Affective lability in psychosis spectrum disorders: characteristics and correlates

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LIST OF STUDIES

Study I

Affective lability across psychosis spectrum disorders

Høegh, M.C., Melle, I., Aminoff, S.R., Laskemoen, J.F., Büchmann, C.B., Ueland, T., Lagerberg, T.V. (2020). *European Psychiatry*, 63(1), e53, 1–8, https://doi.org/10.1192/j.eurpsy.2020.44

Study II

Characterization of affective lability across subgroups of psychosis spectrum disorders

Høegh, M.C., Melle, I., Aminoff, S.R., Haatveit, B., Olsen, S.H., Huflåtten, I.B., Ueland, T., Lagerberg, T.V. (2021). *International Journal of Bipolar Disorders*, 9:34, https://doi.org/10.1186/s40345-021-00238-0

Study III

Affective lability and social functioning in severe mental disorders

Høegh, M.C., Melle, I., Aminoff, S.R., Olsen, S.H., Lunding, S.H., Ueland, T., Lagerberg. T.V. (2022). *European Archives of Psychiatry and Clinical Neuroscience,* https://doi.org/10.1007/s00406-022-01380-1

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ALS-SF	Affective lability Scale Short Form
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUDIT	Alcohol Use Identification Test
BDI	Bipolar Disorder, type I
BDII	Bipolar Disorder, type II
CDSS	Calgary Depression Scale for Schizophrenia
DBT	Dialectical Behavior Therapy
DGLM	Double Generalized Linear Model
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text
DUB	Duration of Untreated Bipolar Disorder
DUDIT	Drug Use Disorder Identification Test
DUP	Duration of Untreated Psychosis
GWAS	Genome Wide Assocation Study
HPA	Hypothalamic Pituitary Adrenal
IDS-C	Inventory of Depressive Symptoms Clinician Rated
MANCOVA	Multivariate Analysis of Covariance
MANOVA	Multivariate Analysis of Variance
MRI	Magnetic Resonance Imaging
NORMENT	Norwegian Center for Mental Disorders Research
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PTSD	Posttraumatic Stress Disorder
RDoC	Research Domain Criteria
SCID	Structured Clinical Interview for DSM-IV
SFS	Social Functioning Scale
TOP	Thematically Organized Psychosis Research
YMRS	Young Mania Rating Scale

SUMMARY

Affective lability entails rapid, excessive and unpredictable changes between different affective states. It has been found to be prevalent in the general population as well as in many psychiatric disorders, and has consistently been associated with poor clinical and functional outcome. In psychotic disorders, including schizophrenia- and bipolar spectrum disorders, there is limited knowledge about the level, structure, dispersion and correlates of affective lability, in particular in the schizophrenia spectrum group.

The current thesis is comprised of three studies with the overall aim of providing new insight into the construct of affective lability in psychotic disorders. Participants for the studies were included from the Thematically Organized Psychosis (TOP) research study in Oslo and affective lability was measured by the Affective Lability Scale Short Form (ALS-SF). The ALS-SF yields a total score of affective lability, in addition to scores on three subdimensions covering fluctuations between anxiety-depression, depression-elation and anger and normal mood. In *study I*, we compared the level of affective lability in individuals with either schizophrenia- or bipolar spectrum disorders and healthy controls, and investigated whether there were specific sociodemographic and clinical correlates of affective lability in the two patient groups. In *study II*, we investigated whether there were differences in the level and structure of affective lability in the different psychotic disorders, and if this was independent of current symptoms status and other putative confounding variables. In addition, we explored the dispersion of affective lability within each diagnostic subgroup and possible differences in dispersion between the groups. In *study III,* the aim was to explore the relationship between affective lability and social functioning in psychotic disorders. We wanted to see whether such a link was specific to subdimensions of affective lability, as well as independent of other well-established predictors of social impairments in psychosis.

We found that affective lability was significantly higher in schizophrenia- and bipolar spectrum disorders compared to healthy controls from the same catchment area and that it was equally high in the two patient groups. Affective lability was further associated with current positive

psychotic- and depressive symptoms in the schizophrenia spectrum group, and with alcohol use disorders, current depressive symptoms and non-use of antipsychotics in the bipolar spectrum group (*study I*). In the more specific diagnostic subgroups, we found that affective lability was highest in bipolar II disorder (BDII) and equally high in bipolar I disorder (BDI) and schizophrenia, also when controlling for current symptom levels. Affective fluctuations between anxiety-depression and depression-elation were most prominent in all subgroups. The heightened levels of affective lability did not appear to be driven by individuals with extreme scores and no differences between the dispersions of affective lability in the diagnostic subgroups were found (*study II*). Finally, we found that elevated affective lability in the anxiety-depression dimension was significantly associated with reduced social functioning even when controlling for other robust predictors of social functioning (*study III*).

Collectively, the findings reported in this thesis expand and provide new knowledge about affective lability in psychotic disorders. Through the three studies, we have found that affective lability is a prominent illness feature in psychotic disorders which appears to increase the risk for a more arduous illness burden as well as for reduced social functioning. Consequently, our findings suggest that there should be increased focus on assessment and treatment of affective lability in clinical practice with patients with both schizophrenia- and bipolar spectrum disorders.

1 Introduction

Affect can be thought of as the broad and general sense of feeling that we experience during the course of every day, a sort of barometer that lets us know how we are doing [1, p. 72]. The roots of the concept of affect can be traced back to the German physiologist and psychologist Wilhelm Wundt. Wundt referred to affect as "simple feelings" (gefühl) that arise from internal bodily sensations, such as feeling pleasant versus unpleasant and/or activated versus subdued [2, 3, p. 2., 4]. Although much debate about the conceptualization of affect has followed, Wundt's initial ideas have inspired theorists in the field of affective science, and mounting evidence suggests that they still hold their ground today [2, 5]. Affect is thought to be constantly and ever-presently with us, even when we are not aware of it, as a property of consciousness embedded in the constant conversation between the brain and the body [1, p. 73., 6, 7]. By nature, affect ebbs and flows in magnitude, and fluctuations are thus to be expected. However, the experience of very rapid, excessive and unpredictable changes in affective states, which is often referred to as affective lability, can be an indication of an affective disturbance that may be pathological in nature. Hence, it is perhaps not surprising that such lability in affect has been found to be more frequent among those with mental disorders compared to those without [8-10]. Further, affective lability has consistently been associated with negative clinical and functional outcomes across a host of different disorders [11-13]. In the current thesis, the aim is to investigate to which degree and in what manner this affective disturbance manifests itself in the severe mental disorders in the schizophrenia- and bipolar spectrum.

In schizophrenia- and bipolar spectrum disorders, research into pathophysiological mechanisms and potential treatment targets span centuries [14, 15]. Although considerable treatment progress has been made to ameliorate the most prominent psychotic- and mood symptoms, many individuals with these disorders still struggle with social, vocational and daily-life functioning [16, 17]. Consequently, there is a need to explore and characterize other illness mechanisms that may be involved in order to optimize treatment outcomes. From clinical experience with patients with both schizophrenia- and bipolar spectrum disorders, unstable affect or "having mood swings" beyond more established mood episodes is a

common complaint, and often one of the first things mentioned upon entering treatment. In general, affective disturbances are highly prioritized as treatment targets by individuals with these disorders [18, 19]. Yet, there is limited research investigating the role of specific features of affective disturbances, such as affective lability, in these populations, albeit seemingly for somewhat different reasons. In schizophrenia spectrum disorders, the role of affect has generally received less attention, whereas in bipolar spectrum disorders the primary clinical and research focus has traditionally been on the defined mood episodes despite the fields' growing recognition of the prominence of other affective disturbances as well. Over the past years, there has been accumulating evidence that highlights the many overlaps between schizophrenia- and bipolar spectrum disorders, also in terms of affective disturbances. This has resulted in the conceptualization of "psychosis spectrum disorders" which will be discussed in more detail below. The overall aim of the current thesis is to shed light on the level, structure and distribution of affective lability across psychosis spectrum disorders, as well as its putative clinical and functional correlates. For the sake of simplicity, the term psychotic disorders will be used throughout to refer to psychosis spectrum disorders, including both schizophrenia- and bipolar spectrum disorders, although psychosis is not a prerequisite for a diagnosis of bipolar disorder (see section 1.1.3). Hopefully, the findings presented in the thesis will lead to further research investigating the clinical utility of targeting affective lability in treatment of individuals with psychotic disorders.

1.1 Psychosis spectrum disorders and the continuum model

Historically, there has been a conceptual and categorical divide between the "non-affective" versus "affective" psychotic disorders. The origins of this dichotomy can be traced back to Emil Kraepelin (1856-1926) who divided psychotic disorders into two separate entities due to differences in illness course and outcome; dementia praecox (schizophrenia) and manic-depressive illness (bipolar disorder) [20]. The Kraepelinian distinction has been influential for psychiatric nosology and has sparked much debate and controversy over the years [21-23]. It was first challenged by Eugen Bleuler who emphasized the importance of affect and aimed to extend the borders of schizophrenia to "the group of schizophrenias" [24]. Over time, there has been a gradual shift towards a more dimensional understanding of psychotic disorders. Schizophrenia is still considered to be more severe than bipolar disorder, but the disorders

are thought to exist on a continuum with predominantly psychotic symptoms on one end and predominantly affective symptoms on the other [25, 26]. This change in perception has largely been brought about by accumulating evidence of shared genetic susceptibility between schizophrenia- and bipolar disorders [27-31], in addition to substantial overlap in clinical characteristics such as positive and negative psychotic symptoms [32-34], affective disturbances [35-39], impairments in neurocognition [40-42], risk of substance use [43-45], suicide [46] and early death due to cardiovascular disorders [47, 48]. Studies have also found metabolomics evidence and inflammatory marker alterations supporting the continuum model [49, 50]. The overlap between the disorders is further reflected in clinical practice where standard treatment typically consists of a combination of antipsychotic medication and psychosocial interventions [51, 52]. This illustrates that the boundaries between these diagnostic categories are not precise, nor likely to be a reflection of single disease entities, but perhaps suggestive of a more general psychosis or "psychosis-proneness" phenotype [53, 54]. Such a view is in line with the Research Domain Criteria (RDoC) framework for organizing research initiated by the National Institute of Mental Health [55, 56]. RDoC propagates transcending the boundaries of traditional nosology when investigating the biological and psychosocial basis of core features in mental health. Recently, and relevant for this thesis, affect regulation has been proposed as a new domain in the RDoC framework [57]. A focus on key transdiagnostic factors that contribute to development and maintenance of different forms of psychopathology may contribute to a personalized approach to classification and treatment in the future; a precision medicine for psychiatry [58].

1.1.1 Epidemiology and etiology

Psychotic disorders are severe mental disorders with a lifetime prevalence exceeding 3% [59, 60] and are associated with substantial morbidity and mortality [61-64]. The disorders typically have their onset in late adolescence or early twenties, and are heterogeneous syndromes with highly variable clinical presentations and outcomes. While some individuals experience a relapsing-remitting illness course where illness episodes are followed by stable periods with regained functioning, others have persistent signs and symptoms of the disorders that continue to interfere with functioning over time. In general, the former appears to be more characteristic for bipolar disorders [65], whereas the latter is more representative for

schizophrenia [66]. Despite decades of research, the precise etiology and underlying pathophysiology of psychotic disorders is still largely unknown. However, there is a consensus that the disorders are likely to develop as a consequence of a complex interplay between underlying genetic vulnerability and environmental stressors [14, 15, 67, 68]. Heritability estimates for both schizophrenia and bipolar disorders are high, around 80% [69, 70]. Recent genome-wide association studies (GWAS) have revealed a substantial degree of polygenicity with the likely involvement of a large number of genetic loci [71-73]. Each of the loci appear to have small effects and act together with a multitude of potential biological and psychosocial risk factors or -markers. These include pre- and postnatal complications, neurodevelopmental abnormalities, childhood trauma, urbanicity, migration and substance use [14, 61, 62, 74]. Furthermore, neuroimaging studies have demonstrated structural and functional brain abnormalities in cortical volume and –thickness, white matter integrity deficits and decreased fronto-parietal network connectivity in schizophrenia and bipolar disorders [75]. Albeit more pronounced in schizophrenia than in bipolar disorder, these abnormalities collectively point in the direction of shared neurobiological underpinnings with primary differences in quantity rather than quality of deficits [76]. This also applies to neurocognitive impairments which have been found across all cognitive domains (including memory, executive function, attention and processing speed) and appear to be stable over time irrespective of fluctuations in symptom severity [77, 78].

Of the known environmental risk factors for psychosis, exposure to environmental hazards and childhood trauma in particular appears to increase the risk substantially [79]. Childhood trauma has been implicated in the dysregulation of the hypothalamic pituitary adrenal (HPA) axis observed in these disorders which is presumed to play an important role with respect to etiology [80, 81]. Specifically, early adverse events may render the individual vulnerable to later stress through increased and sustained glucocorticoid release. In addition, such events can induce changes in neurotransmitter pathways involving dopamine, GABA and glutamate that may alter the balance between inhibitory and excitatory states in the brain [73, 82]. Together, the association between inherent vulnerability and acquired stress (environmental/psychological/biological) may result in aberrant functioning of brain circuits leading to symptom formation [14, 15, 67, 83].

1.1.2 Psychotic symptoms

Psychotic symptoms entail a loss of contact with reality, often expressed through the presence of hallucinations and/or delusions. *Hallucinations* are abnormal sensory perceptions or experiences that occur in the absence of stimulation of the relevant sensory organ and can occur in any sensory modality (auditory, visual, olfactory, gustatory, tactile, somatic, kinesthetic) [84, p. 18]. Auditory hallucinations, hearing voices in particular, are the most prevalent type of hallucinations in both schizophrenia and bipolar disorder [85]. *Delusions* are overvalued or false fixed beliefs that are not attributed to an individual's social or cultural background and are held with extraordinary conviction, despite evidence to the contrary [86, p. 10]. Delusional themes are highly variable and can include persecution/paranoia, grandeur, somatic changes, jealousy/love, passivity phenomena (thoughts/actions are controlled by an external agent) and religious deliberations. Persecutory delusions have been reported to be most common in schizophrenia and delusions of grandiosity are the most prevalent in bipolar disorder, but both types frequently occur across diagnoses along with somatic delusions and delusions of guilt [87]. Hallucinations and delusions are closely linked grave impairments in reality testing that can develop gradually over time or have an abrupt onset, they can be brief and episodic or more or less continuous [84, p. 9., 85].

Collectively, hallucinations and delusions are the most evident and dramatic manifestations of psychotic disorders and are called *positive symptoms* because they are "in excess" of normal experiences. These symptoms have traditionally been the main targets for pharmacological treatment interventions [88]. *Negative symptoms*, on the other hand, refer to a reduction in, or presumed lack of, normal experiences. Negative symptoms are manifested as flattened affect, social withdrawal (asociality), poverty of speech (alogia), lack of initiative and motivation (avolition) and loss of pleasure (anhedonia). Negative symptoms can be severely debilitating as they are difficult to treat and tend to be long-lasting [89-91]. In acute phases, *disorganized thinking, -speech and -behavior* is also common, along with *excitative symptoms* such as agitation and impulsivity [92, 93]. The psychotic symptoms outlined here are present to varying degrees in the diagnoses included in the sample presented in this thesis, which will be described below.

1.1.3 Diagnostic classification of psychotic disorders

Despite the significant overlaps highlighted in the sections above, the categorizations between psychotic disorders into schizophrenia- and bipolar spectrum disorders are upheld in the current diagnostic classification systems. They are also still highly relevant and useful in a clinical context [94-96]. Consequently, the diagnostic criteria for schizophrenia- and bipolar spectrum disorders will be outlined separately in the sections below.

The three studies that are included in this thesis are part of the larger Thematically Organized Psychosis (TOP) research study at the Norwegian Center for Mental Disorders Research (NORMENT). In the TOP study, the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) [97] is used to establish schizophrenia- and bipolar spectrum disorder diagnoses as part of a thorough clinical interview covering current symptom state as well as previous illness history. As a result, the DSM-IV is also the basis for all considerations regarding diagnoses in the current thesis.

Schizophrenia spectrum disorders

According to the DSM-IV classification, schizophrenia spectrum disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychotic disorder Not Otherwise Specified (NOS) [97]. The symptoms associated with schizophrenia spectrum disorders are organized into five main domains in the DSM-IV: *delusions* (e.g. paranoid, grandiose, delusions of reference), *hallucinations* (e.g. auditory, visual, tactile), *disorganized speech* (e.g incoherence, frequent derailment), *grossly disorganized or catatonic behavior*, and *negative symptoms* (e.g affective flattening, avolition, social withdrawal). For a diagnosis of *schizophrenia*, two (or more) of these symptoms must be actively present for a duration of at least one month (or less if successfully treated) as a general rule, but only one symptom is necessary if delusions are bizarre or if auditory hallucinations consist of a voice keeping a running commentary on the individual's thoughts or behaviors. The symptoms must result in significant loss of functioning, with continuous signs of the disorder lasting for a minimum of six months. Further, schizoaffective disorder and mood disorder with psychotic features must also be excluded, along with psychotic disturbances due to a general medical condition or substance use. If the condition meets

criteria for schizophrenia but is limited to between one and six months in duration, a diagnosis of *schizophreniform disorder* will be given. If the duration is one month or less, the diagnosis that follows is *brief psychotic disorder*. *Schizoaffective disorder* is diagnosed when an active phase with psychotic symptoms as described in schizophrenia is accompanied by a concurrent mood episode (major depressive-, manic- or mixed episode). However, hallucinations or delusions must also be present for at least two weeks in the absence of prominent mood symptoms, and the symptoms meeting the criteria for a mood episode must be present for a substantial portion of the total duration of illness. In *delusional disorder*, the clinical picture is dominated by primarily non-bizarre delusions, but no other signs and symptoms of schizophrenia should be observed, although hallucinations can be present if they are related to the theme of the delusions. Finally, a diagnosis of *psychotic disorder NOS* should be used when psychotic symptomatology is present, but the clinician is unable to reach a definite diagnostic conclusion due to inconclusive or contradictory information.

Bipolar spectrum disorders

In the DSM-IV, bipolar and related disorders include bipolar I disorder (BDI), bipolar II disorder (BDII) and bipolar disorder Not Otherwise Specified (BD NOS), and the hallmark symptom domains are mania/hypomania and major depression. The classification into the two main diagnostic categories, BDI and BDII, largely depends on the severity of elevated mood [97]. An episode of *mania* is characterized by a distinct period of abnormally elevated, expansive or irritable mood lasting for at least one consecutive week (or any duration if hospitalization is necessary). Further, three (or four if only irritability is present) of the following symptoms must be present to a significant degree: grandiosity, decreased need for sleep, talkativeness (pressure to speak), flight of ideas (racing thoughts), distractibility, and increase in goal-directed activity/psychomotor agitation or excessive involvement in pleasurable activities with potential for harmful consequences. Finally, the disturbance in mood must be sufficiently severe to cause marked impairment in occupational- or social functioning, result in hospitalization or have psychotic features such as hallucinations or delusions. The criteria for an episode of *hypomania* are the same as for mania, except for a shorter minimum threshold of duration (at least four days), and the extent of functional impairment caused by the episode

which should *not* be significant. Hypomania is never severe enough to cause hospitalization and cannot be accompanied by psychotic symptoms (this inevitably leads to a classification of mania).

Bipolar disorder generally also includes *major depressive episodes*. Such episodes should last for at least two weeks with persistent depressed mood and/or marked loss of interest/pleasure, accompanied by at least three of the following (four if only depressed mood or loss of interest is present): significant weight loss/gain or decreased/increased appetite, sleep disturbance (insomnia/hypersomnia), psychomotor agitation/retardation, loss of energy, feelings of worthlessness/inappropriate guilt, diminished ability to concentrate/indecisiveness or suicidality (ideation, plan, attempts). Some of these symptoms may take on a delusional quality or be associated with the presence of hallucinations. Further, the symptoms must cause clinically significant distress or impairment in social, occupational or other important areas of functioning. In a *mixed episode*, the criteria are met for a manic episode and for a major depressive episode (except for duration) simultaneously nearly every day during at least a one-week period. *BDI* is characterized by at least one manic or mixed episode, but in most cases includes several major depressive episodes as well. In *BDII*, which is characterized by at least one hypomanic and at least one depressive episode, all elevated episodes are hypomanic. The depressive episodes of both BDI and BDII can be associated with psychotic symptoms which may or may not be mood-congruent. A diagnosis of *BD NOS* is given when the disorder has bipolar features, but do not meet the full criteria for any specific bipolar disorder.

Even though the biphasic mood episodes are the most distinguishing features of bipolar disorders, psychosis is common. In fact, psychotic symptoms are so frequent in acute mania that it has been argued that it should primarily be considered a psychotic state [98]. Psychosis in mania is most commonly characterized by grandiose and expansive delusions which can often have religious or paranoid themes. In bipolar depression, it has been reported that up to 50% of patients experience psychosis irrespective of bipolar disorder subtype [15, 99, p. 59], whereas other studies have found higher rates of psychotic features in depression in BDI compared to BDII [100]. Despite the inconsistencies in prevalence rates, the psychotic

symptoms that appear to be most common in bipolar depression are delusions of guilt and sinfulness [99, p. 71]. Overall, when the bipolar subtypes are compared with respect to lifetime prevalence of psychosis, the rates are typically above 50% for BDI [101] and around 20% in BDII [102], with some variations between studies. With respect to the inclusion of bipolar disorder under the umbrella term psychosis spectrum disorders, the research field is under rapid development with the number of genetic studies accelerating, and the conceptualization might change in the future as a result of new evidence. As noted under section 1.1, the evidence thus far is strong for a genetic overlap between schizophrenia and BDI as well as for the expected overlap between BDI and BDII. However, novel and distinct genetic loci have recently been found for each of the two bipolar disorders indicating a combination of both common and specific risk loci [103].

1.2 Affective lability

Over the years, labile affect has been discussed extensively in the psychiatric literature due to its prominent associations with various forms of psychopathology, in particular borderline personality disorder [10, 104]. However, the definition of affective lability, what it entails and the demarcation of the borders with overlapping constructs such as emotional lability, affective instability and mood instability has been variable and vague. The confusion surrounding terminology has resulted in substantial heterogeneity in how affective lability is understood and assessed. As I will return to in the sections below, there is an increasing focus on clarifying terminology and the current work aims to contribute with a better understanding of affective lability in psychotic disorders that can improve clinical applicability of the construct.

1.2.1 Affect, emotion, mood

The abovementioned definitional and conceptual muddle reflects the general inconsistency in the field of affective science where the terms affect, emotion and mood are often used interchangeably without a clear consensus regarding precise definitions. In the service of clarification, I will define these broader terms before discussing affective lability further.

The current scientific notion of *affect* is largely in line with the Wundtian view of affect as basic feelings that arise from internal bodily sensations [105]. Affect (or core affect) has two main features; valence (unpleasant vs pleasant) and arousal (activation vs inhibition), and the combination of the two gives rise to the affective tone of our subjective experiences [4, 106, pp. 38-40.]. In this sense, affect provides us with information about the state of our body in the world; "a neurophysiological barometer of the individual's relationship to an environment at a given point in time, with self-reported feelings as the barometer readings" [2, p. 171]. Affect is postulated as a broad and overarching concept that is central in emotions and moods, but also universally and constantly present as a feature of consciousness [107]. *Emotions* are affective experiences that are brief and intense. They are typically elicited by, or reactions to, something in the immediate environment, and are the results of a complex set of appraisal processes and responses [108]. Emotions have an important evolutionary function in that they provide us with information about the demands of our environment and help us to respond adequately to them [109]. *Moods* arise when emotional experiences are sustained and extended into longer durations. Moods may be global, nonspecific or diffuse, are not necessarily about an object or an event but when they are, the cause is often temporally distant from the experience of the mood [106, pp. 44-45].

When things go well, affect, emotion and mood swirl around without much effortful need for regulation or reflection. When situational demands exceed our regulatory capacities, however, this may give rise to affective disturbance which is broadly defined as disruptions in the multi-system response (subjective experience, expressive behavior, physiology) of emotions, moods and stress [108, p. 587]. Affective lability is one such affective disturbance that may give rise to, or be indicative of, challenges with affect regulation. In a general sense, affective disturbances are present to a certain degree in a large number (above 40%) of the disorders listed in the DSM-IV [108]. Yet, they are noted in the diagnostic criteria of far fewer. Consequently, proponents of the RDoC framework suggest to look beyond diagnoses and focus on transdiagnostic and dimensional factors that are likely to be relevant illness mechanisms, such as various forms of affective disturbances, in order to understand the many facets of psychopathology [57].

1.2.2 Defining, conceptualizing and measuring affective lability

In their article "How is affective instability defined and measured? A systematic review", Marwaha and colleagues (2014) aimed to clarify inconsistencies around definitions and measurement of instability in affect. After a thorough study selection process, they identified 37 studies that defined and measured affective instability in different clinical populations using the following terms: affective lability, affective dysregulation, emotional dysregulation, emotion regulation, emotional lability, mood instability, mood lability or mood swings. In itself, the share volume of terms illustrates the challenges with heterogeneity in terminology in the field. Several of Marwahas' findings are highly relevant to the present thesis. First, no important differences between the definitions of affective instability specifically versus those for affective lability/dysregulation, mood instability/lability or mood swings were found [110]. This means that although definitions between studies differ and greater specification is needed, they largely focus on similar attributes. In other words, the findings and implications of studies investigating "affective instability" are likely to be relevant for the construct of "affective lability". When referring to previous studies in this field, I will consequently use the term affective lability for consistency even if other terms have been used in the original studies. This will be done as long as the assessment measure utilized captures phenomena in line with the chosen definition of affective lability as presented below.

Second, the key features within the various definitions of affective instability were not disorder-specific, illustrating that operationalization of the construct in the literature is transdiagnostic and relevant to a host of mental disorders, as well as the general population. Finally, their analysis indicates that affective instability is a broad construct that consists of three core elements: *lability, intensity and control*. Their definition of affective instability highlights this: "rapid oscillations of intense affect, with a difficulty in regulating these oscillations and their behavioral consequences" (p. 1802). Of the core elements, only the level of affective lability and affective control, and not affective intensity, have in a later study been found to be significantly different in those with mental disorders compared to those without [8]. Here, higher lability and lower control was associated with having a disorder. This implies that variability in these specific features of affective instability may be particularly relevant to the development and maintenance of psychopathology. Further, the same study found that only affective lability was associated with functioning after adjusting for diagnostic categories

and other important patient characteristics [8], illustrating that affective lability may be an impediment to functional remission.

In the studies that comprise this thesis, I have chosen to use the recent definition of affective lability by Zwicker and colleagues (2019): "the propensity to experience rapid, unpredictable and excessive changes in affect[1]" (p. 446), which was adapted from Gerson and colleagues (1996) [111, 112]. This definition is largely overlapping with that of affective lability in the DSM-IV: "abnormal variability of affect with repeated, rapid, and abrupt shifts in affective expression" [113], as well as the early description of affective lability by Philip Harvey of "changeable affect" [114]. Referring back to the two main features of affect, namely valence and arousal, affective lability may thus conceptually encompass rapid changes in the general feeling of unpleasantness/pleasantness with some degree of activation, as well as rapid changes between more specific affective experiences (irritability/anger/happiness) with various degrees of activation [111]. As affective lability is a construct that cannot be observed directly, its presence is typically determined by self-report instruments that differ in their scope, length and use of categorical versus dimensional conceptualizations. There is currently no gold standard for measuring affective lability, but the Affective Lability Scale (ALS, [114]) is frequently used in the research literature and the short version of the scale is also the instrument used in the studies presented in this thesis. The ALS will be described in detail in the methods section.

1.2.3 Prevalence in the general population and mental disorders

Affective lability appears to be relatively common in the general population, with a prevalence rate of around 14% found in an epidemiological population study from England [115]. It is reported to be more frequently occurring in women and in younger people and appears to gradually decrease with age [115]. Although a limited number of studies have explored the potential implications of having affective lability in general population cohorts, those who

[1] Zwicker uses the term "mood" instead of "affect" and although used interchangeably in the literature, I believe affect best represents the construct of *affective* lability.

have suggest that it is associated with adverse effects such as the onset and continuation of non-suicidal self-injury [116] and suicidal thinking and ideas [115]. In addition, it has been linked to lower vagally mediated heart rate variability which is associated with risk for cardiovascular disease [117, 118]. In mental disorders, affective lability is prevalent and related to a host of negative clinical and functional outcomes. The disorders most commonly associated with affective lability will be discussed in the sections below, with a particular emphasis on psychotic disorders.

Affective lability is a defining feature and a core symptom included in the diagnostic criteria of borderline personality disorder [119], as well as a therapeutic target in treatment [120]. Affective lability in borderline personality disorder is characterized by frequent shifts between normal mood and anger, in addition to fluctuations between depression and anxiety [104, 121-124]. In Attention Deficit Hyperactivity Disorder (ADHD), prevalence rates of affective lability have also been found to be high [125-127], and the same applies to Post-Traumatic Stress Disorder (PTSD) [128, 129]. Furthermore, affective lability has been highlighted as a factor involved in dysregulated eating behavior [130-132]. With respect to major depressive disorder, affective lability has been established as a precursor of depressive episodes, predicting their onset [133]. However, there is surprisingly limited work exploring the specific effects of affective lability in major depressive disorder, despite a reported prevalence of over 60% [115] and aligned findings suggesting that it should be routinely assessed in this population [134-136]. Taken together, affective lability has somewhat different correlates in these disorders, but appears to be associated with a more arduous illness burden.

In psychotic disorders, the majority of the studies have focused on bipolar disorders where disturbances in affective states is a key feature. Comparatively fewer studies have investigated the specifics of prevalence, level, distribution and correlates of affective lability in what has traditionally been referred to as non-affective psychotic disorders, schizophrenia in particular. In bipolar disorders, affective lability has been identified as a precursor of the disorder [137, 138] and as part of the prodromal phase [139-141]. It is present early in the course of illness [142, 143], in euthymia [144], in all polarities of the illness episodes [145-148], as well as in

non-affected relatives [149, 150]. Thus, affective lability appears to be both a risk factor and an inherent part of the disorder itself, in addition to a feature that is exacerbated in illness episodes. It has also consistently been linked to poor prognosis. Here, associations have been found with alcohol use disorders [151], reduced overall functioning and quality of life [152, 153], suicidality [154, 155], anxiety [154, 156], mixed episodes [154], elevated blood pressure [157], and lower likelihood of recovery [158]. Affective lability has been found to be higher in BDII compared to BDI [143, 159, 160]. As it is a prominent feature in both BDII and borderline personality disorder contributing to the overlap in clinical expressions, differentiating between the two disorders can be a challenging diagnostic exercise [161]. Structurally, however, there appears to be some differences, as affective lability in BDII has not been found to be associated with fluctuations in anger [121, 122]. The extent to which this is the case for BDI as well is not known and is one of the areas which we wanted to clarify in this thesis. In the literature, there is also some focus on a phenomenon which is closely related to affective lability, namely affective reactivity. Affective reactivity entails the emotional response to environmental cues, or stress sensitivity [162, 163], and particular emphasis has been put on the process of inhibition/activation in distinguishing between mixed states (dysphoric mania and agitated depression) [164]. From a clinical perspective, this is important as mixed episodes are difficult to treat and linked to negative outcomes [165]. Further, affective hyper-reactivity appears to be connected to unfavorable somatic outcomes, such as inflammation and increased cardiometabolic risk [166-169]. Heightened affective reactivity to both positive and negative stimuli and lower use of adaptive emotion regulation strategies have been noted in a relatively large body of work, particularly pertaining to BDI [170, 171]. In fact, difficulties in downregulating positive affect has been suggested to be the primary driver of mania [172]. The findings are mixed, however, with some studies reporting better outcomes in the face of higher levels of positive affect suggesting that higher positive affectivity is problematic primarily when it induces grave challenges with control and inhibition [173]. Overall, the evidence indicates that difficulty with regulating negative affect is the dimension that is most robustly and uniquely associated with bipolar disorder [173].

In schizophrenia and related disorders, the number of studies that have explicitly investigated affective lability is relatively scarce. The existing studies suggest that it is pronounced, that it

may be a part of the psychotic process either as a precursor, associated feature or as a consequence, and that it may mediate the link between childhood adversity and positive psychotic symptoms [8, 9, 174]. Further, associations with suicidality and self-injury have been found [175-178]. More generally, features of affective dysregulation have been related to the development and maintenance of auditory hallucinations, paranoid delusions as well as other psychotic experiences such as thought interference and passivity phenomena [35, 36, 179, 180]. In addition, affective dysregulation appears to be involved in the risk of transition to, and onset of, clinically relevant psychotic disorder in the general population [181]. In line with this, an affective pathway to psychosis has been proposed whereby aberrant affective reactivity to daily environmental stressors constitutes part of the liability to psychosis, in particular with respect to positive psychotic symptomatology [182, 183].

Collectively, the evidence suggests that affective lability is a dimensional, transdiagnostic construct that is implicated in the origins and features of many mental disorders. It appears to add to the total illness burden and negatively impacts prognosis through significant associations with psychological, interpersonal, clinical, and somatic factors. However, heterogeneity in definitions and measurements of affective lability limits its clinical utility as a treatment target. Thus, more studies are needed to delineate how it can best be understood in different clinical populations, including psychotic disorders.

1.2.4 Etiology of affective lability

The imprecisions concerning the construct of affective lability in the literature also render clarification of underlying mechanisms difficult. Yet, the evidence thus far suggests that a combination of genetic, environmental and psychological factors is at play [12, 13]. In the following sections, the most relevant research findings pertaining to the possible etiology of affective lability will be summarized. The biological and environmental risk factors associated with affective lability are highly intertwined and generally difficult to disentangle from each other, but for the sake of simplicity I have tried to divide them into separate sections based on presumed primacy.

Genetic and neurobiological factors

Results from twin-studies indicate a small to modest influence of genetic factors on affective lability [184, 185]. Recently, 46 independent genetic loci were identified in a large population cohort, along with a heritability estimate based on single-nucleotide polymorphisms (SNP) of ~8% in another study [186, 187]. Further, several studies have found elevated affective lability in healthy relatives of individuals with affective disorders compared to controls, indicating that affective lability may be an endophenotypic trait [111, 153, 188, 189]. A significant overlap with the personality trait neuroticism which has a substantial heritable component has also been found [190], although the two constructs still appear to be phenomenologically distinct [191, 192].

In terms of neurobiological factors, imaging studies have revealed altered amygdala activation and neural connectivity dysfunction associated with affective lability, particularly in the default mode- and salience networks [164, 193-195]. Further, abnormalities in neurotransmitter activity (both serotonergic, cholinergic and noradrenergic) have been noted [10, 12]. More generally, a factor rooted in structural and functional neural deficits that has been suggested to underlie and exacerbate affective disturbances is aberrant affective cognition, often referred to as “hot” (i.e. emotion-laden) cognition [196-198]. In particular, difficulties with facial emotion recognition have been noted as a possible early risk marker of bipolar disorder and also appears to be present in schizophrenia [199, 200]. How challenges with affective cognition might affect affective lability or vice versa is, however, unclear. Finally, studies investigating temperament, which is considered to be a relatively stable and heritable biological trait, suggest that affective lability is one of the temperamental factors that is already observable in newborns [201-203]. In adults, cyclothymic temperament, defined as a relatively permanent instability in mood, thinking and activity [204], has been associated with affective lability and is suggested as a common denominator for the overlap between borderline personality disorder, ADHD and bipolar disorder [205-207].

Environmental and psychological factors

Environmental factors pertaining to the child-caregiver relationship present early in life appear to be central to the development of affective lability [10, 12]. Here, the role of childhood trauma, in particular childhood neglect and abuse, is of specific importance and has been associated with higher rates of affective lability in clinical populations [159, 174, 208-210]. Adaptive affect regulation and modulation of sensitivity to environmental cues in the developing child is largely contingent upon the caregivers' ability to be attuned to changes in affective states and to serve as a self-regulating other [211]. When there is an ongoing failure to meet the needs of the child, such as in neglect, the impact on the development of affect regulation abilities is monumental and has pervasive psychological and neurobiological effects [212, 213]. Notably, maturation of the neuroendocrine system, including the HPA axis, is affected by the quality of early caregiver experiences rendering children exposed to early adversity more likely to have heightened biological and emotional reactivity to contextual demands which again makes it challenging to self-regulate in an adaptive way [214].

Still, there appear to be avenues to affective disturbances that are not based in grave insults. As mentioned in the previous section, there are also inherent factors and predispositions in the child that are likely to play a part and impact the responses of the caregiver in the interactive dyad that provides the base for the emotional responses of the child [211]. In other words, some newborns come into the world with genes and/or temperamental features that leave them particularly sensitive to the environment and may result in frequent displays of distress and soothing difficulties. This in turn will place higher demands on the quality of the child-caregiver relationship and require more sensitivity and a larger contribution on the part of the caregiver [10]. When the affective demands of the child exceed the regulatory capacity of the caregiver, this might contribute to an environment that fosters maladaptive affective responsivity in the caregiver, which over time may result in difficulties managing and processing the child's affect[211]. Several studies drawing on John Bowlby's attachment theory have highlighted the importance of secure attachment for adaptive affect regulation and inversely, the far-reaching negative consequences of insecure attachment styles on the ability to regulate negative affect [215-217]. The latter appears to be an obstacle to forming interpersonal relationships in particular. The specific effect of different attachment styles on affective lability has not been investigated in-depth. However, insecure attachment has been

linked to higher levels of affective disturbances in general in psychotic disorders including ultra-high risk populations, addiction and borderline personality disorder [218-224]. Moreover, insecure attachment and unpredictable and chaotic rearing practices have been found to characterize the family climates of children who have experienced childhood maltreatment [225].

To summarize, the existing research pertaining to the etiology of affective lability suggests that its origins are early in life; rooted in an interplay between an inherent trait and developmental experiences such as early trauma and disturbances in the child-caregiver relationship that further modulates its expression.

1.3 Social functioning in psychotic disorders

Social functioning has been defined broadly as the capacity of a person to function in different societal roles such as homemaker, worker, student, partner, family member or friend [226, 227]. Healthy social relationships are linked to longer, healthier lives and psychological well-being, and appear to be just as crucial for mortality as behavioral risk factors such as smoking, obesity, physical inactivity and high blood-pressure [228]. Yet, the importance of social factors for health is often underestimated [229]. In psychotic disorders, social functioning is an important marker of recovery and a predictor of well-being [230, 231]. In fact, the capacity to socialize and positively engage in social relationships has been shown to be key to the health-related quality of life in this population [232]. As life expectancy has been found to be markedly decreased in psychotic disorders compared to the general population, the health-promoting benefits of social factors are perhaps particularly central [169]. Previous literature has established that social functioning is impaired across diagnoses in psychotic disorders and is predicted by a range of risk factors connected to both individual characteristics and lifetime- and current illness related features [233, 234]. These include core clinical features such as positive-, negative- and depressive symptoms [36, 37, 233, 235-242], male sex [238, 243], impaired premorbid social functioning [244, 245], deficits in neurocognition [235, 246], total number of illness episodes [238, 247], duration of untreated illness [248, 249] and comorbidity, including substance use and anxiety disorders [238, 250-253]. Recent evidence

suggests that there is moderate improvement in social functioning in psychotic disorders overall over time [254], but also that persistent impairments are evident in a substantial group that can already be identified in adolescence [244].

1.3.1 Social functioning and affective lability in psychotic disorders

Our affective worlds are developed, expressed and regulated in a social context through interactions with others [255, pp 3-5]. Social settings are by default ever-changing, ambiguous and unpredictable, and consequently it is necessary to have a clear representation of, and control over, one's own internal affective states to guide appropriate behavior and responses [256]. Affective lability might contribute to make this challenging through increased reactivity and difficulty in maintaining a consistent affective state, and as a result may impede the drive to establish both peripheral and close social connections. In a self-reinforcing manner, the lack of social contact may also increase affective lability as the opportunity to regulate or calibrate through the help of others is lost. Indeed, several studies have found significant associations between various forms of affective disturbances and reduced social functioning in psychotic disorders [146, 153, 257-264]. Still, the specific relationship between affective lability and social functioning in psychotic disorders has, to our knowledge, not been investigated previously.

1.4 Knowledge gaps

The realms of affective lability in psychotic disorders have yet to be fully explored, rendering several knowledge gaps with respect to how prominent such experiences are and how they manifest in the different psychotic disorders that this thesis aims to narrow. First, there is a lack of studies investigating affective lability in psychotic disorders that also includes healthy controls from the same catchment area. As affective lability is common in the general population, this is needed and will contribute to establish if affective lability is indeed a prominent illness feature in psychotic disorders beyond what lies within "normality" and in line with what can be expected based on previous research. There is also a shortage of more specific comparisons of how the level of affective lability varies between different diagnostic subgroups, in particular pertaining to non-affective psychosis. In addition, the

sociodemographic, clinical and functional correlates of affective lability in psychotic disorders are unclear, along with information about how it is structured (i.e. what types of affective fluctuations dominate), and if this varies between diagnostic subgroups. Collectively, these areas of uncertainty limit the clinical utility of affective lability and should be clarified in order to evaluate its potential as a putative treatment target for individuals with psychotic disorders. Also, increased knowledge about affective lability may contribute to a better understanding of illness- and/or symptom mechanisms in psychotic disorders.

2 Aims

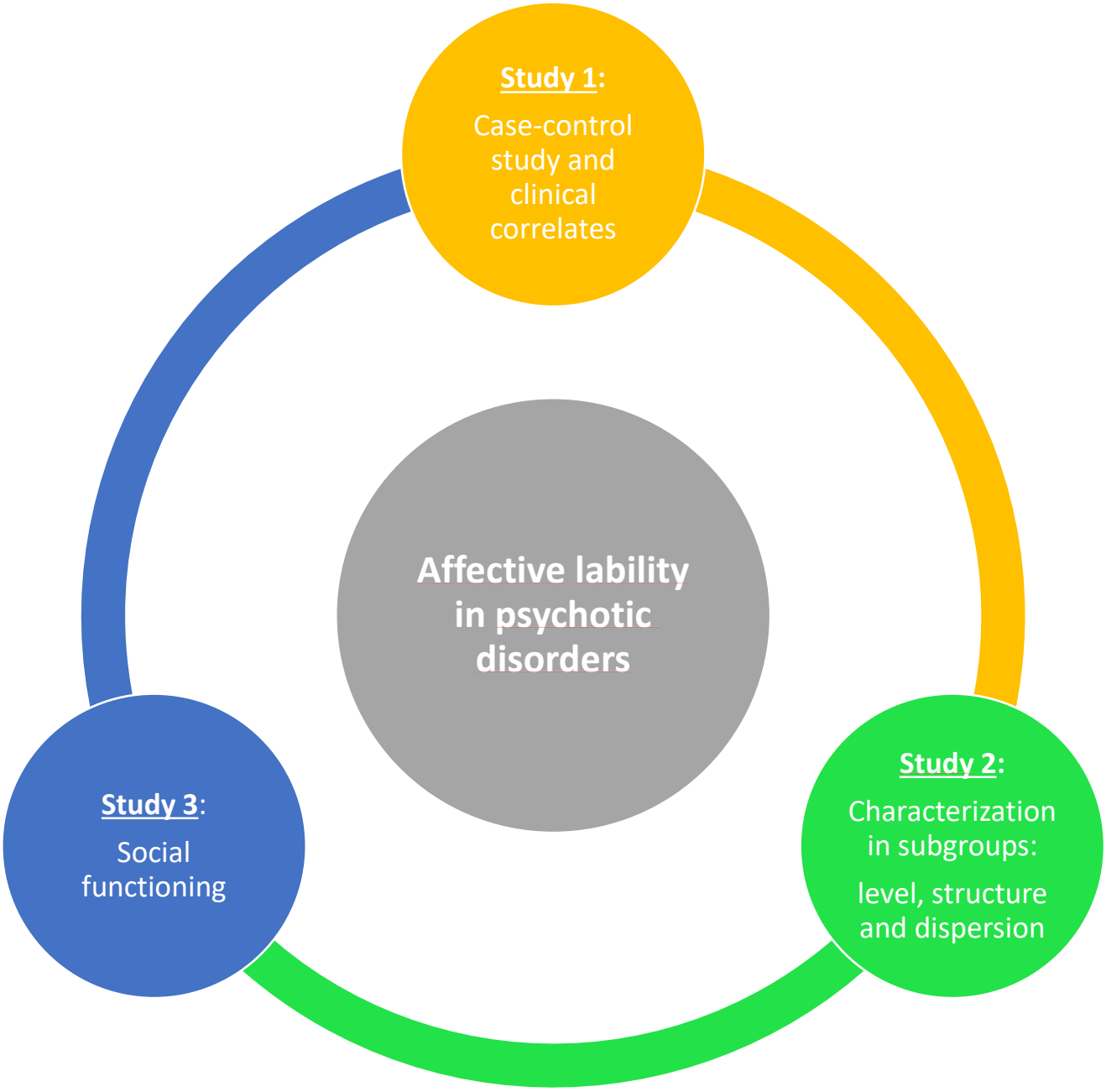
The overall and main aim of the current PhD project was to increase the knowledge about affective lability in psychotic disorders through three specific studies:

In **study I**, the aim was to compare the level of affective lability in individuals with either schizophrenia- or bipolar spectrum disorders and healthy controls. Further, we aimed to explore whether there were specific sociodemographic and clinical correlates of affective lability in the schizophrenia- compared to the bipolar spectrum group.

In **study II**, the first aim was to investigate if there were differences in the level and architecture of affective lability in the different psychotic disorders, and if potential differences remained after controlling for current symptom status and other possible confounders. The second aim was to investigate the dispersion of affective lability within each diagnostic category, as well as to establish if there are differences in dispersion between the diagnostic groups.

In **study III**, we aimed to investigate the relationship between affective lability and social functioning in psychotic disorders, and to explore whether such a putative association was specific to subdimensions of affective lability. We hypothesized that affective lability would be associated with social functioning independent of other pre-defined and well-established predictors of social impairments.

2.1 Study overview



3 Material and methods

3.1 Design and research setting

The three studies presented in this thesis are part of the larger translational TOP study at the NORMENT Center in Oslo (Norway), and used naturalistic cross-sectional data collected between the time periods of October 2006 to September 2019. NORMENT is a cross-disciplinary research Center of Excellence (CoE) funded by the Research Council of Norway, and aims to clarify the causes and mechanisms underlying severe mental disorders. The center is organized as a collaboration between the host institution University of Oslo and the University of Bergen, Oslo University Hospital and Haukeland University Hospital. The studies included in this thesis are rooted in the Mechanisms of Psychopathology group headed by Trine Vik Lagerberg where the primary aim is to expand the understanding of mechanisms underlying the significant symptom variation observed in psychotic disorders over time and between individuals. The TOP study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and is conducted in line with the Helsinki declaration of 1975 (as revised in 2008 and 2013). For more information about NORMENT, please refer to https://www.med.uio.no/norment/om/arsrapport/norment-annual-report-2020.pdf.

3.2 Participants and recruitment procedures

In the TOP study, participants are recruited based on diagnosis, i.e. psychosis spectrum, including both schizophrenia- and bipolar spectrum disorders. Consequently, individuals with non-psychotic bipolar disorder are also included. Potential participants are consecutively recruited from psychiatric inpatient- and outpatient units in a catchment area that is comprised of all the major hospitals in Oslo and surrounding regions. All individuals with mental health problems in Norway receive public mental health care in their catchment area and as such the representability of the TOP sample is considered to be very good. Healthy control participants from the same catchment area as the patient group are recruited through random selection using national statistical records. The Primary Care Evaluation of Mental Disorders questionnaire [265] is used to screen control participants for a history of mental disorders, ongoing drug or alcohol use, in addition to history of mental disorders in first-

degree relatives. Those who have ongoing substance use, mental disorders or first-degree relatives with schizophrenia, bipolar disorder or major depressive disorders are not included. All participants in the TOP study must be between 18-65 years and speak a Scandinavian language. General exclusion criteria are intelligence quotient (IQ) below 70 and prior history of severe head trauma or other organic brain pathology. Thorough information about the purpose of the study emphasizing its voluntary nature and the opportunity to withdraw at any time is given verbally and in writing before the participants sign the consent form that is a prerequisite for participation. Economic compensation of NOK 500 to cover travel and other expenses related to participation is provided. The short version of the ALS, the ALS-SF, is part of the standard TOP clinical protocol and was used to assess affective lability in studies I-III. Only the individuals who had completed the ALS-SF were eligible for the studies (further description of the study samples is outlined below). The ALS-SF was initially introduced in a TOP study sub-protocol for participants with first-episode mania. A few years later, it was included in the main TOP protocol (i.e. to individuals with other diagnoses than BDI).

3.3 Study samples

Overall, studies I-III used highly overlapping samples, with the exception of the inclusion of healthy control participants (n=140) in study I. Due to newly added participants included in the time period from January 2018 to September 2019, the total n for the patient group increased from n=222 in study I to n=297 in study II. Four of the 297 participants did not have sufficient data on the scale that was used to measure social functioning, the Social Functioning Scale (SFS), and were therefore not included in study III, rendering a total n of 293. For an overview of the distribution of diagnostic subgroups in each study, please refer to appendix I. A subsample (n=43) of the current study sample has previously been included in a study investigating the association between affective lability and alcohol use disorder in bipolar spectrum disorders [151].

3.4 Measures

3.4.1 Clinical assessments

All clinical assessments in the TOP study are carried out by clinical psychologists, psychiatrists or medical doctors who have completed a three-month training and quality assurance program developed at the University of California, Los Angeles, USA [266]. In addition, all interviewers receive supervision by senior researchers and participate in regular diagnostic consensus meetings led by Professor of Psychiatry and NORMENT core researcher (CR) Ingrid Melle. The TOP clinical interview protocol is extensive, covering sociodemographic information, diagnostic assessment using the Structured Clinical Interview for DSM-IV (SCID) modules A-E [267], symptomatology, substance use, physical health and medication. Supplementary information from medical records and close relatives is collected if needed. Diagnostic reliability is assessed with regular intervals and has been found to be very good with Cohen's kappa for diagnosis ranging between 0.92 and 0.99 across different assessment teams [268]. In addition to clinical assessments and a general medical examination, all participants undergo a neuropsychological evaluation.

3.4.2 Assessment of core symptoms

All assessments of psychotic- and affective symptoms in the three studies in this thesis were interview-based. The level of psychotic symptoms (positive, negative, general) was assessed by the well-established Positive and Negative Syndrome Scale (PANSS) [269]. Here, 30 items are rated on a scale from 1-7 where a score of ≥4 is indicative of clinically relevant psychotic symptoms. Consequently, a high total score is reflective of a higher symptom burden. With respect to depressive symptoms, they were assessed with the Inventory of Depressive Symptoms Clinician Rated (IDS-C) [270] for participants with bipolar spectrum disorders and the Calgary Depression Scale for Schizophrenia (CDSS) [271] for participants with schizophrenia spectrum disorders in study I. The IDS-C has 30 items covering the nine symptom domains used to characterize a major depressive episode in DSM-IV and is rated from 0 (not present) to 3 (severe). The CDSS is a 9-item scale rated from 0-4 in the same manner. In study II and III, depressive symptoms were assessed using the depression item (G6) from the general scale of the PANSS as this measure was available for all participants

irrespective of diagnosis. The rating for G6 is based on the answer to one opening question ("how has your mood been in the past week, mostly good or mostly bad?") followed by 1 to 11 questions to determine the extent of the depressive state and its behavioral consequences. To assess the presence of manic symptoms over the past two days from the interview date, the Young Mania Rating Scale (YMRS) [272] was used in all three studies. The YMRS consists of 11 items rated from 0-4 with higher scores indicating more severe symptoms.

3.4.3 Assessment of affective lability

The ALS was originally developed by Harvey and colleagues [114] and consists of 54 items aiming to capture how typical it is for an individual to fluctuate between different affective states. It was later adapted into a short form, the ALS-SF, which consists of 18 items and is preferred due to its reduced length. This version has largely replaced the original [273]. The ALS-SF is highly correlated with the original scale and has been found to have good psychometric properties across different clinical populations and in the general population [188, 274, 275].

The ALS-SF captures the total level of affective lability reported by the study participants (the sum of all item responses divided by 18), as well as subscores covering fluctuations between three subdimensions: anxiety-depression, depression-elation, and anger and normal mood. Consequently, it provides details regarding the potential architecture of affective lability and whether its presence is primarily driven by specific- or a combination of affects. The 18 items of the scale are rated on a 4-point Likert scale ranging from 0 ("very uncharacteristic of me") to 3 ("very characteristic of me"). Five of the items refer to shifts in anxiety-depression, eight refer to shifts in depression-elation and the final five items cover shifts between anger and normal mood. Of note, the eight items that comprise the depression-elation dimension have two items that strictly reflect elation/elevation in mood (item numbers 13 and 17), whereas the remaining items encompass shifts between experiences of decreased and increased energy/activation/distractibility that can occur in mania/hypomania but which do not necessarily involve elated mood per se. The items of the ALS-SF encompass *subjective experiences* (e.g. "One minute I can be feeling OK and then the next minute I'm tense, jittery, and nervous"), *physiological perceptions* (e.g. "There are times when I'm so mad that my heart

starts pounding and/or I start shaking and then shortly afterwards I feel quite relaxed") and *behaviors* (e.g. "I shift back and forth between being very unproductive and being just as productive as every-one else"). Please refer to appendix II to see all of the items of the ALS-SF.

3.4.4 Assessment of social functioning

In study III where the aim was to investigate associations between affective lability and social functioning, the interpersonal domain of the Social Functioning Scale (SFS) was used to measure the level of social functioning. The SFS is a self-report scale that was developed to assess social adjustment in schizophrenia [276], but it has also been validated for use in bipolar disorder [277]. The SFS is a lengthy scale with 76 items that yields a full-scale score as well as scores on seven subscales. Each subscale is standardized and normalized to a scaled score with a mean of 100 and a standard deviation of 15, and the full-scale score is calculated as the mean of the scaled scores of the seven subscales. Overall, the psychometric properties for the scale are reported to be good and to be highly correlated with clinician-rated measures of functioning [278-280]. The interpersonal domain is comprised of subscale 1) *Withdrawal* covering social engagement (amount of time spent alone, likelihood of initiating conversations, social avoidance) and subscale 2) *Interpersonal functioning* which assesses interpersonal behavior (number of friends, romantic relationships, quality of communication). A higher score is indicative of a higher level of functioning. The interpersonal domain has been found to have good ecological validity, particularly in terms of capturing social avoidance and social isolation [281]. Please refer to appendix III to see the items included in this domain.

The choice to use the interpersonal domain rather than the full-scale score was made because scales 3) *Pro-social activities* and 4) *Recreational activities* which combined comprise the activity domain have been found to have low ecological validity as well as to include items that are perhaps not directly relevant to social functioning [281]. Furthermore, scales 5) *Independence competency*, 6) *Independence performance* and 7) *Employment* are not directly reflective of *social* functioning but rather encompass skills for independent living (budgeting, preparing a meal, shopping for groceries etc.) and ability to work/study which were not of primary interest in this respect.

3.4.5 Assessment of other relevant clinical symptoms and variables for studies I-III

In order to shed light on affective lability in psychotic disorders as outlined in the aims of the three studies, several symptoms and variables were assessed and included as putative confounding variables. Identification of potential confounders between the independent and dependent variables is necessary so that these can be adjusted for in the statistical analyses and thereby increase the likelihood that an observed relationship is as specific and precise as possible. The rationale for the choice of variables for each study was as follows:

In *study I*, the aim was to investigate the level of affective lability in schizophrenia- or bipolar spectrum disorders and healthy controls. Based on previous research, sex and age were considered to be possible confounding variables [115, 282], along with number of years in education. Further, we aimed to explore whether there were specific sociodemographic and clinical correlates of affective lability in the schizophrenia spectrum as compared to the bipolar spectrum group. Here, duration of illness, medication use and current core symptoms (psychotic, manic, depressive) were considered as potential correlates to affective lability in both diagnostic groups as all of these factors could putatively influence the level of affective lability. In addition, alcohol- and cannabis use disorders have previously been found to be associated with affective lability in a study by our group [151] and thus these variables were also considered.

In *study II*, the aim was to investigate if there were differences in the level and architecture of affective lability in the different psychotic disorders, and if potential differences remained after controlling for current symptom status and other possible confounders. Here, current core symptoms (psychotic, manic, depressive), substance use status and sex were considered possible confounders, along with current level of anxiety. The latter variable was chosen as associations between anxiety and affective lability has previously been found in bipolar disorders [154].

In *study III*, the aim was to investigate putative associations between affective lability and social functioning in psychotic disorders, and if such an association was independent of other well-established predictors of social impairments. The persistence, frequency and level of affective and psychotic symptoms, both current and over the lifetime, has previously been found to influence social functioning in both schizophrenia- and bipolar spectrum disorders [36, 37, 233, 236-241, 260]. As such, total number of illness episodes, duration of illness, presence of psychotic episodes (lifetime) and current symptoms (psychotic, manic, depressive) were considered as potential confounders. In addition, associations between social functioning and sex [238, 243], poor premorbid social functioning [244, 245], neurocognitive deficits [235, 246], duration of untreated illness [248, 249] and comorbidities such as substance use and anxiety [238, 250-253] have been found and these variables were consequently also considered as potential confounders. The variables chosen for study I-III are described in more detail below:

Duration of illness in years

Duration of illness was estimated based on the age of onset of the first SCID-verified episode of psychosis for schizophrenia spectrum disorders and first affective episode for bipolar spectrum disorders in all three studies.

Substance use

In study I, lifetime alcohol- and cannabis substance abuse or dependence diagnoses were established according to the DSM-IV criteria using module E of the SCID. In studies II and III where current substance misuse was considered potentially confounding variables, the self-report forms Alcohol Use Disorders Identification Test (AUDIT) [283] and the Drug Use Disorders Identification Test (DUDIT) [284] were used.

Medication use

Current use of antipsychotic-, antidepressant- or mood stabilizing medication was obtained through the clinical interview and medical records and included in study I since all of these categories of pharmacological agents are known to have mood stabilizing properties [285]. Here, a dichotomous variable (current use yes/no) was created for each of the three classes of medications.

Anxiety symptoms

In studies II and III, the level of current anxiety symptoms was measured by the anxiety item G2 in the general scale of the PANSS where the rating is based on one initial question ("have you been feeling worried or nervous in the past week?"), followed by 1 to 6 questions depending on the response.

Duration of untreated illness in weeks

For study III, an estimate of duration of untreated illness was calculated for all diagnostic groups. In schizophrenia spectrum disorders, duration of untreated psychosis (DUP) was calculated as the number of weeks from the first SCID-verified psychotic episode to adequate treatment. Here, adequate treatment was considered as antipsychotic medication in adequate doses for more than 12 weeks or until remission, or admission to hospital for psychosis. For bipolar spectrum disorders, duration of untreated bipolar disorder (DUB) was based on the number of weeks from the first SCID-verified episode of mania/hypomania to adequate treatment; mood-stabilizing medication or antipsychotics in adequate doses for more than 12 weeks or until remission, or hospital admission for treatment of mania. DUP and DUB were then combined into one variable, duration of untreated illness, to use for the whole sample.

Total number of illness episodes

For study III, the total number of illness episodes was calculated as the sum of all recorded and SCID-I verified illness episodes (depressive, hypomanic, manic, mixed and psychotic). If psychotic symptoms were present in an affective episode, this was counted as one single episode.

Lifetime psychosis

Since previous research has indicated a relationship between psychotic symptoms and lower functioning and the sample in study III also included individuals with bipolar disorder who have never had a psychotic episode, a categorical psychosis lifetime variable was made. The variable was scored yes/no according to whether a SCID-verified psychotic episode was ever recorded.

Premorbid social adjustment

In study III, premorbid social adjustment was assessed based on scores on the social domain in childhood from the Premorbid Adjustment Scale (PAS) [286]. PAS is a clinician-rated instrument that assesses social and academic impairment on a scale ranging from 0 (no impairment) to 6 (severe impairment) in childhood (age 0-11), early adolescence (age 12-15), adolescence (age 16-18) and adulthood (age 19+). The premorbid period is defined as time from birth up until 6 months before the onset of mental disorder. Only the childhood subscale was used to avoid overlap with the prodromal phase that is common in psychotic disorders. Further, we only used the social domain of the childhood subscale as this was most relevant to the outcome of interest, namely social functioning in adulthood [287].

3.5 Statistical analyses

The Statistical Package for the Social Sciences (SPSS) was used for all statistical analyses, version 24 for study I and version 26 for studies II and III. For study II, the Graphpad Prism tool (GraphPad Software, La Jolla California USA, version 8.0 for Windows) was used to create

violin plots, and R (R core team, 2017) was used to conduct double generalized linear models. A significance level of $p \leq 0.05$ (two-tailed tests) was employed for all analyses.

To examine the distribution of variables, preliminary analyses were carried out. Normality of data was evaluated by inspections of histograms and Q-Q plots. Demographic and clinical characteristics of the sample were investigated with descriptive statistics, including means with standard deviations or frequencies with percentages as fitted. Although data was complete for the main outcome variables (ALS-SF and SFS interpersonal), certain other variables had missing data. Consequently, the *exclude cases pairwise* option was selected where a case was excluded from a given analysis if data was missing for that particular analysis yet included in all other analyses with existing data. Group comparisons of demographic and clinical variables were conducted using one-way analyses of variance (ANOVA), independent samples t-tests, and chi-square tests where appropriate. In correlational analyses, Pearson and Spearman correlations were carried out for normally distributed variables and skewed distributions, respectively. Effect sizes were calculated using eta square (study I), partial eta square (study II) and r square change (study III).

In *study I*, an ANOVA was carried out to investigate differences in the total level of affective lability between the groups, with Tukey's honestly significant difference (HSD) test for post-hoc comparisons. This was followed by an analysis of covariance (ANCOVA) to adjust for the potential effect of gender, which was differentially distributed across groups. Further, Z scores were calculated for all the ALS-SF dimensions by using the means and the standard errors of the mean for the healthy controls as baseline. Separate correlational analyses for the schizophrenia- and bipolar spectrum groups were then carried out to investigate relationships between the demographic and clinical variables and the total ALS-SF scores. This was followed by separate standard multiple regression analyses where the demographic and clinical variables shown to be significantly associated with affective lability were entered as independent variables.

In *study II*, a multivariate analysis of variance (MANOVA) with Bonferroni post-hoc tests was performed to investigate group differences in total- and subdimension affective lability. This was followed by a multiple analysis of covariance (MANCOVA) to see if statistically significant group differences in affective lability remained when current symptoms, substance use status and sex were entered as covariates. Further, a one-way repeated measures ANOVA was carried out for each diagnostic group to investigate which of the ALS-SF subdimensions contributed most to the total affective lability. Finally, the ALS-SF scores for all dimensions were plotted into the Prism tool in Graphpad and converted into violin plots to illustrate score dispersions within groups, and double generalized linear models (DGLM) were conducted in R to test if score dispersions were significantly different between groups.

In *study III*, bivariate correlational analyses were performed to investigate the association between the SFS interpersonal domain and the ALS-SF dimensions, as well as the relationship between SFS interpersonal and demographic and clinical variables. This was followed by a hierarchical multiple regression analysis where the SFS interpersonal dimension was entered as the dependent variable and all the variables that were significantly associated with the SFS score were entered block-wise as independent variables. The three ALS-SF dimensions were entered in the last block. There were no indications of problematic multicollinearity between the ALS-SF subdimensions (tolerance≥.35 and VIF≤2.9 for all dimensions). Scatterplots did not indicate interaction effects between the presence of lifetime psychosis/diagnostic group and affective lability on the SFS interpersonal. Still, to further exclude that the relationship between affective lability and social functioning differed in the diagnostic subgroups, follow-up subgroup analyses were carried out according to current diagnostic nomenclature: schizophrenia spectrum (schizophrenia, schizophreniform, schizoaffective, psychosis NOS; n=123) and bipolar spectrum (BDI and BDII; n=170). Following the same procedure as for the total sample, bivariate analyses for the two groups were performed first, followed by separate forced entry hierarchical regressions where the variables that were significantly associated with the SFS interpersonal score were entered one by one. Here, the total score of the ALS-SF was used in the multivariate analyses for both groups instead of the three ALS-SF subdimension scores to adjust the number of variables in the models to the smaller subsample sizes.

4 Summary of results

4.1 Study I: Affective lability across psychosis spectrum disorders

In study I, we aimed to investigate the level of affective lability in a sample of 222 individuals with either schizophrenia- or bipolar spectrum disorders (n=88 and n=134 respectively) and 140 healthy controls. We also investigated whether there were specific sociodemographic and clinical correlates of affective lability in the schizophrenia- compared to the bipolar spectrum group.

We found that there was a significant difference in the total level of affective lability between the groups and that the effect size calculated by eta^2 was large (0.37). This was followed by post-hoc tests which revealed significantly lower scores for the healthy control group compared to the two patient groups. However, there were no significant differences between the schizophrenia- versus the bipolar spectrum group. Correcting for sex which was differently distributed across groups, with more men in the schizophrenia spectrum group, did not alter the results. The mean ALS-SF score levels ranged from 0.69-1.34 for the schizophrenia spectrum group, 0.85-1.33 for the bipolar spectrum group and 0.14-0.39 for the healthy controls. With respect to correlates of affective lability in the patient groups, we found that affective lability was independently and significantly associated with higher current positive psychotic- and depressive symptoms in the schizophrenia spectrum group. In fact, current positive psychotic- and depressive symptoms were the only two variables that were significantly associated with affective lability in the bivariate analyses in this group. Sex, age, duration of illness, lifetime alcohol- and drug use disorder, negative symptoms and medication use were not, and were consequently not included in the multivariate analysis. Although the final regression model was highly significant (p=.001), it explained only a modest proportion of the total variance (15.7%). In bipolar spectrum disorders, affective lability was significantly and independently associated with higher current depressive symptoms, having an alcohol use disorder, as well as with non-use of antipsychotic medication. The associations between affective lability and manic symptoms, duration of illness and antidepressant medication found in the bivariate correlation analyses were not upheld in the multivariate analysis. The final regression model was significant (p=.001) and explained 30.3% of the total variance.

4.2 Study II: Characterization of affective lability across subgroups of psychosis spectrum disorders

In study II, the aim was to further characterize affective lability in specific subgroups of psychosis spectrum disorders to reveal putative differences in ALS-SF levels (both total- and subdimension), and to explore which of the ALS-SF subdimensions contribute most to the total affective lability in each group. In addition, we aimed to investigate if potential differences remained after controlling for current symptoms. Finally, we wanted to examine the dispersion of ALS-SF scores within- and between groups. The sample consisted of 297 patients and included the following subgroups: schizophrenia (n=76), BDI (n=105), BDII (68) and a mixed psychosis group (n=48, including psychosis NOS [n=32] and schizoaffective disorder [16]). We chose to combine psychosis NOS and schizoaffective disorder into one "mixed" group as the sample sizes were relatively small and the diagnoses typically include a heterogeneous mix of patients with both psychotic- and affective symptoms. Of the total sample in the study, n=222 were also included in study I.

We found that there was a statistically significant difference in affective lability between the groups on the total ALS-SF score as well as all of its subdimensions. Here, post-hoc analyses showed that the BDII group had higher scores compared to all of the other groups for total affective lability as well as for the depression-elation dimension. The scores of the BDII group on the anxiety-depression dimension was also significantly higher than those of the schizophrenia- and the BDI groups, but not the mixed psychosis group. On the anger dimension, the BDII group had significantly higher scores compared to schizophrenia and the mixed psychosis groups, but not the BDI group. There were no significant differences between the schizophrenia and BDI groups on any dimension of the ALS-SF. Further, the overall differences in affective lability remained statistically significant even after adjusting for the effects of sex, current symptom- and substance use status, with the exception of the difference between the mixed psychosis and BDII groups which no longer remained for the total-, depression-elation- and anger domains. With respect to putative differences in the architectural structure of affective lability, the anxiety-depression and depression-elation dimensions contributed most to the total affective lability in all of the diagnostic groups. There were no significant differences in the score dispersions between the groups and the scores

were not clustered around the minimum or maximum but rather around the median score. This indicates that the heightened affective lability is generalizable to the groups as a whole and not driven solely by subgroups with extreme scores in any of the diagnostic groups.

4.3 Study III: Affective lability and social functioning in severe mental disorders

In study III, we aimed to investigate the relationship between affective lability and social functioning as measured by the interpersonal domain of the Social Functioning Scale, taking into account other previously identified predictors of social impairment. We also wanted to explore whether potential associations were specific to subdimensions of affective lability. We used the same sample of individuals with psychosis spectrum disorders from study II, but due to potential errors in the SFS scores in four participants, the final n was 293.

Overall, we found that there was a significant association between all of the ALS-SF subdimension scores and the SFS interpersonal score. After controlling for potential confounders such as current symptoms, duration of untreated illness, total number of illness episodes as well as premorbid social functioning in childhood, a significant association remained for the anxiety-depression dimension only. In the regression model, reduced social functioning was further significantly associated with higher levels of current positive- and negative symptoms, in addition to reduced premorbid social functioning. The follow-up bivariate analyses in diagnostic subgroups (schizophrenia- and bipolar spectrum) showed that a higher ALS-SF total score was significantly associated with reduced social functioning in both groups. In the separate forced entry hierarchical multiple regression analyses, the ALS-SF total score was no longer significantly associated with social functioning in the schizophrenia spectrum group after correcting for the level of positive psychotic symptoms. There was also, however, a significant association between the level of positive psychotic symptoms and the ALS-SF total score. Hence, the analysis indicated that the effect of ALS-SF on the SFS score was mediated through positive psychotic symptoms in this group. Further, reduced social functioning was significantly associated with reduced social functioning in childhood and higher levels of current negative symptoms. In the bipolar spectrum group, the multivariate analyses showed that elevated affective lability was the strongest predictor of lower social

functioning. In addition, there was a significant association between higher level of current positive psychotic symptoms and reduced social functioning.

5 Discussion

The studies included in this thesis were conducted using cross-sectional data from the naturalistic TOP study. The main findings of the three studies included in this thesis will be discussed in relation to existing research, methodological considerations, clinical and research implications, as well as strengths and limitations.

5.1 Affective lability and psychotic disorders

Study I is, to our knowledge, the largest to date which has explored affective lability in a sample of patients with psychotic disorders that also included a sample of healthy control participants from the same catchment area. As pointed out by Marwaha and colleagues (2018), one of the major shortcomings in the literature has been the lack of comparable data, i.e. from the same cultural population, from individuals without mental disorders, rendering it difficult to establish the boundaries between putatively "normal" and "abnormal" affective lability. Our findings show that patients with psychotic disorders had significantly higher levels of affective lability compared to the control group, and that the levels of the control group were consistently low on all dimensions of the ALS-SF. The levels we found for the control group correspond with those of previous studies and indicate that affective lability scores well below 1 (0-0.50) is what can be expected in an adult sample of people without mental disorders. With respect to the comparison between schizophrenia- and bipolar spectrum disorders, we found no significant differences in the total level of affective lability. Based on previous studies and the centrality of affective disturbances in bipolar disorder, we expected the level of affective lability to be elevated here, but it was somewhat surprising that the level was the same in schizophrenia spectrum disorders. This indicates that affective lability is an equally prominent clinical feature in what is traditionally known as "non-affective" psychotic disorders. Yet, the affective dimension has historically been overlooked in research on schizophrenia spectrum disorders and investigations into specific affective traits, states and dispositions have been few and far between [38, 288, 289]. When investigated, the focus has primarily been on the alterations in emotional expression and experience manifested through the negative symptoms flat affect and anhedonia [290], as well as the related diagnostic and phenomenological conundrum of depression in schizophrenia [36, 291]. It appears, however,

that there might be much to gain from broadening the research horizon to include a wider range of affective disturbances as well.

The aim of study I was also to investigate whether there were specific clinical or demographic characteristics that were associated with affective lability in the two patient groups. In both groups, having higher levels of current depressive symptoms was significantly associated with elevated affective lability. The directionality of this association cannot be inferred from the study design, but irrespective of whether elevated affective lability leads to an increase in depressive symptoms or vice versa, the combination of the two is likely to result in a more arduous illness burden. One might speculate that the observed association between affective lability and depression is due to a phenomenological overlap as the ALS-SF contains elements pertaining to experiences of depression. We believe that the likelihood of this is limited, however, for three reasons: a) the overall level of depression in both patient groups was relatively low (34.1% and 27.6% above cut-off for moderate depression in schizophrenia- and bipolar spectrum respectively), b) the items in the ALS-SF clearly refer to rapid *switches* between depressive- and other affective states, not depressive symptoms per se, and c) affective lability has also been found in periods of euthymia in bipolar disorder indicating the presence of trait-like features that are not simply a function of elevation in symptom levels [144].

The prevalence of affective lability in individuals with schizophrenia who are in remission has not been investigated thus far. However, the schizophrenia spectrum group had clinical symptom scores corresponding to a categorization of “mildly ill” [292] and a significant difference between the schizophrenia group and healthy controls was still found. As a result, we believe that there is reason to infer that affective lability is indeed an illness feature that is present across different symptomatic levels in schizophrenia spectrum disorders in line with what has previously been found in bipolar disorder. Furthermore, elevated affective lability was also associated with higher current positive psychotic symptoms in this group. Again, we cannot confirm the direction of this association, but clarifying the interplay between affective lability and psychotic symptoms in future longitudinal studies appears important. If affective

lability does increase the risk for reality distortion, this would be further support for the theory of an affective pathway to psychosis [182]. In fact, there is now mounting evidence that challenges with affect regulation, especially pertaining to negative affect, may be implicated in the formation, development and persistence of positive psychotic symptoms, delusions in particular [293, 294]. This is highly relevant from a clinical perspective as affective disturbances are treatable targets that can be areas of focus early in the illness course or even before the unfolding of clear-cut symptoms in clinical high-risk samples. Potential clinical implications will be discussed in further detail in section 5.6.

Associations between affective lability and having an alcohol use disorder was found in the bipolar spectrum group, a link that we have also shown previously in a sample partially overlapping with the current [151]. One can speculate that the link with alcohol abuse may potentially develop as a response to affective lability in line with the self-medication hypothesis [295]. Conversely, alcohol abuse may destabilize the affective regulatory circuitry in bipolar disorder leading to increased affective lability [296], but this should be investigated further. Regardless of directionality, the relationship between affective lability and alcohol was not found in the schizophrenia spectrum group and therefore suggests that the causes and/or consequences of elevation in affective lability may be diagnosis-specific. In the bipolar spectrum group, we also found associations between higher affective lability and non-use of antipsychotic medication. There may be different explanations for the observed association: a) it could be an indication that antipsychotic medication has mood-stabilizing properties in bipolar disorder beyond that of reducing the risk for full-blown affective episodes, supporting and extending earlier findings to a group with relatively low symptom levels [285], or b) there could be diagnostic differences in affective lability within the bipolar-spectrum group that mediate this association as individuals with BDII are less likely to be prescribed antipsychotic medication compared to individuals with BDI. The latter hypothesis will be discussed in further detail in the section below. Interestingly, current use of mood stabilizers and antidepressant medication was not found to be significantly associated with affective lability in the multivariate analyses of the bipolar group, perhaps indicating that these pharmacological agents may have limited effects on affective lability despite efficacy in stabilizing mood episodes [52]. Nonetheless, we cannot exclude the possibility that some individuals with

initially very high levels of affective lability might have experienced reductions in levels by using mood stabilizers or antidepressants. In the schizophrenia spectrum group, no significant association between affective lability and antipsychotic medication was found. One may speculate that antipsychotic medication does not have an effect on affective lability in this group or, conversely, the result may also be a type II error as the majority of the group (81.8%) used antipsychotic medication at the time of assessment. Our findings underscore the uncertainty regarding the potential of standard psychopharmacological treatment in efficiently reducing affective lability in psychotic disorders and the need for further studies, something which will be discussed in section 5.6.

5.2 The architecture of affective lability: structure and dispersion in subgroups

In study II, the objective was to further characterize and explore if and how affective lability varied between the specific disorders included in the psychosis spectrum, and if putative differences would remain after controlling for current symptoms. Furthermore, we aimed to investigate the dispersion of the ALS-SF scores within each diagnostic group and if there were differences in dispersion between groups. We found that the level of affective lability was markedly elevated in BDII compared to BDI and schizophrenia, with the mixed psychosis group in the middle with scores not significantly different from BDII, BDI or schizophrenia. This replicates previous findings of higher levels of affective lability in BDII compared to BDI [159, 160]. It also adds to the knowledge by showing that this difference remains even when controlling for current depressive and manic symptoms. Consequently, the results imply that there are some trait-like differences between BDI and BDII here, perhaps tying affective lability more closely to the core of BDII. Further, our findings show that the BDI group is in fact more similar to schizophrenia than it is to BDII when it comes to both total and subdimension affective lability as measured by the ALS-SF. This is in line with the notion of the continuum model of substantial overlap between the traditional “non-affective” and “affective” psychotic disorders when it comes to affective disturbances, in addition to the already established genetic similarities [72]. Also, it suggests that the bipolar disorder types should be investigated separately, at least when addressing specific illness features such as affective lability.

What can the high affective lability in BDII be attributed to? As discussed in study II, individuals with BDII appear to be somewhat less atypical in terms of neurobiology, genetics and cognition compared to BDI and schizophrenia [297-301]. Further, a study looking at emotion regulation deficits in euthymic individuals with BDI versus BDII using functional MRI and diffusion-tension imaging found abnormalities in neural connectivity in emotion regulation circuitry in BDI, but not in BDII [302]. Albeit in need for replication in larger samples, the results are suggestive of well-preserved emotion regulation capacities in BDII, at least from a neural perspective. Thus, it might be that the high affective lability is rooted in environmental or clinical risk factors that may be more specific to BDII. As highlighted in the introduction of the thesis, childhood trauma is a risk factor for affective lability that has been investigated in several clinical populations. The prevalence rates of childhood trauma are, however, reported to be approximately the same in BDI- and BDII [303, 304]. The presence of a comorbid anxiety disorder is also likely to increase affective lability, but the rates appear to be at the same level here as well albeit some inconsistent findings [305]. When it comes to comorbid ADHD, the findings are mixed with some studies indicating similar levels [306, 307], whereas others have found higher levels in BDI [308] or BDII [309]. With respect to substance use disorders, there are some indications of slightly higher rates in BDI, but the difference between the groups appears to be marginal [310]. A more plausible reason for elevated affective lability is perhaps the more frequent and severe borderline personality comorbidity observed in BDII [161, 311], possibly in combination with the added burden of higher rates of depressive symptoms and episodes [309]. Unfortunately, the rates of comorbid borderline personality disorder were not investigated in the current study. Finally, the presence of specific combinations of personality traits or -profiles in BDII could perhaps also play into the elevation in affective lability observed [312, 313], something which should be investigated in future studies.

Since the conceptualization of affective lability entails rapid fluctuations between different affective states, it is of interest to explore which types of fluctuations are most prominent in different disorders for putative therapeutic interventions to be as targeted as possible. As mentioned under section 1.2.3, previous studies have looked at the structure of affective lability in borderline personality disorder compared to BDII using the ALS-SF and found that fluctuations involving anger appear to be what mainly separates the two [104, 144]. Little has

been known about the structure of affective lability in schizophrenia and BDI, however. Our findings are novel in this respect and show that shifts between anxiety-depression and depression-elation were the most typical for both schizophrenia, BDI, BDII, as well as the mixed psychosis group. The scores for the anger dimension were low for all groups and are noteworthy for a few reasons. Firstly, this adds support to earlier findings suggesting that fluctuations in anger are not representative of affective lability in BDII. As inter-episodic affective lability can be one source of confusion in the differential diagnosis of bipolar- versus borderline personality disorder, using the ALS-SF anger dimension as a screening tool may aid in distinguishing between the two and as such have valuable clinical potential.

Secondly, the low scores on the anger dimension for the schizophrenia group approximate what has been found in healthy controls [268]. There has been substantial media coverage about the propensity for aggressive behavior and violence associated with schizophrenia [314]. The items of the ALS-SF covering the anger dimension involve experiences of the ability to control one's temper and its physiological and behavioral manifestations, i.e. "There are times when I am so mad that I can barely stop yelling and other times shortly afterwards when I wouldn't think of yelling at all". Our results indicate that rapid, unpredictable fluctuations between these experiences of anger and normal mood as well as subsequent outwards behavioral manifestations of anger are not common in schizophrenia (nor in BDI and BDII). One may consequently speculate that the risk of impulsive acts due to a tendency to experience frequent bursts of anger or aggression appears to be limited, at least in clinical populations with low symptom levels. This is in line with new research in the field [315]. Collectively, the centrality of affective shifts involving depression suggests that affective lability as measured by the ALS-SF is primarily associated with internalizing versus externalizing problems and behaviors in psychotic disorders.

Neuroticism has been postulated to be at the core of internalizing pathology [316], is characterized by negative affectivity and has been found to be distinct from, yet significantly related to, affective lability in previous studies [191, 192]. Interestingly, these studies found that the difference in neuroticism and affective lability was mainly attributed to an interpersonal style characterized by anxiousness and avoidance in the former versus acting

out/externalization in the latter in samples of individuals with personality disorders as well as undergraduate students. Our findings of a closer relationship between affective lability and internalizing problems tentatively suggest that the overlap between neuroticism and affective lability might in fact be more pronounced than previously assumed, at least in psychotic disorders. This is in line with a previous study which found affective lability to be the most distinctive feature of neuroticism, in addition to being the feature that was most significantly linked to highest psychological distress [190].

Study II also investigated the dispersion of the ALS-SF scores within the different diagnostic categories and found that scores were clustered around the median for all dimensions in all groups. Furthermore, there were no significant differences in the dispersion between the diagnostic groups. This indicates that despite overall differences in ALS-SF levels, affective lability is likely to be present to some degree in a substantial proportion of individuals with these diagnoses, not just in subgroups with extreme scores. The opposite seems to be true for healthy control samples (where having a mental disorder is an exclusion criteria) where scores typically center around 0 when measured by the ALS-SF, with some extreme deviations [8, 268]. As such, our findings further support the notion of affective lability as an illness feature that, albeit seemingly non-specific and transdiagnostic in nature, still appears to be a rather specific marker of psychopathology. If replicated, routine screening for affective lability in general medical practice may be of value to identify the individuals who might benefit from focusing on mental health related issues in further evaluation and treatment.

5.3 Affective lability and social functioning

In study III, the aim was to investigate the putative relationship between affective lability and social functioning in psychotic disorders, which to our knowledge has not been explored previously. In general, there is a paucity of studies investigating the role of specific features of affective disturbances on social functioning in psychotic disorders and this is unfortunate as such disturbances might be viable treatment targets. We found a significant association between higher scores on the anxiety-depression dimension of the ALS-SF and reduced social functioning that was independent from well-established predictors of social functioning in

psychotic disorders. The other dimensions of the ALS-SF were also significantly associated with social functioning in the bivariate analyses, but significance was lost when potential confounders were taken into account. These results extend the findings of study II with respect to the centrality of negative affective shifts (anxiety-depression), and suggest that rapid fluctuations between different internalizing thoughts/behaviors may be more disruptive to social functioning compared to externalizing problems that can arise from fluctuations involving elation or anger. Also, larger fluctuations in affective states has in itself been linked to high levels of negative affect [173] and may potentially create a vicious cycle with reciprocally negative interactions. In the follow-up analyses in the diagnostic subgroups (schizophrenia- and bipolar spectrum), we found that the significant association between higher affective lability and reduced social functioning was lost in the schizophrenia spectrum group after correcting for positive psychotic symptoms. In addition, there was a statistically significant association between elevated affective lability and higher positive psychotic symptoms which we also found in study I. Taken together, we interpret this finding as a mediation effect, i.e. that the impact of psychotic symptoms on social functioning may be driven by elevated affective lability, which would be in line with the notion of an affective pathway to psychosis. However, the cross-sectional design does not exclude the possibility that high levels of positive symptoms can be followed by elevated affective lability.

The results of study III underline the importance of achieving symptom remission as higher levels of current positive and negative psychotic symptoms contributed the most to reduced social functioning in the total sample. Furthermore, based on the above-mentioned findings that elevated affective lability is associated with higher levels of positive psychotic symptoms in the schizophrenia spectrum group, one could speculate that a reduction in affective lability might be beneficial for social functioning directly as well as by means of reducing positive symptoms. Also, while the levels of current affective symptoms (depressive and manic) were associated with social functioning in the bivariate analyses, statistical significance was not upheld when entered into the multiple regression model for the total sample together with affective lability. Tentatively, this is interpreted as support for the presence of “trait-like” features of affective lability that are independent of elevation in symptom levels and as such contribute to poor social functioning. Our findings are in line with those of Grove and

colleagues (2016) who found elevated negative affect to be highly predictive of social functioning irrespective of other predictors across psychotic disorders, including bipolar disorder [258]. However, their measures of negative affect were all state-dependent (using time intervals ranging from "current moment" to "in the past month") and did not include features that are conceptualized to be more trait-like, such as affective lability. Consequently, our results add to the literature by providing more knowledge about the functional implications of specific affective disturbances in psychotic disorders.

When it comes to the exact mechanisms by which affective lability exerts its effects on social functioning, more research is necessary. As we speculated in the discussion section of study III, however, affective lability may negatively impact the ability to sustain and return to an adaptive affective baseline which can be taxing over time and potentially contribute to adverse health effects [10, 168, 169]. Further, this pattern with elevated affective lability and a slow return to a neutral physiological state could foster coping behaviors that are counterproductive to social functioning, such as withdrawal and disengagement. Tentative support for such an hypothesis is found in an early study showing an association between increased autonomic arousal and lower scores on the interpersonal domain of the SFS in individuals with schizophrenia [317]. The maladaptive "non-approach" behaviors will typically result in social avoidance over time and as such interfere with the drive to forge and maintain social connections. Adding to this negative spiral, social situations may be triggering to a host of different affective experiences as they are by nature unpredictable and ambiguous. To guide appropriate behavioral responses, a clear representation of one's own internal affective state is necessary [256], something which can be made distinctively more difficult by elevated affective lability. The frequent and unpredictable affective shifts place great demands on the ability to differentiate, categorize and label affective states in a precise way and may result in low emotional granularity/awareness [318] which has also been associated with challenges with social functioning [319-322]. With reference to the theoretical process model of affect regulation by Gross, one may thus speculate that affective lability disrupts the first and important *identification* stage of affect regulation [323]. This stage requires a representation- and evaluation of ongoing affective states in order to decide if a change in affect is appropriate, something which is hypothesized to be a prerequisite for selection of adaptive

affect regulation strategies. Taken together, affective lability may render social interactions taxing while features related to social settings may in turn increase affective lability, generating negative cascades that contribute to impairments in social functioning.

5.4 General and overarching discussion

Overall, the three studies that comprise the present thesis shed light on the level, structure and distribution of affective lability in psychotic disorders. To sum up, our results show the following:

- Affective lability is elevated in patients with psychotic disorders compared to healthy controls.
- The level of affective lability is the same in schizophrenia- and bipolar spectrum disorders, but the road to affective lability may be diagnosis-specific as the associations with clinical characteristics appear to be partly different.
- In diagnostic subgroups, the level of affective lability is highest in BDII and the same in BDI and schizophrenia, even when controlling for current symptoms.
- Affective fluctuations between anxiety-depression and depression-elation are most prominent in all diagnostic subgroups.
- The heightened levels of affective lability do not appear to be driven by a limited number of individuals with extreme scores, and there are no differences between diagnostic subgroups in the dispersion of affective lability.
- Higher levels of fluctuations between anxious and depressive states are independently associated with lower social functioning, i.e. after controlling for other well-established predictors of social functioning.

The results of the present thesis consequently add to the mounting literature that highlights affective lability as a common and transdiagnostic illness feature in many mental disorders, extending it to the broader spectrum of psychotic disorders. The studies provide new knowledge about the architecture and correlates of affective lability in psychotic disorders that may have both clinical and research implications which will be discussed in section 5.6. Conclusions about the underlying etiological mechanisms of affective lability in psychotic

disorders, and whether these are different or the same as in other disorders, are still elusive. Despite this, tentative speculation regarding how affective lability might be a pathway for the onset of psychotic experiences can be drawn from the work of neuroscientist Lisa Feldman Barrett and the theory of constructed emotion [324]. Returning to the concept of affects; the ever-present and basic feelings of pleasure or displeasure/calmness or agitation, the brain is constantly trying to make sense of their meaning in relation to what is going on around us in the world [2]. With elevated affective lability, the process of sense-making might be more taxing and unpredictable, leaving us to treat affect as information about the world instead of our *experiences* of the world, a phenomenon termed affective realism [1, pp. 75-78]. Consequently, if affective fluctuations are predominantly unpleasant or negative as appears to be the case with affective lability, this may result in a vulnerability to see the world as inherently unpleasant and negative as well; to use feelings as evidence for the actual state of our reality. Further, this again alters what we see and hear [325-328], providing negative feedback-cycles that may restructure our experiences of the surroundings in line with the aberrant salience hypothesis. Here, dopaminergic dysfunction renders incorrect assignment of salience to innocuous stimuli, something which has been hypothesized to be central in the development of psychosis [329, 330]. Although most of the research on aberrant salience pertains to schizophrenia, some studies have found evidence for the hypothesis in BDI as well [331, 332]. It is important to note that a possible pathway from affective lability via affective realism to aberrant salience and finally psychotic symptom formation has not been tested directly. However, based on related findings of associations between negative affect and elevated stress sensitivity, aberrant salience and positive psychotic symptoms, this may be a fruitful avenue to explore in future research [333-336]. Interestingly, the brain areas that have been implicated in neuroimaging studies of affective lability, namely neural connectivity dysfunction in the default mode- and salience networks, are the same as those typically associated with aberrant salience [193-195, 337, 338]. Collectively, the putative “affective lability pathway” to psychosis may be relevant for schizophrenia and BDI where the overlap is large with respect to both the structure and level of affective lability. In BDII, where psychosis is less frequent and the level of affective lability is significantly higher, the mechanisms tying affective lability to adverse illness course and outcome may be different as suggested in section 5.1.

5.5 Methodological considerations

There are several methodological issues that should be noted pertaining to the sample, potential confounding factors and the measurements used in study I-III which are relevant to the conclusions that can be drawn from the results. These will be discussed below.

5.5.1 Study sample and representability

All clinical participants in the TOP study are recruited from psychiatric inpatient- and outpatient units in a catchment area comprised of the major hospitals in Oslo and surrounding regions. The Norwegian mental health system is publicly funded and all individuals with mental health problems of a certain severity have access to specialized public mental health care in their catchment areas.

The structure of the mental health system in Norway ensures that the TOP study population has a high degree of representability for individuals with schizophrenia- and bipolar spectrum disorders across different socioeconomic backgrounds and illness phases. Still, there are some aspects that might impact generalizability. Participation in the TOP study is based on informed consent to take part in thorough and elaborate clinical interviews, neuropsychological- and somatic assessments and magnetic resonance image scanning. Hence, those who are not considered able to give informed consent due to severe psychotic symptoms are not approached for participation. Also, clinicians in the psychiatric units may be reluctant to referring individuals with very severe symptoms and impairments for other reasons as well. Furthermore, patients who are generally high-functioning might have difficulty taking time off work or be reluctant to associate themselves with a study of severe mental disorders. Consequently, the possibility of a selection bias in both directions cannot be ruled out. However, considerable efforts are made by the study recruitment- and assessment teams to be accessible and flexible and adjust the interview setting, -length and complexity to fit the needs of the participants as well as possible. Also, the members of the teams regularly attend meetings in the different psychiatric units to aid identification of eligible participants and to provide verbal and written information about the study to both clinicians and potential candidates.

The mean levels of current symptoms of the participants in studies I-III are generally low, indicating that the sample consisted of individuals who were relatively stable symptom-wise. Yet, there was still considerable variation in the level of symptoms, illness duration and –course, and use of medication in the sample. As such, participants with both severe and very mild symptoms, those with short and long illness duration and one to multiple illness episodes, as well as drug naïve vs those with polypharmacy were all included. We therefore believe that the findings from this thesis are largely generalizable to individuals with psychotic disorders who are treated in a mental health care setting.

5.5.2 Confounding factors

In the planning of the studies that the thesis is comprised of, substantial effort was made to identify and control for potentially confounders of associations between affective lability and the variables of interest. How these variables were selected and used in the statistical analyses are described under section 3.4. There are, however, two relevant variables that warrant further mention, namely sleep and neuroticism. Both of these factors have been associated with affective lability in previous studies, but were not assessed in the TOP study and thus could not be included in the analyses.

Sleep

Sleep problems have been found to be associated with affective lability in several studies [339-341], and it has been suggested that the association between affective lability and increased risk for developing a depressive episode is at least partially mediated via sleep disturbances [133]. Although not specific to affective lability, higher levels of negative affect have also been found to mediate the link between insomnia and increased paranoia in a small sample of individuals with psychotic disorders [342]. In addition, bidirectional relationships between chronobiological disturbances and affective temperaments (including cyclothymia) in BDII have been found [343]. Sleep disturbance is a relatively new area of research interest in the TOP study and the clinical protocol that was used when recruiting the participants in studies I-III did not include specific sleep assessments/questionnaires. As such, we had no standard

sleep measure available. Since sleep was not a primary outcome of interest, accounting for sleep disturbances through creating a sleep variable based on items from clinical symptom assessments or similar was beyond the scope of the current thesis.

Neuroticism

As discussed in the introduction section of the thesis, there appears to be strong links between affective lability and the personality trait neuroticism, but how this plays out in psychotic disorders is not known. Genetic overlap between neuroticism and schizophrenia has been established [344] and several studies suggest that neuroticism is higher in bipolar disorder than in the general population [345-347], rendering this an interesting path for further research. Unfortunately, we did not have any personality measures available and consequently could not investigate potential associations with affective lability in our sample.

5.5.3 Measurements

To ensure that the research questions in study I-III were answered properly, the quality and the aptness of the measures used were of high importance. As described in the methods section, the application of diagnostic tools for the studies in this thesis have been quality-assured by thorough training and calibration, and the other clinical measures have been applied extensively and psychometrically evaluated across many comparable studies. When it comes to the main outcome measures, the ALS-SF and the SFS, some methodological issues need to be discussed in further detail and will be outlined below.

The Affective Lability Scale Short Form (ALS-SF)

As noted in section 3.4.3, the ALS-SF is used frequently and has been found to have good psychometric properties in different populations across several studies. However, there are some specific challenges pertaining to the scale that should be mentioned: the lack of validated cut-off scores and potential sources of error associated with operationalization of the scale. When interpreting the ALS-SF scores, there are no given points of reference nor

published validation studies that establish what are likely to be valid cut-off values for "manageable" or "problematic" affective lability. The reference points 0 and 3 indicate "not present" and "highly present", but what constitutes high, moderate, or low affective lability beyond these extreme endpoints is not defined. Establishing clinical cut-off values have multiple purposes such as aiding the evaluation of treatment needs and facilitating communication. As of now, it is largely up to the individual researcher or clinician to define and interpret the meaning of the scores, which can be challenging when comparing studies and in clinical practice. Over the past years, more knowledge has been gained regarding what appears to be typical levels of affective lability for certain clinical populations, as well as for healthy controls [8]. We believe that study I and II make a significant contribution to the field in this respect by highlighting what is potentially high and low affective lability in psychotic disorders. Yet, there is a need for further clarification in even larger samples to increase the generalizability of the interpretations of the ALS-SF scores and to establish a standardization for psychotic disorders specifically but also more generally.

In terms of potential sources of error associated with the operationalization of the ALS-SF, the respondents are asked to make a judgement about how *characteristic/typical* the different claims/items are for them, without the presence of a specific time interval (such as "in the last week" or "over the past six months"). Also, a threshold with respect to what constitutes "typical" is not provided, i.e. how many times/how often this must occur in order for it to be called typical. The background for why a time interval is not given is that affective lability is thought to be a persistent trait that is present irrespective of state. Still, making such general assessments about the internal workings of one's own emotional life can be challenging for the respondent. More specifically, it presupposes that one is capable of separating how one "usually" is from how one is doing "here and now". This demands a substantial degree of insight and can be particularly difficult if the respondent is on the verge of, or in the midst of, an ongoing illness phase where the risk of "affective bias" is large. Hence, controlling for current symptom states as we have done in studies I-III is important when interpreting the results. It can also be useful to note other circumstances present at the time of testing that can potentially affect what the respondent characterizes as typical affective fluctuations, such as somatic illness, effect of medication and substance use. Finally, there appears to be some

cross-cultural variations in affective lability that might influence how scores should be interpreted in different countries. A previous study from our research group used both a Norwegian and French bipolar sample when investigating the psychometric properties of the ALS-SF and found that the French sample had significantly higher scores on the ALS-SF for patients as well as healthy controls [188]. There was still a significant difference between patients and controls in both countries, but this indicates that results should be interpreted with some caution when comparing scores from different countries. With respect to study I-III, the majority of the participants in our sample were born in Norway and as such there is little reason to believe that the findings should be confounded by cultural variations although this cannot be fully excluded. Despite its limitations, the ALS-SF has the major strengths that it is a frequently used, psychometrically sound and multidimensional assessment scale of affective lability that can provide insight and understanding of the construct in different populations. Indeed, many studies targeting affective lability have used single items measurements, such as the SCID-II item "Do you have a lot of sudden mood changes?", which captures the construct with much less detail. There has been some debate about the discriminant validity of the ALS-SF subdimensions [275], yet different dimensions appear to dominate in different diagnostic categories (e.g. borderline personality disorder vs BDII) and the dimensions also affect functioning differentially as illustrated by the results in study III. Further, we found no indications of multicollinearity between the dimensions. As such, there is reason to believe that the dimensions are of meaningful specificity despite putative phenomenological overlap.

The Social Functioning Scale (SFS)

The Norwegian version of the SFS has, like its English counterpart, been found to have good psychometric properties and is frequently used to measure social functioning in severe mental disorders [277]. Nonetheless, there are some challenges with the scale that deserve mentioning. Firstly, it is comprised of 76 items which makes it relatively time-consuming to fill in and may pose a challenge for individuals with cognitive deficits. A short version of the scale was developed [348], but has gained little momentum and consequently the original version has not been replaced. In the TOP study, the self-report scales are typically filled in during a

clinical session where the interviewer is present to help clarify any uncertainties and assist if needed. As such, we believe that the test setting facilitates appropriate use of the scale. Secondly, as the scale was developed in 1990 and has not been revised since then, it does not incorporate social media activity; a limitation it shares with the majority of the measures of social functioning that are currently in use in the field [349]. This is problematic as social media is now an important arena for social interaction, and the scale might consequently lose valuable information about the broader social reality of the respondents. Future research should encompass social media use in its assessments of social functioning in psychotic disorders. Finally, it is worth noting that the SFS is a self-report scale and not an "objective" measure of social disability. However, in study III we were interested in the participants own perceptions, i.e. subjective experiences, of their social functioning as this is closely linked to subjective well-being and quality of life [226]. As such, we believe the SFS interpersonal domain to be an appropriate outcome measure. In addition, self-report has previously been found to provide valid and reliable assessments of social functioning [258, 350], even in patients with poor insight [351], and is likely to yield a representative indication of actual level of functioning.

Assessment of symptoms of anxiety and depression in study II and III

In study II and III, the level of current symptoms of anxiety and depression were measured by items from the general scale of the PANSS (G2 and G6 respectively). As mentioned in section 3.4 regarding measures, the PANSS is a well-established scale for measuring symptom severity in schizophrenia, but it is also widely used in schizoaffective- and bipolar disorder, in addition to other disorders where psychosis can occur [352]. Since PANSS is not primarily a measure developed to assess anxiety and depression it may not fully capture these symptom dimensions. Thus, we cannot completely rule out the possibility that current symptoms still could have influenced the association between affective lability and diagnostic group/social functioning. However, we believe that this is unlikely at least when it comes to depressive symptoms as the mean level was not significantly different between the diagnostic groups. Further, the sample as a whole appears to be characterized by low levels of current depressive symptoms ranging from 2.3-2.7 which is indicative of minimal symptoms (≥3=mild depression)

[292]. This corresponds well with the relatively low levels we found in study I using more comprehensive scales. With respect to anxiety, the levels were significantly different between the groups and needed to be adjusted for in the analyses by using the measure of anxiety symptoms that we had available. Overall, the mean levels of current anxiety symptoms were also low (ranging from 2.5-3.3), indicating minimal to mild symptoms.

5.6 Clinical and research implications

We believe that the findings from this thesis may have several implications for clinical practice and future research that will be outlined below.

Clinical implications

Our results illustrate that affective lability is a prevalent and distinctive illness feature present in all subgroups of psychotic disorders that is associated with clinical symptoms and functional outcome. As such, our findings suggest that it could be important to screen for affective lability in clinical practice to identify those individuals who might benefit from an additional focus on affective lability in treatment. As noted in the introduction of the thesis, many patients with psychotic disorders find affective disturbances burdensome and give high priority to tackling these issues in treatment [18, 19]. Accordingly, a focus on affective lability might be useful in terms of enhancing adherence and satisfaction with treatment in addition to the putative benefits related to reducing affective lability in itself. Using the already well-established ALS-SF as a screening tool is likely to be feasible as it is readily available, short and relatively easy to administer and fill in. Further, the multidimensional nature of the scale will aid in pinpointing what types of affective fluctuations are most dominant in order to target and personalize interventions as much as possible.

With respect to intervention efforts, there is considerable uncertainty regarding the potential of standard pharmacological treatment in efficiently reducing affective lability [52]. However, there are several psychosocial interventions that appear promising. Dialectic behavioral therapy (DBT) is widely used in borderline personality disorder where affective lability is also

a core feature [119], and has an explicit focus on affect regulation skills training including mindfulness practices [120]. Studies have indicated that mindfulness-based meditation interventions, both brief and long-term, may reduce negative affective responses, increase positive affective responses and reduce behavioral avoidance, as well as promote affective stability and awareness [353, 354]. DBT has already been tried out in bipolar disorder and the results indicate that it is a feasible adjunct treatment that may reduce affective dysregulation and –reactivity [355-359]. In line with this, different forms of mindfulness-based interventions aiming to improve affect regulation have also been tested in both bipolar disorder and schizophrenia, with indication of therapeutic potential [360-363]. In fact, cultivation of more adaptive affect regulation strategies has been found to be feasible even in patients with acute psychotic symptoms in an experimental setting [364]. More studies are needed to evaluate if these findings can be generalized to daily life situations, but digital interventions hold promise as a putative translational link from the clinic to the real world [365, 366].

Furthermore, based on our findings of a possible link with internalizing problems, one can speculate that efforts to reduce negative affect, enhance positive affect and increase emotional granularity and awareness may be other promising avenues to decrease affective lability in psychotic disorders [364, 367-369]. In addition, such skills training is likely to generalize to more universal distress as well, which might be beneficial for quality of life. On this note, although speculative, the implications of reducing affective lability may be particularly beneficial for suicidality. Severe mental disorders account for a large proportion of suicide attempts- and deaths across the world [370], and affective lability is associated with increased risk [116, 128, 155, 175, 177, 371, 372]. Many of the risk factors for suicidality in these populations cannot be targeted in treatment (family history of suicide, childhood trauma, early age of onset) or have proven challenging to treat efficiently, such as bipolar depressions [373]. Consequently, identifying novel targets that may be modifiable by treatment is important to reduce suicide risk in these disorders. Targeting affective lability could prove beneficial in this regard through its links to suicidality both independently and as a mediator of other risk factors such as childhood trauma [154, 374] and substance use [375]. Nevertheless, it is important to note that despite promising results in reducing affective disturbances more generally, none of studies referenced in this section have explicitly

targeted affective lability. Accordingly, more research is needed to assess the feasibility, acceptability and efficacy of interventions that aim to reduce affective lability thorough various types of emotion regulation skills training in psychotic disorders.

Research implications

As noted in section 5.1, it is not possible to conclude on the direction of the observed association between affective lability and clinical symptoms (positive psychotic symptoms, depression) based on the results of this thesis. Hence, future research should try to clarify this interplay; does affective lability increase the risk for reality distortion and depression, or does higher symptom load lead to elevated affective lability, or a combination of both? If support is found for the former association, this tentatively suggests that efforts to reduce affective lability might reduce the severity of the illness course in psychotic disorders.

Although speculative, considering the possibility that affective lability is a risk factor and/or basis for formation of affective and psychotic symptoms, it may also be fruitful as a very early intervention measure to minimize the risk of transition to psychosis and/or depression in certain individuals. Longitudinal studies with frequent assessments of affective lability and relevant symptom domains in parallel in transdiagnostic samples would help in untangling the extent of the primacy of affective lability in different populations so that interventions can be tailored accordingly. Furthermore, such studies could also clarify whether the causal pathways leading to elevated affective lability are different in the different diagnostic subgroups as suggested by the specific links to clinical symptoms in study I. For example, it would be interesting to see whether sleep disturbances are more pronounced in BDII compared to BDI as this could perhaps contribute to explain some of the elevation in affective lability observed in the BDII group. To our knowledge, only one study has specifically addressed this so far [376]. In fact, a study of complex interplays has already been initiated at NORMENT through the use of the newly launched digital illness monitoring smartphone app “MinDag”. Here, affective lability and emotional reactivity is registered by individuals with psychotic disorders alongside self-assessments of affective- and psychotic symptoms, sleep, substance use and daily activities/social functioning. The study is in its initial phase and we aim to digitally phenotype the interplay between affective lability and core illness features over time, along with other

relevant psychological and behavioral dimensions. Please refer to the following link to read more about the project:

https://www.med.uio.no/norment/english/research/projects/MinDag/index.html.

5.7 Limitations and strengths

In section 5.5 concerning methodological considerations, I have already discussed some of the major limitations and strengths of the studies reported in this thesis. I will sum up and highlight these below.

The main overall limitation of study I-III pertains to the cross-sectional design which precludes conclusions about causality. Replication of the findings in larger longitudinal studies is needed before any firm assumptions about directionality between affective lability and clinical symptoms as well as social functioning can be made. Further, the ALS-SF and SFS are based on self-report which means that the risk of recall- and response bias cannot be ruled out. However, with regards to affective lability, this phenomenon is considered to be best captured by self-report, and consequently, to our knowledge, there is no validated clinician-rated measure of affective lability available. In addition, we did not have information regarding putative comorbid anxiety disorders, personality disorders and ADHD. Also, the measures used for anxiety and depressive symptoms in study II and III are based on a scale primarily developed for assessing psychotic symptoms.

The main overall strength of the three studies in this thesis is the relatively large and well-characterized, representative and transdiagnostic nature of our sample, which also included a healthy control sample from the same catchment area in study I. All participants went through detailed assessments with thorough and structured diagnostic evaluations by trained clinical researchers, and high inter-rater reliability with regards to both diagnosis and current symptoms further strengthen the results. Both the ALS-SF and the SFS are multidimensional scales with sound psychometric properties. The ALS-SF provides rich insight and understanding of the construct of affective lability, while the SFS offers the opportunity to specifically evaluate the level *social* functioning.

6 Conclusions

Through the three studies presented in this thesis, we have expanded the knowledge of, as well as provided novel insights about, the construct of affective lability in psychotic disorders. We have found that affective lability is higher in psychotic disorders compared to healthy controls and confirmed previous findings of higher affective lability in BDII compared to BDI. Further, we have shown that the level of affective lability is equally high in BDI and schizophrenia, something which to our knowledge has not been established before. Also, we have provided a more granular understanding of how affective lability appears to be structured in psychotic disorders, emphasizing the importance of fluctuations between negative affective states. In addition, we have found that elevated affective lability appears to be a characteristic feature across psychotic disorders and not something that is driven by subgroups of individuals with extreme levels. Finally, we have shown a specific and independent association between elevated affective lability in the anxiety-depression dimension and reduced social functioning in psychotic disorders.

Returning to the metaphor of affect as a barometer for how we are doing, affective lability can be thought of as an inherent obstacle to deciphering the barometer readings. Over time, this can be psychologically and metabolically taxing, as well as impede and disrupt the ability for adaptive affect regulation. Based on previous research and the findings of the present thesis, it seems plausible to conceptualize affective lability as a non-specific underlying trait to a host of different mental disorders which in combination with specific risk genes and environmental factors can increase the predisposition for the development and/or maintenance of psychotic disorders. Overall, the findings of this thesis highlight the importance of affective lability as an illness feature in psychotic disorders that should be assessed in clinical practice, in addition to providing an impetus for exploring the potential of affective lability as a putative treatment target in the future.

7 References

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8 Appendices

8.1 Appendix I: Study samples: number of participants in each study.

	Study I	Study II	Study III
Healthy controls	140		
Schizophrenia	42	62	62
Schizophreniform	13	14	13
Schizoaffective	8	16	16
Psychosis NOS	25	32	32
BDI	89	105	102
BDII	37	68	68
BD NOS	8*		
Total	**362**	**297**	**293**

*Due to the low number of participants with BD NOS (n=8), these were recoded into BDI (n=5) or BDII (n=3) in studies II and III based on whether a SCID-verified manic episode was ever recorded.

8.2 Appendix II: Items of the ALS-SF

1. At times I feel just as relaxed as everyone else and then within minutes I become so nervous that I feel light-headed and dizzy.

2. There are times when I have very little energy and then just afterwards I have about the same energy level as most people.

3. One minute I can be feeling OK and then the next minute I'm tense, jittery, and nervous.

4. I frequently switch from being able to control my temper very well to not being able to control it very well at all.

5. Many times I feel nervous and tense and then I suddenly feel very sad and down.

6. Sometimes I go from feeling extremely anxious about something to feeling very down about it.

7. I shift back and forth from feeling perfectly calm to feeling uptight and nervous.

8. There are times when I feel perfectly calm one minute and then the next minute the least little thing makes me furious.

9. Frequently, I will be feeling OK but then I suddenly get so mad that I could hit something.

10. Sometimes I can think clearly and concentrate well one minute and then the next minute I have a great deal of difficulty concentrating and thinking clearly.

11. There are times when I am so mad that I can barely stop yelling and other times shortly after-wards when I wouldn't think of yelling at all.

12. I switch back and forth between being extremely energetic and having so little energy that it's a huge effort just to get where I am going.

13. There are times when I feel absolutely wonderful about myself but soon afterwards I often feel that I am just about the same as everyone else.

14. There are times when I'm so mad that my heart starts pounding and/or I start shaking and then shortly afterwards I feel quite relaxed.

15. I shift back and forth between being very unproductive and being just as productive as every-one else.

16. Sometimes I feel extremely energetic one minute and then the next minute I might have so little energy that I can barely do a thing.

17. There are times when I have more energy than usual and more than most people and then soon afterwards I have about the same energy level as everyone else.

18. At times I feel that I'm doing everything at a very slow pace but then soon afterwards I feel that I'm no more slowed down than anyone else.

Anxiety-depression dimension items: 1, 3, 5, 6, 7.

Depression-elation dimension items: 2, 10, 12, 13, 15, 16, 17, 18.

Anger dimension items: 4, 8, 9, 11, 14.

8.3 Appendix III: Items of the SFS interpersonal domain

Subscale 1: Withdrawal[2]

1. What time do you get up each day?
   Before 9
   9-11 o'clock
   11-13 o'clock
   After 13 o'clock

2. On average, how many hours do you spend alone in one day?
   0-3 hours
   3-6 hours
   6-9 hours
   9-12 hours (or more)

3. When you are together with others, how often will you start a conversation?
   Almost never
   Rarely
   Sometimes
   Often

4. How often do you leave the house (for any reason)?
   Almost never
   Rarely
   Sometimes
   Often

5. How do you react to the presence of strangers/people you don't know?
   Avoid them
   Feel nervous
   Accept them
   Like them

[2] Items 1 and 2 are rated from 3-0, items 3-5 are rated from 0-3.

Subscale 2: Interpersonal behavior[3]

1. How many friends do you have at the moment?

   0

   1

   2

   3+

2. Do you have a partner?

   Yes

   No

3. How often are you able to carry out a proper conversation with someone?

   Almost never

   Rarely

   Sometimes

   Often

4. How easy or difficult do you find it talking to people at the moment?

   Very easy/quite easy

   Average

   Quite difficult

   Very difficult

[3] Item 1 is rated from 0-3 and item 2 is rated yes=3, no=0. The scores of the two items are then combined. Item 3 is rated from 0-3 and item 4 is rated from 3-0. All items are adapted from the Norwegian version of the SFS.

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Affective lability across psychosis spectrum disorders

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Abstract

Background. Despite apparent clinical remission, individuals with psychotic disorders often experience significant impairments across functional domains. Thus, there is a need to search beyond management of core symptoms to optimize treatment outcomes. Affective dysregulation is considered a risk factor for poor clinical and functional outcomes in many mental disorders, but research investigating such features in psychosis, particularly in schizophrenia, is limited. We aimed to investigate the level of affective lability (AL) in participants with schizophrenia- and bipolar spectrum disorders ($n = 222$) compared to healthy controls ($n = 140$), as well as clinical correlates of AL in the diagnostic groups.

Methods. The Affective Lability Scale (ALS-SF) was used to measure total score of AL and subscores covering the domains of anxiety/depression, depression/elation, and anger. An analysis of covariance was performed to compare the ALS-SF total score between groups, correcting for potential confounders, as well as standard multiple regression analyses for diagnosis-specific investigations of the relationship between AL and demographic and clinical features.

Results. Both the schizophrenia- and bipolar spectrum group had significantly higher ALS-SF total score compared to controls ($p < 0.001$), and no significant differences between the patient groups were found. In the schizophrenia group, current psychotic and depressive symptoms were significantly and independently associated with AL ($p = 0.012$ and $p = 0.024$, respectively).

Conclusions. The findings indicate that AL is elevated in psychotic disorders and that it transcends diagnostic boundaries. Further research into the causal relationship between psychotic and affective symptoms and AL, as well as its role as a potential therapeutic target in psychosis spectrum disorders, is warranted.

Introduction

Affective instability (AI) is common in the general population and even more prevalent among persons with mental disorders [1,2]. AI can be defined as rapid oscillations of intense affect with difficulty regulating these oscillations or their behavioral consequences [3], and is considered a central feature of affective dysregulation. The presence of AI in addition to a mental disorder is linked to a more complex and severe illness course and outcome. Research has demonstrated associations with higher rates of compulsory hospital admissions, longer in-patient hospital stays, increased frequency of hospital admissions [4], more frequent suicidal ideation and suicide attempts [5,6], alcohol use disorders (AUD) [7,8], and reduced cognitive and work functioning [9].

The term AI has been used interchangeably with affective lability (AL), mood or emotional instability, and mood swings [3]. The use of different definitions and measurement tools between studies limits the possibility to compare findings across different study populations. As a consequence, it is hard to determine if the negative outcomes associated with AI has consistent implications across diagnoses, or whether the effects pertain to specific mental conditions [10]. In an attempt to clarify these issues, the construct AI has been conceptualized into three core components: the *intensity* of affective responsiveness [11], the ability to *control* affective states [12], and *AL* [3]. Of these components AL, the tendency to experience prominent and unpredictable changes in mood [13], is most commonly investigated and appears to have the highest impact on outcome [10].

Individuals with psychotic disorders, schizophrenia-spectrum (SCZ) and bipolar spectrum (BD) disorders in particular, often struggle with psychosocial, vocational, and daily-life functioning even when acute phase affective and psychotic symptoms have diminished [14,15]. Thus, it is necessary to search beyond management of the core clinical symptoms of the disorders to optimize treatment. As this is the case for many mental disorders, the National Institute of Mental

Health has proposed a dimensional framework for research, the Research Domain Criteria (RDoC). RDoC aims to improve our limited understanding of the development and maintenance of psychopathology by transcending the boundaries of traditional diagnostic nosology [16]. Consequently, it seeks to combine biological and behavioral components of both normal and abnormal functioning in a singular framework to construct valid phenotypes for mental disorders. Affect regulation, and challenges with such, is a potential mechanism underlying more overt psychopathology, and has recently been suggested as an important new domain within this matrix [17]. As AL has been linked to poor functional outcome in mental disorders, addressing this construct in research could help determine its validity as a clinical treatment target.

Few studies to date have explored AL in psychotic disorders, with the bulk focusing on lability in BD where dysregulation of affect is a core feature. Here, AL belongs to a constellation of symptoms preceding the development of the disorder [18], is present early in the course of illness [19], in manic and mixed episodes [20], but also in periods of euthymia [21]. Hence, AL appears to be both a trait- and state-dependent factor that is associated with poor prognostic outcomes [21,22]. Our research group has previously found relationships between elevated AL and clinical correlates such as AUD, childhood trauma, suicidality, mixed episodes and anxiety, as well as intact executive functioning in BD [7,19,23,24]. In nonaffective psychotic disorders, especially schizophrenia, knowledge concerning the prevalence, distribution, and clinical correlates of AL is scarce [25]. The few existing studies looking explicitly into AL suggest that it is common, and that it may mediate the link between childhood adversity and positive psychotic symptoms [4,10,25]. More broadly, features of affective dysregulation have been associated with both the emergence and persistence of paranoid delusions, auditory hallucinations and other psychotic experiences such as passivity phenomena and thought interference [26–29]. As a consequence, the effects of AL may be of substantial clinical significance in psychotic disorders, but a richer understanding is needed.

Furthermore, there is mounting evidence of considerable overlap between SCZ and BD when it comes to genetic susceptibility and clinical symptomatology [30,31]. A previous study suggests that the level of AL is the same in nonaffective psychotic disorders and BD [10]. To what extent AL is linked to the same sociodemographic factors and clinical symptoms across these diagnostic groups is, however, not known. Also, AL is likely to exist on a continuum from normality to pathology [32], yet few studies looking into AL in severe mental illness have included at-risk populations or healthy controls (HC), with some notable exceptions [10,13,33,34]. This makes it difficult to identify the threshold where AL is so severe that it becomes pathological with need for treatment.

The present study thus seeks to address some of these knowledge gaps concerning AL in psychotic disorders. More specifically, we aim to investigate the distribution and level of AL in individuals with either SCZ or BD and HC. Furthermore, we aim to explore whether there are specific sociodemographic and clinical correlates of AL in the SCZ group, as compared to the BD group.

Methods

Participants

We included 222 patients with severe mental disorders, including SCZ ($n = 88$; schizophrenia [$n = 42$], schizophreniform [$n = 13$], schizoaffective [$n = 8$], psychosis Not Otherwise Specified (NOS) [$n = 25$]) and BD ($n = 134$; BD I [$n = 89$], BD II [$n = 37$], and BD NOS [$n = 8$]), and 140 HC who participated in the Thematically Organized Psychosis (TOP) research study at the Norwegian Center for Mental Disorders Research (NORMENT), Oslo University Hospital in Norway. Recruitment to the study is primarily via psychiatric inpatient and outpatient units in a catchment area consisting of all the major hospitals in the Oslo area, and has been ongoing since 2003. HC participants were drawn randomly from the population registers in the Oslo region. To be included in the study, all patients had to meet diagnostic criteria for a Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnosis of schizophrenia- or bipolar spectrum disorder and be able to give informed consent. Before consenting, thorough information about the purpose of the study was given to all participants both orally and in writing, emphasizing the voluntary nature of the study and the opportunity to withdraw at any time. HC were screened with the Primary Care Evaluation of Mental Disorders [35] for a history of physical and mental disorders, ongoing drug or alcohol use and history of severe mental disorders in first-degree relatives. Both patients and HC had to be within the age range of 18–65 years. Exclusion criteria for all participants were intelligence quotient (IQ) below 70, a history of severe head trauma and insufficient understanding of a Scandinavian language. For the current study, only patients and HC who completed the Affective Lability Scale (ALS) [36] were included. A subsample of the current BD group has previously been included in a study of AL and AUD in BD [7]; it is here included in a re-analysis to highlight the differences between SCZ and BD.

The TOP study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and is conducted in line with the Helsinki declaration of 1975, as revised in 2008.

Clinical assessments

All clinical evaluations were carried out by trained clinical psychologists, psychiatrists, or medical doctors. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I disorders, modules A–E. Diagnostic reliability is assessed with regular intervals in the TOP study and has been found to be very good with Cohen's kappa for diagnosis in the range between 0.92 and 0.99 across different assessment teams. Current psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) [37], depressive symptoms with the Inventory of Depressive Symptoms Clinician Rated (IDS-C) [38] for participants in the BD group and the Calgary Depression Scale for Schizophrenia (CDSS) [39] for participants in the SCZ group, and manic symptoms with the Young Mania Rating Scale (YMRS) for participants in the BD group [40]. Internal consistency scores for all of the symptom measures used in the study are presented in Table 1. Lifetime alcohol (AUD) and cannabis (CUD) substance abuse or dependence diagnoses were established according to DSM-IV criteria.

Affective lability

We used ALS-SF [41], the short version of the ALS, to capture shifts between normal mood (euthymia) and the domains of anxiety-depression, depression-elation, and anger. Both the ALS and the ALS-SF, which is highly correlated with the original scale, have been found to have good psychometric properties [32,36,42]. The ALS-SF consists of 18 items which are rated on a four-point Likert scale ranging from 0 ("very uncharacteristic of me") to 3 ("very

Table 1. Internal consistency of the symptom measures

Symptom measure	Cronbach's alpha
PANSS	0.876
IDS-C	0.795
YMRS	0.767
CDSS	0.828
ALS-SF	0.947

Abbreviations: ALS-SF, Affective Lability Scale-Short Form; CDSS, Calgary Depression Scale for Schizophrenia; IDS-C, Inventory of Depressive Symptoms-Clinician Rated; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

characteristic of me"). Five of the items refer to shifts in anxiety/depression, eight refer to shifts in depression/elation, and the final five items concern shifts between anger and normal mood. The scale yields a total score of AL (the sum of all item responses divided by 18), as well as subscores for the three affective domains.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 24). A significance level of $p \leq 0.05$ (two-tailed tests) was employed for all tests. Bivariate analyses including a one-way analysis of variance, independent samples *t*-test, and chi-square tests were conducted to compare the groups on demographic and applicable clinical variables, including the level of AL, measured by the ALS-SF total score. For the latter variable, a Tukey's honestly significant difference (HSD) test was used for post-hoc comparisons, followed by an analysis of covariance to adjust for potential confounders of the relationship between group and the ALS-SF total score. Effect size was calculated using eta square. *Z*-scores were calculated for all of the ALS domains using the means and the standard errors of the mean for the HC as baseline.

Bivariate correlational analyses were then conducted separately for SCZ and BD to investigate relationships between the demographic and clinical variables and the ALS total score. Pearson correlation was used for normally distributed variables and Spearman's rho for non-normally distributed variables. Demographic variables included gender, age and number of years in education. Clinical variables included duration of illness, current symptoms and medication use. The current symptom variables were chosen in order to examine the relationship between ALS and the core symptoms of SCZ and BD. PANSS positive domain was used to assess psychotic symptoms for both groups, while PANSS negative domain is more prevalent in schizophrenia and was used for SCZ only together with the CDSS. Correspondingly, the IDS-C and the YMRS were chosen for BD. Duration of illness was included to investigate whether the level of AL increases over the course of the illness. Current use of antidepressant (AD) and antipsychotic (AP) medication, in addition to use of mood stabilizers for the BD group, was included since all of these classes of pharmacological agents are known to have stabilizing properties [43]. As associations between AUD and CUD and increased AL in BD have previously been found by researchers from our group [7], these variables were also considered. Lastly, we conducted separate standard multiple linear regression analyses for the ALS-SF total score for SCZ and BD. The clinical and demographic variables shown to be significantly associated with AL in bivariate analyses were entered as independent variables.

Results

Demographics and clinical characteristics of the sample

Demographics for SCZ, BD, and HC as well as clinical characteristics for the two diagnostic groups are presented in Table 2. There was a significant difference in gender between the groups, with more women in the BD group compared to HC ($p = 0.041$). In terms of clinical features, the SCZ group had significantly higher total PANSS scores as well as a higher prevalence of AP medication use, a

Table 2. Demographics and clinical characteristics.

	SCZ (n = 88)	BD (n = 134)	HC (n = 140)		
	Mean (SD)	Mean (SD)	Mean (SD)	Statistics	p-value
Age, years	30.3 (9.7)	30.5 (10.3)	32.3 (9.4)	$F = 1.669$, $df = 2$	0.190
Female sex, *n* (%)	41 (46.6)	77 (57.5)	60 (42.9)	$X^2 = 6.154$, $df = 2$	**0.046** BD > HC
Education, years, median	14 (3.2)	15 (2.8)	15 (2.0)	$F = 2.617$, $df = 2$	0.074
Duration of illness, years	5.2 (5.2)	10.4 (9.1)		$t = 4.383$, $df = 216$	**0.000**
PANSS—total	57.1 (14.9)	44.4 (8.4)		$t = 8.282$, $df = 218$	**0.000**
IDS-C—total	n.a.	16.5 (10.9)			
CDSS—total	4.39 (4.317)	n.a.			
% > cut-off for moderate depression	34.1[a]	27.6[a]			
YMRS—total	n.a.	3.5 (5.0)			
Lifetime AUD, *n* (%)	6 (6.8)	16 (11.9)		$X^2 = 4.542$, $df = 1$	**0.033**
Lifetime CUD, *n* (%)	6 (6.8)	16 (11.9)		$X^2 = 1.561$, $df = 1$	0.213
Antipsychotic use, n (%)	72 (81.8)	64 (47.8)		$X^2 = 25.961$, df = 1	**0.000**

Abbreviations: AUD, alcohol use disorder; BD, bipolar spectrum disorder; CDSS, Calgary Depression Scale for Schizophrenia; CUD, cannabis use disorder; HC, healthy controls; IDS-C, Inventory of Depressive Symptoms-Clinician Rated; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia spectrum disorder; YMRS, Young Mania Rating Scale.[a]CDSS cut-off for moderate depression ≥ 6, IDS-C cut-off for moderate depression ≥ 22.

shorter duration of illness and significantly less AUD than the BD group.

ALS-SF scores in the diagnostic groups as compared to HC

There was a significant difference in the ALS-SF total score between the groups ($F = 107{,}258$, $p < 0.001$), with a large effect size ($eta^2 = 0.37$). Post-hoc comparisons tests showed significantly lower scores for the HC group compared to the SCZ group ($p < 0.001$) and the BD group ($p < 0.001$), but no significant differences between the two diagnostic groups ($p = 0.903$). Correcting for gender, which was differently distributed across groups, did not alter the results. Mean scores for the three groups on all of the ALS-SF subscales are presented in Table 3 and standardized ALS-SF total scores for the clinical groups relative to HC are shown in Figure 1.

Associations between ALS-SF total score and demographic and clinical variables in the SCZ group

In the SCZ group, bivariate analyses showed that the ALS-SF was significantly associated with current positive psychotic symptoms and depressive symptoms, but not with gender, number of years in education, age, duration of illness, negative symptoms, AUD, CUD, AD medication use or AP medication use (see Table 4 for correlation coefficients).

In the subsequent multivariate analysis, the ALS-SF total score was significantly and independently associated with higher current positive psychotic and depressive symptom scores (model $F = 7.840$, $df = 2$, $p = 0.001$) (Table 5).

Table 3. Raw scores for ALS-SF subdomains across the sample

	SCZ	BD	HC
	Mean (SD)	Mean (SD)	Mean (SD)
ALS total	1.16 (0.67)	1.19 (0.73)	0.26 (0.29)
ALS anxiety-depression	1.34 (0.82)	1.32 (0.89)	0.14 (0.26)
ALS depression-elation	1.34 (0.73)	1.33 (0.74)	0.39 (0.39)
ALS anger	0.69 (0.78)	0.85 (0.79)	0.17 (0.51)

Abbreviations: ALS-SF, Affective Lability Scale-Short Form; BD, bipolar spectrum disorder; HC, healthy controls; SCZ, schizophrenia spectrum disorder.

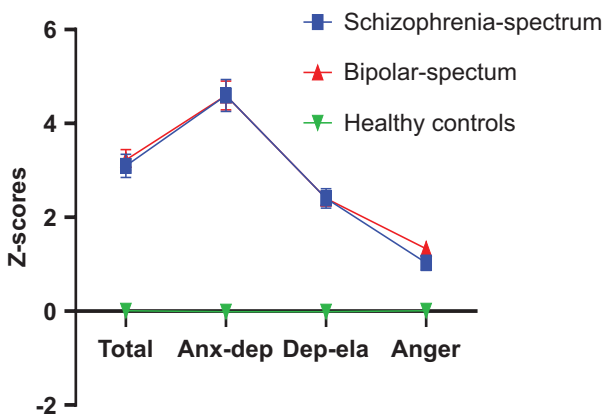

Figure 1. Affective Lability Scale-Short Form score distribution: *Z*-scores for the clinical groups relative to the HC group.

Table 4. Bivariate correlation coefficients between ALS-SF total score and demographic and clinical variables in the SCZ group

	ALS-SF total	Sex	Years of education	Age	Duration of illness	PANSS P	PANSS N	CDSS	AUD	CUD	AD	AP
ALS-SF total	1.000	$r_s = 0.107$, $p = 0.322$	$r = -0.158$, $p = 0.142$	$r_s = -0.008$, $p = 0.939$	$r_s = 0.177$, $p = 0.106$	**$r_s = 0.351$, $p = 0.001$**	$r_s = 0.033$, $p = 0.759$	**$r_s = 0.347$, $p = 0.001$**	$r_s = 0.151$, $p = 0.161$	$r_s = 0.052$, $p = 0.634$	$r_s = 0.091$, $p = 0.399$	$r_s = -0.115$, $p = 0.284$

Abbreviations: AD, antidepressant medication; ALS-SF, Affective Lability Scale-Short Form; AP, antipsychotic medication; AUD, alcohol use disorder; CDSS, Calgary Depression Scale for Schizophrenia; CUD, cannabis use disorder; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia spectrum disorder.

Table 5. Multiple linear regression analysis on the relationship between ALS-total score and clinical variables in SCZ

Covariates	Beta	t-test	p-value	95% CI for B	
				Lower bound	Upper bound
PANSS positive	0.266	2.582	**0.012**	0.009	0.070
CDSS total	0.237	2.293	**0.024**	0.005	0.069

R^2 for the final model = 0.157; $N = 87$ due to missing values.
Abbreviations: ALS-SF, Affective Lability Scale; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia spectrum disorder.

Associations between ALS-SF total score and demographic and clinical variables in the BD group

In the BD group, bivariate analyses showed that the ALS-SF was significantly associated with current depressive symptoms, AUD, AP medication use, use of AD medication, duration of illness and current manic symptoms, but not with gender, age, number of years in education, current positive psychotic symptoms, CUD or use of mood stabilizers (see Table 6 for correlation coefficients).

In the subsequent multivariate analysis, the ALS-SF total score was significantly and independently associated with higher current depressive symptom scores and with having an AUD. Also, individuals not using AP medication had higher scores compared to those with AP medication use. The final model was significant ($F = 8.936$, $df = 6$, $p < 0.001$) (Table 7).

Discussion

To the best of our knowledge, this is the largest study to date exploring AL across a clinical sample of patients with SCZ and BD disorders compared to HC from the same catchment area. Our main findings were that the patients had significantly higher levels of AL compared to HC, but that there were no significant differences between the SCZ and BD groups with respect to the total level of AL. In BD, where affective dysregulation is inherent to the disorder itself, one would expect elevated AL, but our results indicate that AL is an equally relevant clinical feature in SCZ. This observation calls for further attention to AL both within research and clinical care, and the current study also adds to the knowledge of AL in psychotic disorders by investigating its relationship with clinical characteristics.

We found that depression was significantly associated with elevated AL in both diagnostic groups. Depressive symptoms are troublesome in their own right, but our findings also demonstrate that they are linked to increased lability in affect, which may further add to the illness burden. As the ALS-SF contains several items pertaining to depressive experiences, one might suspect that the observed association is due to a phenomenological overlap. However, the depressive experiences entailed in the ALS-SF refer to rapid *switches* between depressive and other emotional states such as normal mood or anxiety, not depressive symptoms per se. Depression in schizophrenia has long been a diagnostic conundrum, with accumulating evidence of it being intrinsic to the illness rather than a comorbidity [44]. Yet, despite its prevalence and prominence, there are limited studies investigating treatment alternatives for depression in schizophrenia. Although the causal directions are unknown, targeting AL and other features of affective dysregulation could potentially provide a buffer against depression [27]. Conversely, AL may also be a facet or consequence of depression. As we state in the introduction, AL has been found in periods of euthymia in BD [21], indicating that there are features of AL that are more "trait-like" and not simply a function of elevation in symptom levels. In schizophrenia, the prevalence of AL in non-symptomatic patients is not known and needs to be investigated further. However, the clinical symptom scores of our SCZ group indicate that the majority is in the "mildly ill" category [45], and yet we still found a statistically significant difference in AL between patients and HC. We tentatively interpret this in support of the claim that AL is a risk factor for psychopathology, and that intervention efforts are needed. Also, a relationship between AL and increased positive psychotic symptoms was found in the SCZ group. Clarifying this interplay is important: do psychotic symptoms increase AL or does AL increase the risk for reality distortion? The latter would be in line with the notion of an affective pathway to psychosis [46]. To investigate these relationships, longitudinal studies with frequent assessments of AL and psychotic and depressive symptoms in parallel are necessary.

We have previously explored clinical correlates of AL in individuals with BD [7,23,24]. In the current study, we also investigated the relationship between AL and the most commonly used psychopharmacological agents and found that AL was lower in individuals with BD using AP medication. Our results support those of Cipriani et al. [43] indicating that AP medication has good mood-stabilizing properties in BD and extend the findings to a group of BD patients with fairly low levels of depressive and manic symptoms. The observed association was, however, not present in the SCZ group. This may suggest that AP medication does not have the same mood-stabilizing effect in SCZ, but could also be a statistical ceiling-effect since the majority of the SCZ group used such medication. The association between AUD and AL in the BD group, a link we have shown previously [7], was not found in the SCZ group. This could be a type II error, as only six individuals in the SCZ group had AUD. Taken together, the findings suggest that although the level of AL was equally high across diagnoses in our sample, the paths leading to this elevation may be diagnosis-specific.

There are no proposed or validated cut-off scores for evaluating the severity of AL. Previously, mean ALS-SF total and subscale scores in the range of 0.38–0.86 for HC, 1.16–1.66 for patients with BD and 1.25–1.65 for patients with nonaffective psychosis respectively, have been found by Marwaha et al. [10], which correspond well with our results. Future studies should aim to establish severity cut-off values for the ALS-SF as this would be useful both for clinical purposes and in research. From a clinical perspective, exploring the implications of AL in psychotic disorders may be fruitful since affective disturbances are considered burdensome and highly prioritized as treatment targets by service users, even more so than positive psychotic symptoms [47,48]. Focusing on aspects of affective dysregulation might consequently lead to increased satisfaction with, and corresponding adherence to, treatment.

Table 6. Bivariate correlation coefficients between ALS-SF total score and demographic and clinical variables in the BD group

	ALS-SF total	Sex	Years of education	Age	Duration of illness	PANSS P	IDS-C	AUD	CUD	AD	AP	MS	YMRS
ALS-SF total	1.000	$r_S = 0.147$, $p = 0.091$	$r_S = -0.001$, $p = 0.988$	$r_S = -0.020$, $p = 0.817$	**$r_S = 0.341$, $p < 0.001$**	$r_S = 0.138$, $p = 0.113$	**$r = 0.421$, $p < 0.001$**	**$r_S = 0.175$, $p = 0.043$**	$r_S = 0.056$, $p = 0.523$	**$r_S = 0.175$, $p = 0.043$**	**$r_S = -0.347$, $p < 0.001$**	$r_S = -0.067$, $p = 0.440$	**$r_S = 0.237$, $p = 0.006$**

Abbreviations: AD, antidepressant medication; ALS-SF, Affective Lability Scale-Short Form; AP, antipsychotic medication; AUD, alcohol use disorder; BD, bipolar spectrum disorder; CUD, cannabis use disorder; IDS-C, Inventory of Depressive Symptoms-Clinician Rated; MS, mood stabilizers; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

Table 7. Multiple linear regression analysis on the relationship between ALS-total score and demographic and clinical variables in BD

				95% CI for B	
Covariates	Beta	t-test	p-value	Lower bound	Upper bound
IDS-C total	0.331	4.151	**0.000**	0.012	0.033
YMRS total	0.020	0.262	0.793	−0.020	0.026
Duration of illness	0.124	1.543	0.126	−0.003	0.023
AP use	−0.261	−3.263	**0.001**	−0.614	−0.150
AD use	0.068	0.866	0.388	−0.139	−354
AUD	0.155	2.041	**0.043**	0.009	0.616

R^2 for the final model = 0.303; $N = 128$ due to missing values.
Abbreviations: AD, antidepressant medication, ALS, Affective Lability Scale; AP, antipsychotic medication, AUD, lifetime alcohol use disorder; BD, bipolar spectrum disorder; IDS-C, Inventory of Depressive Symptoms—Clinician Rated; YMRS, Young Mania Rating Scale.

Limitations and strengths

Our findings must be interpreted in light of some limitations. The ALS-SF is a self-report instrument which makes it vulnerable to recall- and response bias. Also, we cannot make causal attributions about the associations between the clinical variables and elevated AL due to the cross-sectional nature of the study. Furthermore, an investigation of potential differences in AL between the different diagnoses included in the SCZ and BD groups would have been informative, but this was not possible due to small sample sizes. The study also has several strengths; it is the largest study to date looking at AL in a transdiagnostic, representative, well-characterized and relatively young sample of individuals with psychotic disorders, as well as HC.

Conclusions

Our results illustrate that AL is markedly elevated in psychotic disorders and that it transcends diagnostic boundaries. In the SCZ group, AL was associated with higher levels of current depressive and positive psychotic symptoms. In BD, in addition to previously known relationships to AUD and depressive symptoms, AL was less prominent in individuals using AP medication. Further research is needed to establish whether elevated AL increases affective and/or psychotic symptom load in these patient groups or vice-versa. Nevertheless, our findings indicate that AL may be a relevant therapeutic target in psychotic disorders and that it is warranted to investigate how strategies aiming to promote affective stability, such as emotion regulation skills training, could be integrated in the treatment of these patient populations.

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Conflict of Interest. The authors report no conflicts of interest.

Data Availability Statement. The data that support the findings of this study will be made available upon request.

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Characterization of affective lability across subgroups of psychosis spectrum disorders

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Abstract

Background: Affective lability is elevated and associated with increased clinical burden in psychosis spectrum disorders. The extent to which the level, structure and dispersion of affective lability varies between the specific disorders included in the psychosis spectrum is however unclear. To have potential value as a treatment target, further characterization of affective lability in these populations is necessary. The main aim of our study was to investigate differences in the architecture of affective lability in different psychosis spectrum disorders, and if putative differences remained when we controlled for current symptom status.

Methods: Affective lability was measured with The Affective Lability Scale Short Form (ALS-SF) in participants with schizophrenia (SZ, n = 76), bipolar I disorder (BD-I, n = 105), bipolar II disorder (BD-II, n = 68) and a mixed psychosis-affective group (MP, n = 48). Multiple analyses of covariance were conducted to compare the ALS-SF total and subdimension scores of the diagnostic groups, correcting for current psychotic, affective and anxiety symptoms, substance use and sex. Double generalized linear models were performed to compare the dispersion of affective lability in the different groups.

Results: Overall group differences in affective lability remained significant after adjusting for covariates (p = .001). BD-II had higher affective lability compared to SZ and BD-I (p = .004), with no significant differences between SZ and BD-I. There were no significant differences in the contributions of ALS-SF dimensions to the total affective lability or in dispersion of affective lability between the groups.

Conclusions: This study provides the construct of affective lability in psychosis spectrum disorders with more granular details that may have implications for research and clinical care. It demonstrates that despite overlap in core symptom profiles, BD-I is more similar to SZ than it is to BD-II concerning affective lability and the BD groups should consequently be studied apart. Further, affective lability appears to be characterized by fluctuations between depressive- and other affective states across different psychosis spectrum disorders, indicating that affective lability may be related to internalizing problems in these disorders. Finally, although the level varies between groups, affective lability is evenly spread and not driven by extremes across psychosis spectrum disorders and should be assessed irrespective of diagnosis.

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Background

Affective lability, the propensity to experience rapid, unpredictable and excessive changes in affective states (Zwicker et al. 2019), is a central and common feature of affective instability that is associated with negative outcomes across psychiatric disorders (Patel et al. 2015; Marwaha et al. 2013a, 2014a, 2018; Broome et al. 2015a,b; McDonald et al. 2020). As a consequence, affective lability and other elements of affective instability are gradually becoming recognized as dimensional and transdiagnostic constructs in line with the Research Domain Criteria (RDoC) project of The National Institute of Mental Health (NIMH) (Broome et al. 2015b; Insel et al. 2010; Fernandez et al. 2016).

Due to the considerable overlap in the symptomatology and etiology of schizophrenia and bipolar disorder, the Kraepelinian dichotomy is increasingly being questioned (Craddock and Owen 2010; Pearlson 2015). Consequently, investigating the full spectrum of these disorders—referred to as psychosis spectrum disorders—is recommended when exploring both biomarkers and clinical features (Guloksuz and Os 2018). Still, studies investigating affective lability thus far have focused on bipolar disorder (BD), which is likely to be due to the fluctuations in affective states inherently tied to a BD diagnosis. Affective lability has been found to be both a trait- and a state-dependent factor in individuals with bipolar I (BD-I) and bipolar II (BD-II) disorders. It is present in periods of euthymia (Henry et al. 2008), early in the course of illness (Aminoff et al. 2012), in all polarities of the illness episodes (Henry et al. 2003; Gershon and Eidelman 2015; Faurholt-Jepsen et al. 2015; Verdolini et al. 2019), as well as in non-affected relatives (Hafeman et al. 2016; Birmaher et al. 2013). Due to its associations with adverse clinical correlates such as alcohol use disorders (AUD) (Lagerberg et al. 2017), suicidality (Aas et al. 2017; Ducasse et al. 2017), anxiety disorders (Aas et al. 2017), cardiometabolic risk (Dargel et al. 2018) and inflammation (Dargel et al. 2017), there is mounting evidence that affective lability may be a relevant therapeutic target in BD.

In schizophrenia (SZ), there has previously been limited emphasis on the prevalence and correlates of affective lability, despite indications that it can be a prominent facet of psychotic experiences (Patel et al. 2015; Marwaha et al. 2014b). Indeed, in our recently published study investigating affective lability across psychotic disorders, we found that affective lability was markedly elevated in individuals with SZ and BD compared to healthy controls, with equally high elevations in both groups (Høegh et al. 2020). Also, affective lability was significantly and independently associated with higher levels of positive psychotic- and depressive symptoms in SZ, and with higher levels of AUD and depressive symptoms in BD. This suggests that affective lability adds to the total illness burden across psychosis spectrum disorders. The findings highlight that increased awareness of affective lability in both research and clinical care is warranted.

To further elucidate the mechanisms of affective lability and its potential value as a treatment target consistent with personalized approaches to psychiatry, it is of interest to explore how and if affective lability varies between the specific disorders included in the psychosis spectrum. In line with this, a few previous studies with relatively small samples, as well as two larger studies, have found higher affective lability in individuals with BD-II compared with BD-I (Faurholt-Jepsen et al. 2015, 2019; O'Donnell et al. 2018; Marwaha et al. 2016). Knowledge about the expression of affective lability in SZ and how this expression overlaps with the broader psychosis spectrum, however, is scarce. Also, it is unclear if there are certain types of lability in affect that are more prominent in the different psychosis spectrum disorders. The presence of anxiety, for example, has been found to be high in both individuals with BD and SZ (Karpov et al. 2016; Achim et al. 2011), but to which extent it is part of the composition of affective lability in the various disorders is not known. For potential intervention efforts to be as targeted as possible, more precise knowledge about which affects that appear to be involved in the lability in the different diagnostic subgroups is needed.

Using the same sample as in our previous study (Høegh et al. 2020) together with newly added participants, we are now able to further explore affective lability measured by The Affective Lability Scale Short Form (ALS-SF) across specific psychosis spectrum disorders. These include SZ, BD-I, BD-II in addition to a mixed "psychosis-affective" (MP) group including schizoaffective disorder and psychotic disorders not otherwise specified (psychosis NOS) with prominent mood symptoms. Here, we aim to investigate if these groups exhibit differences in the architecture of affective lability that could aid further characterization of this phenomenon in psychosis spectrum disorders. We also aim to investigate whether putative differences in affective lability between the diagnostic groups are primarily

mediated by differences in their current symptomatology. Finally, we explore potential variations in affective lability within the diagnostic categories in the psychosis spectrum, i.e. between individuals with the same type of disorder, by examining the within-group dispersion of ALS-SF scores, and whether this differs between the diagnostic groups. Such an investigation has, to our knowledge, yet to be conducted in this population and will highlight whether affective lability appears to be driven by subgroups with extreme scores or is more evenly spread within and across the different diagnostic groups.

Accordingly, we seek to investigate affective lability in four diagnostic groups within the psychosis spectrum: SZ, BD-I, BD-II and MP, and more specifically to:

1. Investigate (a) if there are differences in the total- and subdimension scores of ALS-SF between the groups, (b) if potential differences remain after controlling for current symptoms, and (c) which of the ALS-SF subdimensions contribute most to the total affective lability score in each of the diagnostic groups.
2. Investigate the dispersion of the ALS-SF scores within each diagnostic category and if there are differences in dispersion between the diagnostic groups.

Material and methods

Design

The current study is part of the larger Thematically Organized Psychosis (TOP) study at the Norwegian Center for Mental Disorders Research (NORMENT) in Oslo, Norway. Recruitment to the TOP study has been ongoing since 2003 and potential participants are referred via psychiatric inpatient and outpatient units, including specialized psychosis units as well as community teams, in a catchment area that is comprised of all the major hospitals in Oslo. As such, the overall representability of the sample is considered to be very good. The participants are given thorough information about the voluntary nature of the study and the possibility to withdraw at any time. The participants included in the study have to meet diagnostic criteria for a Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnosis of schizophrenia- or bipolar spectrum disorder and provide informed consent. Both individuals with established diagnoses and individuals who are diagnosed for the first time are included in the study. Further inclusion criteria are intelligence quotient (IQ) above 70, no prior history of severe head trauma and sufficient understanding of a Scandinavian language (Ringen et al. 2008).

Participants

The sample for the current study was comprised of two hundred and ninety-seven participants with psychosis spectrum disorders from the TOP study, and only participants who had completed the ALS-SF were included. The ALS-SF was originally introduced in a TOP study sub-protocol for participants with first episode mania, and a few years later included in the main protocol (i.e. to patients with other diagnoses than BD-I). It was mainly presented for participants with low levels of current affective symptoms. The diagnostic grouping in the current study was as follows: SZ (including schizophreniform [n = 14]) n = 76, BD-I n = 105, BD-II = 68 and MP (including psychosis NOS [n = 32] and schizoaffective disorder [n = 16]) n = 48. The rationale for combining psychosis NOS and schizoaffective disorder into one "mixed" group was that these categories typically include patients with both psychotic- and affective symptoms that are diagnostically more heterogeneous than the other groups (Santelmann et al. 2015, 2016; Widing et al. 2020). Of the present sample, n = 222 were used in our previous study investigating affective lability across the psychosis spectrum (Høegh et al. 2020), and are now re-analyzed along with the newly added participants to shed light on putative differences in affective lability between the specific psychotic disorders.

Clinical assessments

The diagnoses in the study were established by the Structured Clinical Interview for DSM-IV axis I disorders (SCID-1), modules A-E (First et al. 1995) which was carried out by trained medical doctors, psychiatrists or clinical psychologists. In the TOP study, diagnostic reliability is assessed with regular intervals and Cohen's kappa for diagnosis in the range between 0.92 and 0.99 has been found across different assessment teams. To assess current symptom state, the positive subscale of the Positive and Negative Syndrome Scale [PANSS (Kay et al. 1987)] was used for positive psychotic symptoms, and the depression item (G6) and the anxiety item (G2) in the general scale of the PANSS were used for depressive- and anxiety symptoms, respectively. PANSS G6 and PANSS G2 were chosen because they were the only measures of depression and anxiety that were collected at the same time point as the ALS-SF for all participants. The rating for G6 is based on the answer to one initial question ("how has your mood been in the past week, mostly good or mostly bad?") followed by 1–11 follow-up questions concerning the extent of the depressive state and its behavioral consequences. For G2, the rating is based on the same algorithm; one initial question ("have you been feeling worried or nervous in the past week?") and then

1 to 6 follow-up questions depending on the response to the first question. The Young Mania Rating Scale [YMRS (Young et al. 1978)] was used to assess manic symptoms. The Alcohol Use Disorders Identification Test [AUDIT (Saunders et al. 1993)] was used to evaluate the degree of harmful alcohol consumption, and drug related problems were measured with the Drug Use Disorders Identification Test [DUDIT (Berman et al. 2005)]. Duration of illness was estimated based on the age of onset of the first SCID-verified episode of psychosis for SZ and MP, and the first SCID-verified affective episode for BD-I and BD-II.

The Affective Lability Scale Short Form (ALS-SF)

To measure affective lability, we used the ALS-SF (Oliver and Simons 2004). The ALS-SF captures the total level of affective lability reported by an individual, but also subdimensions of affective lability covering oscillations between three subdomains: anxiety-depression, depression-elation and anger and normal mood. Thus, the scale provides an indication of whether affective lability is predominantly driven by specific- or a combination of affects. The ALS-SF has been found to have good psychometric properties (Aas et al. 2015; Look et al. 2010) and is widely used across different clinical populations. The 18 items of the scale are rated on a four-point Likert scale ranging from 0 ("very uncharacteristic of me") to 3 ("very characteristic of me") and yields a total score of affective lability as well as scores for the three subdomains. There are no validated cut-off scores for evaluating the severity of affective lability, but in our previous study we found mean ALS-SF total and subscale scores in the range of 0.17–0.39 for healthy controls, 0.85–1.33 for individuals with BD, and 0.69–1.34 for individuals with SZ (Høegh et al. 2020). This corresponds well with what has been found in at least one similar study (Marwaha et al. 2018).

Statistical analyses

Descriptive statistics, including means with standard deviations or frequencies with percentages where relevant, were used to investigate demographical and clinical characteristics of the different diagnostic groups. The groups were then compared using one-way between-groups analyses of variance (ANOVA) and chi-square tests. The Tukey's honestly significant difference (HSD) test was used for post-hoc comparisons where appropriate. To investigate group differences in the level of affective lability as measured by scores on the total- and subdimensions of the ALS-SF, a one-way between-groups multivariate analysis of variance (MANOVA) was conducted with Bonferroni post-hoc tests. A multiple analysis of covariance (MANCOVA) was then carried out to investigate if statistically significant group differences in affective lability remained significant when current symptom and substance use status were entered as covariates. The variables which were significantly associated with diagnostic group and/or with the ALS-SF domains in bivariate correlation analyses were entered as covariates. The selected covariates were as follows: current level of positive psychotic symptoms (PANSS P), manic symptoms (YMRS), depression (PANSS G6), anxiety (PANSS G2), alcohol use (AUDIT) and drug use (DUDIT) (see Table 1 for correlation coefficients). In addition to the symptom and substance use variables, sex was entered as a covariate as there was a significant difference in the number of females in the different groups and previous research has indicated that affective lability is higher in females in general (Marwaha et al. 2013b; Winkler et al. 2004). Age, which has also been found to be associated with affective lability previously (Broome et al. 2015b), was not associated with the diagnostic groups or with the ALS-SF scores in our sample and therefore not included in further analyses. Effect sizes were calculated by partial eta squared. To investigate which of the ALS-SF subdimensions contributed the most to the total affective lability, a one-way repeated measures ANOVA was performed for each group. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 26) was used for all statistical analyses and a significance level of $p \leq 0.05$ (two-tailed tests) was employed. For aim 2, ALS-SF scores for all dimensions for each diagnostic group were plotted into the Graphpad Prism tool (GraphPad Software, La Jolla California USA, version 8.0 for Windows) and converted into violin plots to illustrate score distributions. To further investigate variability in the ALS-SF scores, double generalized linear models (DGLM, $Y \sim Dx, \sim Dx$) were carried out using R (R core team 2017) to test if the ALS-SF score dispersions were significantly different between groups (for more detailed information see Additional file 1).

Table 1 Bivariate correlation analyses

	PANSS P	PANSS G2	PANSS G6	AUDIT	DUDIT	YMRS	SEX
ALS-SF total	$r_s = 0.174^{**}$	$r_s = 0.381^{**}$	$r_s = 0.305^{**}$	$r_s = 0.153^{**}$	$r_s = 0.227^{**}$	$r_s = 0.282^{**}$	$r_s = 0.136^{*}$

ALS-SF affective lability scale short form, *PANSS P* positive and negative syndrome scale positive subscale, *PANSS G2* positive and negative syndrome scale anxiety item, *PANSS G6* positive and negative syndrome scale depression item, *AUDIT* the alcohol use disorders identification test, *DUDIT* the drug use disorders identification test, *YMRS* young mania rating scale. *$p < 0.05$, **$p < 0.001$

Results

Demographics and clinical characteristics of the sample

Demographic and clinical characteristics for SZ, BD-I, BD-II and MP are presented in Table 2. A statistically significant difference in sex between the groups was found, with fewer women in the SZ group compared to remaining groups. There were also significantly more women in the BD-II compared to the BD-I group. In addition, the duration of illness between the groups was significantly different; the BD-I and BD-II groups had been ill longer than the SZ and MP groups ($p < 0.001$ and $p < 0.05$, respectively). Regarding clinical features, there were statistically significant differences between the groups for PANSS total, PANSS P, YMRS, G2 anxiety and AUDIT (see Table 2).

Affective lability in the diagnostic groups: total and subdimension scores

The mean scores for the ALS-SF dimensions for the different diagnostic groups are presented in Fig. 1. The MANOVA showed that there was a statistically significant difference in affective lability between the groups for all of the ALS dimensions: ALS-total $F = 8.446$, $df = 3$, $p < 0.001$; ALS anxiety-depression $F = 9.298$, $df = 3$, $p < 0.001$; ALS depression-elation $F = 7.281$, $p < 0.001$ and ALS anger $F = 4.252$, $p = 0.006$. Effect sizes were moderate; partial $eta^2 = 0.080$, 0.087, 0.069 and 0.042, respectively.

Post-hoc analyses with Bonferroni revealed that the BD-II group had significantly higher affective lability scores compared to all of the other groups for the ALS total ($p < 0.05$) and depression-elation ($p < 0.05$) dimensions. For the ALS anxiety-depression dimension, the scores for the BD-II group were significantly higher than those of the BD-I and SZ groups ($p < 0.001$ for both), but not the MP group ($p = 0.060$). Finally, the BD-II group had significantly higher scores compared to the SZ group ($p = 0.006$) and the MP group ($p = 0.042$) groups, but not the BD-I group ($p = 0.089$) on the anger dimension. There were no significant differences in the scores for the SZ and BD-I groups on any dimension ($p = 1.000$).

Results from multivariate analyses

The overall differences in affective lability between the groups remained statistically significant also after adjusting for the effects of sex, current symptom- and substance use status: ALS total $F = 5.305$, $df = 3$, $p = 0.001$; ALS anxiety-depression $F = 6.139$, $df = 3$, $p < 001$; ALS depression-elation $F = 4.432$, $df = 3$, $p = 0.005$ and ALS anger $F = 4.184$, $df = 3$, $p = 0.006$. Again, the effect sizes were moderate with partial eta^2 of 0.057, 0.067, 0.048 and 0.046. Post-hoc group comparisons with Bonferroni showed that the difference in AL between BD-II versus SZ and BD-I remained statistically significant for the ALS total ($p = 0.004$ for both SZ and BD-I), anxiety-depression (SZ $p = 0.038$, BD-I $p = 0.001$) and depression-elation dimensions (SZ $p = 0.031$, BD-I $p = 0.006$). The difference between BD-II and SZ on the anger domain also remained statistically significant ($p = 0.004$). The difference between the MP group and the BD-II group no longer remained statistically significant for the total-, depression-elation- and anger domains after adjusting for covariates.

Contributions of the ALS-SF subdimensions to the total score

In all of the diagnostic groups, the one-way repeated measures ANOVAs with Bonferroni post-hoc tests showed that the anxiety-depression and depression-elation dimensions contributed most to the total affective lability, with no significant differences in the level of scores between these dimensions in any group ($p = 1.000$ for SZ and BD-I, $p = 0.225$ for BD-II, $p = 0.814$ for MP). Across the board, the anger dimension was found to contribute significantly less to the total score compared to the anxiety-depression and depression-elation dimensions ($p < 0.001$).

Dispersion of affective lability scores within and between the diagnostic groups

The score distributions for all dimensions of the ALS-SF for the four diagnostic groups are shown in Fig. 2a–d. The median score is illustrated by a vertical straight line. The double generalized linear models found no significant differences ($p > 0.05$) in the score dispersions between any of the groups in any of the domains, indicating that despite differences in mean ALS-SF scores between groups, the dispersion in the scores was the same (for more information see Additional file 1).

Discussion

The construct of affective lability refers to the propensity to experience rapid, unpredictable and excessive changes in affective states (Zwicker et al. 2019). The main aim of the current study was to investigate differences in affective lability between different psychosis spectrum disorders. Our results show that individuals with BD-II had markedly elevated levels of total- and subdimension affective lability compared to BD-I and SZ, even when correcting for sex, the level of current symptoms and substance use. Affective lability in the MP group, on the other hand, was not significantly different from BD-II nor SZ or BD-I when the covariates were taken into account. There were no statistically significant differences between individuals with BD-I and SZ for any ALS-SF dimension and these two groups

Table 2 Demographics and clinical characteristics

	SZ *(n = 76)*	BD-I *(n = 105)*	BD-II *(n = 68)*	MP *(n = 48)*	Statistics	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Age, years	29.8 (9.2)	31.6 (11.2)	29.4 (9.2)	29.5 (8.3)	F = 0.971, df = 3	0.407
Female sex, n (%)	27 (35.5)	56 (53.3)	47 (69.1)	27 (56.3)	$X^2 = 16.608$, df = 3	*0.001* SZ < all, BD-II > BD-1
Education, years	14.3 (3.1)	15.0 (2.9)	16.0 (2.8)	14.6 (3.1)	F = 1.950, df = 3	0.122
Duration of illness, years	4.1 (6.2)	9.9 (9.8)	13.1 (8.7)	6.1 (7.2)	F = 15.785, df = 3	*0.000* BD-I and BD-II > SZ, MP
PANSS—total	56.2 (15.6)	42.1(8.4)	43.0 (8.2)	53.8 (14.2)	F = 30.356, df = 3	*0.000* SZ, MP > BD-I, BD-II
PANSS—P	12.8 (4.8)	9.0 (2.5)	9.1 (2.6)	12.1 (3.8)	F = 28.431, df = 3	*0.000* SZ, MP > BD-I, BD-II
Depression (PANSS item G6)	2.3 (1.2)	2.3 (1.4)	2.7 (1.4)	2.4 (1.3)	F = 2.167, df = 3	0.092
Anxiety (PANSS item G2)	2.8 (1.2)	2.7 (1.3)	3.3 (1.4)	2.5 (1.2)	F = 3.599, df = 3	*0.014* BD-II > BD-I, MP
YMRS—total	3.5 (4.2)	2.3 (3.4)	3.0 (4.2)	1.7 (2.3)	F = 2.699, df = 3	*0.046**
AUDIT total	5.1 (4.9)	8.1 (7.1)	8.5 (6.4)	5.3 (5.1)	F = 5.648, df = 3	*0.001* SZ < BD-I, BD-II; MP < BD-II
DUDIT total	*3.1 (6.9)*	*3.6 (7.1)*	*2.8 (5.6)*	*3.2 (7.1)*	*F = 0.237, df = 3*	*0.871*

Statistically significant group differences are highlighted in italic

SZ schizophrenia, *BD* bipolar disorder, *MP* mixed psychosis, *PANSS* positive and negative syndrome scale, *YMRS* young mania rating scale, *AUDIT* the alcohol use disorders identification test, *DUDIT* drug use disorders identification test

*Post-hoc tests were non-significant

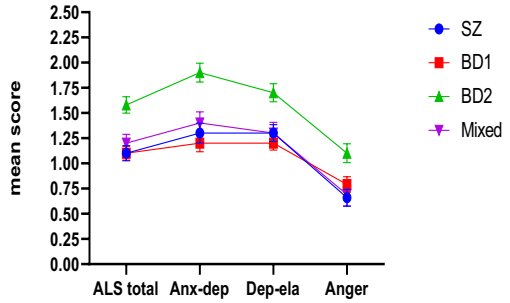

Fig. 1 ALS-SF mean and SEM scores. *SEM* standard error of the mean, *SZ* schizophrenia, *BD* bipolar disorder, *ALS-SF* affective lability scale short form, *anx-dep* anxiety-depression domain, *dep-ela* depression-elation domain

had very similar score patterns throughout. This suggests that despite the overlap in core affective symptom profiles of BD-I and BD-II, the BD-I group is more similar to SZ than it is to BD-II concerning levels of affective lability. Further, since we controlled for current symptoms, our findings imply that there are some trait-like differences between the disorders with respect to affective lability, where elevated affective lability is perhaps more inherently tied to BD-II compared to the other psychosis spectrum disorders.

Given that individuals with BD-II are more similar to healthy controls when it comes to neurobiology, genetics and cognition compared to BD-I and SZ (MacQueen et al. 2005), one can speculate if the high affective lability is based in environmental or clinical risk factors specific to BD-II. For instance, childhood trauma has been found to be associated with affective lability (Aas et al. 2014), but the prevalence rates of trauma are reported to be at the same level in individuals with BD-I and BD-II (Palmier-Claus et al. 2016; Janiri et al. 2015). The presence of comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) and anxiety disorders is also likely to increase affective lability (Broome et al. 2015a; Aas et al. 2017), but again the rates are at the same level in BD-I versus BD-II (Pataki and Carlson 2013; Bennett et al. 2019; Brus et al. 2014; Pavlova et al. 2015). It is perhaps more plausible that the elevation in affective lability

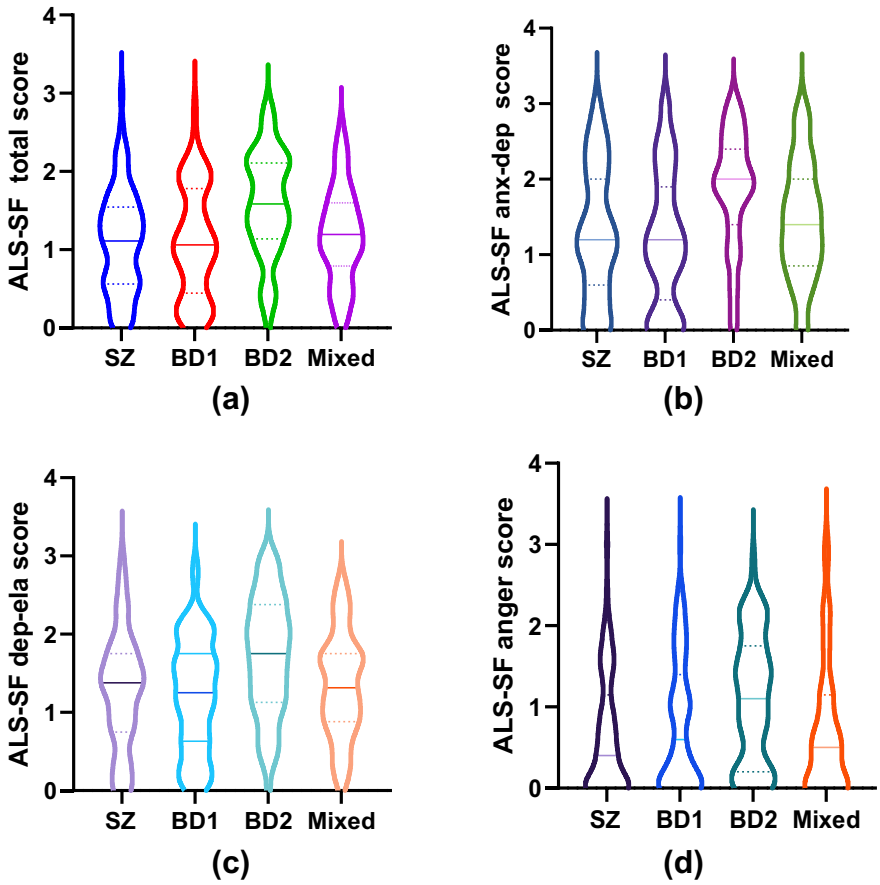

Fig. 2 **a**–**d** ALS-SF score distribution: **a** ALS-SF total score, **b** anxiety-depression dimension, **c** depression-elation dimension, **d** anger dimension. *SZ* schizophrenia, *BD* bipolar disorder, *ALS-SF* affective lability scale short form, *anx-dep* anxiety-depression dimension, *dep-ela* depression-elation domain

observed in individuals with BD-II is associated with more frequent and severe borderline personality traits (Saunders et al. 2020) and/or higher rates of depressive episodes and symptoms (Karanti et al. 2020), but this needs to be investigated further. In addition, affective lability, anxiety disorders, borderline personality disorders and BD-II appear to be more prevalent in women compared to men, and there may be some interrelationships here that are worthwhile looking into in future research. Regardless of origin, it seems important to investigate the BD groups separately with regards to affective lability. When it comes to the similarities between individuals with BD-I and SZ, this may not be surprising at least from a genetic point of view, given the established overlap between BD-I and SZ (Tamminga et al. 2013; Tesli et al. 2014). It is, however, important to keep in mind that both individuals with BD-I and SZ also present with higher affective lability rates than healthy controls (Høegh et al. 2020).

With respect to the architecture of affective lability, oscillations between anxiety-depression and depression-elation were the most typical for all groups. In our previous study, we found significant associations between affective lability and current depression in both SZ and BDs (Høegh et al. 2020). We now extend these findings to show that even when controlling for the level of depressive symptoms, significant between-group differences in affective lability persist. Somewhat surprisingly, we found that fluctuations between depression and elation were also prevalent, even in individuals with SZ, along with fluctuations involving anxiety. This is in line with the dimensional perspective of psychosis that has been found in previous research showing a large degree of symptomatic overlap between disorders (Os and Kapur 2009). The mean scores of the SZ, BD-I and MP groups on the anger dimension were low (0.66, 0.79 and 0.69, respectively). Although the anger score for the BD-II group was higher (1.08), it is still comparatively low relative to the BD-II scores for the other dimensions. Collectively, this is an indication that affective lability is related to more internalizing versus externalizing problems and behaviors in psychotic disorders, which is different from the pattern found in for example borderline personality disorder where rapid shifts involving anger appear to be more characteristic (Henry et al. 2001; Koenigsberg et al. 2002).

To our knowledge, the dispersion of ALS-SF scores in the different psychosis spectrum disorders has not previously been investigated. The violin plots showing the full distributions of the data confirm that the scores seem to be relatively evenly dispersed in all groups, i.e. the scores are not clustered around the minimum or maximum but rather around the median score. Hence, the level of affective lability in the groups does not appear to result primarily from the presence of subgroups of patients with extreme scores, but to represent the typical score pattern for each disorder. Visually, the shape of the distribution of scores in the BD-II group stands out, especially for the anxiety-depression dimension. Yet, the statistical analyses revealed no significant differences between the groups with regards to dispersion. This indicates that although the level varies between groups, affective lability is evenly spread and not driven by extremes across psychosis spectrum disorders and should be routinely assessed irrespective of diagnosis.

Limitations and strengths

The present study must be interpreted in light of some limitations. The cross-sectional nature of the study implies that we cannot make causal attributions about the association between diagnostic group and affective lability. In addition, data on comorbid anxiety disorders, personality disorders and ADHD are lacking, and the measures used for anxiety and depressive symptoms are based on a scale primarily developed for assessing psychotic symptoms. Hence, the possibility that current symptoms still could have influenced the association between affective lability and diagnostic group cannot be ruled out completely. However, we believe that the likelihood of this is limited due to the relatively low levels of anxiety and depressive symptoms. Further, the risk of recall- and response bias cannot be ruled out as the ALS-SF is a self-report instrument. The study also has several strengths; it has a large, diagnostically well-characterized sample covering the psychosis spectrum, and uses a multidimensional assessment scale of affective lability that provides a richer insight and understanding of the construct.

Conclusions

Our results illustrate that affective lability is more prominent in individuals with BD-II compared to SZ and BD-I, and that this is not explained by differences between the groups in sex, levels of affective-, psychotic- or anxiety symptoms or severity of substance use. BD-II thus appears to be a particularly vulnerable diagnostic group with respect to affective lability. No differences in affective lability were found between individuals with BD-I and SZ. The results further add information about the structure of affective lability in these disorders emphasizing the significance of fluctuations between depressive- and other affective states. The findings also show that there is an even dispersion of affective lability scores within each diagnostic group, and that the dispersion also appears to be largely equivalent across groups. Overall, the study provides the concept of affective lability in psychotic disorders with more granularity by showing differences and similarities between diagnostic groups that may have implications for both research and clinical practice.

Abbreviations

ALS-SF: Affective Lability Scale Short Form; SZ: Schizophrenia; BD: Bipolar disorder; RDoC: Research Domain Criteria; NIMH: The National Institute of Mental Health;

AUD: Alcohol Use Disorder; MP: Mixed Psychosis group; Psychosis NOS: Psychosis Not Otherwise Specified; TOP: Thematically Organized Psychosis Study; NORMENT: Norwegian Center for Mental Disorders Research; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition; SCID: Structured Clinical Interview for DSM-IV; PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale; AUDIT: Alcohol Use Disorders Identification Test; DUDIT: Drug Use Disorders Identification Test; ANOVA: Analysis of Variance; HSD: Honestly Significant Difference test; MANOVA: Multivariate Analysis of Variance; MANCOVA: Multivariate Analysis of Covariance; SPSS: Statistical Package for the Social Sciences; DGLM: Double Generalized Linear Models; ADHD: Attention-Deficit/Hyperactivity Disorder.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40345-021-00238-0.

Additional file 1: Double Generalized Linear Models.

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Authors' contributions
MCH and TVL designed the study. MCH conducted the data analyses and drafted the manuscript. TVL contributed with data analyses and -interpretation and with revising the paper. IM initiated the study and together with TU provided input concerning data analyses and interpretation of results. BH conducted the double generalized linear model analyses. SRA, MCH, SHO and IBH collected data. All authors were involved in critically reviewing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study will be made available upon reasonable request.

Declarations

Ethics approval and consent to participate
The TOP study is conducted in line with the Helsinki declaration of 1975 (as revised in 2008 and 2013) and has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants must be able to provide informed consent before entering the study.

Consent for publication
Not applicable.

Competing interests
The authors report no conflicts of interest.

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III

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ORIGINAL PAPER

Affective lability and social functioning in severe mental disorders

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Abstract
Social functioning is impaired in severe mental disorders despite clinical remission, illustrating the need to identify other mechanisms that hinder psychosocial recovery. Affective lability is elevated and associated with an increased clinical burden in psychosis spectrum disorders. We aimed to investigate putative associations between affective lability and social functioning in 293 participants with severe mental disorders (schizophrenia- and bipolar spectrum), and if such an association was independent of well-established predictors of social impairments. The Affective Lability Scale (ALS-SF) was used to measure affective lability covering the dimensions of anxiety-depression, depression-elation and anger. The interpersonal domain of the Social Functioning Scale (SFS) was used to measure social functioning. Correlation analyses were conducted to investigate associations between affective lability and social functioning, followed by a hierarchical multiple regression and follow-up analyses in diagnostic subgroups. Features related to premorbid and clinical characteristics were entered as independent variables together with the ALS-SF scores. We found that higher scores on all ALS-SF subdimensions were significantly associated with lower social functioning ($p < 0.005$) in the total sample. For the anxiety-depression dimension of the ALS-SF, this association persisted after controlling for potential confounders such as premorbid social functioning, duration of untreated illness and current symptoms ($p = 0.019$). Our results indicate that elevated affective lability may have a negative impact on social functioning in severe mental disorders, which warrants further investigation. Clinically, it might be fruitful to target affective lability in severe mental disorders to improve psychosocial outcomes.

Keywords Affective lability · Social functioning · Psychotic disorders · Schizophrenia spectrum · Bipolar spectrum · Affective lability Scale Short Form (ALS-SF)

Introduction

Social functioning, defined as the capacity of a person to function in different societal roles such as homemaker, worker, student, partner, family member or friend [1, 2], is an important marker of recovery and a predictor of quality of life in severe mental disorders [3, 4]. Social impairments are present across schizophrenia- and bipolar spectrum disorders and appear to be driven by a range of factors. A better understanding of the different paths leading to social impairment is important to tailor and personalize interventions for the individual patient. Affective disturbances, defined broadly as disruptions in the subjective experience, expressive behavior and physiology of emotions and mood [5], are taxing and highly prioritized as treatment targets by the patients [6–8]. Several studies have found significant associations between various forms of dysregulated affect and reduced social functioning in patients with both non-affective and affective psychotic disorders [9–15]. This association appears to be independent of other risk factors such as neurocognitive- and social cognitive deficits, indicating that affective dysregulation may uniquely contribute to social impairments in psychosis. As human emotions are developed, expressed and regulated in interaction with others, it is perhaps not surprising that challenges with affect regulation make social contexts and situations particularly burdensome [16].

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Still, there is a paucity of studies investigating the role of specific facets of affective dysregulation for social functioning in severe mental disorders [17, 18]. Affective lability refers to the propensity to experience rapid, excessive and unpredictable changes in affective states and is associated with poor clinical and functional outcome in many psychiatric disorders [19, 20]. In a sample partially overlapping with that of the current study, we have previously found that affective lability is elevated in schizophrenia- and bipolar spectrum disorders compared to healthy controls [21]; with the highest level in bipolar II disorder (BDII) and equally high levels in schizophrenia and bipolar I disorder (BDI) [22]. Hence, affective lability appears to be a common illness feature across these disorders, with potential consequences for clinical outcome.

To clarify the relationship between affective lability and social functioning in severe mental disorders, other known risk factors for social impairment must be taken into consideration. Predictors of social impairment appear similar across the disorders, and range from individual characteristics through lifetime- and current illness-related features [23, 24]. As social impairment is higher in schizophrenia compared to schizoaffective- and bipolar disorders [23], the presence and/or prominence of psychotic symptoms may be of relevance. This is supported by findings of larger functional impairment in patients with bipolar disorder with psychotic symptoms compared to those without [25–27]. Nonetheless, the severity of affective symptoms, depressive in particular, also seems to predict social functioning across diagnoses [28–33]. Hence, core clinical symptoms, both current and over the lifetime, appear to be central to social functioning in these populations. In addition, there are several other shared risk factors for social impairments highlighted in the literature. These include male sex [34, 35], poor premorbid social functioning [36, 37], neurocognitive deficits [25, 38], total number of illness episodes [28, 39], duration of untreated illness [40, 41], negative symptoms including apathy [23, 33, 42] and comorbidity such as substance use and anxiety [28, 43–46].

Here, we aim to investigate the relationship between affective lability and social functioning in severe mental disorders, and to explore whether this putative relationship is specific to subdimensions of affective lability. To our knowledge, this relationship has not been investigated previously. We hypothesize that affective lability will be associated with social functioning independent of other pre-defined predictors of social impairment across severe mental disorders.

Methods

Participants

The study sample was comprised of two hundred and ninety-three participants with severe mental disorders (schizophrenia [$n=62$]; schizophreniform [$n=13$]; schizoaffective [$n=16$]; BDI [$n=102$]; BDII [$n=68$]; psychosis Not Otherwise Specified (NOS) [$n=32$]), recruited through the Thematically Organized Psychosis (TOP) research study at the Norwegian Center for Mental Disorders Research (NORMENT) in Oslo, Norway. Recruitment to the TOP study is consecutive and still ongoing via psychiatric inpatient and outpatient units in a catchment area that is comprised of all the major hospitals in Oslo. All participants in the study must meet diagnostic criteria for a Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnosis of schizophrenia- or bipolar spectrum disorders and be able to give informed consent. In addition, exclusion criteria are intelligence quotient (IQ) below 70, prior history of severe head trauma and insufficient understanding of a Scandinavian language. In the current study, only participants who had completed the Affective Lability Scale—Short Form (ALS-SF) and the Social Functioning Scale (SFS) were included.

The TOP study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and is conducted in line with the Helsinki declaration of 1975 (as revised in 2008 and 2013).

Diagnostic assessment

The Structured Clinical Interview for DSM-IV axis 1 disorders (SCID; modules A-E) [47] was used to establish diagnoses in the study as part of a thorough clinical assessment carried out by clinical psychologists, medical doctors in psychiatric residency or psychiatrists. All clinical personnel in the study undergo an extensive 3-month training and quality assurance program in the use of SCID and the Positive and Negative Syndrome Scale (PANSS) developed at the University of California, Los Angeles, USA [48] before being allowed to carry out clinical interviews with diagnostic assessments, irrespective of previous clinical training. Diagnostic reliability across different groups of assessment teams have demonstrated a Cohen's kappa for diagnosis in the range between 0.92 and 0.99.

The Social Functioning Scale (SFS)

The Social Functioning Scale is a self-report scale that was originally developed to measure social adjustment in patients with schizophrenia, tapping areas of functioning that are crucial to community living [49]. It has later been validated for use with other severe mental disorders, including bipolar disorder, and has been found to have sound psychometric properties, as well as to correlate highly with clinician-rated measures of functioning [3, 24, 50–53]. The scale is comprised of 76 items that are rated on a Likert scale and yields a total score of overall functioning after illness debut, as

well as scores on seven subscales: (1) social engagement/withdrawal (amount of time spent alone, likelihood of initiating conversations, social avoidance); (2) interpersonal behavior (number of friends, romantic relationships, quality of communication); (3) prosocial activities (engagement in common social activities, e.g. going to the cinema); (4) recreation (engagement in hobbies/activities); (5) independence-competence (ability to maintain independent living, e.g. shopping for groceries); (6) independence-performance (performance of skills required for independent living); (7) employment/occupation (or being a full-time student). Each subscale is standardized and normalized to a scaled score (SS) with a mean of 100 and a standard deviation of 15, and the full-scale score is calculated as the mean of the SSs of the seven subscales [49]. The first two subscales combined are referred to as the SFS interpersonal domain. This domain has been found to have good ecological validity and to capture social isolation and social avoidance in particular [54], which are in themselves risk factors for depression, loneliness and other negative health outcomes [16]. The 3rd and 4th subscales comprise the activity domain, and although it includes single items that may reflect social functioning (i.e. whether you have visited friends), it has been found to have low ecological validity [54]. The remaining three subscales are not reflective of *social* functioning per se, but rather encompass skills for independent living (budgeting, preparing a meal, etc.) and ability to work/study which were not of primary interest in this respect. Consequently, only the interpersonal domain was used for the present study as this domain best represents our outcome measure of interest, namely social functioning. A higher score on the SFS interpersonal domain is indicative of a higher level of functioning.

The Affective Lability Scale Short Form (ALS-SF)

We used the Affective lability Scale Short Form (ALS-SF) [55] to measure affective lability. The scale, which is filled in by the participant, yields a total level of affective lability, in addition to subscores covering fluctuations between three subdimensions; anxiety-depression, depression-elation and anger-normal mood. The scale contains 18 items that are rated on a 4-point Likert scale ranging from 0 ("very uncharacteristic of me") to 3 ("very characteristic of me") and has been found to have good psychometric properties [21, 56, 57]. Of the items, five refer to shifts in anxiety-depression, eight refer to shifts in depression-elation and the final five items cover shifts between anger-normal mood. The ALS-SF yields subscores for the three subdimensions in addition to a total score of affective lability (the sum of all item responses divided by 18). In the current study, we chose to investigate the subdimensions in the total sample as opposed to the composite (total) ALS-SF score to more specifically address if there are certain types of affective lability that appear to be linked to social functioning.

Potential confounders of the relationship between social functioning and affective lability

The following variables are previously established predictors of social functioning considered potential confounders of the relationship between social functioning and affective lability in the current analyses. With respect to individual characteristics we investigated: sex, premorbid social functioning based on scores on the social domain in childhood from the Premorbid Adjustment Scale (PAS) [58, 59], as well as overall cognitive ability measured by the Wechsler Abbreviated Scale of Intelligence (WASI, [60]). More specific investigations of the role of cognitive deficits on social functioning were beyond the scope of the current study. Features related to illness course included estimation of duration of illness which was based on the age of onset of the first SCID-verified episode of psychosis for schizophrenia, schizophreniform, schizoaffective and psychosis NOS, and the first SCID-verified affective episode for BDI and BDII. We also calculated an estimate for the duration of *untreated* illness. For schizophrenia, schizophreniform, schizoaffective and psychosis NOS, duration of untreated psychosis (DUP) was calculated as the number of weeks from the first SCID-verified psychotic episode to adequate treatment (antipsychotic medication in adequate doses/admission to hospital for psychosis). For BDI and BDII, the duration of untreated bipolar disorder (DUB) was based on the number of weeks from the first SCID-verified episode of mania/hypomania to adequate treatment (mood-stabilizing medication or antipsychotics in adequate doses/hospital admission for treatment of mania). DUP and DUB were combined into one variable, duration of untreated illness, to use in the analyses of the whole sample. Further, the total number of illness episodes was calculated as the sum of all recorded illness episodes (depressive, hypomanic, manic, mixed, psychotic). Based on previous indications of a relationship between psychotic symptoms and lower social functioning and since the present sample also included individuals with bipolar disorder who have never had a psychotic episode, a categorical psychosis lifetime variable was made which denoted the lifetime history of a SCID-verified psychotic episode. With respect to current symptom states, they were assessed with the following: positive psychotic symptoms with the positive subscale of the PANSS [61], negative symptoms with the negative subscale of the PANSS, manic symptoms with the Young Mania Rating Scale (YMRS [62]), and depressive symptoms were assessed with the depression item (G6) in the general scale of the PANSS. To measure comorbid anxiety symptoms, the anxiety item (G2) from the general scale of the

PANSS was used. These items from the general scale of the PANSS were chosen because they were the only measures of depression and anxiety collected at the same time point as the ALS-SF and the SFS for all participants. We further used the Alcohol Use Disorders Identification Test (AUDIT, [63]) and the Drug Use Disorders Identification Test (DUDIT, [64]) to measure the degree of harmful substance use since associations between reduced social functioning and substance use has previously been found [65, 66].

Statistical analyses

Demographic and clinical characteristics of the sample were investigated with descriptive statistics, including means with standard deviations or frequencies with percentages as fitted. Pearson and Spearman's correlations were conducted to investigate the relationship between the SFS interpersonal domain and ALS-SF dimensions. Correlational analyses were also performed to investigate the relationship between the SFS interpersonal and demographic as well as clinical variables that have been established as predictors of social functioning in previous research. This was followed by a hierarchical multiple linear regression analysis for the SFS interpersonal score entering all the variables that were significantly associated with the SFS score. The analysis was conducted block-wise to investigate the proportion of variance explained by affective lability specifically. Here, premorbid social adjustment was entered first, the illness course variables (duration of untreated illness, total number of illness episodes) next, followed by the current symptom- and comorbidity variables (positive- and negative symptoms, manic symptoms, depression and anxiety) and finally all of the ALS-SF subdimensions in the last block. There were no indications of problematic multicollinearity between the ALS-SF subdimensions (tolerance ≥ 0.35 and VIF ≤ 2.9 for all dimensions). Based on our previous findings of higher levels of affective lability in BDII versus BDI and schizophrenia [67] and lower levels of social functioning in schizophrenia and psychotic versus non-psychotic bipolar disorder, we anticipated a possible interaction effect between lifetime psychosis and affective lability on social functioning. However, visual inspections of a scatterplot of the relationship between SFS and ALS-SF split by the dichotomous psychosis lifetime variable (Fig. 1) did not indicate an interaction between ALS-SF and psychosis lifetime on social functioning. Thus, we did not include such an interaction term in the regression analysis. As there could be differences between the diagnostic groups in terms of social functioning and to further disentangle putative relationships, follow-up analyses were also carried out in diagnostic subgroups according to current diagnostic nomenclature: schizophrenia spectrum (schizophrenia, schizophreniform, schizoaffective, psychosis NOS; $n = 123$) and bipolar spectrum (BDI and BDII; $n = 170$). Here, separate bivariate analyses for the two groups were performed to investigate the association between social functioning and affective lability, in addition to the other relevant demographic and clinical variables. The variables that were significantly associated with the SFS interpersonal score in bivariate analyses for each group were then entered into separate forced entry hierarchical multiple regression models. Due to lower n when the sample was split, the total score of the ALS-SF was used in the multivariate analyses for both groups to ensure enough statistical power when all predictor variables were entered. An interaction term between affective lability and diagnostic subgroup on social functioning was not included as a scatterplot did not indicate the presence of such an interaction (Fig. 2).

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 26) and a significance level of $p \leq 0.05$ (two-tailed tests) was employed.

Results

Demographics and clinical characteristics of the sample

Demographic and clinical characteristics of the sample are presented in Table 1. There were 82 participants without lifetime psychosis; 25/102 (24.5%) in BDI and 57/68 (83.8%) in BDII.

Bivariate analyses in the total sample

Overall, although correlation coefficients are low to moderate, the analyses revealed significant associations between all of the ALS-SF subdimension scores and the SFS interpersonal score (anxiety-depression $p < 0.001$, depression-elation $p = 0.003$, anger $p < 0.001$), as well as the total score ($p < 0.001$). The SFS interpersonal score was further significantly associated with current manic symptoms, current positive and negative psychotic symptoms, current anxiety and depressive symptoms, duration of untreated illness, total number of illness episodes, as well as premorbid social functioning in childhood (see Table 2 for correlation coefficients). The SFS interpersonal score was not associated with sex, age, illness onset at or before 18, duration of illness, IQ, alcohol- or drug misuse, or the psychosis lifetime variable.

Results from multivariate analyses in the total sample

After controlling for potential confounders, higher scores on the anxiety-depression dimension of the ALS-SF were significantly and independently associated with lower social

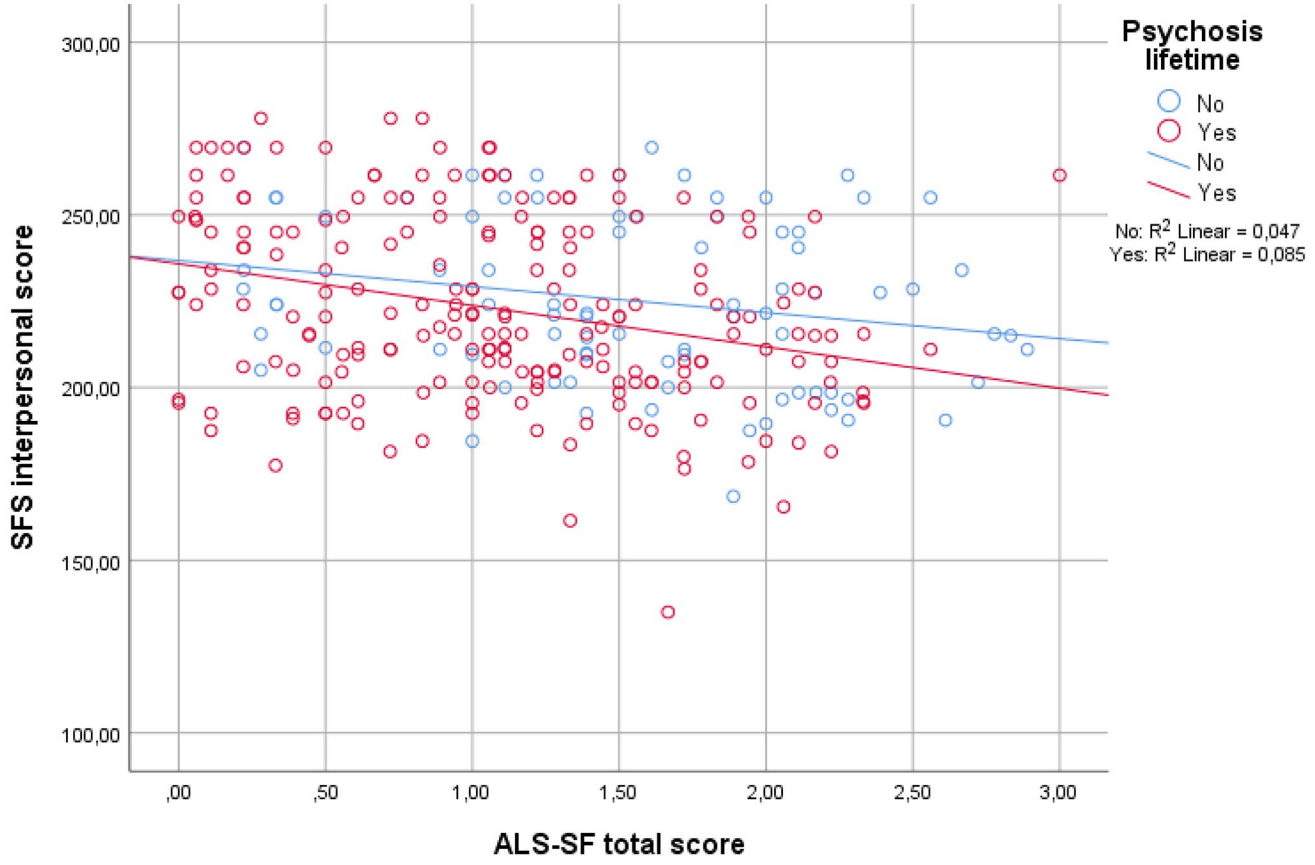

Fig. 1 The relationship between affective lability and social functioning split by the presence of lifetime psychosis

functioning ($p = 0.019$; model $F = 8.249$, df = 11, $p < 0.001$). In addition, higher levels of current positive- and negative symptoms and lower premorbid social adjustment were significantly associated with lower social functioning (R^2 for the final model = 0.298; PANSS N p < 0.001; PANSS P $p = 0.008$; PAS-S $p = 0.009$, see Table 3). The depression-elation and anger dimensions of the ALS-SF were not significantly associated with social functioning after controlling for potential confounders ($p = 0.306$ and $p = 0.627$, respectively). The R^2 change for the ALS-SF dimensions block was 3.1%, which is a statistically significant contribution (Sig. F change 0.027). The R^2 change for the first block with individual characteristics (PAS-S) was 4.2%, the illness course variables block was 1.9%, and the current symptoms block was 20.6%.

Follow-up bivariate analyses in diagnostic subgroups

Overall, elevated affective lability was significantly and negatively associated with social functioning in both the schizophrenia- and the bipolar spectrum groups (ALS-SF total score $p < 0.01$, see Table 2). With respect to the ALS-SF subdimensions, the anxiety-depression and the anger dimensions were significantly associated with the SFS in the schizophrenia spectrum group ($p = 0.001$ and $p = 0.006$, respectively). The SFS was further significantly associated with current positive and negative psychotic symptoms, current anxiety and depressive symptoms, premorbid social adjustment in childhood and duration of untreated illness in this group. In the bipolar spectrum group, the association between affective lability and social functioning was significant for all subdimensions ($p \leq 0.001$). Here, current anxiety and depressive symptoms and positive and negative psychotic symptoms were also significantly associated with the SFS.

Results from follow-up multivariate analyses in diagnostic subgroups

In the schizophrenia spectrum group, lower social functioning was significantly associated with lower premorbid social functioning in childhood and higher levels of current negative symptoms ($p < 0.001$ and $p = 0.001$, respectively; model $F = 9.281$, df = 7, $p < 0.001$, R^2 for the final model = 0.394), in addition to trend level associations for

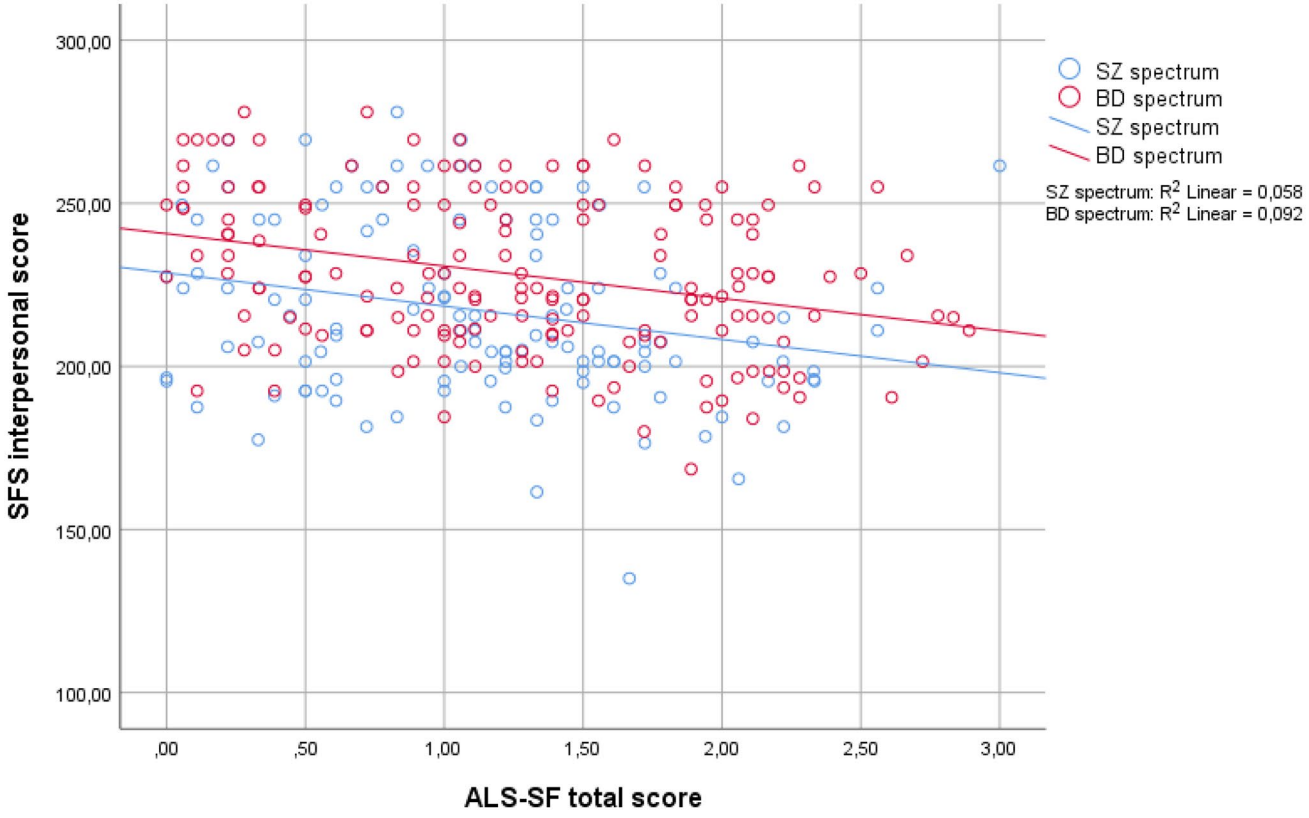

Fig. 2 The relationship between affective lability and social functioning split by diagnostic group

higher levels of current positive psychotic- ($p=0.055$) and depressive symptoms ($p=0.053$). Affective lability (ALS-SF total score) was no longer significantly associated with social functioning after correcting for the level of positive symptoms ($p=0.685$). There was also a statistically significant association between the ALS total score and the level of positive psychotic symptoms. The analysis thus indicated that the effect of the ALS on the SFS score was mediated through positive psychotic symptoms. In the bipolar spectrum group, elevated affective lability was the strongest predictor of reduced social functioning ($p=0.004$; model $F=6.432$, df = 5, $p<0.001$; R^2 for the final model = 0.164). In addition, a higher level of current positive psychotic symptoms was also significantly associated with reduced social functioning in the bipolar spectrum group ($p=0.031$). Please refer to supplementary information for regression tables for the subgroups.

Discussion

Affective lability and social functioning in the total sample

In the current study, we found that higher scores on the anxiety-depression dimension of the ALS-SF were significantly associated with lower social functioning in severe mental disorders. Albeit accounting for a modest part of the total variance, this association remained at a level of statistical significance even when we controlled for other well-established predictors of social functioning such as premorbid social functioning, duration of untreated illness, and level of current symptoms. We have previously found that affective lability in our sample was characterized by fluctuations between both anxiety-depression and depression-elation across diagnostic groups [22]. However, only fluctuations between anxiety- and depressive symptoms appear to be directly linked to social functioning. As a majority of the sample (58%) consisted of individuals with bipolar disorder, it was somewhat surprising that an association between the depression-elation dimension and social functioning was not found. This might be an indication that internalizing thoughts and behaviors related to negative affectivity are more disrupting to social functioning compared to

Table 1 Demographics and clinical characteristics

	Total sample, $n=293$	Schizophrenia-spectrum, $n=123$	Bipolar-spectrum, $n=170$	Statistics	p value
	Mean (SD)	Mean (SD)	Mean (SD)		
Age (years)	30.1 (9.9)	29.7 (8.9)	31 (10.5)	$t=-1.092$, df = 284	0.276
Female sex, *n* (%)	157 (53.0)	53 (43.1)	101 (59.4)	$X^2=7.625$, df = 2	**0.006** BD > SZ
SFS interpersonal	223.4 (25.9)	217.1 (27.4)	227.9 (24.1)	$t=-3.586$, df = 291	**0.000 BD > SZ**
Duration of illness, years[a]	8.6 (9.0)	4.9 (6.6)	11.2 (9.5)	$t=-6.675$, df = 288	**0.000** BD > SZ
IQ (WASI)[b]	108 (13.4)	104 (14.8)	110.9 (11.5)	$t=-4.277$, df = 204	**0.000** BD > SZ
Total number of illness episodes	9.4 (16.2)	3.9 (4.8)	13.4 (19.9)	$t=-5.981$, df = 196	**0.000** BD > SZ
Onset of illness ≤ 18 years, *n* (%)	123 (42.0)	25 (20.3)	98 (57.6)	$X^2=40.813$, df = 1	**0.000** BD > SZ
Duration of untreated illness, weeks[c]	47 (145.3)	75 (173.3)	22 (109.5)	$t=2.764$, df = 226	**0.008** SZ > BD
Premorbid social functioning (PAS)[d]	1.9 (2.3)	2.1 (2.4)	1.8 (2.3)	$t=1.196$, df = 286	0.233
Psychosis lifetime, *n* (%)	214 (72.1)	123 (100)	88 (52)	$X^2=82.386$, df = 1	**0.000** SZ > BD
PANSS—total	47.8 (13.3)	55.4 (15.1)	42.3 (8.3)	$t=8.702$, df = 175	**0.000** SZ > BD
PANSS—Positive	10.4 (3.9)	12.6 (4.4)	8.9 (2.5)	$t=8.488$, df = 178	**0.000** SZ > BD
PANSS—Negative	11.2 (4.8)	14.0 (5.7)	9.2 (2.5)	$t=8.797$, df = 157	**0.000** SZ > BD
Depression (PANSS item G6)	2.4 (1.3)	2.3 (1.2)	2.5 (1.4)	$t=-1.448$, df = 291	0.149
Anxiety (PANSS item G2)	2.8 (1.3)	2.7 (1.2)	3.1 (1.4)	$t=-1.688$, df = 291	0.092
YMRS—total[e]	2.6 (3.6)	2.7 (3.6)	2.5 (4.1)	t = .490, df = 288	0.624
AUDIT[f]	6.8 (6.0)	5.2 (4.9)	8.1 (6.5)	$t=-4.116$, df = 282	**0.000** BD > SZ
DUDIT[g]	3.2 (6.6)	3.2 (7.1)	3.2 (6.4)	$t=-.068$, df = 281	0.946
ALS-SF—total	1.2 (0.71)	1.1 (0.65)	1.3 (0.73)	$t=-1.890$, df = 291	0.060
ALS-SF anxiety-depression	1.4 (0.87)	1.3 (0.83)	1.5 (0.90)	$t=-1.168$, df = 291	0.244
ALS-SF depression-elation	1.4 (0.74)	1.3 (0.71)	1.4 (0.76)	$t=-1.453$, df = 291	0.147
ALS-SF anger	0.80 (0.78)	0.67 (0.75)	0.90 (0.80)	$t=-2.559$, df = 291	**0.011**

SFS Social Functioning Scale, *WASI* Wechsler Abbreviated Scale of Intelligence, *PAS* Premorbid Adjustment Scale, *PANSS* Positive and Negative Syndrome Scale, *YMRS* Young Mania Rating Scale, *AUDIT* The Alcohol Use Disorders Identification Test, *DUDIT* Drug Use Disorders Identification Test, *ALS-SF* Affective Lability Scale Short Form

Statistically significant *p* values are in bold

[a]99% ($n=290$) participants had data on duration of illness

[b]93% ($n=273$) participants had data on IQ

[c]78% ($n=228$) had data on duration of untreated illness

[d]98.2% ($n=288$) participants had data on PAS

[e]99% ($n=290$) participants had data on YMRS

[f]96.9% ($n=284$) participants had data on AUDIT

[g]96.6% ($n=283$) participants had data on DUDIT

Table 2 Bivariate correlation analyses

	Total sample SFS interpersonal	Schizophrenia-spectrum SFS interpersonal	Bipolar-spectrum SFS interpersonal
Sex	$r_s = 0.032$	$r_s = 0.152$	$r_s = -0.126$
Age	$r_s = 0.020$	$r_s = -0.031$	$r_s = -0.016$
IQ	$r = 0.117$	$r = -0.003$	$r = 0.133$
PANSS P	$r_s = -0.391^{**}$	$r_s = -0.426^{**}$	$r_s = -0.203^{**}$
PANSS N	$r_s = -0.399^{**}$	$r_s = -0.470^{**}$	$r_s = -0.236^{**}$
PANSS G2	$r_s = -0.236^{**}$	$r_s = -0.295^{**}$	$r_s = -0.236^{**}$
PANSS G6	$r_s = -0.174^{**}$	$r_s = -0.212^{*}$	$r_s = -0.208^{**}$
YMRS	$r_s = -0.142^{**}$	$r_s = -0.161$	$r_s = -0.111$
AUDIT	$r = 0.092$	$r = 0.103$	$r = 0.011$
DUDIT	$r_s = -0.041$	$r_s = -0.013$	$r_s = 0.019$
Psychosis lifetime	$r_s = -0.052$	n0.a	$r_s = 0.092$
Premorbid social functioning	$r_s = -0.218^{**}$	$r_s = -0.308^{**}$	$r_s = -0.125$
Duration of untreated illness	$r_s = -0.197^{**}$	$r_s = -0.229^{*}$	$r_s = -0.051$
Total number of illness episodes	$r_s = 0.175^{**}$	$r_s = 0.098$	$r_s = 0.046$
Duration of illness	$r_s = 0.034$	$r_s = -0.076$	$r_s = -0.035$
ALS-SF total	$r = -0.244^{**}$	$r = -0.240^{**}$	$r = -0.303^{**}$
ALS-SF anxiety-depression	$r = -0.283^{**}$	$r = -0.308^{**}$	$r = -0.304^{**}$
ALS-SF depression-elation	$r = -0.171^{**}$	$r = -0.103$	$r = -0.265^{**}$
ALS-SF anger	$r = -0.208^{**}$	$r = -0.246^{**}$	$r = -0.249^{**}$

SFS Social Functional Scale, *PANSS P* Positive and Negative Syndrome Scale Positive subscale, *PANSS N* Positive and Negative Syndrome Scale Negative subscale, *PANSS G2* Positive and Negative Syndrome Scale anxiety item, *PANSS G6* Positive and Negative Syndrome Scale depression item, *YMRS* Young Mania Rating Scale, *AUDIT* The Alcohol Use Disorders Identification Test, *DUDIT* The Drug Use Disorders Identification Test, ALS-SF Affective Lability Scale Short Form, $^{*}p < 0.05$, $^{**}p < 0.01$

Table 3 Multiple linear regression analysis on the relationship between social functioning and affective lability in the total sample

Covariates	Beta	*t* test	*p* value	95% CI for B	
				Lower bound	Upper bound
Premorbid social functioning	− 0.156	− 2.656	**0.009**	− 3.034	− 0.449
Duration of untreated illness	0.004	0.064	0.949	− 1.057	1.128
Total number of illness episodes	0.034	0.553	0.581	− 0.140	0.249
Anxiety (PANSS G2)	− 0.068	− 0.959	0.339	− 4.101	1.417
Depression (PANSS G6)	− 0.051	− 0.746	0.456	− 3.618	1.631
PANSS P	− 0.211	− 2.685	**0.008**	− 2.431	− 0.373
PANSS N	− 0.249	− 3.650	**0.000**	− 2.072	− 0.619
YMRS	0.001	0.016	0.987	− 0.924	0.938
ALS-SF anxiety-depression	− 0.229	− 2.357	**0.019**	− 12.487	− 1.113
ALS-SF depression-elation	0.091	1.027	0.306	− 2.922	9.274
ALS-SF anger	− 0.039	− 0.486	0.627	− 6.610	3.995

PANSS G2 Positive and Negative Syndrome Scale anxiety item, *PANSS G6* Positive and Negative Syndrome Scale depression item, *YMRS* Young Mania Rating Scale, *PANSS P* Positive and Negative Syndrome Scale Positive subscale, *PANSS N* Positive and Negative Syndrome Scale Negative subscale *ALS-SF* Affective Lability Scale Short Form

Statistically significant *p* values are in bold

externalizing problems that may arise as a result of fluctuations in elation.

In line with some previous studies [25, 26], higher levels of current psychotic symptoms (both positive and negative) contributed the most to reduced social functioning in the total sample, highlighting the importance of achieving symptom remission. From an illness course perspective, whether the participants had previous psychotic episodes or not in their

lifetime did not appear to influence the level of social functioning. In an earlier study, we found that elevated affective lability was associated with higher levels of positive psychotic symptoms in schizophrenia spectrum disorders, although directionality could not be inferred [21]. Based on the past and current findings, one may, however, speculate that targeting affective lability in treatment might be beneficial for social functioning in psychotic disorders directly but also via reducing positive psychotic symptoms. Interestingly, while affective symptoms (depressive and manic) were associated with social functioning in the bivariate analyses, their statistical significance was not upheld when entered together with affective lability into the multivariate regression model. We tentatively interpret this as support for the claim that affective lability in the anxiety-depression dimension is indeed a "trait-like" illness feature associated with social functioning independent of elevation in symptom levels.

Affective lability and social functioning in diagnostic subgroups

The follow-up analyses in diagnostic subgroups showed that the significant association between affective lability and social functioning was lost in the schizophrenia spectrum group when other predictors of social functioning were entered into the regression model. Further analyses indicated that the effect of affective lability on social functioning was largely mediated through positive psychotic symptoms in the schizophrenia spectrum group. As noted above, we have also previously reported a significant association between elevated affective lability and increased positive psychotic symptoms in schizophrenia spectrum disorders [21]. Since elevated affective lability is considered a more stable trait that may increase the risk for reality distortion, in line with the notion of an affective pathway to psychosis [68], we interpret our findings as mediation. However, the cross-sectional study design does not rule out the possibility that high levels of positive psychotic symptoms are followed by higher affective lability. More studies, preferably using longitudinal designs, are needed to clarify these relationships in schizophrenia spectrum disorders. In the bipolar spectrum group, on the other hand, affective lability remained significantly and independently associated with social functioning even when the other predictors were taken into account. Nonetheless, as our previous study showed that the level of affective lability is significantly different in BDI versus BDII disorders [22], this finding warrants further investigation in larger samples to tease out if the association between affective lability and social functioning is the same irrespective of bipolar subtype.

Putative mechanisms underlying the relationship between affective lability and social functioning

Healthy social relationships are tied to longer, healthier lives and improved psychological well-being [69]. Thus, improving social functioning should be an important treatment goal in all psychiatric disorders. In fact, research indicates that social factors such as social support and social integration are at least as important for mortality as well-established behavioral risk factors such as smoking, obesity, physical inactivity and high blood-pressure [70]. In severe mental disorders, where life expectancy has been found to be substantially decreased compared to the general population, the health-promoting effects of social factors are perhaps particularly crucial [68–70]. The results of the current study indicate that elevated affective lability may be an obstacle to harvesting the benefits of social interactions, although the directionality and the exact mechanisms by which this may exert its effects are, thus far, unclear.

Negative affect has been found to predict social functioning across schizophrenia and bipolar disorder, and high levels of negative affect have been linked to greater fluctuations in affective states [10, 71]. This has again been associated with delayed return to a more adaptive affective baseline which can result in adverse health effects [72–74]. One can speculate that a pattern with elevated affective lability, high levels of negative affect and slow return to a neutral physiological state could give rise to a vicious cycle, fostering coping behaviors that are counterproductive to social functioning, such as withdrawal, avoidance and disengagement. Over time, this may interfere with the drive to forge and maintain both peripheral and close social connections [75–78], which is deleterious to well-being and longevity [79, 80]. Feeding into this potential negative cycle, social settings are in themselves triggering to a host of different affective experiences due to their ever-changing, ambiguous and unpredictable nature. Successful social navigation is therefore contingent upon having a clear representation of one's own internal affective state to guide appropriate behavior and responses [81]. Elevated affective lability might make it distinctively more difficult to differentiate, categorize and label affective states in a precise and specific way, i.e. result in low emotional granularity [82], which has further been associated with social dysfunction [83–86]. Collectively and tentatively, affective lability may contribute to steering individuals away from the social world while features in the social world, in turn, may increase affective lability, generating negative interactions that contribute to impairments in social functioning.

Limitations and strengths

The findings of the present study must be interpreted in light of some limitations. Causal attributions are precluded due to the cross-sectional nature of the study and data on comorbid disorders such as personality disorders, ADHD and anxiety disorders are lacking. In addition, since this is a naturalistic study, the participants have typically received a broad range, as well as different combinations, of pharmacological and psychosocial treatments that would be very difficult to control for in the statistical analyses. Furthermore, as the ALS-SF and the SFS are based on self-report, there is a risk for recall- and response bias that cannot be ruled out. Finally, the measures used for anxiety and depressive symptoms are based on a scale primarily developed for assessing psychotic symptoms. Hence, the possibility that current symptoms still could have influenced the association between affective lability and social functioning cannot be ruled out completely. However, we believe that the likelihood of this is limited due to the relatively low levels of anxiety and depressive symptoms. The study also has several strengths; it demonstrates that there are associations between affective lability and social functioning in a large, diagnostically well-characterized sample of participants with severe mental disorders while accounting for many other well-documented confounding variables. To our knowledge, this has not been shown previously.

Conclusions

Our results indicate that elevated affective lability may have a negative impact on social functioning in severe mental disorders. If replicated, this could have important clinical implications as affective lability can be targeted in treatment through various forms of emotion regulation skills training. Future research should address whether a therapeutic focus on affective lability could be one pathway towards improving social outcomes in severe mental disorders.

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Author contributions MCH and TVL designed the study. MCH conducted the data analyses and drafted the manuscript. TVL contributed with data analyses and -interpretation and with revising the paper. IM initiated the study and together with TU provided input concerning data analyses and interpretation of results. SRA, MCH, SHO and SHL collected data. All authors were involved in critically reviewing the manuscript before approving the final version.

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Availability of data and materials The data that support the findings of this study will be made available upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The TOP study is conducted in line with the Helsinki declaration of 1975 (as revised in 2008 and 2013) and has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Consent to participate All participants must be able to provide informed consent before entering the study.

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