Chapter 2
Combining clinical stage and pathophysiological mechanisms to understand illness trajectories in young people with emerging mood and psychotic syndromes

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Summary

- Traditional diagnostic classification systems for mental disorders map poorly onto the early stages of illness experienced by young people, and purport categorical distinctions that are not readily supported by research into genetic, environmental and neurobiological risk factors.
- Consequently, a key clinical challenge in youth mental health is to develop and test new classification systems that align with current evidence on comorbid presentations, are consistent with current understanding of underlying neurobiology, and provide utility for predicting outcomes and guiding decisions regarding the provision of appropriate and effective care.
- This chapter outlines a transdiagnostic framework for classifying common adolescent-onset mood and psychotic syndromes, combining two independent but complementary dimensions: clinical staging, and three proposed pathophysiological mechanisms.
- Clinical staging reflects the progression of mental disorders and is in line with the concept used in general medicine, where more advanced stages are associated with a poorer prognosis and a need for more intensive interventions with a higher risk-to-benefit ratio.
- The three proposed pathophysiological mechanisms are neurodevelopmental abnormalities, hyperarousal and circadian dysfunction, which, over time, have illness trajectories (or pathways) to psychosis, anxious depression and bipolar spectrum disorders, respectively.
- The transdiagnostic framework has been evaluated in young people presenting to youth mental health clinics of the University of Sydney's Brain and Mind Centre, alongside a range of clinical and objective measures. Our research to date provides support for this framework, and we are now exploring its application to the development of more personalised models of care.

Despite the vast majority of major mental disorders having their onset in adolescence or early adulthood,[1] current diagnostic frameworks often map poorly onto the early stages of illness. Young people commonly experience less specific syndromes with mixed clusters of symptoms that do not clearly fit within specified categories and thresholds.[2–5] Further, diagnostic categories in these frameworks (based exclusively on sets of presenting symptoms) are assumed to represent independent clinical categories. However, comorbidity is the rule rather than the exception in young people, and research regarding genetic, environmental and neurobiological risk factors does not readily support current assumptions regarding classification.[6–11]

Considering the inadequacies of current diagnostic classification systems, an important clinical challenge is to derive new diagnostic frameworks. These should be consistent with the current understanding of developmental epidemiology and neurobiology, reflect the experiences of individuals across the course of illness, and provide utility when used in a clinical setting for facilitating informed decisions regarding care and treatment. In response to this challenge, we have developed a transdiagnostic framework incorporating two independent but complementary dimensions to classify common mood and psychotic syndromes in young people (Box 1). These two dimensions are clinical stage, reflecting the severity and persistence of illness, and pathophysiological mechanisms, reflecting the proposed underlying mechanisms of illness and their individual trajectories (or pathways). These two dimensions are key tools for the assessment of clinical presentation within our larger multidimensional framework (Chapters 1 and 3) and are intended to be used as adjuncts to formal diagnosis. We describe these dimensions in detail in this chapter, and also present data from the University of Sydney's Brain and Mind Centre (BMC) Optymise Youth Cohort — a group of young people who were included in a longitudinal study tracking multidimensional outcomes for the duration of their engagement with youth mental health clinics at the BMC (Chapter 1).[12,13]

Clinical staging

The concept of clinical staging is widely used and accepted in various areas of medicine (eg, oncology) in which it is inappropriate to treat conditions based on an ambiguous illness category (eg, treating all presentations of breast cancer equally). Rather, staging attempts to place an individual on a continuum from risk to end-stage disease and then determines treatment using evidence-based pathological boundaries. Applying the same concept in mental health, it is not optimal to plan preventive, early intervention strategies and/or treatment plans based on broad illness categories such as schizophrenia or major depression. The use of clinical staging in mental health care is supported by preliminary evidence that suggests there are different patterns of response to specific interventions at different points along the continuum of mental illness.[14–17] Further, levels of impairment in young people presenting for mental health care are high, despite being at early stages of mental disorders and often not meeting formal diagnostic criteria.[18–22] This highlights a need to intervene with stage-appropriate care to reduce this distress and disability, and to prevent progression to later stages. In contrast to previous research (eg, early-psychosis research), the emphasis in our clinical staging framework is on transdiagnostic transition from earlier to later stages of illness, rather than transitions to full-threshold disorders within narrow diagnostic bands. Clinical stages in our model are an adjunct to formal diagnosis, and the demarcation between stages does not equate

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to the cut-off points for threshold diagnoses according to standard diagnostic classification systems (eg, *Diagnostic and statistical manual of mental disorders*[23] and International Classification of Diseases[24]).

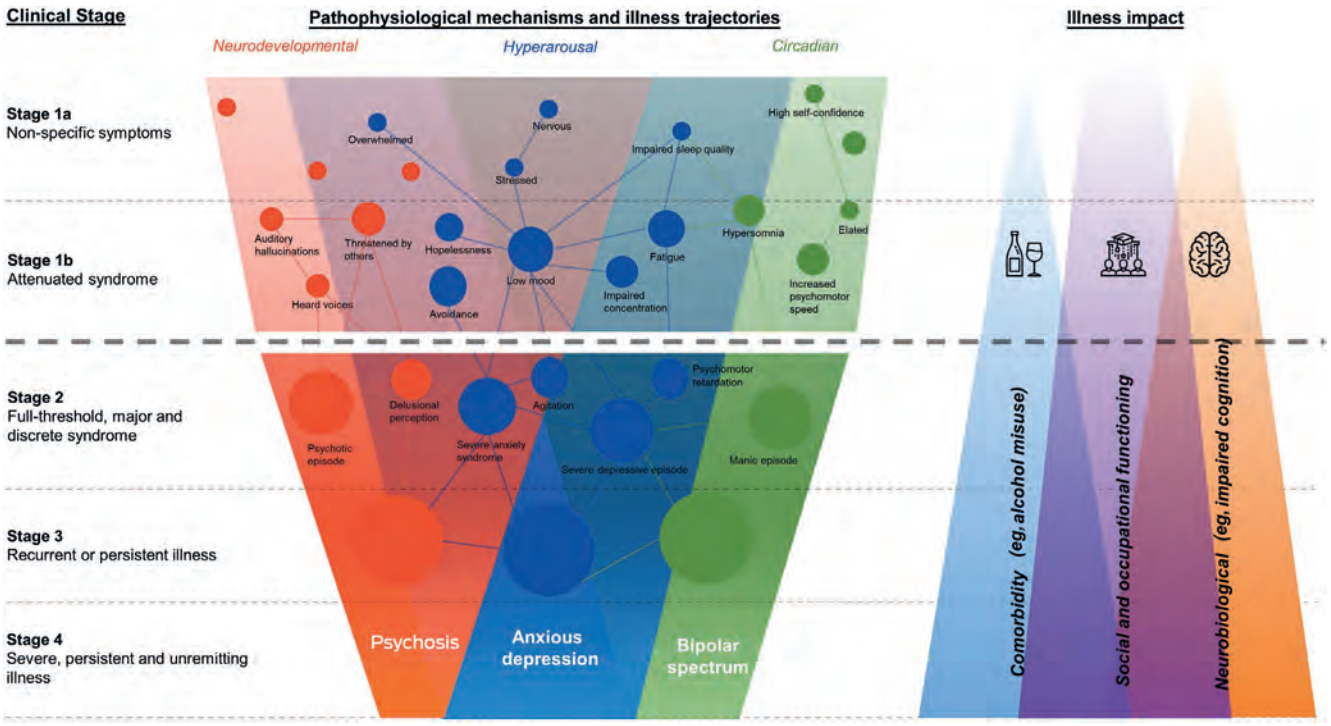
Illness progression in clinical staging

Clinical staging can be applied to young people (aged 12–30 years) with mood and psychotic syndromes (including anxiety, depression, bipolar disorder, psychosis) presenting for mental health care. Earlier stages are characterised by lower rates of impairment and are associated with a lower risk of progression to more severe, disabling or persistent disorders. As with clinical staging in other areas of medicine, intervention at earlier stages is more likely to result in positive treatment outcomes. One key distinction is the differentiation between those in early phases (stages 1a and 1b) and those who have reached a higher threshold of disorder (stage 2 and above). Stage 2 is our proposed cut-off point for more persistent disorders requiring further specific and intensive clinical care and treatment.[5,16,17] Another key distinction is made in the earlier stage 1 disorders where we differentiate "attenuated syndromes" (stage 1b) — which often, but not always, meet criteria for specific mood or anxiety disorders according to diagnostic criteria — from more non-specific anxiety or depressive symptoms (stage 1a). Transitions across stage 1a to 1b and stage 2 are largely driven by severity of illness, whereas transitions to stage 3 and 4 are largely driven by persistence and recurrence of illness. While it is possible to recover from an acute episode of illness, individuals cannot move backwards across clinical stages once a threshold is reached. In instances of uncertainty about the appropriate stage, assessors are encouraged to rate down, assigning the earlier clinical stage until more evidence of progression becomes apparent. A decision tree outlining key clinical decisions (between stage 1 and 2, and between stage 1a and 1b) is provided in Box 2, and detailed descriptors of each stage are provided in Box 3. We have previously demonstrated the inter-rater reliability of clinical staging using this structured approach.[5]

The distinction between early stage 1 syndromes and more developed stage 2+ illnesses represents a key boundary between non-specific syndromes that may or may not progress, and more specific discrete disorders that are expected to persist or recur if appropriate intervention is not provided. This is particularly important across the adolescent period, when transient mood instability is common, and many experiences that may be considered "depressive syndromes" at early adolescent ages will spontaneously remit by late adolescence or early adulthood. In support of this, Box 4 illustrates recent data in a community-based cohort of adolescents showing that most depressive syndromes that meet the criteria for "caseness" in early adolescence (age 12 or 14 years) do not continue into later adolescence (age 16 years).[25] In the context of development, it is thus important to use appropriate levels of monitoring and care for those at early clinical stages with the expectation that most will not experience progressive continuation of illness.

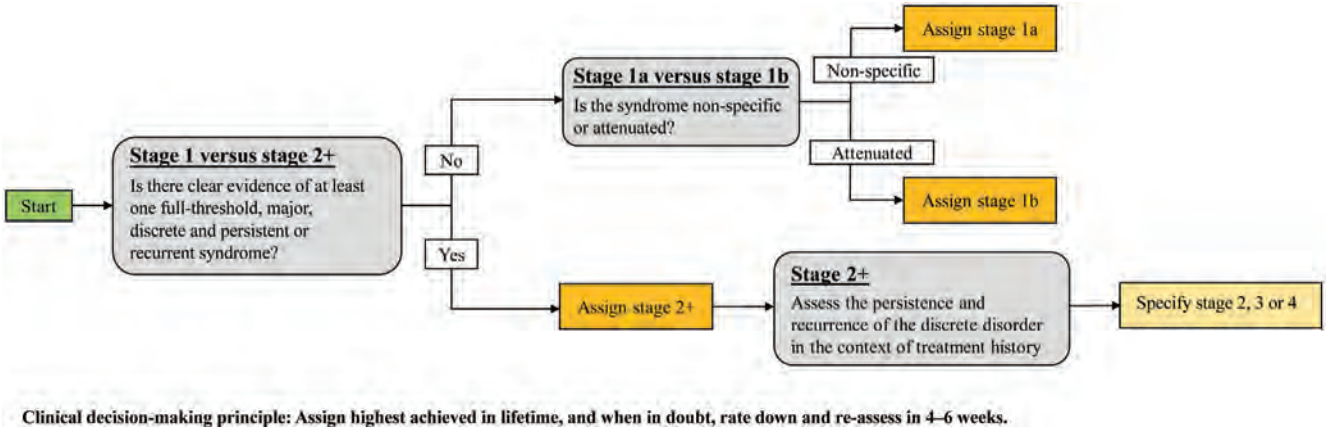
At later clinical stages, recovery is expected to be less common and more difficult. One key aspect of recovery from mental illness is return to a normal level of functioning. Using the Social and Occupational Functioning Assessment Scale (SOFAS) as an indicator of functional recovery in the BMC's Optymise

1 Transdiagnostic framework of clinical stages, proposed pathophysiological mechanisms, and illness trajectories for the onset and course of adolescent-onset mood and psychotic syndromes*



Icons from www.flaticon.com: wine bottle/glass made by srip; team education made by Eucalyp; brain made by Freepik. * Circles represent symptoms. Some examples of symptoms in the model, symptom clustering and illness trajectories (shown by joining lines) are provided. Increasing symptom burden occurs as syndromes progress to later clinical stages of illness and more discrete disorders (represented by larger circles and a more solid background). Colours represent proposed pathophysiological mechanisms with three key pathways to illness subtypes: neurodevelopmental–psychosis, hyperarousal–anxious depression, and circadian–bipolar spectrum. Progression to later stages of illness is also accompanied by increasing illness impacts including comorbidity, impairment in social and occupational functioning, and neurobiological deficits. ◆

2 Decision tree used to assign clinical stage*



* This is intended to be used in conjunction with Box 3 to assist in assigning clinical stage to young people receiving mental health care. The first key decision is between stage 1 and stage 2+, with young people at stage 2+ likely to require more specific and intensive interventions. For those at stage 1, the second key decision is between stage 1a and stage 1b, to determine whether the illness is at an early, non-specific stage with a low risk of progression, or has developed into an attenuated syndrome with a greater need for monitoring and intervention to prevent progression. The specification of stage 2, 3 or 4 in those assigned stage 2+ is a secondary distinction that may be made to provide more detail on the illness and treatment history. ◆

Youth Cohort, Box 5 shows differences in recovery rates across stages (unpublished data). A greater proportion of those at earlier stages achieve functional recovery (as indexed by a SOFAS score in the normal range [ie, ≥ 70]) during the course of care, with functional recovery rates of 54% for stage 1a, 32% for stage 1b, and 24% for stage 2+ (Box 5). Further, those at earlier stages who do functionally recover, do so at a faster rate than those at later stages, starting with less functional impairment and achieving functional recovery earlier in the course of care. It should be noted that these data only represent those who continue to engage with care, so they cannot provide insight into recovery rates for young people who are no longer engaged with care. Nevertheless, these results highlight the importance of intervening early in the course of illness to maximise positive outcomes. Thus, the use of clinical staging, as an adjunct to formal diagnosis, may help guide decisions regarding the provision of appropriate and effective care options (Chapter 4).

Illness extension in clinical staging

Most clinical staging models employed in mental health settings have evolved primarily as a means of describing disease progression (ie, severity and persistence of illness).[26,27] Often this means that attempts are made to include other phenomena — such as metabolic disturbances, alcohol or other substance misuse, or other problems that are significantly associated with mental disorders — in the progression dimension. While this approach is understandable, it has created some problems when trying to employ a transdiagnostic framework.[28] An alternative is to try to separate disease extension from disease progression. While disease progression refers to worsening of the syndrome itself, disease extension refers to the spread of the syndrome to have wider reaching effects on multiple outcomes (analogous to the spread of physical disease to other areas of the body). It is important to stress, however, that this idea is an emerging concept. Nevertheless, as is seen in oncology (where, for example, tumour-node-metastasis models chart progression across several dimensions), it is expected that there is a range of disease extension that may occur within each stage. Therefore, in addition to an individual's clinical stage, the degree of extension may help inform clinical decisions such as additional treatments targeting specific concerns (Chapter 4).

Clinical and objective validation of clinical staging

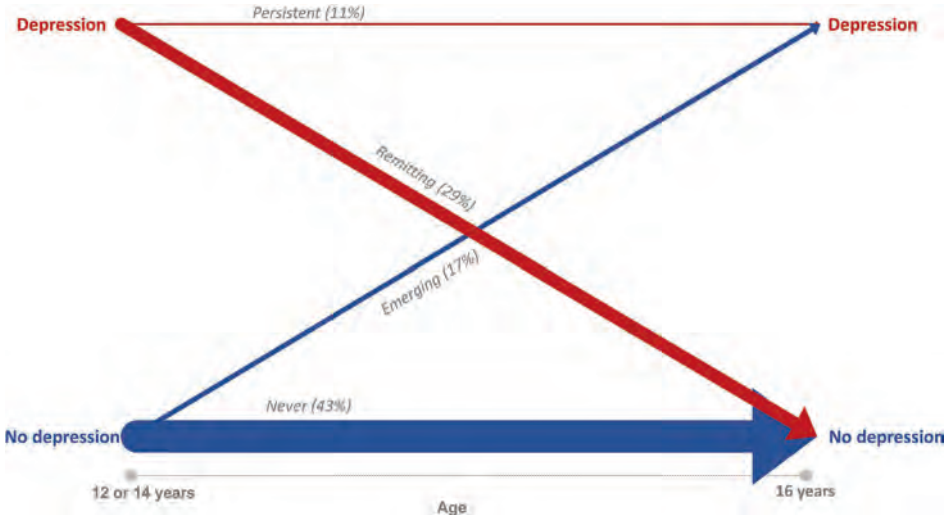
In the BMC's Optymise Youth Cohort, we previously examined multiple clinical and objective factors in relation to clinical stage. It is clear from our studies that later stages are associated with greater distress and disability, and more functional impairment.[18,19,22,29] Increased functional impairment at later stages is partially to be expected cross-sectionally because current levels of functioning are part of the clinical presentation used to assess clinical stage. However, those at later stages also remain functionally impaired longitudinally, highlighting the need for more intensive care for those at later stages. For example, we have found that, compared with stage 1a, those classified as stage 1b remain significantly impaired following 10 sessions of treatment despite greater service use, modest decreases in psychological distress and improvement in functioning.[30] The first 3 months of treatment has been highlighted as a critical window for intervention in which most transitions from stage 1b to stage 2+ occur.[31] Our data show that by 12 months, about 17% of those at stage 1b will have transitioned to a later stage.[31] Among those classified as stage 1b, there are diverse patterns of symptomatic and functional change, with 25–30% showing reliable improvement, 10% showing reliable deterioration, and most showing neither linear improvement nor deterioration of symptoms and functioning when followed up for 6 months.[32] Recently, we have reported in the BMC's Optymise Youth Cohort that of those presenting to care at stage 1a, only 3% progress to stage 2+ by time last seen, whereas 13% of those presenting at stage 1b progress to stage 2+.[13] In our longitudinal work, transition to later stages has been found to be predicted by negative symptoms, psychotic-like experiences, manic-like experiences, circadian disturbance, self-harm, lower social functioning, and lower engagement in education or employment.[13,30]

3 Guidelines and detailed criteria for clinical stage*

Clinical stage	Definition and clinical features	Additional information
Stage 1a: non-specific symptoms	Functioning — episode of illness is having a mild to moderate impact on social, educational or occupational function **plus** Depression — mild to moderate levels of depressive ideation without specific features indicative of more disabling syndromes **and/or** Anxiety — mild to moderate levels of arousal without significant or persistent avoidant behaviour	• May include those with earlier childhood-onset symptoms who have re-presented or had worsening of symptoms during the adolescent period • May include those with earlier onset neurodevelopmental or attentional disorders who now present with anxiety or depressive symptoms in the adolescent years • Typically, adolescent or early adult populations assessed in primary care or educational settings or identified by screening in relevant primary care, employment or educational settings of relevant populations; may be referred to specialist settings for further assessment
Stage 1b: attenuated syndrome	Functioning — episode of illness is having a moderate to severe impact on social, educational or occupational function **plus** Depression — depressive syndromes of moderate severity without specific features indicative of a stage 2 syndrome **and/or** Anxiety — specific and more severe symptoms of anxiety, such as the development of specific avoidant behaviour **and/or** At-risk mental states — hypomanic symptoms and/or attenuated or brief psychotic symptoms Comorbidity — syndromes may be somewhat mixed in terms of their symptoms or complicated by alcohol or other substance misuse	• May include those who meet diagnostic criteria for specific anxiety disorders, major depressive disorder or bipolar II disorder • The presence of regular, deliberate self-harm without overt suicidal intent may occur in this stage; this includes impulsive low lethality overdose occurring in the context of psychosocial stressor and in the absence of severe depression • Treatment may have already commenced and/or the person may have been referred for further specialised assessment • Some degree of treatment with an antidepressant, antipsychotic or mood-stabilising agent is common, particularly where there has been limited access to specialised psychological therapies
Stage 2: full-threshold, major and discrete syndrome	Functioning — episode of illness is clearly having an ongoing and major impact on social, educational or occupational function **plus** Mania — clear manic syndrome during a specific illness event (hypomanic symptoms or brief hypomanic syndromes alone do not constitute a discrete disorder) **and/or** Psychosis — clear psychotic syndrome for more than 1 week **and/or** Depression — features indicative of more severe depressive syndromes including psychomotor retardation, marked agitation, impaired cognitive function, severe circadian dysfunction, psychotic features, brief hypomanic periods, severe neuro-vegetative changes, pathological guilt or severe suicidality **and/or** Anxiety — anxiety complicated by at least moderate to severe concurrent depressive syndromes; typically associated with significant or persistent avoidant behaviour, marked agitation, fixed irrational beliefs, overvalued ideas, attenuated psychotic symptoms, or substantial and persistent substance misuse Comorbidity — syndrome may remain mixed in phenomenological terms, not necessarily matching a single or discrete DSM-style disorder or corresponding to a specific cut-off point on a specific rating scale for anxiety, depressive, manic or psychotic symptoms; the primary discrete syndromes may co-occur, including significant and clear symptoms (depressive, manic or psychotic) in the context of a more severe persistent syndrome; and the significant comorbidity may include alcohol or other substance misuse, abnormal eating behaviour or other relevant psychological syndromes	• Moderately severe mood or anxiety disorders that are complicated by significant and persistent alcohol or other substance misuse may reach this stage • Typically, patients with discrete disorders have been referred to specialist services for further assessment or have been managed extensively by suitably qualified primary care or other interdisciplinary services • If the patient has been hospitalised for treatment, then typically they would have met the criteria for this stage • If the patient required very intensive outpatient care due to suicidal or homicidal intent, plan or history of attempt, florid or persistent psychotic or very severe depressive symptoms (eg, psychomotor change or psychotic features), they would have been likely to have met the criteria for this stage
Stage 3: recurrent or persistent illness	Functioning — over at least a 12-month period after entry to relevant specialist or enhanced primary care services, there has been clear evidence that the illness course has resulted in marked worsening in social, educational or occupational function due to persistence or recurrence **plus** Symptoms — either incomplete remission from discrete disorder at 12 months after entry to care following a reasonable course of treatment (of at least 3 months' duration), or recurrence of discrete disorder after period of complete recovery (having fully recovered for at least 3 months)	• Includes those with discrete disorders who are assessed and specifically treated for at least 3 months, but with poor response or incomplete response to treatment • May include those with discrete disorders who have fully recovered but then relapse to the full extent described in Stage 2
Stage 4: severe, persistent, and unremitting illness	Functioning — illness course is associated with clear evidence of marked deterioration in social, educational or occupational function due to persistence or recurrence **plus** Symptoms — severe, persistent and unremitting illness assessed after at least 24 months of engagement with relevant specialised clinical services and provision of a reasonable range of medical, psychological and social interventions	• Includes those with chronic, deteriorating severe depressive, bipolar, and/or psychotic illness, which may be complicated by alcohol or other substance misuse, that has persisted without remission for at least 2 years

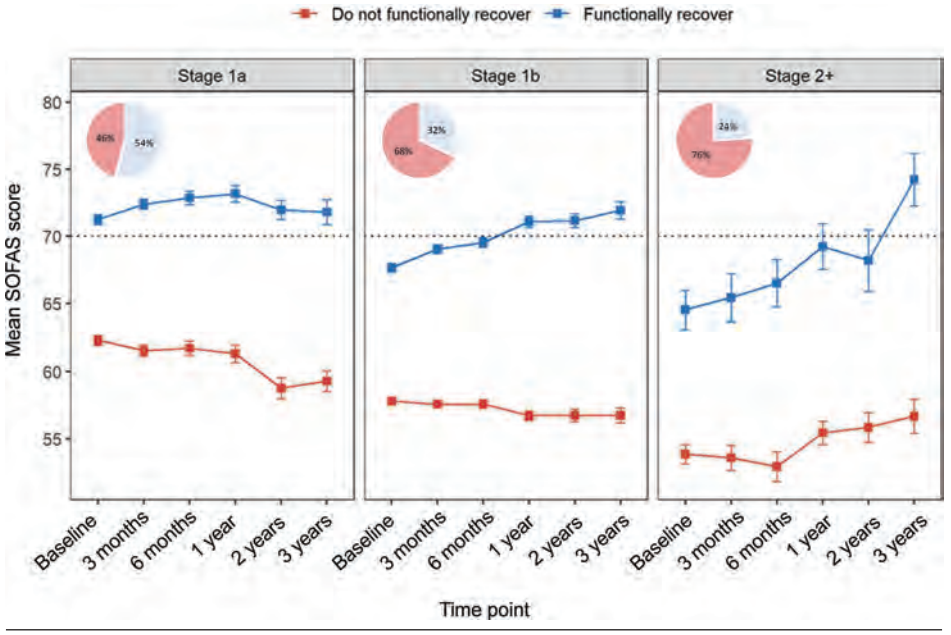
DSM = *Diagnostic and statistical manual of mental disorders.* * Adapted from Hickie and colleagues.[5] Each stage is defined by a degree of functional impairment as well as severity and persistence of symptoms. Although symptom type is noted in the clinical descriptors, clinical stages are not expected to coincide with traditional diagnostic categories. It is highly likely that young people in the early phases of illness will have mixed symptoms that range across various diagnostic categories. Consequently, young people with the same formal diagnosis (eg, major depressive episode) may be rated as being at different clinical stages based on symptom profile, symptom severity, level of disability, need for hospitalisation and comorbid symptoms. ◆

4 Proportions of transient and persistent illness across adolescence*



* Adapted with permission from Scott and collegues.[25] Blue lines indicate no depression at first visit, red lines indicate depression at first visit, and most cases of depression at 12 or 14 years remit by 16 years. ◆

5 Functional recovery over time in the Brain and Mind Centre's Optymise Youth Cohort presenting to primary mental health care*



SOFAS = Social and Occupational Functioning Assessment Scale. * Unpublished data from 2162 young people with at least 1 month of follow-up after presentation to care. Those who do functionally recover (blue lines) are compared with those who do not functionally recover (red lines) for each clinical staging group. Pie charts indicate the proportions of young people at each stage who do and do not functionally recover, in blue and red, respectively. Functional recovery is indexed by a SOFAS score of ≥70 by time last seen. Squares represent mean values and error bars indicate standard error of mean. ◆

In our research examining objective factors related to clinical stage, we have used measures of neuropsychological function, brain structure and function, sleep–wake behaviours and circadian rhythms. This research has focused on the two major clinical stages of illness surrounding key transitions (ie, stage 1b and stage 2+) with the aim of determining the objective features that characterise the major demarcation point in adolescent-onset mood and psychotic syndromes. Our key findings to date, linking stage with clinical and objective measures, are summarised in Box 6.

Cross-sectionally, we have reported neuropsychological performance to be impaired in those at stage 2+ relative to controls, with those at stage 1b showing an intermediate profile, and the most prominent impairments being for verbal memory and executive functioning.[34] Longitudinal follow-up of neuropsychological performance indicates that change in these measures is generally similar between those at stages 1b and 2+, despite those at stage 2+ being significantly more impaired at baseline.[35] However, those at stage 1b show significant improvement in verbal memory compared with those at stage 2+, who show slight deterioration in verbal memory at follow-up,[35] suggesting that verbal memory may be a particularly sensitive neuropsychological measure for distinguishing between earlier and later stages.

We have conducted two neuroimaging studies demonstrating structural differences between clinical stages. One of these studies showed that those at stage 2+ presented with decreased grey matter volumes within distributed frontal brain regions compared with controls and those at stage 1b; most prominently, this was in an overlapping region bounded by the superior and middle frontal gyri on the right side.[36] The second study showed that those at stages 1b and 2+ presented with significant disruption in white matter integrity in the left anterior corona radiata, particularly in the anterior thalamic radiation, compared with healthy controls.[37] These studies provide some support for delineating earlier stages from later stages of illness, given that there are measurable changes in the brain associated with stage 2 disorders, which to some degree can be differentiated from stage 1b disorders.

Using actigraphy monitoring to measure average rest and activity timing over several days, we have also found differences in sleep–wake behaviours between those at different clinical stages of illness. This is characterised by delayed sleep timing in those at stage 1b and stage 2+ compared with controls, with more severe delays in those at stage 2+ compared with those at stage 1b.[38] To explore the biological basis of these behavioural sleep–wake delays, we have examined evening dim-light melatonin secretion to quantify circadian rhythm parameters. This study showed that the timing of the evening rise in melatonin secretion did not differ between stages, but reduced levels of evening melatonin and shorter

6 Supporting evidence for clinical staging from the Brain and Mind Centre's Optymise Youth Cohort

Measurement domain and study design	Key findings
Clinical domain, cross-sectional design	• Later clinical stages are associated with greater impairment in social and occupational functioning,[18,19,22,29] greater symptom severity,[22,29] greater distress[18,19] and greater disability[19]
Clinical domain, longitudinal design	• Psychological distress abates and functioning improves in stage 1 patients following 6–10 sessions of care, but stage 1b patients remain impaired[30] • Stage 1b patients make and miss more appointments than stage 1a patients[33] • Those who present at later stages have a greater rate of transition[5,13] • Predictors of transition include being female, negative symptoms, psychotic-like experiences, manic-like experiences, circadian disturbance, self-harm, lower social functioning, and lower engagement in education or employment[13,30] • Within stages, there are diverse ranges of individual symptomatic and functional change over time with only a small proportion of patients showing reliable deterioration or improvement at 6-month follow-up[5,32]
Neuropsychological domain, cross-sectional design	• Stage 1b and 2+ patients are both impaired across neuropsychological measures compared with controls, with greater impairments in stage 2+ patients compared with stage 1b patients[34,35] • The greatest impairments in stage 2+ patients are found in tests of verbal memory and executive functioning[34,35]
Neuropsychological domain, longitudinal design	• Neuropsychological measures either improved or did not significantly change at follow-up in stage 1b and 2+ patients[35] • Verbal memory improved in stage 1b patients relative to stage 2+ patients at follow-up[35] • The proportion of young people showing improvement or deterioration in neuropsychological variables did not differ between stages 1b and 2+[35]
Neuroimaging domain, cross-sectional design	• Both stage 1 and 2+ patients have a reduction in grey matter volume in frontal brain regions compared with controls[36] • Stage 2+ patients have more extensive grey matter loss in frontal brain regions compared with stage 1 patients, with the greatest loss occurring in a region bounded by the right superior and middle frontal gyri[36] • Diffusion tensor imaging showed both stage 1 and 2+ patients have disrupted white matter integrity in the left anterior corona radiata, with a greater extent of these white matter microstructural changes in stage 2+ patients[37]
Circadian domain, cross-sectional design	• There is a progressive increase in the proportion of young people with delayed sleep phase at later clinical stages, with significantly later sleep times in stage 1b and 2+ patients compared with controls[38] • Stage 2+ patients have reduced evening melatonin secretion and altered timing of melatonin onset relative to sleep compared with stage 1b patients;[39] this reduced melatonin secretion is also associated with lower subjective sleepiness and impaired verbal memory in those at stage 2+

phase angles (time differences) between the melatonin rise and sleep onset were apparent in those at stage 2+ compared with those at stage 1b.[39] These studies suggest that disruptions to circadian rhythms, associated with delays in sleep timing, may be a marker of more developed mental illness.

Together, these findings are consistent with a neuroprogressive model of illness, with greater deficits and abnormalities across various objective measures at later stages of illness. In general, these abnormalities are not associated with clinical or functional measures, indicating that these neuropsychological, neuroimaging, sleep–wake behaviour and circadian rhythm features may distinguish stages of illness independent of current mental state. This provides some initial support for clinical staging as a valid representation of putative phenotypes (ie, clinical phenomena and objective markers) with distinct underlying neurobiology, although replication of findings in independent samples is now required.

Proposed pathophysiological mechanisms

A lack of knowledge surrounding the optimal meta-structure for differentiation of major mental disorders has hindered progress in research into objective markers of illness risk, progression, and response to treatment.[40–43] Consequently, there is a need to identify pathophysiologically based phenotypes in broad transdiagnostic populations to advance our understanding of how disorders develop and guide decisions regarding the provision of appropriate and effective care options (Chapter 4). This is particularly important in the early stages of mood and psychotic syndromes where clinical phenotypes often do not meet diagnostic thresholds and are not reliably distinguished in conventional frameworks. Focusing on adolescents and young adults close to the onset of these disorders has the added advantage of reducing confounding factors related to chronicity, secondary morbidity and prolonged exposure to treatments.

We propose at least three common illness trajectories (or pathways) in young people with mood and psychotic syndromes which may represent underlying pathophysiological mechanisms.[29] These pathophysiological mechanisms emphasise neurodevelopmental impairments, heightened arousal and stress sensitivity, and circadian rhythm dysregulation (Box 1). In young people presenting with any type of mood and psychotic syndrome, our model is used to allocate one of these three proposed pathophysiological mechanisms on the basis of the clinical presentation.[29,44] Any cases with significant manic-like symptoms or significant atypical features (eg, reduced activation and energy, prolonged sleep or prolonged fatigue) are allocated to the "circadian–bipolar spectrum" illness subtype. This subtype is derived from probabilistic and dimensional models that differentiate mood disorder presentations that are more likely to follow a bipolar course, characterised by atypical features, circadian disturbance, and dysregulated activation and energy including increased need for sleep.[45–49] Cases of adolescent-onset mood and psychotic syndromes with a current primary psychotic disorder or a history of childhood-onset significant and persistent developmental difficulties (such as an autism spectrum disorder, specific learning disability, or low intelligence quotient) are allocated to the "neurodevelopmental–psychosis" illness subtype. It is important to note that neurodevelopmental difficulties can also occur outside the context of mood and psychotic syndromes, and that cases are not allocated a position within this framework unless a mood and psychotic syndrome is present. This neurodevelopmental–psychosis subtype is consistent with meta-structures proposed for the redevelopment of diagnostic

7 Supporting evidence for pathophysiological mechanisms from the Brain and Mind Centre's Optymise Youth Cohort

Illness subtype	Proposed neurobiological features	Key findings
Neurodevelopmental–psychosis	• Childhood neurodevelopmental disorders • Cognitive impairment • Psychotic features	• More likely to be male and older at presentation to services[29] • Lower premorbid intelligence quotient and performance on neuropsychological measures, especially mental flexibility and verbal learning and memory[29] • Disproportionately represented in a data-driven cluster characterised by global neurocognitive impairment and lower functioning over 3 years (unpublished data) • Poorer social and occupational functioning at baseline and over the first 6 months of care, and less likely to be at early clinical stages of illness[29,60] • More likely to have a family history of psychotic disorders[29]
Hyperarousal–anxious depression	• Childhood anxiety • Heightened stress sensitivity • Adolescent depressive syndromes	• Those who have unipolar depressive disorders are more likely to report social anxiety compared with those who have bipolar-type illness[61] • More likely to have a family history of depressive disorders[29] • Reduced rates of alcohol or other substance misuse in those without psychotic or bipolar syndromes[62]
Circadian–bipolar spectrum	• Disrupted sleep–wake behaviours and circadian rhythms • Delayed sleep–wake timing • Atypical or bipolar spectrum symptom profile	• More likely to be female[63] • Delayed sleep–wake timing common and more pronounced in those who have bipolar-type illness compared with those who have unipolar mood disorders and controls[64,65] • Other sleep disturbances in bipolar-type illness include long sleep duration and more disturbed sleep[64] • Abnormal melatonin secretion patterns also reported in those who have bipolar-type illness[65] • Sleep–wake cycle disturbances predict increases in manic symptoms longitudinally[66] • More likely to have a family history of bipolar and anxiety disorders[29] • Family history of bipolar disorder is also associated with sleep–wake cycle disturbances[67] • Suicidal thoughts and behaviours have also been linked to bipolar-type illness[68]

classification systems,[40,50,51] and is based on evidence linking neurodevelopmental abnormalities with increased risk of developing psychotic phenomena.[52–55] Remaining cases, typically those reporting childhood anxiety and later stress sensitivity with evolving depressive disorder symptoms are allocated to the "hyperarousal–anxious depression" illness subtype. This is also the default subtype for those without clear evidence of a circadian–bipolar spectrum or neurodevelopmental–psychosis subtype. It is aligned with research emphasising stress sensitivity in anxiety and unipolar mood disorders, and with models of neural fear circuitry, prolonged stress responses, and glucocorticoid-dependent arousal.[56–59]

It is important to note that the three proposed pathophysiological mechanisms do not represent mutually exclusive pathways, and individuals may shift between pathways over time. Across all stages of illness, there is a degree of overlap between the three pathways, as illustrated in Box 1. In early clinical stage, this is demonstrated by mixed presentations of non-specific symptoms. At later clinical stages, syndromes may be more specific, but are often accompanied by comorbid conditions (such as alcohol or other substance misuse), greater functional impairment and neurobiological effects. Previous research from the BMC's Optymise Youth Cohort supporting these three proposed pathophysiological mechanisms is summarised in Box 7.

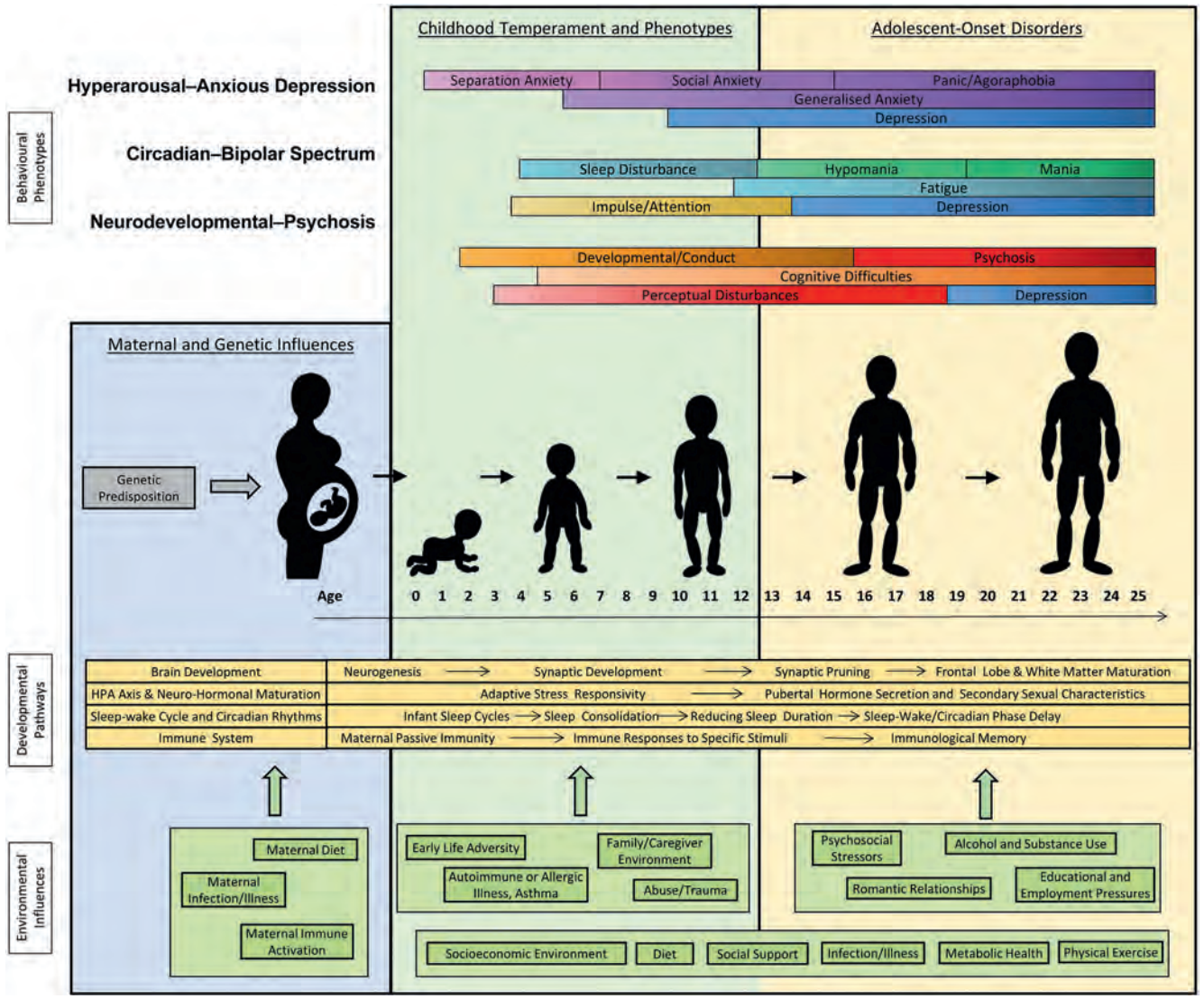
Our previous research has shown that those in the neurodevelopmental–psychosis subtype are more likely to be male, are older at presentation to services, and present with less severe anxiety and depressive symptoms, distress, and suicidality.[29] This subtype also presents with poorer social and occupational functioning, lower premorbid intelligence quotient, and poorer performance on neuropsychological measures (including marked dysfunction on tests of mental flexibility and verbal learning and memory). Further, we have found that a cluster of young people with global neuropsychological impairment and poorer functioning over 3 years are more likely to have psychotic illness (unpublished data).

When examining young people in our cohort who have a bipolar course of illness (circadian–bipolar spectrum subtype), we have reported that a greater proportion present with a delayed sleep–wake profile (>60%) compared with those who have unipolar mood disorders (30%) and controls (10%).[64] Circadian rhythm abnormalities appear to accompany these sleep–wake delays, with reduced and delayed evening melatonin secretion profiles in young people who have bipolar illness compared with those who have unipolar illness.[65] A neurobiological basis for these circadian abnormalities is supported by associations between delayed rhythms and neurochemical alterations.[69,70] Analysis of sleep–wake behaviours and circadian rhythms in a transdiagnostic sample further corroborates the presence of this subtype with delayed sleep and circadian rhythms, which is not exclusively restricted to a bipolar diagnosis according to traditional classification systems.[71–73] In addition, we have found in our longitudinal research that sleep–wake disturbances are predictive of increased manic symptoms at follow-up.[66]

Overall, this research provides initial support for three proposed pathophysiological mechanisms and pathways, with differing objective profiles between groups. The validity of the pathophysiological mechanisms is also supported by our findings that the neurodevelopmental–psychosis subtype is more likely to have a family history of psychotic disorders and less likely to have a family history of depression, while the circadian–bipolar spectrum subtype is more likely to have a family history of anxiety and bipolar disorders, and the hyperarousal–anxious depression subtype is more likely to have a family history of depression.[29] A family history of bipolar disorder has also been linked to specific subjective and objective sleep–wake cycle disturbances in our cohort, including increased sleep time and more variable sleep–wake patterns.[67]

As illustrated in Box 8, the pathways are expected to have different patterns of onset of clinical characteristics across development, with evolving behavioural presentations and increasing comorbidity. The evolution of mood and psychotic syndromes occurs in the context of age-dependent developmental and

8 Age-dependent behavioural phenotypes in the context of developmental pathways and environmental influences*



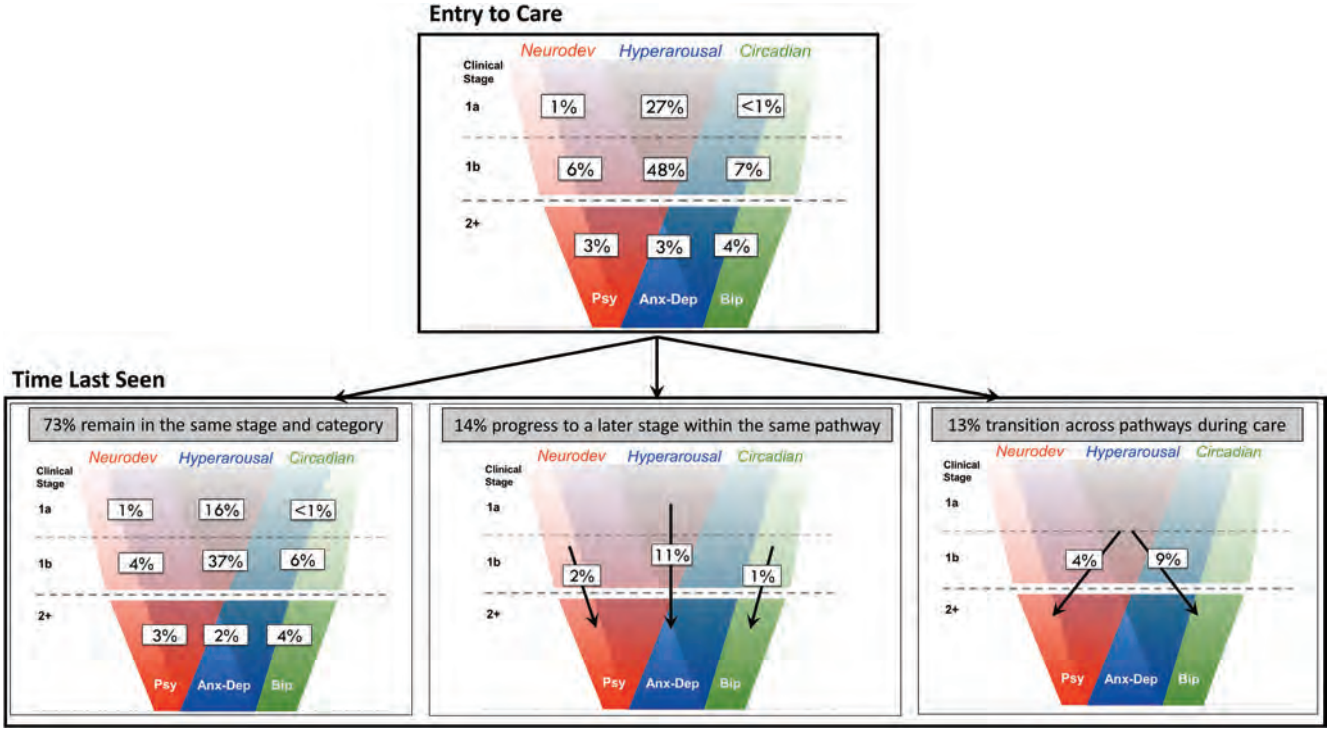
HPA axis = hypothalamic–pituitary–adrenal axis. * The behavioural phenotypic expression of mood and psychotic syndromes typically follows one of three proposed pathophysiological mechanisms with different presenting syndromal features across development. The development and maturation of biological systems provides an age-dependent context in which these interactions occur. Genetic predispositions interact with various environmental influences across development from the prenatal period to young adulthood. Some environmental influences are specific to certain developmental periods (eg, early life adversity) while others may be present across development or may have varied influence at different phases (eg, socioeconomic environment, diet, etc, as shown in green box at base of figure, are influences during both childhood and adolescence). ◆

environmental influences. That is, genetic predispositions interact with different environmental exposures across the lifespan, including psychosocial stressors, traumatic events, physical health insults, and educational, occupational or socioeconomic pressures. Progressive development of various biological systems, including neural, hormonal, circadian and immune maturation, influence these interactions to generate complex individual presentations with the onset of diverse clinical phenomena at different points along the life course.

Combining clinical staging and proposed pathophysiological mechanisms for a transdiagnostic framework

The combination of clinical staging and the proposed pathophysiological mechanisms into one transdiagnostic framework is shown in Box 1. Assigning individuals to a location in the framework is intended to assist in clinical decisions regarding appropriate care and treatment (Chapter 4). Tracking movement or progression in the framework over time will enable a greater understanding of individual illness trajectories and key intervention points. Box 9 shows the distribution and movement of the BMC's Optymise Youth Cohort across clinical stages and proposed pathophysiological mechanisms (unpublished data). At baseline, 28% are at stage 1a, 61% are at stage 1b and 10% are at stage 2+; 78% are classified as being in the hyperarousal–anxious depression pathway, 11% in the circadian–bipolar spectrum pathway and 11% in the neurodevelopmental–psychosis pathway. Over the course of care, 27% progress across stages and between pathways, including 14% progressing to later stages within the same trajectory and 13% progressing between pathways (typically through the development of psychotic, hypomanic or manic phenomena, with or without stage progression). Accordingly, while the three proposed pathophysiological mechanisms represent common pathways in which most individuals remain over time, there are multiple unique trajectories

9 Distribution across clinical stage and the three proposed pathophysiological mechanisms of young people in the Brain and Mind Centre's Optymise Youth Cohort at baseline and transitions across the course of care*



Anx-Dep = anxious depression. Bip = bipolar spectrum. Neurodev = neurodevelopmental. Psy = psychosis. * Unpublished data from 2259 young people with at least 1 month of follow-up after entry to care. Most young people first present in the hyperarousal–anxious depression pathway, and at earlier clinical stages. Across the course of care, 14% progress to a later stage within the same pathway, and 13% transition across pathways, typically from earlier stages of hyperarousal–anxious depression to later stages of circadian–bipolar spectrum or neurodevelopmental–psychosis pathways. ◆

within the model that an individual may take across the course of their illness. Box 10 illustrates three case examples of potential illness trajectories over time, reflecting movement from non-specific symptoms into more specific and severe syndromes.

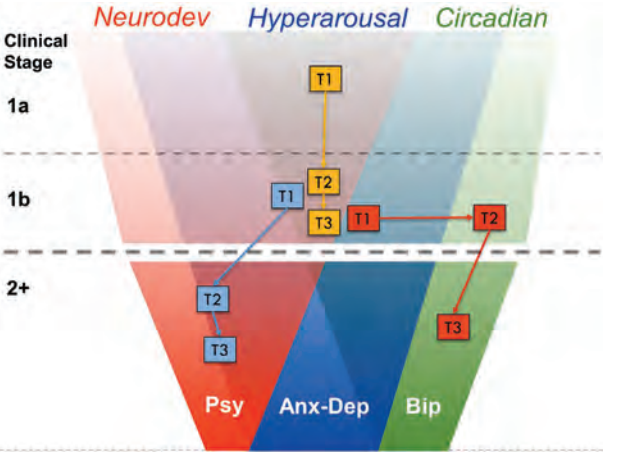
Limitations

This transdiagnostic framework is intended to be applied to adolescent-onset mood and psychotic syndromes in young people presenting for mental health care. It does not encompass all mental illness presentations (eg, eating disorders) or young people who have persistence of their childhood onset disorders (eg, autism spectrum disorders and attention deficit hyperactivity disorder) without development of a subsequent adolescent-onset mood and psychotic syndrome, although these may exist as precursors or comorbid conditions. While the research to date is promising, further validation of the objective underpinnings of clinical stages and pathophysiological mechanisms is necessary to support the framework and inform treatment implications. The potential utility of this framework for improving clinical care for mental illness in young people is a focus of ongoing research at the BMC.

Conclusion

Our transdiagnostic framework combining two independent but complementary dimensions of clinical staging and pathophysiological mechanisms in common adolescent-onset mood and psychotic syndromes is supported by clinical, neuropsychological, neuroimaging, sleep–wake behaviour and circadian rhythm evidence from the BMC's Optymise Youth Cohort. It is important that future research clarifies any longitudinal relationships between objective correlates of both clinical stages and the proposed pathophysiological mechanisms in young people with mental illness. Prospective biological research is

10 Case examples of common illness trajectories over time*



Anx-Dep = anxious depression. Bip = bipolar spectrum. Neurodev = neurodevelopmental. Psy = psychosis. * T1, T2 and T3 represent time points. Yellow indicates a typical hyperarousal–anxious depression illness trajectory, developing from non-specific to attenuated syndrome but not progressing to a discrete disorder. Blue indicates a typical neurodevelopmental–psychosis illness trajectory, initially presenting with stage 1b general depressive syndrome and then progressing to more severe psychotic-type illness. Red indicates a typical circadian–bipolar spectrum illness trajectory, initially presenting with stage 1b anxious depression symptoms, then developing a presentation of circadian disturbance before progressing to a more distinct later stage bipolar-type syndrome. ◆

also needed to validate the distinctions between stages and pathways in our model and compare our proposed boundaries to other clinical or data-driven subtypes. Further elaboration of this framework could provide a greater understanding of the underlying clinical and objective features of these disorders. It also has the potential to inform advances in treatment development and personalising care options. Compared with the use of traditional diagnostic classification systems in isolation, it could underpin the development of much more personalised, youth-relevant models of care.

1 Gore FM, Bloem PJN, Patton GC, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 2011; 377: 2093–2102.

2 McGorry PD. Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. *Schizophr Res* 2010; 120: 49–53.

3 McGorry PD, Yung AR, Bechdolf A, et al. Back to the future: predicting and reshaping the course of psychotic disorder. *Arch Gen Psychiatry* 2008; 65: 25–26.

4 McGorry P. Issues for DSM-V: clinical staging. A heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. *Am J Psychiatry* 2007; 164: 859–860.

5 Hickie IB, Scott EM, Hermens DF, et al. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry* 2013; 7: 31–43.

6 Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Rev Genet* 2012; 13: 537–551.

7 Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. *Neuron* 2012; 74: 990–1004.

8 Waszczuk MA, Zavos HM, Gregory AM, et al. The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry* 2014; 71: 905–916.

9 Kendler KS, Aggen SH, Knudsen GP, et al. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *Am J Psychiatry* 2011; 168: 29–39.

10 Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. *Mol Psychiatry* 2016; 21: 717–721.

11 Eaton NR, Rodriguez-Seijas C, Carragher N, et al. Transdiagnostic factors of psychopathology and substance use disorders: a review. *Soc Psychiatry Psychiatr Epidemiol* 2015; 50: 171–182.

12 Iorfino F, Hermens D, Cross SPM, et al. Delineating the trajectories of social and occupational functioning of young people attending early intervention mental health services in Australia: a longitudinal study. *BMJ Open* 2018; 8: e020678.

13 Iorfino F, Scott EM, Carpenter JS, et al. Clinical stage transitions in persons aged 12 to 25 years presenting to early intervention mental health services with anxiety, mood and psychotic disorders. *JAMA Psychiatry* 2019; https://doi.org/10.1001/jamapsychiatry.2019.2360 [Epub ahead of print].

14 Scott J. Bipolar disorder: from early identification to personalized treatment. *Early Interv Psychiatry* 2011; 5: 89–90.

15 Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry* 2006; 188: 313–320.

16 McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry* 2006; 40: 616–622.

17 McGorry PD, Purcell R, Hickie IB, et al. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007; 187: S40–S42. https://www.mja.com.au/journal/2007/187/7/clinical-staging-heuristic-model-psychiatry-and-youth-mental-health

18 Scott EM, Hermens DF, Glozier N, et al. Targeted primary care-based mental health services for young Australians. *Med J Aust* 2012; 196: 136–140. https://www.mja.com.au/journal/2012/196/2/targeted-primary-care-based-mental-health-services-young-australians

19 Hamilton BA, Naismith SL, Scott EM, et al. Disability is already pronounced in young people with early stages of affective disorders: data from an early intervention service. *J Affect Disord* 2011; 131: 84–91.

20 Burgess PM, Pirkis JE, Slade TN, et al. Service use for mental health problems: findings from the 2007 National Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry* 2009; 43: 615–623.

21 Rickwood DJ, Telford NR, Parker AG, et al. headspace – Australia's innovation in youth mental health: who are the clients and why are they presenting? *Med J Aust* 2014; 200: 108–111. https://www.mja.com.au/journal/2014/200/2/headspace-australias-innovation-youth-mental-health-who-are-clients-and-why-are

22 Purcell R, Jorm AF, Hickie IB, et al. Demographic and clinical characteristics of young people seeking help at youth mental health services: baseline findings of the Transitions Study. *Early Interv Psychiatry* 2015; 9: 487–497.

23 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, Va: APA, 2013.

24 World Health Organization. International statistical classification of diseases and related health problems. 11th revision. Geneva: WHO, 2018. https://icd.who.int/browse11/l-m/en (accessed Sept 2019).

25 Scott J, Davenport TA, Parker R, et al. Pathways to depression by age 16 years: examining trajectories for self-reported psychological and somatic phenotypes across adolescence. *J Affect Disord* 2017; 230: 1–6.

26 McGorry P, Keshavan M, Goldstone S, et al. Biomarkers and clinical staging in psychiatry. *World Psychiatry* 2014; 13: 211–223.

27 Shah J, Scott J. Concepts and misconceptions regarding clinical staging models. *J Psychiatry Neurosci* 2016; 41: E83–E84.

28 Scott J, Leboyer M, Hickie I, et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. *Br J Psychiatry* 2013; 202: 243–245.

29 Hickie IB, Hermens DF, Naismith SL, et al. Evaluating differential developmental trajectories to adolescent-onset mood and psychotic disorders. *BMC Psychiatry* 2013; 13: 303.

30 Cross SP, Hermens DF, Hickie IB. Treatment patterns and short-term outcomes in an early intervention youth mental health service. *Early Interv Psychiatry* 2016; 10: 88–97.

31 Cross SPM, Scott J, Hickie IB. Predicting early transition from sub-syndromal presentations to major mental disorders. *BJPsych Open* 2017; 3: 223–227.

32 Cross SP, Scott JL, Hermens DF, et al. Variability in clinical outcomes for youths treated for subthreshold severe mental disorders at an early intervention service. *Psychiatr Serv* 2018; 69: 555–561.

33 Cross SPM, Hermens DF, Scott J, et al. Differential impact of current diagnosis and clinical stage on attendance at a youth mental health service. *Early Interv Psychiatry* 2017; 11: 255–262.

34 Hermens DF, Naismith SL, Lagopoulos J, et al. Neuropsychological profile according to the clinical stage of young persons presenting for mental health care. *BMC Psychology* 2013; 1: 8.

35 Tickell AM, Lee RSC, Hickie IB, et al. The course of neuropsychological functioning in young people with attenuated vs discrete mental disorders. *Early Interv Psychiatry* 2017; 13: 425–433.

36 Lagopoulos J, Hermens DF, Naismith SL, et al. Frontal lobe changes occur early in the course of affective disorders in young people. *BMC Psychiatry* 2012; 12: 4.

37 Lagopoulos J, Hermens DF, Hatton SN, et al. Microstructural white matter changes are correlated with the stage of psychiatric illness. *Transl Psychiatry* 2013; 3: e248.

38 Scott EM, Robillard R, Hermens DF, et al. Dysregulated sleep-wake cycles in young people are associated with emerging stages of major mental disorders. *Early Interv Psychiatry* 2014; 10: 63–70.

39 Naismith SL, Hermens DF, Ip TK, et al. Circadian profiles in young people during the early stages of affective disorder. *Transl Psychiatry* 2012; 2: e123.

40 Andrews G, Goldberg DP, Krueger RF, et al. Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychol Med* 2009; 39: 1993–2000.

41 Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. *BMC Med* 2013; 11: 132.

42 Cuthbert BN. Research domain criteria: toward future psychiatric nosologies. *Dialogues Clin Neurosci* 2015; 17: 89–97.

43 Hickie IB, Scott J, Hermens DF, et al. Clinical classification in mental health at the

cross-roads: which direction next? *BMC Med* 2013; 11: 125.

44 Hickie IB, Naismith SL, Robillard R, et al. Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. *BMC Med* 2013; 11: 79.

45 Woo YS, Shim IH, Wang HR, et al. A diagnosis of bipolar spectrum disorder predicts diagnostic conversion from unipolar depression to bipolar disorder: a 5-year retrospective study. *J Affect Disord* 2015; 174: 83–88.

46 Scott J, Murray G, Henry C, et al. Activation in bipolar disorders: a systematic review. *JAMA Psychiatry* 2017; 74: 189–196.

47 Mitchell PB, Goodwin GM, Johnson GF, et al. Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disord* 2008; 10: 144–152.

48 Akiskal HS, Benazzi F. Atypical depression: a variant of bipolar II or a bridge between unipolar and bipolar II? *J Affect Disord* 2005; 84: 209–217.

49 Han KM, De Berardis D, Fornaro M, et al. Differentiating between bipolar and unipolar depression in functional and structural MRI studies. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; 91: 20–27.

50 Goldberg DP, Andrews G, Hobbs MJ. Where should bipolar disorder appear in the meta-structure? *Psychol Med* 2009; 39: 2071–2081.

51 Andrews G, Pine DS, Hobbs MJ, et al. Neurodevelopmental disorders: cluster 2 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009; 39: 2013–2023.

52 Bombin I, Mayoral M, Castro-Fornieles J, et al. Neuropsychological evidence for abnormal neurodevelopment associated with early-onset psychoses. *Psychol Med* 2013; 43: 757–768.

53 Keshavan MS. Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *J Psychiatr Res* 1999; 33: 513–521.

54 Peralta V, de Jalon EG, Campos MS, et al. The meaning of childhood attention-deficit hyperactivity symptoms in patients with a first-episode of schizophrenia-spectrum psychosis. *Schizophr Res* 2011; 126: 28–35.

55 Piper M, Beneyto M, Burne TH, et al. The neurodevelopmental hypothesis of schizophrenia: convergent clues from epidemiology and neuropathology. *Psychiatr Clin North Am* 2012; 35: 571–584.

56 McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; 12: 342–348.

57 Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry* 2004; 161: 195–216.

58 Bennett MR. Stress and anxiety in schizophrenia and depression: glucocorticoids, corticotropin-releasing hormone and synapse regression. *Aust N Z J Psychiatry* 2008; 42: 995–1002.

59 Hansell NK, Wright MJ, Medland SE, et al. Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. *Psychol Med* 2012; 42: 1249–1260.

60 Crouse JJ, Chitty KM, Iorfino F, et al. Exploring associations between early substance use and longitudinal socio-occupational functioning in young people engaged in a mental health service. *PLoS ONE* 2019; 14: e0210877.

61 Scott EM, Hermens DF, Naismith SL, et al. Distinguishing young people with emerging bipolar disorders from those with unipolar depression. *J Affect Disord* 2013; 144: 208–215.

62 Hermens DF, Scott EM, White D, et al. Frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental healthcare: a cross-sectional study. *BMJ Open* 2013; 3: e002229.

63 Scott EM, Hermens DF, White D, et al. Body mass, cardiovascular risk and metabolic characteristics of young persons presenting for mental healthcare in Sydney, Australia. *BMJ Open* 2015; 5: e007066.

64 Robillard R, Naismith SL, Rogers NL, et al. Delayed sleep phase in young people with unipolar or bipolar affective disorders. *J Affect Disord* 2013; 145: 260–263.

65 Robillard R, Naismith SL, Rogers NL, et al. Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *Eur Psychiatry* 2013; 28: 412–416.

66 Robillard R, Hermens DF, Lee RS, et al. Sleep-wake profiles predict longitudinal changes in manic symptoms and memory in young people with mood disorders. *J Sleep Res* 2016; 25: 549–555.

67 Scott J, Naismith S, Grierson A, et al. Sleep-wake cycle phenotypes in young people with familial and non-familial mood disorders. *Bipolar Disord* 2016; 18: 642–649.

68 Iorfino F, Hermens DF, Cross SPM, et al. Prior suicide attempts predict worse clinical and functional outcomes in young people attending a mental health service. *J Affect Disord* 2018; 238: 563–569.

69 Naismith SL, Lagopoulos J, Hermens DF, et al. Delayed circadian phase is linked to glutamatergic functions in young people with affective disorders: a proton magnetic resonance spectroscopy study. *BMC Psychiatry* 2014; 14: 345.

70 Robillard R, Lagopoulos J, Hermens DF, et al. Lower in vivo myo-inositol in the anterior cingulate cortex correlates with delayed melatonin rhythms in young persons with depression. *Front Neurosci* 2017; 11: 336.

71 Carpenter JS, Robillard R, Hermens DF, et al. Sleep-wake profiles and circadian rhythms of core temperature and melatonin in young people with affective disorders. *J Psychiatr Res* 2017; 94: 131–138.

72 Carpenter JS, Robillard R, Lee RS, et al. The relationship between sleep-wake cycle and cognitive functioning in young people with affective disorders. *PLoS One* 2015; 10: e0124710.

73 Robillard R, Carpenter JS, Rogers NL, et al. Circadian rhythms and psychiatric profiles in young adults with unipolar depressive disorders. *Transl Psychiatry* 2018; 8: 213. ■