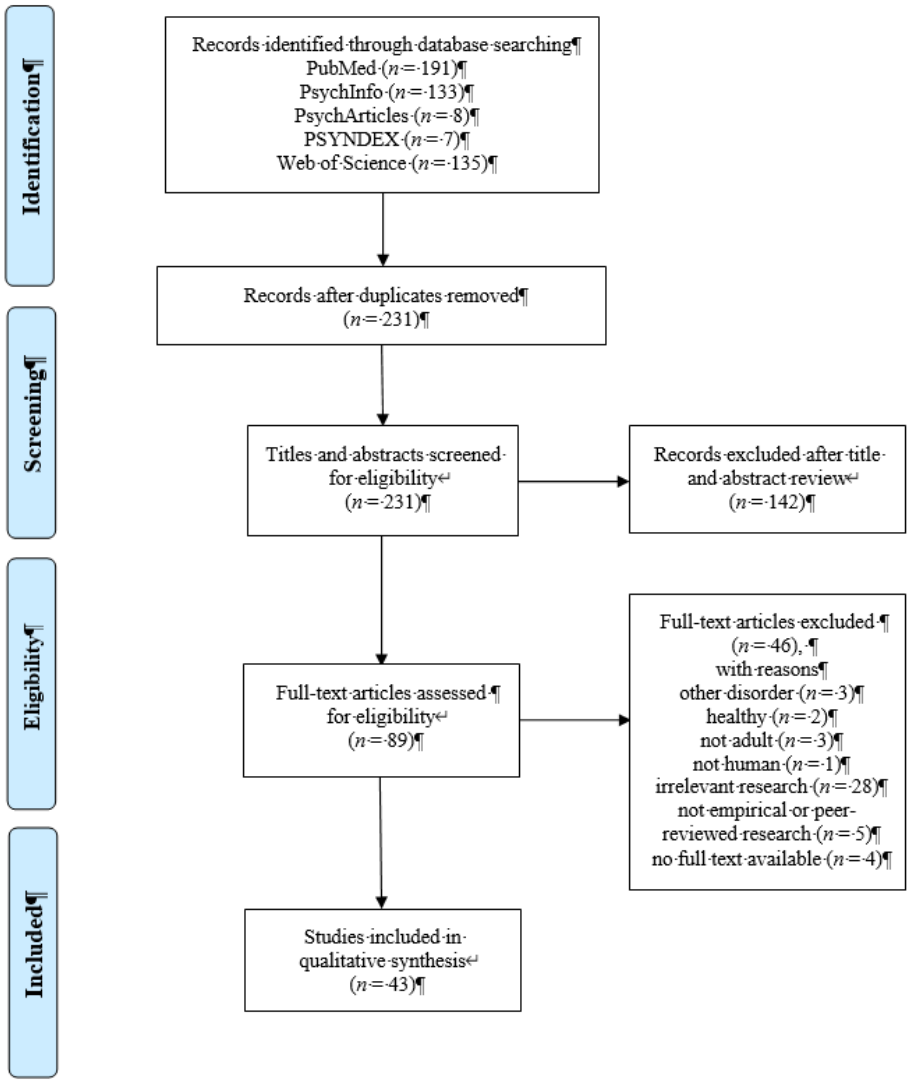

Figure 1 PRISMA flow diagram.

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Supplementary Material A

Mood and Anxiety Disorders within the Research Domain Criteria framework of Positive and Negative Valence Systems: a scoping review

Sarah Jane Böttger*, Bernd R. Förstner, Laura Szalek, Kristin Koller-Schlaud, M. D., Michael A. Rapp, M. D., Ph. D., Mira Tschorn, M. D.

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1 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their	5

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	-
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	5
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	5
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	5-9
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	5-9
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	9
Limitations	20	Discuss the limitations of the scoping review process.	10
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	11
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	12

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplementary Material B

Mood and Anxiety Disorders within the Research Domain Criteria framework of Positive and Negative Valence Systems: a scoping review

Sarah Jane Böttger*, Bernd R. Förstner, Laura Szalek, Kristin Koller-Schlaud, M. D., Michael A. Rapp, M. D., Ph. D., Mira Tschorn, M. D.

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1 Scoping review protocol

Scoping Review Details	
Scoping Review Title:	Mood and Anxiety Disorders within the Research Domain Criteria framework of Positive and Negative Valence Systems: a scoping review
Scoping Review Objectives:	Scoping literature review of mood and anxiety disorders in relation to positive and negative valence
Scoping Review Questions:	What is the state of published research investigating the role of PVS and NVS in MAD using the RDoC framework?
Inclusion/Exclusion Criteria	
Population:	Individuals with symptoms of mood (depression, bipolar) or anxiety (anxiety, phobia) disorders; adults (18 years and older)
Concept:	Outcome measures of positive valence or positive affect, and negative valence or negative affect, with reference to RDoC; all units of analysis (genes, molecules, cells, circuits, physiology, behavior, self-report)
Context:	Open
Type of evidence source:	Empirical research; peer-reviewed publications
Covidence®: Title and abstract screening	
Keywords for inclusion [a]:	depression, bipolar, anxiety, phobia, phobic, panic, human, adults, positive valence, negative valence, positive valence systems, negative valence systems, RDoC, research domain criteria, threat, fear, loss, nonreward, anhedonia, trauma, guilt, crying, rumination, sadness, withdrawal, shame, worry, morbid thoughts, aggression, reward, habit, drive, self-report, schedule, questionnaire, interview, scale, molecule, cell, circuit, physiology
Keywords for exclusion:	animal, rats, mice, rodents, children, infants, youth, pediatric schizophrenia, borderline, PTSD, OCD, autism

Study tags for inclusion:	RDoC, genetic measures, molecule measures, neuronal measures (circuit measures), behavior measures, self-report measures, paradigms, positive valence, negative valence, depression, bipolar, anxiety, phobia
Covidence®: Full-text screening	
Exclusion reasons:	wrong population (other disorder), wrong population (healthy participants), wrong population (age), wrong population (animal studies), wrong domain(s) assessed (irrelevant research), irrelevant to research objectives (irrelevant research), no empirical research, research not found (no full text available)
Data charting process	
Evidence source details and characteristics:	Author/s, publication year, country, language, research design, disorder, aim, (outcome) measures, RDoC domain and (sub-)constructs, findings relevant to the research objectives
Details extracted from source of evidence:	Disorder, domain, constructs, subconstructs, units of analysis, elements, findings

The Scoping review protocol was developed using the Joanna Briggs Institute recommendations (Peters et al., 2020). NVS = Negative Valence Systems; PVS = Positive Valence Systems; RDoC = Research Domain Criteria; OCD = Obsessive-compulsive disorder; PTSD = Post-Traumatic Stress Disorder.

[a] A selection of keywords of the Positive Valence Systems and Negative Valence Systems domains, constructs, subconstructs and elements of different units of analysis were handpicked in accordance to the RDoC matrix (NIMH, 2023).

2 REFERENCES

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Supplementary Material C

Mood and Anxiety Disorders within the Research Domain Criteria framework of Positive and Negative Valence Systems: a scoping review

Sarah Jane Böttger*, Bernd R. Förstner, Laura Szalek, Kristin Koller-Schlaud, M. D., Michael A. Rapp, M. D., Ph. D., Mira Tschorn, M. D.

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1 Search Strategy

A detailed search strategy for all sources searched is presented in the following tables 1-3.

Table 1: Search Strategy used (via EBSCOhost) in PsychInfo, PsychArticles and PSYNDEX

Search component	Search terms	Search results on April 26, 2021 (*N*)			Search results on January 21, 2023 (*N* (additional *n*))		
		PsychInfo	PsychArticles	PSYNDEX	PsychInfo	PsychArticles	PSYNDEX
Search 1							
S1	AB ("depression" or "depressive disorder*" or "depressive symptom*" or "major depressive disorder") OR AB "affective disorder*" OR AB "mood disorder*" OR AB ("bipolar disorder*" or "bipolar" i or "bipolar ii" or "manic depression" or "bipolar affective disorder*" or "bipolar depression") OR AB ("mania" or "manic" or "manic episode") OR AB ("anxiety disorder*" or "anxiety") OR AB ("phobia" or "phobic disorder*") OR AB ("panic disorder*")	428,433	16,065	21,023	466,901	17,461	23,517
S2	AB "rdoc" OR AB "research domain criteria"	695	40	32	829	53	51
S3	AB "positive valence" OR AB "negative valence"	1,528	126	173	1,736	148	210
S4	S1 AND S2 AND S3	49	2	2	59 (10)	3 (1)	3 (1)
Search 2							
S5	AB "valence" OR AB "affect*" OR AB "emotion*"	734,770	34,792	42,982	806,829	37,630	48,052
S6	S1 AND S2 AND S5	111	7	4	133 (22)	8 (1)	7 (3)
Conjunction of Search 1 and 2							
S7	S4 OR S6	111	7	4	133 (22)	8 (1)	7 (3)

The search was conducted on April 26, 2021 and updated on January 21, 2023. AB = Abstract; rdoc = Research Domain Criteria.

Table 2: Search Strategy used in PubMed

Search component	Search terms	Search results on April 26, 2021 (*N*)	Search results on January 21, 2023 (*N* (additional *n*))
Search 1			
#1	("depression"[Title/Abstract]) OR ("depressive disorder*"[Title/Abstract]) OR ("affective disorder*"[Title/Abstract]) OR ("mood disorder*"[Title/Abstract]) OR ("bipolar"[Title/Abstract]) OR ("bipolar disorder*"[Title/Abstract]) OR ("maniac"[Title/Abstract]) OR ("manic"[Title/Abstract]) OR ("anxiety"[Title/Abstract]) OR ("anxiety disorder*"[Title/Abstract]) OR ("phobia*"[Title/Abstract]) OR ("phobic disorder*"[Title/Abstract]) OR ("panic disorder*"[Title/Abstract])	558,992	635,001
#2	("rdoc"[Title/Abstract]) OR ("research domain criteria"[Title/Abstract])	855	1,061
#3	("positive valence"[Title/Abstract]) OR ("negative valence"[Title/Abstract])	1,238	1,538
#4	#1 AND #2 AND #3	64	86 (22)
Search 2			
#5	("valence"[Title/Abstract]) OR ("affect*"[Title/Abstract]) OR ("emotion*"[Title/Abstract])	2,150,390	2,451,343
#6	#1 AND #2 AND #5	147	191 (44)
Conjunction of Search 1 and 2			
#7	#4 OR #6	147	191 (44)

The search was conducted on April 26, 2021 and updated on January 21, 2023. AB = Abstract; rdoc = Research Domain Criteria.

Table 3: Search Strategy used in Web of Science

Search component	Search terms	Search results on April 26, 2021 (*N*)	Search results on January 21, 2023 (*N* (additional *n*))
Search 1			
#1	(AB="depression") OR (AB="depressive disorder*") OR (AB="bipolar") OR (AB="affective disorder*") OR (AB="mood disorder*") OR (AB="anxiety") OR (AB="phobia") OR (AB="phobic disorder*") OR (AB="panic disorder*")	505,695	585,665
#2	(AB="rdoc") OR (AB="research domain criteria")	649	808
#3	(AB="positive valence") OR (AB="negative valence")	1,577	1,951
#4	#1 AND #2 AND #3	50	68 (18)
Search 2			
#5	(AB="valence") OR (AB="affect*") OR (AB="emotion*")	2,929,932	3,399,188
#6	#1 AND #2 AND #5	105	135 (30)
Conjunction of Search 1 and 2			
#7	#4 OR #6	105	135 (30)

The search was conducted on April 26, 2021 and updated on January 21, 2023. AB = Abstract; rdoc = Research Domain Criteria.

Supplementary Material D

Mood and Anxiety Disorders within the Research Domain Criteria framework of Positive and Negative Valence Systems: a scoping review

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