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Research paper

The psychopathology of mood disorders: implications for identifying neurocognitive intervention targets☆

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ABSTRACT

Background: Neurofeedback and neuromodulation treatments are of increasing clinical interest, but their neurocognitive targets are poorly understood.
Methods: In this review, we will use Jaspers' phenomenological psychopathology combined with modern network analysis to identify neurocognitive treatment targets by focussing on distinctive and necessary symptoms of mood disorders as well as their subsyndromal and prognostic variations.
Results: We discuss the early descriptions of Kraepelin's mixed affective states and suggest a model of four mood states (depressed, anxious, irritable, and elated) and their dynamic evolution and mixing. Blame and praise internalisation and externalisation biases are proposed as key mechanisms underpinning mood states, together with approach/withdrawal-related action tendencies. Whilst self-worth and interest emerge as the most distinctive symptom dimensions, that are necessary for bipolar and recurrent unipolar depressive disorders, we also discuss anxiety as a potential primary symptom in a subgroup of chronic depression. Based on a neuroanatomical model of the conceptual self, anterior temporal and subgenual networks and their importance for self-blame and worthlessness, as well as the hypothesised role of septo-hypothalamic networks for affiliative interest are discussed. The latter is distinguished from ventral striatal networks as relevant for more general approach-related action tendencies and hedonic interest (anticipatory anhedonia). Finally, recent target validation from early-stage fMRI neurofeedback trials are reviewed.
Limitations: It was not feasible to employ a systematic review approach.
Conclusions: Neurofeedback studies are not only of interest as new treatments, but also for enhancing our pathophysiological understanding and could gain clinical impact with ongoing advances in scalable neurotechnologies.

1. Introduction

Neurocognitive interventions for mood disorders, such as functional MRI neurofeedback, are still in their infancy, but have the potential to enhance our pathophysiological understanding as well as broaden our treatment modalities. Here, we will argue that the identification of neurocognitive treatment targets needs to be informed by psychopathology. The term "neurocognitive" will be used to denote neuroanatomical structures and circuits that are strongly associated with a particular psychological function when considering both functional neuroimaging, as well as patient lesion evidence. These cognitive-anatomical components are employed in translational cognitive neuroscience models of more complex functions, which can in turn be related to specific combinations of symptoms (Zahn, 2009). We will use the term "mood states" as reflecting internal propensities to emotionally respond to external and internal stimuli in a way which is determined by the mood state rather than the emotional value of the stimulus only (Zahn, 2024). Thereby, mood states act as filters, explaining their priming effect on mood-congruent emotions and memories (Bower, 1981), also described computationally as a "hyper-prior" (Clark et al., 2018). We will describe the phenomenology of mood states, as well as the cognitive neuroscience of distinctive and necessary symptoms. The last section will review validation studies of neurocognitive targets for depression from available early phase randomised controlled fMRI

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neurofeedback trials (RCTs).

1.1. The phenomenological framework and neurocognitive targets

In 1913, Jaspers, a philosopher and psychiatrist, introduced the philosophical method of phenomenology to clinical psychiatry and his descriptions of subjective experiences as sources of detecting symptoms remain the most systematic and comprehensive ones (Jaspers, 1997). Jaspers was critical of operational diagnostic categories, as now used in the diagnostic statistical manual (DSM) or International Classification of Diseases (ICD) for mental disorders. As these were not intended to be directly defined by their aetiology (i.e. underlying causes, (Kendler and First, 2010)), relating the phenomenology of symptoms with aetiological entities cannot rely solely on operational categories (e.g. "Major Depressive Disorder").

One could therefore argue that diagnostic categories in psychiatry are of limited pathophysiological relevance. To support the replacement of diagnostic categories, however, one would need to provide evidence for an alternative and better way of supporting clinical decisions regarding thresholds for accessing care, prognosis, and treatment selection, which ultimately determine the clinical validity of any pathophysiological model. So far, this has not been demonstrated to our knowledge. For example, although anxiety, unipolar and bipolar depressive disorders share a large degree of symptoms and risk factors, their distinction is nevertheless clinically important for treatment selection (e.g. first-line psychological treatment for anxiety disorders without more severe depression versus additional pharmacological treatment in more severe major depressive disorder (NICE, 2022), as well as increased risk of harm with antidepressant monotherapies in bipolar I disorder (Jelen and Young, 2020) and to make gross prognostic predictions (e.g. higher risk of recurrence in bipolar versus unipolar depression overall, (Burcusa and Iacono, 2007)). Therefore, rather than replacing diagnostic categories, we will identify pathophysiologically relevant symptom combinations (subsyndromes), which could in the future be used for refining classification systems.

Symptoms will be operationally defined as abnormal subjective experiences or objective behaviours which cause suffering or impairment cross-culturally. All our diagnostic categories are based on symptom-complexes (i.e. syndromes), but also contain aetiological constraints, such as temporal association of symptoms with known sufficient organic causes ((APA), 2000). As Jaspers summarised in his chapter on symptom-complexes ((Jaspers, 1963/1959), pp. 582) there are different aspects of the relation of symptoms within a symptom-complex: 1) frequency of symptom co-occurrence, 2) coherence of symptoms by being related to a common aspect or function, and 3) primary symptoms caused by the aetio-pathogenetic process and secondary symptoms emerging from these in an understandable way.

The second aspect, that of symptom coherence, has been emphasized by Carl Schneider (as cited by Jaspers) stating about symptoms: *"Their connectedness must be due to a normal complex of psychic function, which complex has been affected by the illness"*. It is worth revisiting this aspect of symptoms again (Zahn, 2009), now that we have a more advanced knowledge of which underlying functions to examine. To enable this, however, one needs to start by isolating symptom-complexes which are likely to be associated with pathogenetically relevant functions. This endeavour can be supported by learning from the trials and errors of understanding neuropsychological syndromes, such as aphasia, one of the first to be related to focal brain dysfunction by cognitive neurologists and psychiatrists, such as Lichtheim and Wernicke in the late 19th century (reviewed in (Zahn et al., 2006)).

Aphasic syndromes may be conceived of as a combination of primary deficit (negative) and secondary compensation (positive) symptoms (Hughlings-Jackson, 1879), or as a primary deficit, causing another deficit as a secondary symptom. This distinction is important in that compensation symptoms should not be intervention targets. For example, if irritability was a compensation symptom to counter low self-esteem in irritable forms of depression, it would not be a suitable treatment target. The use of aphasic syndromes to study lesion-deficit associations in aphasia has been questioned and instead single symptoms were suggested to correlate better with localised lesions (Dronkers and Ludy, 1998). Whilst this argument may have proved helpful for syndromes primarily defined as a combination of deficit symptoms (e.g. "global aphasia"), those syndromes that are defined as a combination of intact (e.g. repetition) and impaired (e.g. comprehension) abilities, will be more homogenous with regard to underlying impairments (Zahn et al., 2002), because these syndromes describe what cognitive neuropsychologists nowadays call a dissociation of impaired and intact performance between two tasks (Shallice, 1990). Such dissociations were used as evidence for the existence of different cognitive components required for the performance of two tasks that can be affected independently from each other by a lesion.

Thus, symptom-complexes made up of symptoms related to impaired as well as intact functions are more likely candidates for unequivocal relationships with a cognitive component than are single symptoms. This is because single deficit symptoms could have been caused by impairments of multiple cognitive component functions. From the above considerations it follows that a prerequisite for neurocognitive models of symptoms is understanding the functional coherence of symptom co-occurrences or dissociations of symptoms. The next section will examine these for depressive and hypomanic syndromes.

2. Phenomenology and temporal evolution of affective symptoms

2.1. Transculturally stable symptoms of depression and the influence of "endogeneity"

The largest and most systematic transcultural comparison of frequencies of different symptoms, using gold standard semi-structured interviews in patients with clinical diagnoses of depressive disorders has been conducted in the World Health Organisation (WHO) Collaborative study (Sartorius et al., 1980; Sartorius, 1986; Thornicroft & Sartorius, 1993). Symptoms with differences in frequencies between countries in this and other studies were guilt feelings, somatic symptoms and suicidal ideas, but it is unclear whether these reflected cultural variations or different severity levels (Tseng, 2001),pp. 339). The authors of the WHO Collaborative study concluded (Sartorius et al., 1980) on a common core of depressive symptoms in all centres regardless of diagnostic subtypes (Sartorius et al., 1980): "sadness, joylessness, anxiety and tension, lack of energy, loss of interests, experience of loss of the ability to concentrate, and ideas of insufficiency, inadequacy and worthlessness."

"Endogenous" (i.e. more biological) and "psychogenic" (i.e. more psychosocial) forms of depression were distinguished prior to DSM-IV. "Endogenous" depression showed a higher frequency of the following symptoms: "worse in the morning, early awakening, slowness or retardation of thought, psychomotor retardation". The 10-year follow-up study (Thornicroft & Sartorius, 1993) reported marked differences in the course of illness between these groups. The best outcome (one or two reasonably short episodes of depression with complete remission between episodes) was twice as frequent in the "endogenous" group.

This classical question of subdividing depressive disorders and their symptom profiles into those linked more strongly to biological versus psychosocial causes has been investigated in a large Han Chinese sample ($n = 5784$) using an extensive interview to characterise their past major depressive episode, polygenic risk scores, family and trauma history (van Loo et al., 2018). Using modern network analysis methods, there was no evidence of differences in symptom network structure between those with higher and lower genetic and environmental risk, which supports the abandonment of such distinctions in DSM-IV/5 and ICD-10/11. The strength of the study was to include separate items for low self-confidence, self-esteem and the DSM worthlessness/guilt item (see

below) which were associated with hopelessness. Bipolar items were coded separately which was another strength, resulting in a negative partial correlation between hyper- and insomnia, for example. Nervousness/Anxiety was associated with psychomotor agitation and irritability, whereas decreased libido and a loss of interest as well as loss of the ability to enjoy things were associated.

Thus, whilst biological or psychosocial risk factors for depression were not necessarily reflected in characteristic symptoms, the observation that fully remitting and recurring courses of depression were more common in patients with psychomotor retardation and circadian rhythm-related symptoms (Thornicroft & Sartorius, 1993) is valuable to inform our subsequent neurocognitive understanding.

2.2. Transculturally stable symptoms of (hypo)mania

As noted in (Zahn, 2024), there is much less formal evidence from transcultural comparisons of hypomanic and manic symptoms, possibly, because there is less debate about cultural variability and because it is harder to recruit and study patients with mania. A well powered international study of symptom criteria, which controlled for transcultural variations, corroborated the widely assumed transcultural stability of key symptoms used in the DSM with >80 % consistency: elevated mood, increased activity and goal-directed activities, increased self-esteem, decreased sleep and being more talkative (Angst et al., 2011).

2.3. Temporal evolution of affective symptoms

Kraepelin's description of the temporal evolution of manic and depressive symptoms over the course of years of observations in his patients are still widely considered to be the most lucid account of how to explain mixed affective states where some symptoms of depression flexibly recombine with some manic symptoms. These observations of mixed affective states (see Fig. 1) may have contributed to Kraepelin's conceptualisation of what we would now call unipolar depression as part of the same manic-depressive illness spectrum. Modern evidence supports the notion that the boundaries between unipolar and bipolar mood disorders are indeed more fluid than their separation in diagnostic categories and care pathways might suggest, particularly for recurrent major depressive disorder (Angst et al., 2011; Cassano et al., 2004).

From the observations of temporally dissociable affective symptoms, important lessons can be learned for psychological and cognitive neuroscience models of affective disorders. Such temporal dissociations of some symptoms point to their composition of at least partly distinctive neurocognitive components whose prominence can independently increase and decrease over time. Kraepelin postulated three symptom dimensions: mood (empty/depressed, irritable, elated), diminished and increased will/drive & motor activity/restlessness and accelerated and inhibited thought (i.e. mental activity). Whilst there is no reason to dispute the validity of these dimensions, it is obvious that the number of such dimensions needs empirical study using modern statistical methods.

One promising method is network analysis (Robinaugh et al., 2020) which can also be used to investigate the temporal dynamics of symptom networks (Epskamp et al., 2018). The only drawback of these modern approaches (Malgaroli et al., 2021) is their common reliance on opportunistically obtained data using self-report scales which were mostly not designed for assessing individual symptoms and rather reflect DSM diagnostic criteria, such as the Patient Health Questionnaire-9 (First et al., 2002) and this systematically biases the literature against some symptoms. For example, low self-esteem/feelings of inadequacy are considered in conjunction with self-blame and only considered relevant when people report feeling worthless in DSM, but many patients with bothering levels of low self-esteem will still feel worthy with regard to one aspect of themselves and will not endorse feeling worthless in general according to our experience with using our semi-structured interview (Zahn et al., 2015). Likewise, the Inventory of Depressive Symptomatology-30 used in the unique STAR-D and Netherlands Study of Depression and Anxiety (NESDA) studies (van Borkulo et al., 2015) uses one item, called "view of myself" which mixes self-blame and feelings of inadequacy as anchors for different severity levels, thereby precluding network-analyses (Fried et al., 2016) from examining self-blaming feelings separately from feelings of inadequacy. Other studies relied on observer-rated depression scale items (Komulainen et al., 2021), such as the Hamilton depression scale (Hamilton, 1960) which was also not designed for individual symptom assessment and lacks an item assessing feelings of inadequacy/worthlessness for example, but

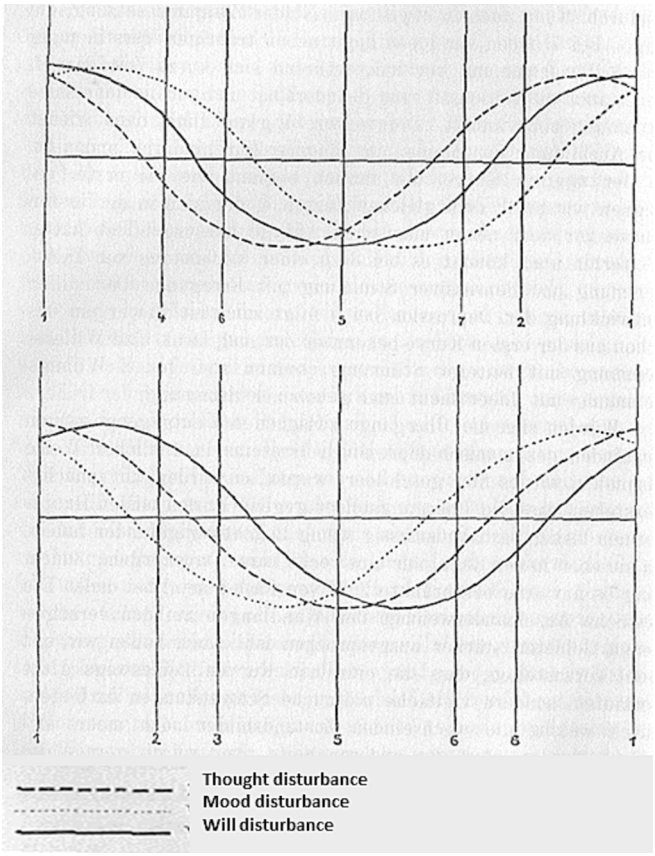

Fig. 1. Kraepelin's concept of mood symptom dynamics.
Kraepelin's Fig. XXIV describes the composition of mixed states in manic-depressive illness (Kraepelin, 1904) and has previously been described in (Zahn, 2024). He conceptualised disturbances of mood, thought and will as independent. He described mood as empty (="verödet"), thought as inhibited and an inability to decide as an expression of depressive will disturbance. Numbers 1 to 7 describe the composition of different mixed states: 1. Mania with flight of ideas, elated mood and urge to be active, 2. Angry/irritable mania is when the elated mood switches into being irritable and sensitive, whilst still having an increased self-esteem, this is accompanied by a mild flight of ideas and restlessness and increased activity, also including excessive smoking or drinking. 3. Depressive agitation is a state when there is a marked impoverishment of thoughts and sad mood, combined with restlessness. 4. A state of an unproductive mania with impoverished thinking. In this state patients feel elated in mood. 5. Depression with an inhibition of thought, sad mood and an inability to make decisions. 6. Manic stupor: patients do not respond, if they speak, they only speak with a low voice to themselves, smile without reason, and are usually calm. They often develop a pressure to talk and a flight of ideas. 7. Within the usual picture of depression, inhibition of thought can be replaced by a flight of ideas. 8. Is not depicted, but Kraepelin notes also an observation of combined symptoms of a flight of ideas together with elated mood and psychomotor inhibition. Sometimes he observed irritability, distractibility, jocularity, flight of ideas and pressure to talk, as well as an increased number of sound associations. At the same time he observed an absence of motor restlessness.

assesses somatic symptoms in more depth than other scales.

One dynamic network study, however, used Beck Depression Inventory-II data (Beck, 1996), which contains items specifically probing different aspects of self-worth and -blame in addition to DSM-relevant symptoms. Patients self-reported their symptoms prior to each therapy session from an RCT comparing Interpersonal and Cognitive therapy for current MDD (Bringmann et al., 2015). Using all the items of the questionnaire from the previous session as predictors of subsequent sessions, whilst controlling for multiple comparisons, they were able to identify directed connections, i.e. a symptom predicting subsequent presence of the same or another symptom.

A further analysis of the so-called "community structure", which considers how densely symptoms are connected with each other relative to others, revealed a two-cluster structure. The analysis of how central each symptom was in terms of network structure, i.e. how many connections it had (betweenness centrality), revealed two symptoms as most connected with others: "Loss of pleasure" and "Past failure". The symptom label "past failure" is somewhat misleading in that the anchors for the scale prompt people to think about the level of generalisation of thinking of themselves like a failure including the past, present and future. Thus, the community structure and centrality analyses both converged on at least two relevant subsyndromes which are key to understanding the dynamics of major depressive disorder: 1) loss of interest and pleasure, as well as energy and somatic symptoms among others, and 2) feelings of inadequacy related to self-criticism.

One limitation of the trial was that it used a wait list control group and this is likely to have biased the study against including more severe and acute forms of depression. Nevertheless, the study's findings of a subsyndromal separation between self-inadequacy- and loss of pleasure-related symptoms was consistently observed also in cross-sectional analyses of depression scale symptom items in difficult-to-treat MDD (Harrison et al., 2021) and more formally shown by statistically comparing the strength of the connection between worthlessness and other symptoms related to self-blame versus those related to loss of pleasure in both a large Chinese community and clinical MDD case control study (Harrison et al., 2022). This strong connection between feelings of worthlessness, guilt and self-blame on the symptom checklist-90 was also demonstrated in a European community sample as distinct from other symptoms (Blanken et al., 2018). The authors concluded that feelings of worthlessness are a so-called "stabilising symptom" in network analytical terms. They defined these as "symptoms with many and strong connections within a community", which "could be thought of as the core of a community", where "community" refers to symptoms which are more strongly connected with each other than with other symptoms.

So whilst, there is convergent evidence for at least two dissociable subsyndromes of depression as in the Bringmann et al. study, most studies found somatic symptoms to form separate subsyndromes (Fried et al., 2016), which would then constitute a third symptom cluster. One limitation of many self-report scales, however, is that they do not separate increases and decreases in sleep or appetite, therefore limiting the construct validity of the individual items.

2.4. Distinctiveness of affective subsyndromes between diagnostic categories

Currently, "trans-diagnostic" approaches to symptoms are becoming more influential as many symptoms are overlapping between diagnostic categories and one could assume a common pathophysiology irrespective of diagnosis. Whilst this is a valid approach to identify trans-diagnostic treatment targets which could relate to general risk factors such as early life trauma, this does not replace the search for distinctive ("pathognomonic") symptoms to define and validate diagnostic categories, given their superior prognostic and therapeutic validity compared with transdiagnostic symptoms (see above). The aim of this section is to examine the evidence for distinctiveness of affective symptoms and subsyndromes for major depressive and hypomanic mood states compared with affective symptoms occurring in other diagnostic categories.

Important empirical evidence was provided as part of the Association for Methodology and Documentation in Psychiatry (Bobon et al., 1983). Using factor analytical methods in independent cohorts of inpatients without restrictions regarding their diagnosis, syndrome definitions were based on reproducible association of individual symptoms within syndromes (Pietzcker et al., 1983). Interestingly, across centres, affective rigidity, lack of drive and social withdrawal were associated in a syndrome together with other symptoms which were labelled "apathy syndrome", whereas the manic syndrome included "excessive social contact" apart from previously described symptoms of flight of ideas, euphoria, exaggerated self-esteem, increased drive, motor restlessness, logorrhoea. The "depressive syndrome" included: rumination, feeling of loss of feeling, felt loss of vitality, depressed mood, hopelessness, feelings of inadequacy, feelings of guilt, inhibition of drive, worse in the morning, interrupted sleep, shortened sleep, early waking, decreased appetite. The validation studies showed that depressive and apathy syndromes were only somewhat distinctive between schizophrenia and depressive disorders (Pietzcker et al., 1983). Similar results of a high rate of overlap in major depressive syndromes and symptoms such as lack of self-confidence between people with schizophrenia and major depressive disorder were also obtained in studies (Hafner et al., 2005) using another phenomenological psychopathology-based assessment instrument, the Present State Examination (PSE, (Wing, 1980)).

Despite confirming a high frequency of major depressive symptoms overall in schizophrenia, Serretti et al. (Serretti et al., 2004) also detected distinctive aspects, which could be explained by using a different instrument, the Operational Criteria for Psychotic Illness checklist (OPCRIT; developed by (McGuffin et al., 1991)) with a lifetime perspective. They compared depressive symptom profiles between groups of people with MDD (n = 389), bipolar disorder (n = 511), delusional disorder (n = 93), and schizophrenia and "excessive self-reproach" (defined as (McGuffin et al., 1991): "extreme feelings of guilt and unworthiness" was the least frequent in the schizophrenia group (3.9 % of n = 358), but highly consistent in the MDD group (93.3 % of n = 389). Loss of energy/tiredness and pleasure on the other hand were present in around a third of people with schizophrenia, clearly rendering them less distinctive.

Loss of interest was assessed as a separate symptom from pleasure on the WHO SCAN/PSE (Health, 1994) and is listed in ICD-10 as a separate symptom of depressive episodes, and on the BDI-II. Following the combination of loss of interest and pleasure into one item on the DSM-II-R, IV and 5, many instruments use a combined item, however. This includes the PHQ-9, as well as the The Comprehensive Assessment of Symptoms and History (CASH, (Andreasen et al., 1992)). Snaith reviewed the history of anhedonia in depression and pointed to the importance of its inclusion in the DSM-II-R and a relative lack of attention to it before (Snaith, 1993). He pointed out that a "failure to experience pleasure", which he defines "anhedonia" as, referring to a 19th century definition by Ribot, should not be confused with a loss of interest. He pointed to the core importance of anhedonia not only to melancholic depression, but also to negative symptoms of schizophrenia and flattened affect, which is also reflected on the CASH (Andreasen et al., 1992). A search for studies investigating loss of interest independently of pleasure in Schizophrenia revealed no studies specifically referring to those in the abstract or title.

2.5. Conclusions: consistent and distinctive affective subsyndromes

In the previous sections, we have summarised the evidence on phenomenology, transcultural stability, consistency and coherence of symptoms of mood disorders with a relative scarcity of evidence on manic mood states and temporal evolution of symptoms over short periods of time, as well as a systematic bias towards convenience samples

which lack gold standard instruments for assessing symptoms. Despite, these limitations, the following conclusions can be drawn for our further pathogenetic considerations, when considering evidence from other disorders (Table 1).

Only symptoms within four dimensions were identified as necessary for both hypomanic and depressive episodes: mood and energy, as well as self-worth and interest. Another symptom dimension is necessary according to DSM-5 for hypomania: activity, which was not the case prior to DSM-5, as increased activity may enhance diagnostic specificity, but is not necessarily present in all forms of mild hypomanic episodes to a clear extent (Grunze et al., 2021). One could consider activity, however, as a secondary symptom of other symptom dimensions, particularly energy, and people with unipolar major depression may often exhibit relatively normal levels of activity in areas of importance to them, when symptom levels are not at the severe end. This observation was confirmed when examining data from our antidepressant advisor studies in difficult-to-treat current MDD (see Supplementary results, (Fennema et al., 2023; Harrison et al., 2022)). As expected, a lack of energy/drive (using semi-structured interview as in (Zahn et al., 2015)) was associated with lower psychosocial functioning. Despite this, around half of our patients lacked relevant work impairments despite major depressive episode symptoms and lack of energy.

Table 1
Features of affective subsyndromal dimensions.

Symptom dimension	Polarity	Episode polarity-distinctive	Disorder-distinctive	Necessary
Self-worth	bi-	yes	yes	yes
Interest	bi-	yes	yes	yes
Mood	multi-	yes	only hypomania	yes
Energy	bi-	yes	only hypomania	yes
Activity	bi-	yes	only hypomania	no
Hope	bi-	yes	yes	no
Blame	bi-	yes	yes	no
Pleasure	bi-	yes	no	no
Sleep	multi-	yes	only bipolar	no
Formal Thought	bi-	yes	only bipolar	no
Numbness	uni-	yes	no	no
Anxiety	uni-	yes	no	no
Appetite	bi-	only when decreased	no	no
Aggression	bi- (self/other)	yes	no	no
Sociability	bi-	yes	no	no

Listed are all symptom dimensions for which there is evidence of transcultural consistency and relevance to mood disorders as described in this article. Symptom dimensions can have two poles (bipolar), for example decreased and increased appetite, or they can be unipolar, for example normal or increased levels of anxiety. Mood is a multipolar dimension if one considers elated, depressed, and irritable mood states. Sleep is considered a multipolar symptom dimension here, because an inability to sleep (common in depression) is classed as a different pole from a reduced need for sleep (common in hypomania). Episode polarity distinctiveness refers to whether the pole on the symptom dimension is distinct for different polarities of an episode (i.e. hypomanic and depressive episode). For example, self-worth is increased in hypomania and decreased in depression. Mixed episodes are not considered here, because per definition they would mix symptoms of different polarity at the same time. Syndrome distinctiveness considers whether a symptom dimension is distinctive in degree/persistence or quality for disorders which include major mood episodes (including non-organic and organic or substance-induced mood disorders which are per DSM indistinguishable in symptoms, even if that is debatable), as opposed to people whose symptoms meet the diagnostic criteria for other disorders such as anxiety disorders, or substance use disorders, but who are not experiencing major mood episodes. Schizophrenia poses a particular conundrum in that it also includes major depressive syndromes and its aetiological relationship with major depressive disorder is unclear. Further, the table uses the evidence reviewed in this article for the consistency of symptoms to determine whether they are necessary for mood disorders. None of the symptom dimensions are considered sufficient for mood disorders in that a major mood episode always requires a combination of symptom dimensions. For example, depressed mood is a consistent symptom but occurs in other conditions which are not associated with major mood episodes, for example dysthymia, or chronic anxiety disorders and is therefore classed as necessary but not sufficient for a major depressive disorder. Some symptoms are distinctive and necessary for bipolar rather than unipolar mood disorders only, such as changes in activity.

Given the above, we will focus on the four dimensions that are necessary for both depressive and hypomanic episodes, the energy and mood dimensions may be distinctive of hypomania when one considers persistence and degree, particularly of elated mood states, compared with emotional liability in people with attention hyperactivity deficit syndromes (Brus et al., 2014) for example, but they are not distinctive for depressive episodes in that lack of energy to similar degrees/persistence and of similar quality may occur across a range of neuropsychiatric disorders without other core depressive symptoms. For example, people with negative symptoms of schizophrenia but without major depressive syndromes can show a marked lack of energy (Kulhara et al., 1989), the same is true of people with chronic fatigue syndrome (Matthews et al., 1991) which may occur independently of a full depressive syndrome. Furthermore, low mood although more persistent and bothering in more severe forms of depression is hard to distinguish qualitatively from depressed mood occurring in people with a range of disorders such as chronic anxiety disorders (Wang et al., 2023). This leaves us with two necessary symptom dimensions that are also distinctive for both poles of mood episodes:

Self-worth: although persistently low self-esteem/feelings of inadequacy are common in people with other disorders such as social phobia and can then be indistinguishable from pre-cursor states of depressive episodes to which social phobia pre-disposes (Lipsitz and Schneier, 2000), the degree of self-domain overgeneralisation and quality is distinct in depressive episodes even when people do not always endorse feeling "worthless" as stipulated by DSM-IV/5 for a diagnostically relevant level of feelings of inadequacy. This is derived from observations using our moral emotion interview (Zahn et al., 2015), where most MDD patients described at least a moderate level of inadequacy (which may be related to their own standards rather than in comparison with others) and feeling inadequate regarding most aspects of themselves. Increased self-esteem is distinctive of hypomania even when present in milder forms in patients with pre-existing low self-esteem. For example, in patients with pre-existing social phobia and subsequent hypomania, as we have observed several times, but by using the internal reference, there is no other syndrome in which such an increase in self-esteem compared with one's usual self occurs. The OPCRIT item of self-reproach found to be highly distinctive between schizophrenia and MDD (Serretti et al., 2004) also includes low self-worth. Furthermore, low self-esteem has been reliably identified as a prospective risk factor for major depressive disorder (Ormel et al., 2004).

Interest: loss of interest is a necessary and consistent symptom of depressive episodes which is dissociable from worthlessness and entails a lack of anticipated rewarding aspects of activities or goals but also a loss of interest in duties which one usually feels obligated to carry out. Although, one can fulfil the DSM-criteria for a major depressive episode without a loss of interest or pleasure in all or almost all activities, loss of interest is present in almost all patients with a major depressive episode in our clinical experience and this is corroborated by a network analysis in current MDD showing it to be present in 86 % of patients and being the most central (i.e. most highly co-occurring) symptom (Park and Kim, 2020) with loss of energy/tiredness being the only other more consistent depressive symptoms on the BDI-II in a Korean sample. Similarly to milder forms of low self-esteem, a loss of interest may also be encountered in other conditions such as schizophrenia. Yet, the painful quality of losing one's interest is distinctive of depressive episodes compared with negative symptoms in schizophrenia which were described as affect

flattening, apathy and loss of pleasure without specific mention of loss of interest (Kulhara et al., 1989). Similarly, in psychopathological systems following Jaspers (Zahn, 2024), there is a distinction between the painful "feeling of loss of feeling", commonly found in major depressive disorder (Zahn et al., 2015), versus apathy as not caring anymore about things but not being bothered by this, which was not present in MDD, but found in patients with frontotemporal neurodegenerative conditions typically (Zahn and Burns, 2017). Loss of interest is also common in disorders related to substance use or behavioural addictions, but a closer observation shows that this is better described as a narrowing of interest towards the substance or addictive behaviour which replaces other interests (Sprong et al., 2019). Both schizophrenia (Hafner, 2007) and addiction-related disorders (Hettema et al., 2003), however, increase the risk of depressive episodes which does not invalidate a distinctiveness in degree and quality of the symptom dimension. Increased interest is a consistent symptom of hypomanic episodes and distinct due to the intra-individual reference point even if not always problematic.

As summarised in Table 1, none of the other symptom dimensions are necessary for both mood disorder poles as well as disorder-distinctive. If we assume a common primary pathophysiology for all bipolar and recurrent unipolar disorders, this means that they are unlikely to be primary symptom dimensions, i.e. those linked most closely to mood disorder pathophysiology (Zahn, 2024). Undoubtedly, MDD, however, is not aetiologically homogenous and from epidemiological studies it was shown that around half of patients with MDD only have one lifetime episode, whereas around 15 % developed a chronic course (Eaton et al., 2008). In contrast 35 % with recurrent forms of MDD were more likely to develop bipolar disorder with higher levels of recurrence and high recurrence levels were considered a bipolar characteristic (Angst et al., 2011).

More chronic and treatment-resistant forms of MDD are associated with more prominent anxiety symptoms (Fava Maurizio et al., 2008). Anxiety disorders may precede the onset of major depressive episodes later in life (Gundel et al., 2018; Hettema et al., 2003) and co-morbid anxiety disorders render full remission less likely (Dold et al., 2017). This raises the question of whether the previous notion of a primarily anxious ("neurotic") form of depression should be revisited, where anxiety could be a primary symptom (Wolpe, 1988). What is certainly observable in many patients is that anxiety is managed by avoidance which then leads to a lower probability of positive feedback and success in social and work situations (referred to as demoralization in (Cosci and Fava, 2021), thereby potentially causing feelings of inadequacy as a secondary rather than primary symptom.

Anxiety, however, is unlikely to be a distinguishing symptom between patients with primary and secondary feelings of inadequacy, because depressive anxiety is often linked to the fear of failure due to feelings of inadequacy (Zahn, 2024), thus one either needs to characterise the quality of anxiety or the time course in relation to major depressive episodes. This shows that consistent and distinctive symptoms of depression such as feelings of inadequacy/worthlessness do not necessarily reflect primary symptoms as they could also be a common end of different pathogenetic starting points. Given the difficulty of carrying out population-based cohort studies assessing individual symptoms, the causal relationships between symptoms may not always be directly investigated.

3. Cognitive neuroscience of distinctive and necessary symptoms of mood disorders

The previous section has identified interest and self-worth as two dissociable symptom dimensions which are necessary and have distinctive qualities for recurrent forms of unipolar and bipolar mood disorders. This does not mean, however, they are necessarily primary symptom dimensions in all forms of mood disorders, particularly chronic forms of unipolar depression with preceding anxiety disorders, but the above evidence provides a strong rationale for identifying their cognitive-anatomical substrates as treatment targets. Self-worth and interest as described below are likely reliant on partly overlapping, as well as partly dissociable frontal-temporal-subcortical networks described in our previous models of social knowledge and motivation (see Fig. 4, reproduced from (Zahn et al., 2025)).

3.1. Cognitive neuroscience aspects of self-worth

There is a close relationship between self-worth/-esteem and beliefs one holds about oneself, or the so-called "self-concept" (for a detailed description of its psychology and cognitive neuroscience see (Zahn et al., 2025)). Endorsing more negative concepts describing one's "personality traits" was associated with depressive symptoms (Sakamoto, 1994). Concepts, such as "impolite" are not only used to describe "personality" traits but also social behaviour more generally, which is why we have referred to these as "social concepts" (Zahn et al., 2007) and suggested that the elucidation of their functional neuroanatomy was needed for a more systematic study of the cognitive neuroscience of the „conceptual self' (Gallagher, 2000). Abstract social conceptual representations, independent of their reference to varying action or emotional (e.g. pride, gratitude, guilt or anger) contexts (Zahn et al., 2009b), were shown to rely on the anterior temporal lobe (Binney et al., 2016; Ross and Olson, 2010), particularly its right superior sector (Pobric et al., 2016; Skipper et al., 2011; Zahn et al., 2007, 2009a, 2017).

In contrast, the sequential-context dependent knowledge of social actions/events and goals which abstract social concepts denote were shown to rely on ventral frontal areas in patients with brain lesions (Wood et al., 2005), often extending into the frontopolar cortex (BA10), which also concurred with fMRI studies in neurologically healthy participants (Krueger et al., 2007). More specifically, neurodegeneration of the frontopolar cortex (BA10) was shown to be associated with selective impairments on knowledge of long-term consequences of social behaviour (Zahn et al., 2017).

Of particular relevance within the ventral frontal cortex is the subgenual frontal area, as it exhibits abnormal metabolism, particularly in familial mood disorders (Drevets et al., 1998). The subgenual frontal area is part of the ventral medial prefrontal cortex. The posterior part entails Brodmann Area (BA) 25, further referred to as subgenual cortex, whereas the more anterior portion entails subgenual parts of BA24/32 as part of the anterior cingulate cortex (Zahn et al., 2020). Task-independent functional connectivity of BA25 was shown to predict response to psychological versus pharmacological treatment (Dunlop et al., 2017) and prognosis in difficult-to-treat depression (Fennema et al., 2024a).

We have interpreted reproducible increases in anterior subgenual cingulate activations to self-blame-evoking stimuli in individuals prone to guilt as relevant for causal agency attributions that are particularly important for negative emotions such as guilt and anger (Lythe et al., 2022) and this region has also been associated with prediction errors to social feedback which lower one's self-esteem (Will et al., 2017). Weiner has pointed to the importance of causal attributions for our interpretation of failure (Weiner, 1985) and this was integrated into the revised learned helplessness model of depression as a tendency to make global, internal and stable negative attributions of causality to oneself, predicted to reduce one's self-worth and increase overgeneneral self-blame-related feelings (Abramson et al., 1978).

This has led to the hypothesis that integration of social conceptual information in the right anterior temporal lobe with causal agency information in the subgenual frontal region, reflected in functional connectivity, was key to enabling differentiated blame and thus guarding against overgeneral forms of self-blame and the ensuing reductions of self-worth. This was first confirmed in people with no history of mood disorders (Green et al., 2010) and then in people with remitted MDD displaying reduced right superior anterior temporal-anterior subgenual cingulate connectivity compared with never-depressed controls for guilt versus anger/indignation (Green et al., 2012), which was associated

with self-hate. A subsequent prospective study, however, detected a more posterior region, the subgenual cortex (BA25), which unexpectedly exhibited increased connectivity for self- versus other-blame with the right anterior temporal lobe in medication-free MDD patients at high risk of recurrence (Lythe et al., 2015). We confirmed the pre-registered prediction that this neural signature is likely to reflect a fully remitting form of MDD with higher risk of recurrence but better chance of remission (Fennema et al., 2023). A longitudinal investigation is underway to determine whether this is a signature of trait vulnerability or is modulated by depressive state (Fennema et al., 2024d).

3.2. Cognitive neuroscience aspects of interest

The "mesolimbic" dopaminergic projections from the midbrain ventral tegmental area to the ventral striatum/nucleus accumbens were shown to play a central role in anticipating reward values (Schultz, 2000), also referred to as ("wanting") and thus motivating approach-related actions (Berridge and Robinson, 1998) which are likely to play a key role in the cognitive neuroscience of interest. Hedonic aspects of interest are often disrupted in MDD and often conceptualised as "anticipatory anhedonia" (Rizvi et al., 2016). In contrast, until recently the notion of a specialised neural basis for affiliative motivational states was not considered. Bortolini et al. adapted a classical task to measure reward anticipation in the ventral striatum/nucleus accumbens and dissociate this from reward outcomes (monetary incentive delay-MID) to affiliative rewards (Bortolini et al., 2021). Whilst confirming the hypothesis based on earlier work (Moll et al., 2012) of a specific response in the septo-hypothalamic area for affiliative rewards across anticipation and outcome phases, both affiliative and non-affiliative reward anticipation engaged the ventral striatum (nucleus accumbens) as well as anterior insula (coding for arousal/salience irrespective of valence according to the model by Knutson et al. (Knutson et al., 2014). Bortolini et al. found medial orbitofrontal activations for affiliative and non-affiliative reward outcomes. This confirmed the prediction of a more specific role of septal and hypothalamic regions in affiliative, including moral/altruistic motivations (Moll et al., 2008). In the educational context, interest as distinguished from curiosity has been studied in its development over time to become a predisposition to be interested in a particular subject (Hidi and Renninger, 2019). Social psychologists have further shown that attributes associated with specific interests such as "being musical", play an important role in one's self-identity and so carry affiliative value, suggesting a link with one's self-concept and self-worth (Zahn et al., 2025).

Despite this potential link, the dissociation of loss of interest and self-worth at least in a subgroup of patients with MDD as previously outlined needs to be understood at the neural level. At a psychological level, both interest as well as self-worth are linked to self-identity and thus to the fronto-temporo-basal forebrain network underpinning moral motivation (Zahn et al., 2020) and self-identity (Zahn et al., 2025). What distinguishes them though is that one can be interested in things that one is only observing or receiving, so interest is not tied to agency and achievement necessarily. Interest as an intrinsic motivation was, however, found to be diminished by external rewards, suggesting that it entails a sense of autonomy even if not agency in causing a rewarding outcome (Deci et al., 1999).

The role of agency is an important distinction in that self-worth is very much linked with causal agency and one's active contribution (Weiner, 1985). One may therefore speculate that loss of interest is independent of the anterior subgenual cingulate cortex and its connectivity, shown to be associated with individual variability in proneness to self-blame and need for control (Lythe et al., 2022; Zahn et al., 2020). Likewise, one could argue that some forms of interest, particularly the hedonic interests are not part of our affiliative identity and have little self-identity value. This could then explain also less reliance on posterior subgenual cortex (BA25) connections, whose activation was most consistently linked with affiliative identity value such as group belongingness (Zahn et al., 2020).

Interestingly, a recent meta-analysis of fMRI studies of neural correlates of reward outcomes in MDD which included social and hedonic reward paradigms found reduced activation in striatal regions (right putamen) and a midline region falling into the septo-hypothalamic area (MNI: $x = 0, y = 2, z = -10$, but was misleadingly labelled as "subgenual cingulate cortex") in adult MDD compared with control participants (Bore et al., 2024). In a meta- and mega-analysis of cross-sectional "resting-state" fMRI studies of MDD, ventral striatal (nucleus accumbens) functional connectivity with orbitofrontal regions and other mesolimbic regions was shown to distinguish recurrent MDD from control groups (Ding et al., 2022).

In summary, hedonic interests are most likely to dissociate entirely from subgenual network dysfunction and mostly rely on the ventral striatal-medial orbitofrontal network, whereas affiliative interests are likely to rely on hypothalamic-BA 25 networks overlapping with those relevant for self-worth but may depend less on the anterior subgenual cingulate cortex (subgenual BA24/32). If this prediction is correct, we should be able to find intact anterior subgenual cingulate – right anterior temporal connectivity in people with loss of interest, but no feelings of inadequacy. Reversely we should find intact ventral striatal-orbitofrontal networks but disrupted anterior temporal-subgenual cingulate connectivity in people with feelings of inadequacy, but preserved hedonic interest, such as in partially remitted MDD. For both symptom domains, major depressive episodes will still need to be distinguished from transient depressive syndromes by the persistence of symptoms. This may be explained by an overall rigidity in the network state underpinning a major depressive episode that cannot be overcome by a competing euthymic or hypomanic network state. This rigidity is possibly explained as an exaggerated decoupling of one's mood state from external stimuli, but it could also be maintained by a loop-like active reinforcement through repetitive thinking. The re-learning of euthymic experiences may require lateral frontal brain regions as has been discussed for social attitudes (Cunningham and Zelazo, 2007).

3.3. Synthesis and model of mood states

To integrate above considerations, a model of mood states is depicted below and their relevant psychological dimensions, as well as their integration into different pathways of developing these mood states. Our model comprises four mood states which can also combine in mixed affective states, one can distinguish them on the bases of three main dimensions as illustrated in Fig. 2 below. One could conceive of affective states as much more complex with multiple dimensions and components (Scherer, 2009), but for simplicity, we have focussed on the clinically most prominent mood states and the most relevant dimensions allowing their distinction. Although valence allows a distinction of elated and depressed mood states, it would not allow for a distinction between anxious, irritable and depressed mood states which can be distinguished with regard to self-worth compared with others which is reduced in depression, increased in elated mood states and somewhere in-between for anxious and irritable mood states. Irritable mood states are mainly distinguished from anxious mood states by entailing approach-related action tendencies (i.e. attack, (Duan et al., 2023)), whereas anxious mood states are associated with withdrawal-related action tendencies (e.g. hiding). This schema of mood states is compatible with Kraepelin's mood state descriptions, and would allow for drive and activity levels, as well as mental speed to dissociate temporally from mood state as Kraepelin has observed. At the same time, approach-related action tendencies entailed in mood states would pre-cede and prepare increases in drive and activity. Anxiety could motivate active withdrawal, whereas depression would be associated with passive inactivity.

Our subsyndromal pathway model is illustrated in Fig. 3. The model draws on the evidence reviewed in previous sections but remains speculative in many parts (see Figure legend).

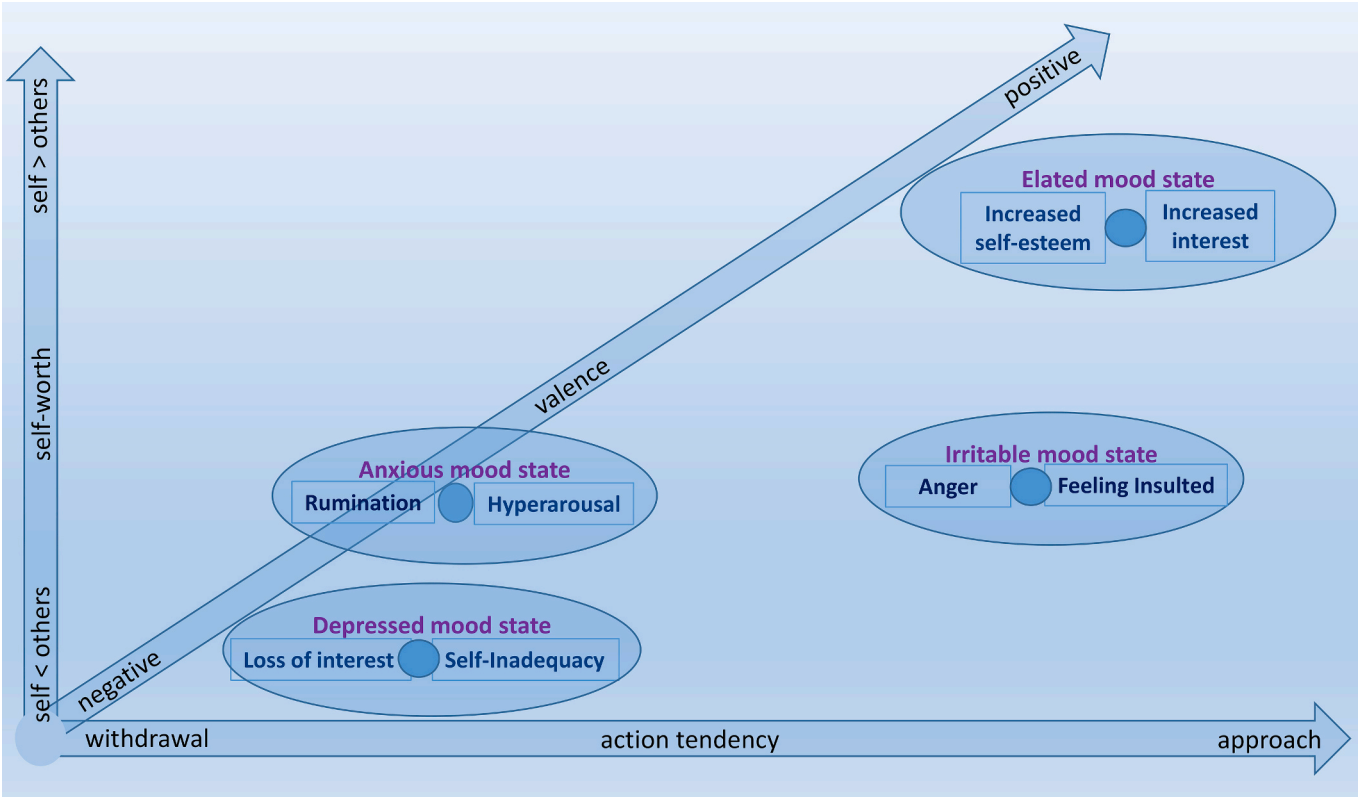

Fig. 2. A 3-dimensional coordinate system for mood states.
Four clinically relevant mood states were defined to account for mixed affective states as well as the observed dissociations as described in the text. Patients can experience elements of different mood states and gradually transition from one mood state to the other. Two hypothesised core symptoms are depicted as constituting each of the four mood states. Loss of interest and feelings of self-inadequacy/worthlessness were highlighted as necessary and distinctive for depressive mood states, which can be distinguished from anxious mood states on the basis of self-worth, relatively pre-served in anxious and irritable mood states. Irritable mood states were conceived of as being similarly negative in valence, yet entailing approach-related action tendencies (attacking others, shown to be reduced in people with depression (Duan et al., 2024) and related to anger (Duan et al., 2022). Irritable mood states were also conceptualised as characterised by feeling defensive in response to self-esteem threats or perceived insults to one's self-concept (Kinderman and Bentall, 1997), often observed in manic anger, but also in people with insecure self-esteem or some forms of atypical depression ("rejection sensitivity"). Anxious mood states were conceptualised as those reported by patients being constantly on edge rather than episodic forms of anxiety with intermediate periods of calm. This hyperarousal is often accompanied by anxious rumination and worry described for generalised anxiety disorder for example (Hirsch and Mathews, 2012). Elated mood states were conceptualised as the polar opposites of depressed mood states with regard to self-esteem, interest, as well as with regard to approach-related motivations enhanced in elated mood states. Elated and irritable mood states were depicted as more closely associated with regard to approach-related motivation and self-esteem, only distinguished by valence. Likewise anxious and irritable mood states are conceptualised as more closely related, mainly distinguished on the action tendencies dimension.

4. Validation of neurocognitive treatment targets in mood disorders

The need to personalise treatment for mood disorders is widely recognised, but reproducible and accurate neurocognitive markers for subtyping mood disorders and thereby better predicting treatment response at the individual level are only in the process of being developed (e.g. (Dunlop and Mayberg, 2014)). Validating a neurocognitive treatment target is a process which would often first rely on cross-sectional comparisons, before showing prospective prediction of clinical outcomes. The final step is to show that the neurocognitive marker can be specifically modulated by a treatment and that this modulation effect is associated with clinical outcomes.

Some neurocognitive markers may be relevant in predicting treatment response but may not correlate with depressive symptom levels and are therefore more likely to relate to vulnerability traits. Both vulnerability traits and depressive state markers could be targeted by treatments, but clinical trials targeting vulnerability traits require longer follow-up periods to determine if normalising the trait marker improves recurrence risk for example. Below we provide examples of functional neuroanatomical treatment target validation studies in MDD that have proceeded to the stage of RCTs.

Our focus here is on fMRI neurofeedback interventions given their functional anatomical specificity, but in principle any RCT that has linked functional anatomy with symptom improvement in response to an intervention is of relevance to neurocognitive target validation (e.g. psychological, pharmacological, neurostimulation). Without measuring the targeted cognitive component alongside neuroanatomical measures, however, it is difficult to ascertain whether the neural changes are related to the presumed function, this is because functionally heterogenous subpopulations of neuronal groups could be modulated in the same anatomical area. Functional near-infrared spectroscopy is a more scalable method with recent advances rendering this of high potential to replace fMRI if the target is cortical (Klein et al., 2024; Kohl et al., 2020). Furthermore, Electroencephalography (EEG) has had a recent renaissance in being considered for neurofeedback due to advances in multivariate analysis methods (Gurevitch et al., 2024). Functional localizer-based neurofeedback drawing on a set of brain regions has been used to enhance positive emotions in MDD (Mehler et al., 2018) which may be powerful from a clinical point of view, but less informative for validating a specific anatomical target. The same applies to the powerful method of multivariate decoding of emotional states using fMRI which can be used to enhance distributed networks related to adaptive emotional states using personalised neurofeedback (Goebel et al., 2024;

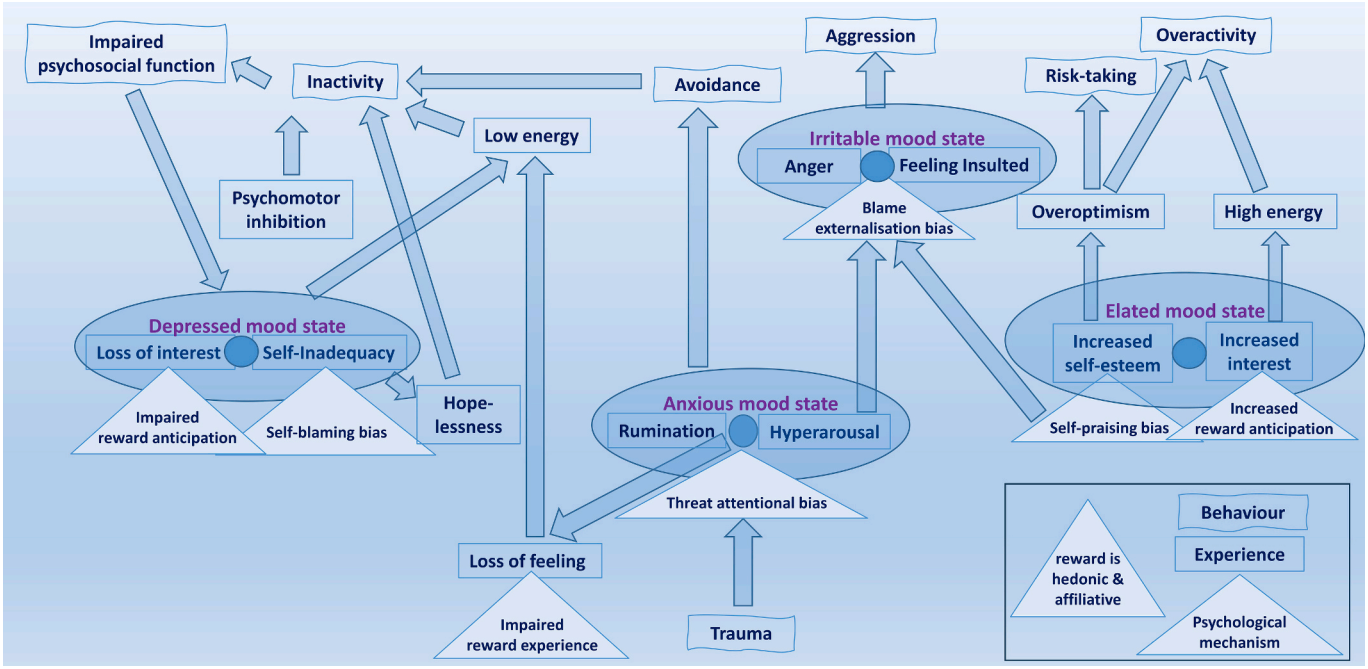

Fig. 3. Mood state pathways.
The model distinguishes subjective experiences from resulting behavioural consequences and proposed psychological mechanisms. Depressed mood states can be the result of anxious mood states via avoidance, reduced activity, and objectively reduced psychosocial functioning which in turn reduces self-worth/inadequacy. The other pathway into a depressed mood state leads from primary self-blaming biases into a sense of self-inadequacy and hopelessness in more severe cases, even in response to minor experiences of failure. Equally important would be a primary impairment in reward anticipation, which could lead to loss of interest as a primary symptom of depressed mood states. Hopelessness, although conceived as linked to self-inadequacy could then reduce activity together with low energy/motivation which would be a result of depressed mood states. Psychomotor inhibition and "inhibition of drive" (Ebert, 1992) as found in people with classical endogenous/melancholic depression (Parker, 2005) where motivation can be intact, but patients feel as if having to work against an inner resistance could be a primary symptom in melancholic forms of depression which would then reduce activity levels. Activity levels could, however, also be reduced by low energy/motivation in people with a feeling of loss of feeling (emotional numbness, (Zahn, 2024)), presumed to also include impaired consummatory anhedonia as a mechanism. Loss of feeling could be a primary symptom in a subgroup of patients with a lack of mood reactivity, but can also be observed in patients in response to anxious mood states as a form of emotional dissociation and potentially a compensation symptom. Anxious mood states would primarily reduce activity levels by entailing withdrawal/avoidance-related action tendencies. The hyperarousal and anxious rumination characterising anxious mood states is hypothesised to result from an attentional biases towards threat-related stimuli and memories typically found in people with posttraumatic stress and generalised anxiety disorders (Hirsch and Mathews, 2012). All causes of inactivity can result in impaired psychosocial functioning and thereby trigger and maintain depressed mood states if this affects self-worth and/or interests. In contrast, irritable mood states have little overlap with depressed mood states and are mainly linked to anxious mood states by hyperarousal rendering people more likely to feel threatened and thus more likely to feel insulted, angry and defensive. Whether irritability is triggered by anxious mood states is predicted by blame externalisation biases according to the model. Although, self-blaming biases are hypothesised to underpin primary feelings of inadequacy, patients with irritable forms of depression are predicted to have secondary feelings of inadequacy with intact blame externalisation when under threat. The primary link between irritable and elated mood states is hypothesised via blame externalisation and self-praising biases as both linked to preserving and enhancing self-esteem, resulting in its more extreme forms in overoptimism and risk-taking behaviour in elated mood states. Increased reward anticipation is hypothesised to cause increased interest, which can result in higher energy which in turn can lead to higher activity levels.

Moll et al., 2014).

4.1. *Amygdala response to emotional salience*

The amygdala has been reproducibly linked to implicit detection of the emotional relevance of perceived stimuli (Sander et al., 2003). fMRI neurofeedback studies have sought to reduce amygdala responses to negative and increase them to positive stimuli. In major depressive disorder, increasing amygdala responses to positive memories has shown promising results in small RCTs (Young et al., 2017), and was shown to enhance effects of CBT (Compere et al., 2023). Decreasing amygdala responses to negative stimuli has shown promise in post-traumatic stress disorder (Zopfs et al., 2024). Although, to our knowledge, it has not been shown how amygdala responses to positive memories relate to interest, work on the role of autobiographical memory in shaping future expectations and thus motivation (Markowitsch and Staniloiu, 2023) suggests that enhancing the salience of positive memories is likely to enhance interest and thereby potentially increase energy and motivation. Reduced positivity and over-general autobiographical memory, however, are a transdiagnostic risk factor for affective disorders (Dalgleish and Hitchcock, 2023) and may be more closely linked to common risk factors such as early life trauma (Gethin et al., 2017).

4.2. *Subgenual frontal and anterior temporal responses to blame*

In two pre-registered proof-of-concept RCTs, subgenual frontal-anterior temporal connectivity whilst experiencing self-blaming feelings in response to autobiographical memory cues were studied. In people with remitted MDD, self-esteem was increased in the active compared with the control fMRI neurofeedback group after one session reinforcing increasing the functional connectivity between the right superior anterior temporal and anterior subgenual cingulate cortex (Zahn et al., 2019). Increased training-induced connectivity correlated with increased self-esteem. In the subsequent trial in difficult-to-treat MDD, reducing connectivity between the right superior anterior temporal and posterior subgenual cortex (BA25) was reinforced in 3 sessions, which did not show superiority over a purely psychological

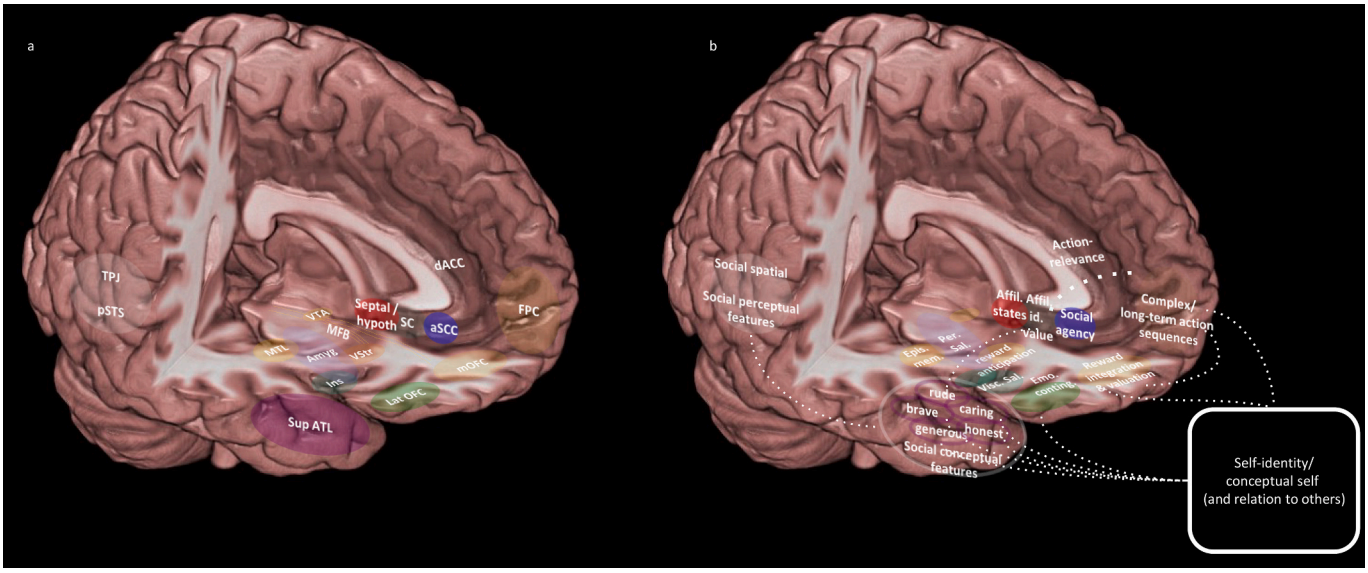

Fig. 4. Neuroanatomical model of the self-concept and motivation.
Depicted is an updated neuroanatomical network model (Event Feature Emotion Complex Model [EFEC]) of social knowledge and moral motivation and its implication for representing the self-concept/self-identity, as well as hedonic and affiliative motivations (reproduced from (Zahn et al., 2025)). This is based on evidence from brain lesions and functional neuroimaging (reviewed in (Moll et al., 2005; Zahn et al., 2020), Figure adapted from (Moll and Schulkin, 2009; Moll et al., 2005; Zahn et al., 2011)). Cortical region: frontopolar cortex (FPC), subgenual cortex (SC, corresponding to Brodmann Area 25), and anterior subgenual cingulate cortex (aSCC, corresponding to subgenual parts of Brodmann Areas 24 and 32), dorsal anterior cingulate (dACC), medial (med) and lateral (lat) orbitofrontal cortex (OFC, with the lateral OFC corresponding to Brodmann Area 47, corresponding to ventrolateral PFC), right superior anterior temporal lobes (sup ATL), and posterior superior temporal sulcus (pSTS), temporo-parietal junction (TPJ). Basal forebrain structures include the amygdala (Amyg), insula (Ins), medial temporal lobe posterior to the amygdala which includes the hippocampus (MTL), hypothalamus, the septal region, ventral striatum (VStr), and midbrain regions such as the ventral tegmental area (VTA) from which the mesolimbic dopaminergic system originates, and which is connected via white matter tracts within the medial forebrain bundle (MFB). Integration across these corticolimbic structures gives rise to event-feature-emotion complexes (EFEC) by temporal binding according to the fronto-temporo-subcortical integration model (Moll et al., 2005). The hypothesised cognitive-anatomical components are the following: (1) Sequential knowledge of actions/events represented within PFC subregions. FPC: complex branching of consequences of actions and ventral PFC regions representing associative knowledge of motivational/emotional states embedded into sequential event/action contexts with medial OFC serving reward integration and valuation and lat OFC representing emotional contingencies; the subgenual cortex representing affiliative identity value/belongingness, and aSCC social agency that is combined with dACC representations of action-relevance/salience to trigger action readiness in supplementary motor areas (not part of the core model) (2) social sensory features stored in pSTS, mental models of social spatial relationships and perspective in the TPJ, and abstract (i.e. context-independent) conceptual knowledge of social behaviour stored in the sup ATL, especially the right hemisphere; (3) central motive or basic emotional states, such as “free-floating” attachment represented by the subcortical structures such as the hypothalamus, the amygdala representing emotional salience of perceived or imagined stimuli (perceptual salience), whilst the insula represents visceral/interoceptive salience and arousal (Jones et al., 2010), the ventral striatum enabling reward anticipation and the medial temporal lobe being relevant for encoding and recollecting self-concept relevant memories within a specific spatio-temporal event context (episodic memories).

intervention control arm (Jaeckle et al., 2021). A secondary analysis, showed, however, that anxious distress features predicted whether patients responded to neurofeedback or the control intervention, which led to the interpretation that the neural signature may have been irrelevant and thus distracting for anxious MDD (Jaeckle et al., 2021). Indeed, a subsequent pre-registered study found anxiety in patients with difficult-to-treat MDD was associated with reduced amygdala responses to positive facial emotions (Fennema et al., 2024b) and that this neural signature of reduced positive emotional perception biases was dissociable from self-blame-selective anterior temporal – BA25 hyperconnectivity measured in the same group, despite both being relevant for predicting prognosis (Fennema et al., 2024c). This pointed to the need to personalise neuromodulation interventions for different patients with MDD.

4.3. Ventral striatal responses to reward

From a cognitive neuroscience perspective, loss of interest and motivation could be approached by providing ventral striatal or hypothalamic neurofeedback for hedonic/general and affiliative reward respectively, but so far to our knowledge the only RCT using ventral striatal neurofeedback in MDD has only been published as a protocol so far and sought to improve bonding in postnatal depression (Eckstein et al., 2019).

4.4. Precuneus/posterior cingulate region and right temporoparietal junction (rTPJ) connectivity in response to repetitive negative thinking

Repetitive negative thinking is a feature of both depressive and anxiety disorders and is often of self-blame-related content in people with MDD (Martínez-Sanchis et al., 2021). It is likely related to biases in autobiographical memory in that it is likely to maintain and enhance negative and overgeneral memories (Raes et al., 2006).

A recent pilot RCT showed that functional connectivity between the retrosplenial cortex (rather than the predicted larger precuneus/posterior cingulate region used for neurofeedback) and right temporo-parietal junction was associated with a greater reduction in Ruminative Response Scale-brooding subscale scores in the current MDD group treated with active fMRI neurofeedback whose scores were significantly reduced after the intervention compared with the sham-treated group (Tsuchiyagaito et al., 2023). A subsequent whole-brain connectivity analysis found a wider network of brain regions probably supporting the treatment effect (Misaki et al., 2024). Whilst undoubtedly, a wider network of brain regions is likely to be modulated even when the neurofeedback reinforces only one particular region, in an RCT against a control neurofeedback intervention, one could nevertheless argue that the modulation of the wider brain network must have been caused by the participants’ response to the neurofeedback signal from the target region. Depressive symptoms were reduced in both active and sham

groups with no differences. The right temporo-parietal junction has been shown to relate to social perspective taking and self-other distinctions (Decety and Grèzes, 2006) and showed abnormal functional connectivity with the right anterior temporal lobe for self- versus other-blame in MDD patients at high risk of recurrence (Lythe et al., 2015). The precuneus/posterior cingulate cortex is the region showing dysfunction early on in Alzheimer's disease and plays a key role in autobiographical and episodic memory retrieval and associated visual imagery (Cavanna and Trimble, 2006). Both regions are therefore of likely relevance for retrieving socially relevant memories which is likely to play a more general role in affective disorders.

4.5. Limitations of neurofeedback evidence

Given the high cost and technical complexity of fMRI neurofeedback, the field has been particularly limited by small sample sizes and the variability in choice of neurofeedback signatures and software, as well as control conditions. Furthermore, it was outside of the scope of this review to undertake a systematic review following standard guidelines and this may have biased the conclusions.

4.6. Conclusions and future perspectives

Although, as this article argues, it is premature to settle on a fixed conceptual framework of cognitive and emotional function domains and link them to specific neuroanatomical and molecular mechanisms, there is increasing progress in identifying relevant neurocognitive components and subsyndromes in mood disorders to inform future neurocognitive treatments. We hope to have shown that valuing our patients' subjective descriptions and careful differential diagnosis continues to be indispensable for understanding pathophysiology. Novel more scalable methods for neuromodulation and neurofeedback, such as functional near-infrared spectroscopy, will improve the statistical power and reproducibility of clinical trials targeting specific neurocognitive components of mood disorders and will thereby allow directly probing their role in mood disorders. These novel imaging methods could thus pave the way for novel cost-effective neurofeedback treatments and contribute to multimodal decision support systems for personalising treatment pathways for mood disorders.

CRediT authorship contribution statement

Roland Zahn: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Role of the funding source

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Declaration of competing interest

RZ is a private psychiatrist service provider at The London Depression Institute and co-investigator on a Livanova-funded observational study of Vagus Nerve Stimulation for Depression. RZ has received honoraria for talks at medical symposia sponsored by Lundbeck, Neuraxpharm as well as Janssen. He has collaborated with EMOTRA, EMIS PLC and Depsee Ltd. He is affiliated with the D'Or Institute of Research and Education, Rio de Janeiro and advises the Scients Institute, USA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119423.

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