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The final scope is to help the translation of most relevant research findings into every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, 4 key-words, one Table or Figure and up to ten references).

Paolo Brambilla, *Section Editor*

Neuropsychological underpinnings of the dynamics of bipolar disorder

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Although we have gained enormous insights into neurobiological and psychological underpinnings of bipolar disorder (BD) symptoms, our knowledge concerning pathogenic mechanisms initiating recurrent affective episodes is still fragmentary. Previous research has highlighted the role of significant life events and social rhythm in recurrent episodes of mania and depression. However, most studies share the drawback of retrospective self-report data, which are prone to recall biases and limited introspective abilities. Therefore, more objective data, such as neuropsychological and neurobiological measures are needed to further unravel the pathogenic mechanisms of the dynamics of bipolar disorder. Previous research has highlighted disturbed emotional reactivity as well as impaired emotion regulation and impulse control as major behavioural characteristics of BD and aberrancies in prefrontal–limbic–striatal networks that have been proposed to be the correlates of these behavioural alterations. However, longitudinal studies assessing these neural and behavioural alterations are rare. Future research should therefore adopt prospective study designs including behavioural and neuroimaging measures underlying cognitive, emotional and motivational deficits in bipolar disorder. Particularly, these measures should be collected continuously at multiple time points as implemented in modern ambulatory assessment tools.

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Bipolar disorder (BD) is a highly severe and chronic mental condition with a lifetime prevalence of 2–4% for its most common subtypes (i.e., type I/II). Given the chronic and episodic course of the disease the prediction of recurrent manic and depressive episodes is a

major, though not adequately resolved clinical and research question. On a phenomenological level the disease is characterised by phases of (hypo)mania, a state of elevated mood, increased energy, risk-taking and reduced sleep and phases of depression, best described by feelings of sadness, hopelessness, loss of energy and reduced sensitivity to positive outcomes. It has been proposed that increased emotional reactivity, deficient emotion regulation and impulse control as well as motivational dysregulation are important

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mechanisms underlying these symptoms (Wessa *et al.* 2014).

BD is considered among the ten most important causes of disease burden worldwide (Whiteford *et al.* 2013) and has been judged the most expensive behavioural health care diagnosis. Hence, it is an important finding that the number of previous episodes and hospitalisations due to full-blown manic and depressive episodes predicts poor functional outcome, more severe cognitive impairments and worse prognosis, as indicated by higher rates of suicidal behaviour (Table 1, Ref. 1, 2). Therefore targeted and tailored improved prevention with respect to relapse into illness episodes would reduce the financial impact of this disease, decrease illness burden for patients and their families and improve patients' social, occupational and cognitive functioning.

The research on inter-episode prodromal symptoms in BD is half a century old and ever since, a few predictors and a number of consistent early signs of recurrent episodes have been identified. Most robustly, relapse is predicted by significant life events (Christensen *et al.*, 2003), but social rhythm disturbances have also been linked to the initiation of recurrent manic episodes (Levenson *et al.* 2013). Further, previous research suggests several early predictive signs for the onset of mania (e.g., reduced need for sleep, increased energy, racing thoughts, overspending and distractibility), depression (e.g., sadness; slowness of movements, talking less and loss of energy) or both illness phases (mood lability, irritability) (Table 1, Ref. 5).

Most of these studies are focused on retrospective self-report data, which imply two important methodological limitations: (1) recall biases and (2) restriction of introspective abilities. To prevent recall biases, real-time reports of symptoms by so-called 'ambulatory assessment (AA) methods' have been proposed to prospectively capture the dynamics of symptoms in chronic mental disorders (Trull & Ebner-Priemer, 2013). In the long run, their application is therefore considered worthwhile in predicting recurrent symptoms and preventing full-blown episodes. In BD research, a handful of studies used such AA methods, suggesting increased intra-individual variability particularly in positive affect and self-esteem measures in BD patients, which distinguished these patients not only from healthy controls but also from patients with major depressive disorder (MDD) (Table 1, Ref. 6). Such increased variability could also explain seemingly contradictory findings of both generally reduced positive affect and greater positive emotionality in BD patients compared with controls (Table 1, Ref. 7, 8). Further, BD patients showed a marked decrease in positive affect when stressed whereas MDD patients displayed a significant increase of

negative affect to stress (Table 1, Ref. 9). These studies provide an important insight into the dynamics of symptoms in BD. However, so far no published AA study has used a prospective design relating to these dynamics recurrence of affective episodes.

Further, we might overcome the issue of limited capability to introspection mentioned above using cognitive, neuropsychological or even neurobiological measures as predictors of recurrent episodes. This has already been done in two studies revealing neuropsychological measures that predict functional outcome or recovery in BD patients (Table 1, Ref. 3). Moreover, the authors showed that patients with impairments in at least one cognitive domain had higher risk to experience a recurrent episode in a shorter time interval (Table 1, Ref. 4). Based on these results, the combination of neuropsychological measures and (repeated) ambulatory assessment appears extremely promising to detect mechanisms predicting the switch into an affective episode.

On a neurobiological level, aberrancies in prefrontal–limbic–striatal networks have been proposed to be the correlate of various aetiological mechanisms of the disease (Phillips & Swartz, 2014), such as disturbed emotional reactivity, impaired emotion regulation (Wessa *et al.* 2014) and impulse control (Swann *et al.* 2009). However, longitudinal data concerning these neural alterations capturing the dynamics of BD is rare. The few existing studies indicate decreased prefrontal activation and/or decreased negative connectivity between prefrontal and limbic brain regions during elevated mood (e.g., Strakowski *et al.* 2011; Cerullo *et al.* 2012), whereas depression is associated with increased activity and connectivity between brain regions mediating emotional appraisal such as insula and amygdala (e.g., Cerullo *et al.* 2012). This pattern is also in line with the assumption that deficits in impulse control known to be mediated by prefrontal brain structures that represent a main feature of mania although increased impulsivity has also been observed across illness phases (e.g., Swann *et al.* 2009). To this end, a very recent longitudinal study investigated a group of bipolar patients in euthymic, manic and depressed states. Here, independent of the symptomatic state, all patients showed decreased activation of the cognitive control network during an emotional conflict task (Rey *et al.* 2014), with a stronger decrease during mania. During euthymia, this decreased response to conflict was only observed during difficult as compared to all task levels in manic and depressed patients.

The present findings underline that we currently face a gap in BD research that only begins to consider the dynamics of recurrent episodes. 'Since the biology, as the symptoms, fluctuates in time' a paradigm shift

Table 1. Example studies of predictors for and early signs of bipolar illness episodes

Study	Sample	Type of study	Assessment/diagnostics	Findings
<i>Significant predictors of recurrent illness episodes in BD</i>				
Martinez-Aran <i>et al.</i> (2004)	40 euthymic BD patients 30 HC	Cross-sectional study	Neuropsychological test battery on premorbid IQ, attention, verbal learning and memory and frontal executive functioning; symptomatology	Euthymic BD patients showed impairments in memory and executive functions. Verbal memory impairment was associated with worse functional outcome, longer illness duration, increased number of manic episodes and prior psychotic symptoms
Finseth <i>et al.</i> (2012)	140 BD-I patients 66 BD-II patients	Retrospective, cross-sectional study	Network Entry Questionnaires including questions on demographic and clinical variables describing the course of the illness, PANSS	Number of hospitalisations due to depression was a significant risk factors of suicide attempts as well as comorbid alcohol/substance use and a history of antidepressant medication- and/or alcohol-induced affective episodes
Martino <i>et al.</i> (2009)	35 euthymic BD patients	Prospective, neuropsychological study	Neurocognitive Battery (verbal memory, attention, executive functions) at study entry; life chart assessment during 12 month follow up; GAF and FAST assessment after 12 months	Predictors of functional outcome: impairments in verbal memory and attention, subsyndromal depressive symptomatology (43% variance explanation)
Martino <i>et al.</i> (2013)	70 euthymic BD patients	Prospective neuropsychological study	Neurocognitive assessment at study entry and division into impaired and not-impaired group; life chart assessment during around 16 months	Patients with impairments in at least one neurocognitive domain showed higher risk to develop a recurrent illness phase compared with non-impaired patients
Sierra <i>et al.</i> (2007)	–	Literature review	Search of studies on prodromes preceding both manic and depressive phases	Most common prodromes for mania: increased activity, elevated mood, decreased need for sleep, more talkative, racing thoughts, increased self-esteem, distractibility, increased sex-drive, increased spending, irritability and alcohol abuse Most common prodromes for bipolar depression: depressive mood, loss of energy, concentration difficulties, negative thinking, decreased sleep, increased sleep, loss of interest in activities, weight loss, loss of appetite, alcohol abuse and suicidal ideas
<i>Ambulatory assessment studies</i>				
Knowles <i>et al.</i> (2007)	18 euthymic BD patients 16 MDD patients 19 HC	Diary study over 1 week	Self-esteem, positive and negative affect were assessed twice a day over 1 week	Greater instability of affect and self-esteem in remitted bipolar patients as compared with unipolar patients and controls
Havermans <i>et al.</i> (2010)	38 euthymic BD patients 38 HC	Experience sampling approach over 6 days	Negative and positive mood states and their reactivity to daily hassles and uplifts	In BD patients mean level of negative affect was higher and positive effect lower compared with healthy controls, reactivity to daily hassles was comparable in both groups; subsyndromal depression increased perceived stress

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Table 1. Continued

Study	Sample	Type of study	Assessment/diagnostics	Findings
Gruber et al. (2013)	31 euthymic BD-I patients 21 remitted MDD patients 32 HC	Experience sampling approach over 6 days	Consecutive assessment of emotionality (positive and negative) and use of emotion regulation strategies	BD-I patients showed increased positive and increased negative emotionality and increased efforts to regulate emotions in everyday life
Myin-Germeys et al. (2003)	42 NAP patients 38 BD patients 46 MDD patients 49 HC	Experience sampling approach	subjective stress reactivity daily hassles, emotional reactivity: changes in positive and negative affect	MDD patients showed an increase in negative affect and BD patients a decrease in positive affect in response to individually perceived stressful situations, whereas NAP patients reported both an increase in negative and decrease in positive affect

NAP = non-affective psychosis; HC = healthy controls.

towards neurobiological assessment at multiple time points over the course of the disease is indispensable, as pointed out in a recent editorial of this journal (Vol. 23, p. 211). Despite considerable challenges when investigating large cohorts of patients over the course of bipolar illness, future research should adopt prospective study designs including behavioural and neuroimaging measures underlying cognitive, emotional and motivational deficits in BD.

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Conflict of Interest

None.

Ethical Statement

The authors declare that no human or animal experimentation was conducted for this work.

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