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The Utility of Clinical Staging in Youth Mental Health Settings

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Abstract

This chapter reviews a clinical staging framework that was developed for youth-onset anxiety, mood, and psychotic disorders. Used for over a decade in early intervention services in Australia, a more restricted version of this framework has been used internationally for specific diagnostic groupings, most notably among youth with psychotic or bipolar disorders. The validity of these different clinical staging frameworks is being assessed within longitudinal cohort, concurrent neurobiological, and specific intervention studies. Preliminary evidence suggests that (a) varying stages of illness are associated with predicted differences in a range of objectively measured neuropsychological, circadian, and structural brain imaging measures; (b) while earlier stages are considered subthreshold disorders from a diagnostic perspective, they are associated with significant reductions in educational, employment, and social participation as well as substantial comorbidity and suicidal thoughts and behaviors; and (c) as predicted by the Sydney model, earlier (subthreshold) stages of illness progress at lower rates to more severe (full-threshold), recurrent, or persistent disorders. Importantly, since approximately 15–30% of young people classified as "attenuated" (subthreshold) syndromes progress to more severe (full-threshold) disorders, this particular group is the most obvious focus for early clinical intervention and secondary prevention trials. The chapter concludes with a discussion of major issues that need to be pursued in future research.

Introduction

Internationally, there is widespread recognition of the premature death and disability attributable to major mental disorders (Bloom et al. 2011; Erskine et al. 2015; Gustavsson et al. 2011). This burden derives from their early age of onset, population prevalence, chronicity, and comorbidity with physical illness and the degree of resultant impairment (Gore et al. 2011; Gustavsson et al. 2011; Lopez et al. 2006). To reduce this burden, earlier identification, more

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effective and more personalized treatments, as well as enhanced long-term care for individuals at risk or in the early phases of developing life-threatening or chronic disorders have been prioritized (Hickie et al. 2013b; Insel 2007, 2009; Lopez et al. 2006; McGorry et al. 2014a; Scott et al. 2012a).

For the major mental disorders, a progressive illness trajectory typically has its onset in late childhood or early puberty and then recurs or continues progressively into adult life (Häfner et al. 2008; Merikangas et al. 2010; Paus et al. 2008). In a significant proportion of these individuals, earlier age-dependent clinical phenotypes will have been evident in childhood (e.g., attentional, anxiety, sleep-wake, somatic, autistic spectrum, or conduct disorders), reflecting significant deviations in brain or psychosocial development. Although 75% of major mental disorders begin before 25 years of age (Gore et al. 2011; Kessler et al. 2005), the diagnostic and research criteria currently being used to identify these subjects have been derived largely from the experiences reported by middle-aged persons with recurring or chronic illness. Often, these midlife phenotypes map poorly onto earlier and less specific phases of the illness experience (Hickie et al. 2013b; McGorry 2007, 2010; McGorry et al. 2008b). For example, young people who go on to develop bipolar disorder rarely present with mania as their first episode of illness. Typically, these young people will have experienced earlier depressive episodes, often with intercurrent periods of emotional instability, suicidal behavior, or brief periods of motor activation throughout their early and mid-adolescent developmental stages (Hafeman et al. 2016; Iorfino et al. 2018; Ratheesh et al. 2017; Scott et al. 2017).

Current diagnostic systems prioritize phenomena such as delusions and hallucinations for psychotic disorders; periods of elevated mood or increased energy for bipolar disorder; and psychomotor slowing, emotional blunting, or cognitive slowing for severe depression. Data from community studies that assess subjects longitudinally from childhood or adolescence emphasize the extent to which many of these phenomena are shared across diagnostic groups over this entire developmental period (Copeland et al. 2013; Kelleher et al. 2012a; Merikangas et al. 2008, 2010, 2012; Murray and Jones 2012; Ormel et al. 2015). A great clinical challenge is to derive new dynamic diagnostic systems that are not only consistent with developmental epidemiology and neurobiology but also useful when applied in everyday clinical practice.

A major response to this challenge has been to apply the general medical concept of clinical staging to the early phases of major mental disorders. In other areas of medicine, it is commonly accepted that it is inadequate to choose treatments, or plan health care, for persons who suffer from conditions that are likely to progress or recur, simply on the basis of broad illness categories (e.g., breast cancer or cardiovascular disease). An assumption of the clinical staging approach is that it is equally meaningless in mental health to plan personalized preventive or early intervention strategies or to select specific treatments simply on the basis of a diagnosis of broad categories, such as schizophrenia, bipolar disorder, or major depression. Indeed, a wealth of evidence indicates

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that subjects at different points along the illness continuum for all of these conditions show quite different patterns of response to various psychological or pharmacological interventions (McGorry et al. 2006, 2007a; Scott 2011; Scott et al. 2006).

Consequently, a range of frameworks for clinical staging have been proposed that can be applied either to all young people presenting for care (Hickie et al. 2013b; McGorry et al. 2006) or to a subset assigned to a "specific" disease category: staging models for major depression (Ruhe et al. 2012; Verduijn et al. 2015), bipolar disorder (Berk et al. 2007; Duffy 2014; Kapczinski et al. 2009), and psychosis-schizophrenia (Agius et al. 2010; Lieberman et al. 2001; McGorry 1995). In addition, staging models have included those who present for clinical care as well as those who may be asymptomatic but "at risk" due to another known risk factor (e.g., family history, prior neurodevelopmental disorder). These various models have been well summarized in the literature (for reviews see Hartmann et al. 2019; McGorry et al. 2018c; Scott et al. 2017).

When staging is applied to single diagnostic groups, the underlying assumption is that a unique pathway or pathophysiology underpins each "independent" or "clinical" category. This assumption is not readily supported by modern epidemiological, psychosocial, family, genetic, or neurobiological risk factor studies, where the same risk factors load on multiple disorders (Buckholtz and Meyer-Lindenberg 2012; Lichtenstein et al. 2009; Sullivan et al. 2012; Waszczuk et al. 2014). In addition, early-onset disorders, such as childhood-onset anxiety, conduct, and developmental disorders (i.e., clinically evident before age 12 years), do not predict specific "adolescent-onset" disorders but rather the full spectrum of later depressive, bipolar, and psychotic disorders (Kim-Cohen et al. 2003). When used in association with a transdiagnostic framework, which includes disorders with high known rates of comorbidity (e.g., anxiety, major mood and psychotic disorders), we propose that clinical staging is more likely to be useful in clinical practice, as it will more closely fit naturally occurring adolescent-onset clinical syndromes, and may prove to have closer links to those underlying pathophysiological processes that underpin these complex syndromes (Hickie et al. 2013c; McGorry et al. 2006).

Utilizing a Transdiagnostic Clinical Staging Framework in Youth Mental Health Services

The clinical staging framework, when applied to young people (12–30 years of age) presenting for health care, proposes that earlier (subthreshold) stages (as compared with more advanced stages) are characterized by lower rates of impairment and predict lower risk of progression to later, more severe, disabling, or persistent disorders. In Australia we have applied this transdiagnostic framework to young people who present for health care and clearly differentiate those in early phases (Stages 1a, nonspecific anxious or depressive symptoms

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or 1b, attenuated syndromes) from those who have reached a higher threshold for disorder (Stage 2 and above). Within the earlier (and assumed typically nonprogressive) Stage 1 disorders, we differentiate the attenuated syndromes (which often meet DSM-IV, DSM-5, or ICD-10 criteria for specific anxiety or mood disorders) from the more nonspecific anxiety and depressive syndromes. A more detailed description of these clinical stages is given in association with Figure 2.1, which outlines a simple and reliable decision tree for making such key distinctions. These decision processes have now been incorporated into our clinical practice systems. We have previously demonstrated the inter-rater reliability of this structured approach (Hickie et al. 2013b). Where there is uncertainty about the appropriate stage to assign, we rate down to the earlier and less severe category.

Importantly, this transdiagnostic approach (Hickie et al. 2013b, 2013c, 2013d; Scott et al. 2013b, 2014b) is consistent with the Research Domain Criteria (RDoC) proposed by the National Institute of Mental Health (NIMH) (Insel et al. 2010; Cuthbert and Insel 2013; Kozak and Cuthbert 2016). That is, clinical stages, in contrast to formal diagnostic categories, may map more reliably onto at least some independent neurobiological processes (and objective measures of those underlying processes). These approaches also place an appropriate emphasis on recognizing developmental trajectories and the active and bidirectional impacts of interaction with the environment.

From a health services perspective, this approach has the advantage of facilitating a more inclusive approach to recruitment. Clinical cohorts, however, are not representative of population-based cohorts as the process of "seeking help" is associated with a range of other demographic (e.g., female gender) and clinical (e.g., suicidal behavior) features. It is consistent, however, with the NIMH recommendation (Casey et al. 2013) that such clinical research should recruit cohorts from common service settings that are also likely to demonstrate appropriate variance along relevant dimensions of interest (e.g., neuropsychological function, cortical or subcortical brain structure).

Issues Related to At-Risk Populations: Stage 0

Clinical staging models variously propose a Stage 0 to be applied to specific "at-risk" populations. These may include young people *not already presenting for clinical care* but who may be at increased risk of developing one or more major disorders. When detected, these cohorts can then be subject to specific systematic evaluation (clinically or neurobiologically). These subgroups may be identified through a variety of strategies:

- Familial relationships with known probands with specific disorders (e.g., adolescent siblings of probands with major mood or psychotic disorders
- First-degree relatives of probands with major disorders

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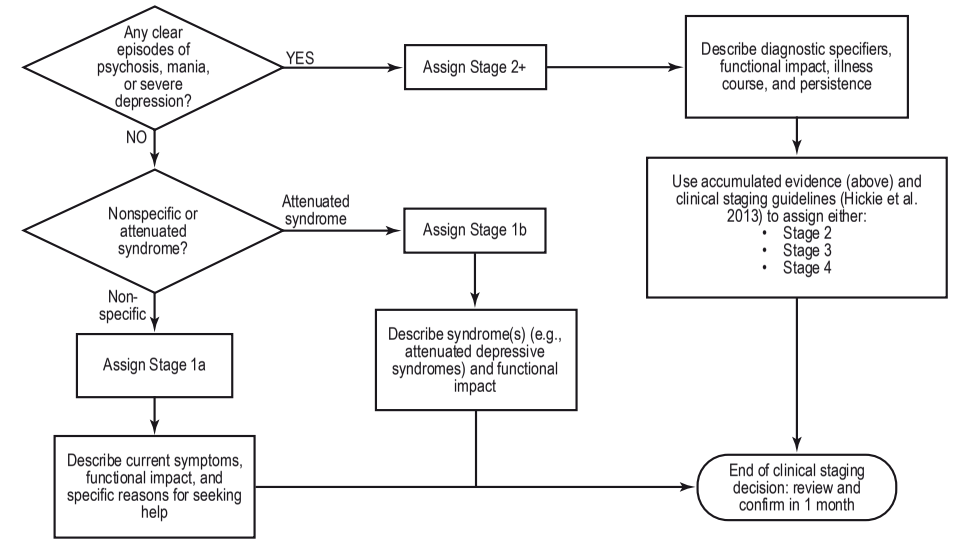

Figure 2.1 Stepwise process taken in clinical services to assign those presenting for care to the appropriate stage. Stage 1a solely indicates nonspecific symptoms of anxiety or depression. By contrast, Stage 1b includes those with "attenuated" syndromes, who present more specific, severe, or comorbid mood or psychotic phenomena. Those who reach Stage 2 have discrete, full-threshold, and severe mood, psychotic, or comorbid syndromes. These disorders are assumed to justify specific clinical interventions and would also be at high risk of progressing to recurrent or persistent states in the absence of effective clinical interventions.

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- Exposure to known developmental risk factors (e.g., maternal exposure to prenatal infection, low birth weight cohorts, childhood exposure to CNS infection)
- Concurrent medical at-risk groups (e.g., hormonal abnormalities including polycystic ovarian syndrome)
- Concurrent alcohol and other substance misuse cohorts

For adolescent-onset mood or psychotic disorders, cohorts consisting of individuals with prior but independent childhood-onset disorders (e.g., attentional, anxiety, or autism spectrum disorders) may be considered as at-risk populations. Further longitudinal studies of relevant developmental cohorts will assist the determination of actual transition rates from such at-risk states to adolescent-onset disorders.

Support for the Clinical Staging Framework

Cross-Sectional and Longitudinal Validation of the Clinical Staging Framework

We have reported extensively on the demographic, clinical (illness type and stage), disability, neuropsychological, brain imaging, and circadian characteristics of a Sydney-based transdiagnostic cohort evaluated over the last decade (see Table 2.1). This is one example of how clinical staging can be used within a cohort to address relevant clinical, neurobiological, and psychosocial issues. These Sydney-based studies have utilized both cross-sectional data with regards to social participation, educational, and employment status as well as longitudinal outcome data characterizing clinical course to test the construct and predictive validity of the transdiagnostic clinical staging model. With regards to levels of impairment, there is clear evidence that earlier stages are associated with lower degrees of functional impairment. This is not unexpected as the clinical phenotype used for staging purposes is, to some degree, inclusive of current levels of function.

Our preliminary longitudinal work using this clinical staging system among young people who present to our primary care services—typically with severe mood or anxiety disorders—indicates that in the short term, those initially classified as Stage 1b, attenuated syndromes, remain significantly impaired following ten sessions of treatment despite using more services and improving modestly (Cross et al. 2016). Within 12 months, approximately 17% of those rated as Stage 1b at initial assessment progress to a later stage (despite receiving clinical care) (Cross et al. 2018b). A significant proportion of these "clinical transitions" occur within the first three months, indicating the need for very close clinical supervision and monitoring following initial presentation. The transition rate varies between pathophysiological pathways: 11% for depression, 40% for psychosis, and 22% for bipolar (Cross et al. 2018b).

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Regardless of the pathway, transition was found to be predicted by NEET (i.e., not in education, employment or training) status and negative symptoms—not by general psychological distress (K10) or positive symptoms. These data are consistent with findings from other studies (Fusar-Poli et al. 2010; Valmaggia et al. 2013).

To advance this work and, more specifically, to plan relevant early intervention and secondary prevention trials, we need to identify more accurately those who may be at particularly high risk of illness progression. Our related work (Scott et al. 2013a, 2014b), which focuses on identifying those subjects in the early course of bipolar disorder, indicates how difficult this is to achieve on the basis of clinical features or neuropsychological testing. Specifically, one study has highlighted the importance of family history of bipolar disorder, psychosis, or substance misuse in predicting this transition (Scott et al. 2013a).

Independent work, based on those at higher risk of developing psychotic disorders, has recognized similar difficulties. Consequently, there is a need to develop more refined clinical criteria to use in related neurobiological, longitudinal, preventive, or specific intervention studies. At this time, we propose that it is necessary to select for more specific phenotypic characteristics that are closer to the syndromal elements that would characterize transition to Stage 2 "full-threshold" disorders or beyond. The existing literature emphasizes that clinical features related to duration of illness, persistence, or recurrence of key symptoms and degree of current impairment may also be predictive.

Neurocognitive and Neuroimaging Evidence to Support Staging

We have conducted a number of studies to determine whether there are neurobiological features that distinguish key stages of illness. To date, these studies have utilized neuroimaging (Lagopoulos et al. 2012, 2013), sleep/circadian (Naismith et al. 2012; Scott et al. 2014a), and neuropsychological (Hermens et al. 2013; Tickell et al. 2017) measures. Across these studies, and consistent with a neuroprogressive model of illness, the data show that those with an attenuated syndrome (compared to controls) have reduced gray matter volumes, compromised white matter integrity, delayed sleep phase, and reductions in neuropsychological performance. By contrast, young people at later stages of illness (i.e., with "full-threshold" or discrete disorders) have significantly greater deficits across these domains. These varying levels of deficits were generally distinct from differences observed in other clinical (including diagnosis, clinical state) or functional (e.g., socio-occupational) measures. This suggests that the staging model may have utility in terms of distinguishing putative phenotypes, particularly with respect to underlying neurobiology. It should be noted that these studies focused on the two major stages of illness in our cohort: attenuated syndrome (Stage 1b) and discrete disorder (2+). The other stages within our model—that is, "nonspecific anxiety or depression" (Stage 1a) and persistent/unremitting disorders (Stage 4)—were intentionally

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Table 2.1 Relationships between clinical stage and demographic, clinical (illness type), disability, neuropsychological, brain imaging, and circadian characteristics in a Sydney-based transdiagnostic youth cohort.

Sample (Stage, N)	Key Results	Other Relevant Information	Reference
	Clinical Studies: Cross-sectional		
1a = 293; 1b = 292; 2 = 121; 3+ = 133	Clinician-rated SOFAS strongly related to stages; later stages have more impaired role function	Stage 2 had highest levels of distress and role function impairment	Scott et al. (2012a)
1b = 286; 2+ = 289	Impairments in functioning and general behavioral disturbance were less marked in 1b compared to 2+	Interaction between stage and tripartite classification; 1b less common in developmental-psychosis	Hickie et al. (2013a)
	Clinical Studies: Longitudinal		
1a = 21; 1b = 112; 2+ = 53	Transition (median = 48 weeks): 11% of 1a; 19% of 1b; 33% of Stage 2	Those who remained within the same stage may have had persistent symptoms or dysfunction or responded to clinical interventions	Hickie et al. (2013b)
1a = 601; 1b = 257; 2+ = 31	Psychological distress (K10) and SOFAS improved over 1–6 to 10 sessions of care for both 1b and 1a	1b remained impaired after 10 sessions; 1a commenced with better SOFAS, less psychological distress	Cross et al. (2016)
1a = 579; 1b = 249	1b made and missed more appointments than 1a	Social functioning best predictor of female attendance; age and stage best predicted male attendance	Cross et al. (2017)
1b = 243	Ca. 17% transitioned to a major mental disorder; independent of syndromal diagnosis, transition more likely in NEET, females, and those with more negative psychological symptoms (e.g., social withdrawal)	NEET status and negative symptoms are modifiable predictors of illness trajectory across diagnostic categories and are not specific to transition to psychosis	Cross et al. (2018b)
1b = 243	Approx. 25–33% of individuals show reliable improvement; ca. 10% show reliable deterioration for both symptoms (K10 and BPRS) and functioning (SOFAS) over six months. Many individuals did not show linear improvement or deterioration.	Individual patterns of symptomatic and functional change are diverse in this group over time, highlighting the importance of routine outcome monitoring in treatment	Cross et al. (2018a)

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Table 2.1 (continued)

Sample (Stage, N)	Key Results	Other Relevant Information	Reference
1a = 21; 1b = 112; 2+ = 53	Transition (median = 48 weeks): 11% of 1a; 19% of 1b; 33% of stage 2	Those who remained within the same stage may have had persistent symptoms/dysfunction or responded to clinical interventions	Hickie et al. (2013b)
	Neuropsychological: Cross-sectional		
1b = 94; 2+ = 100	2+ had most impaired neuropsychological profile; 1b had intermediate profile (cf. controls)	Greatest impairments in verbal memory and executive function.	Hermens et al. (2013)
	Neuropsychological: Longitudinal		
1b = 262; 2+ = 235	Baseline: 2+ worse than 1b in verbal learning, verbal memory, visual memory, set shifting. Both showed stability in processing speed, sustained attention, and visual memory at follow-up	Neuropsychological stability corresponded with stability in clinical and functional status, despite stage of illness	Tickell et al. (2017)
	Neuroimaging: Cross-sectional		
1b = 23; 2+ = 24	2+ had decreased GM in frontal brain regions cf. 1b	Cf. to controls, lb showed similar pattern of GM loss, albeit not to the same degree as their peers in 2+	Lagopoulos et al. (2012)
1b = 73; 2+ = 69	Both 1b & 2+ showed reduced white matter integrity in left ACR; 2+ had additional demyelination	ACR = junction point of 3 major long association fibers; impacts projections from thalamus to frontal lobes	Lagopoulos et al. (2013)
	Neuroimaging: Longitudinal		
1b = 28; 2+ = 16	2+ had markedly reduced levels of melatonin secretion cf. their peers in 1b	In 2+ only, reduced melatonin correlated with poorer verbal memory	Naismith et al. (2012)
1a = 18; 1b = 82; 2+ = 54	Delayed sleep phase (weekdays) increased progressively across illness stages	Older age, medication and later sleep offset strongest predictors of later stage	Scott et al. (2014a)

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excluded from these studies because our aim was to determine the neurocognitive and neurobiological features that occur around the key major demarcation point in this model (i.e., Stage 1b vs. Stage 2+).

Hermens et al. (2013) examined the neuropsychological profiles between young people based on attenuated syndromes (n = 94) compared to those with discrete disorders (n = 100). The latter showed the most impaired neuropsychological profile, with the earlier Stage 1b group showing an intermediate profile compared to controls. Greatest impairments were seen in verbal memory and executive functioning. To address potential confounds created by diagnosis, profiles for those with a mood syndrome or disorder but not psychosis were also examined and the neuropsychological impairments for the Stage 2+ group remained. Thus, the degree of neuropsychological impairment discriminated those with attenuated syndromes from those with a discrete disorder, independent of diagnostic status and current symptoms. Our findings support the notion that neuropsychological assessment is a key tool of clinical evaluation in early stages of major psychiatric illness in young adults. Other studies from our group have illustrated the nature of neuropsychological functioning as a strong predictor of functioning longitudinally, over and above psychiatric symptomatology (Lee et al. 2013, 2014c, 2015). Additionally, more recent studies examining subjects at risk for schizophrenia identified neuropsychological dysfunction as a potential risk factor for illness onset/transition (e.g., executive function, verbal fluency, attention, visual memory, verbal memory, and working memory) (Lin et al. 2013; Maziade et al. 2011; Sumiyoshi et al. 2013).

As a follow-up to our first staging by neuropsychology study, we examined a larger sample (n = 497) of help-seeking young people (aged 21.2, ±3 years; 56% female) of whom 262 were rated as attenuated syndrome (Stage 1b) and 235 as "discrete" or "persistent" disorder (Stage 2+) at baseline (Tickell et al. 2017). Of this sample, 170 individuals (54% at Stage 1b) were reassessed neuropsychologically after 19.8 ±9 months (range: 3–51 months). At baseline, we found that the attenuated and discrete/persistent disorder groups differed significantly in four of the nine neuropsychological measures (verbal learning, verbal memory, visual memory, and set shifting). Despite this, both groups showed similar stability in neuropsychological functioning at follow-up, particularly in processing speed, sustained attention, and visual memory. Furthermore, longitudinal stability in cognition corresponded with increases in socio-occupational functioning. Importantly, we found again (Hermens et al. 2013) that the degree of baseline neuropsychological dysfunction discriminated those with attenuated syndromes from those with a discrete/persistent disorder. Furthermore, stability in neuropsychological functioning corresponded with stability in clinical and functional status, despite stage of illness. This suggests that neuropsychological functioning remains relatively stable in young people with a mental illness and may be a critical window for intervention.

We conducted two neuroimaging studies to examine whether attenuated syndrome and discrete disorder patient groups could be distinguished in terms of gray matter (GM) and white matter (WM) integrity. In a voxel-based

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morphometry study (Lagopoulos et al. 2012), compared to Stage 1b patients (n = 23) and controls (n = 33), Stage 2+ patients (n = 24) were found to have decreased GM volumes within distributed frontal brain regions. The greatest GM loss for Stage 2+ occurred within an overlapping region bounded by the superior and middle frontal gyri on the right side. Additional loss of GM volume was also observed in the inferior aspects of the frontal gyrus as well as the anterior cingulate and the orbitofrontal cortex on the right side and the medial prefrontal cortex midline. Of note, we did not find any evidence of GM loss that extended outside the prefrontal cortex. Overall the findings of this study suggest that, in terms of frontal GM changes, a major transition point may occur in the course of affective illness between early attenuated syndromes and later discrete illness stages.

In a subsequent study (Lagopoulos et al. 2013), we examined WM integrity—more specifically, fractional anisotropy in n = 74 patients in Stage 1b as well as in n = 69 patients in Stage 2+—and compared them with n = 39 healthy controls. Interestingly, we found a significant disruption in WM integrity in the left anterior corona radiata (in particular, the anterior thalamic radiation for both groups of patients) when separately contrasted with healthy controls. Our results suggest that patients with subsyndromal symptoms exhibit discernible early WM changes when compared with healthy control subjects and more significant disruptions are associated with clinical evidence of illness progression. Despite limitations (i.e., mainly cross-sectional studies, relatively small sample sizes, and the potential effects of medication), these studies are collectively consistent with a progression of illness model.

Sleep and Circadian Evidence to Support Staging

Abnormalities in the sleep-wake cycle and circadian rhythms are found across a range of psychiatric disorders and have been highlighted as potentially transdiagnostic factors (Benca et al. 1992; Dolsen et al. 2014; Harvey et al. 2011; Jones and Benca 2015; Karatsoreos 2014). Across adolescence and youth, developmental changes in sleep-wake and circadian systems typically result in delayed sleep and circadian rhythms (Carpenter et al. 2015a; Gradisar et al. 2011), which may predispose the circadian system to be particularly vulnerable to perturbations across this period. In our youth cohort, we have found that delays in sleep timing and increases in wakefulness across the night are found across multiple diagnoses (Robillard et al. 2015). We have also found sleep-wake delays to be particularly prominent in adolescents and youth (Robillard et al. 2014).

To examine sleep-wake cycles in young people at different stages of psychiatric illness, we used actigraphy monitoring to measure average rest and activity timing over multiple days of recording, comparing those with attenuated syndromes (n = 82) and those with discrete disorders (n = 54) to control participants (n = 21) (Scott et al. 2014a). We found delayed sleep timing in both

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patient groups compared to controls, with more severe delays in those with discrete disorders (Stage 2+) compared to those with attenuated syndromes (Stage 1b). The proportion of individuals with a delayed sleep-wake profile also increased across illness stages, with 9.5% of controls, 25.6% of Stage 1b, and 50% of Stage 2+ presenting with delayed sleep-wake. The potential confounding effects of medications (as they increase in complexity, dose, and duration with clinical stage or illness progression) on circadian measures also need to be considered (Robillard et al. 2016b).

In addition to being related to more established and severe illness stages, sleep-wake delays may also be indicative of a more bipolar type of illness, with our research finding delayed sleep phase to be more common in those with bipolar syndromes (over 60%) compared to those with unipolar mood disorders (30%) and controls (10%) (Robillard et al. 2013a). These findings suggest that sleep-wake delays may be an important feature to distinguish between stage of illness as well as being potentially indicative of a specific illness phenotype characterized by circadian dysregulation and bipolar type symptoms. We have also shown sleep-wake disturbances to be predictive of longitudinal outcomes in our cohort. Robillard et al. (2016a) report on 50 young people with sleep-wake assessment (actigraphy) followed up after 11 to 47 months (average 18.9 months). They found that lower sleep efficiency (i.e., more time spent awake during the night) was predictive of worsening of manic symptoms at follow-up, and both shorter sleep and poorer circadian rhythmicity of 24-hour activity patterns were predictive of worsening in verbal memory, demonstrating the utility of sleep-wake assessment in prediction of outcomes.

While disturbance of biological circadian systems is likely to underlie these delays of rest and activity behavior, the direction of causation of these effects is unresolved. In our studies we investigated circadian perturbation by measuring melatonin levels prior to habitual sleep in a subset of participants. While we found no difference in the timing of melatonin secretion across stages of illness, those at Stage 2+ (n = 16) had reduced levels of evening melatonin, compared to those at Stage 1b (n = 28), and shorter phase angles (time differences) between melatonin onset and sleep onset (Naismith et al. 2012). Abnormal phase angles indicate that internal circadian rhythms may not be optimally timed in relation to each other or the external environment, which may be indicative of severe disruption to the circadian system. Reduced evening melatonin secretion may also be a result of circadian misalignment or reflective of reduced circadian rhythm amplitude and weaker circadian signaling. These findings suggest that such disruptions are linked to stage of illness, and the circadian system may become increasingly disrupted with progression of illness. Notably, in this study we did not find any associations between melatonin measures and depressive symptoms, further suggesting that relationships with illness stage may be independent of current symptom levels (Naismith et al. 2012).

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In concordance with the actigraphy findings, we also found reduced evening melatonin in those with bipolar disorders, compared to unipolar depressive disorders, as well as relatively delayed melatonin profiles in those with bipolar disorders (Robillard et al. 2013b). This provides further support for a distinct circadian profile with delayed rhythms and links to bipolar-type symptoms. However, it is important to note that while such a profile may be linked to bipolar-type symptoms, it likely exists across multiple psychiatric diagnoses, rather than being linked to the strict traditional diagnosis of bipolar disorder. In support of this, we used a data-driven technique to identify clusters of individuals in our cohort with similar sleep-wake profiles and found these profiles to be distinct from traditional diagnostic categories (Carpenter et al. 2017b; Carpenter et al. 2015b): those with a profile of delayed sleep demonstrated evidence of delayed biological circadian rhythms of melatonin and core temperature (Carpenter et al. 2017b), thus highlighting a biological basis for delayed sleep-wake presentations.

There is also evidence for interactions between sleep-wake and circadian abnormalities and neural structure and function in this cohort of young people with psychiatric disorders. We have observed links between sleep-wake and circadian disturbances and neuropsychological performance: one study found impaired visual memory in those with a profile of long sleep (Carpenter et al. 2015b) while another found that lower melatonin levels are related to poorer verbal memory functioning in those with discrete disorders (Naismith et al. 2012). An MRI investigation suggests that structural differences in the brain may underlie circadian outputs, with significant correlations between pineal volume and evening melatonin secretion (Carpenter et al. 2017a). We have also linked circadian disturbances with neurochemical changes, using proton magnetic resonance spectroscopy. These studies found that later sleep timing is associated with higher levels of glutamine in the anterior cingulate cortex (Naismith et al. 2014), and that later melatonin onset is associated with lower myo-inositol concentrations in the anterior cingulate cortex (Robillard et al. 2017). These various relationships suggest that observed abnormalities in sleep-wake behavior may reflect disturbed circadian and related neural systems, with potential transdiagnostic relevance to illness progression.

Designing Personalized Treatments Based on These Approaches

Internationally, there is an increasing move to manage actively in clinical settings adolescents and youth who present for care in the early phases of major mood or psychotic disorders. However, the symptom complexes presented are often an admixture of anxiety, depressive, hypomanic, psychotic, or substance misuse-related symptoms (Hickie et al. 2013b) and thus typically do not meet the diagnostic thresholds employed for more specific disorders. The evidence

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base for providing specific treatments for many of these subthreshold or first episode-type disorders is sparse. There is also an increasing desire to link interventions more closely to underlying developmental or specific pathophysiological pathways (Hickie et al. 2013b, c, d). While we have proposed the potential utility of adapting a clinical staging strategy to guide assessment and treatment selection for such early or less-differentiated cases of major mood or psychotic disorders, our view is that this approach is adjunctive to more conventional diagnostic practice. Consequently, we have developed preliminary approaches to plotting both clinical stage and major pathophysiological pathways, while proposing likely objective neurobiological markers that can be tracked concurrently (Figure 2.2).

We propose three major developmental trajectories, putatively linked with more specific (but not mutually exclusive) pathophysiologies: anxiety-depression, circadian-mania/fatigue, and neurodevelopmental-psychotic (Hickie et al. 2013a). These trajectories recognize preceding childhood-risk phenotypes and differential patterns of comorbidity, notably differential ages of onset of alcohol or other substance misuse. Within such a model, the majority of our work is located currently at the threshold between Stages 1b and 2, and it

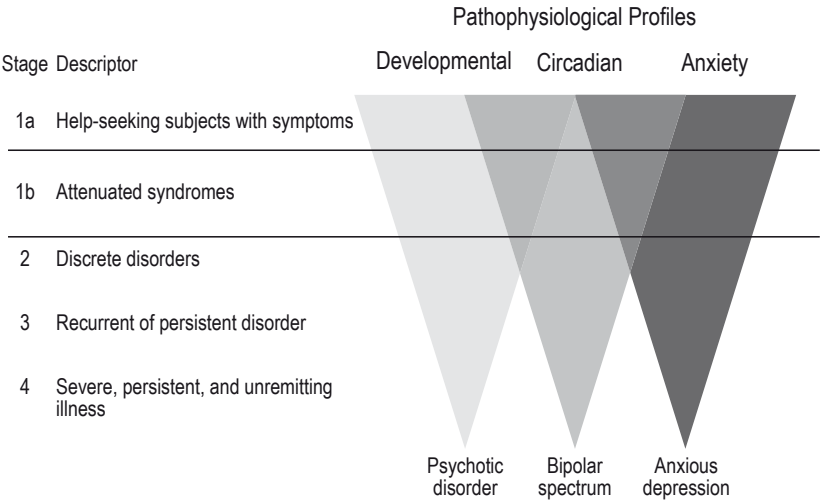

Figure 2.2 Clinical staging model for postpubertal onset and course of major mental disorders: developmental, circadian, or anxiety pathophysiological pathways progress from nonspecific to discrete syndromes. Overlap is evident between all three pathophysiological profiles in the early stages. Key neurobiological measures are neuropsychology (traditional, social cognitive, impulsive, and decision making), magnetic resonance imaging (magnetic resonance spectroscopy, diffusion tensor imaging, voxel-based morphometry, and cortical thickness), and circadian (dim light melatonin onset and actigraphy).

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draws extensively from youth recruited uniquely through our enhanced headspace services and affiliated research clinics.

Complementary to this pathway model, we have commenced the development of a treatment selection model (Table 2.2), demonstrating the capacity to prioritize psychological, social, and behavioral approaches so that later pharmacological approaches can be chosen which may be most relevant to the underlying pathophysiological pathway (inferred from the observed phenotype or concurrent neurobiological testing). For example, 24-hour sleep-wake cycle behavioral interventions or melatonin-based antidepressants may be preferred for some depressive disorders in those who have phenotypic, actigraphic, or laboratory-based evidence of underlying circadian disturbance. This approach is the subject of ongoing clinical testing and refinement. Most recently, we have demonstrated that resolution of underlying circadian disturbance in response to circadian-informed psychological and medical therapies is strongly correlated with resolution of depressive symptoms (Robillard et al. 2018).

Table 2.2 Putative stepped-care therapies for relevant depressive subtypes. Cognitive behavioral therapy (CBT), interpersonal therapy (IPT), cognitive behavioral case management (CBCM), meta-cognitive therapy (MCT), selective serotonin reuptake inhibitor (SSRI), selective serotonin and norepinephrine reuptake inhibitors (SNRI), d-cycloserine (DCS), dialectic behavior therapy (DBT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), individual placement and support (IPS).

Depression Type	First Line Therapy: Psychological or Behavioral	Second Line Therapy: Pharmacological	Experimental Therapies
Anxious depression	CBT, IPT, problem solving, e-health based anxiety management, exposure therapy, CBCM, MCT	SSRIs, SNRIs	Fish oils, DCS, oxytocin, ketamine
Circadian-fatigue depression	Behavioral regulation, physical activity, sleep-wake cycle/circadian-CBT, rumination-focused CBT, DBT, CBCM, MCT	Melatonin, melatonin analogues, lithium, pregabalin, lamotrigine	Sleep deprivation suvorexant, stimulants, modafinil, TMS, tDCS, ketamine, fish oils
Developmental psychosis	Problem-solving, social skills training, cognitive training, social recovery therapy, CBCM, MCT, IPS	Atypical antipsychotics	Ketamine, cannabidiol, oxytocin, novel neuropeptides, hormonal therapies, fish oils

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Conclusion

Over the last decade, a variety of staging frameworks have been proposed for application in youth and early intervention mental health settings. In our Sydney-based studies, we have been able to test the clinical utility and predictive validity of clinical staging, when applied to young people presenting with anxiety, mood, or psychotic syndromes. The range of studies conducted to date provides a firm evidence base for further elaboration of a transdiagnostic model. The following are of greatest importance:

- longitudinal studies that evaluate the ongoing relationships between independent neurobiological correlates of clinical stage and illness progression,
- the design and implementation of stage-specific secondary prevention trials, and
- the testing of the clinical utility of stage-specific and pathophysiologically orientated treatment options.

Compared with practice based on traditional diagnostic systems, it appears that we can now use clinical staging to underpin the development of much more personalized and youth-relevant models of care. Major research questions, however, remain:

- *Longitudinal course*: Are there specific points along the staging continuum beyond which illness extension, progression, or enduring impairment is highly probable? Is it clear that interventions with lower risk of adverse effects, provided earlier in the course of illness, will actually result in prevention of illness extension or progression to later stages?
- *Alignment with existing diagnostic frameworks*: At present, there is poor concordance with current thresholds for formal (full-threshold) diagnosis or alignment with those entities that underpin clinical practice guidelines (e.g., major depression, bipolar disorder, schizophrenia as defined in DSM-5 or ICD-10).
- *Validation against independent neurobiological, interventional, and psychosocial measures*: To date, the literature remains largely cross-sectional and hence extremely limited. Most work has focused solely on individuals with psychotic syndromes. Longitudinal studies that utilize more heterogeneous cohorts of young people are required.
- *Relevance to clinical practice*: The extent to which new clinical staging systems result in better stratified guides to optimal and more personalized treatment selection, and prognostic statements, has not yet been clearly demonstrated.
- *Relevance to health system development*: Whether these systems can be used to facilitate early intervention for young people, and provide more effective health care, has yet to be demonstrated. The earlier clinical

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stages within the frameworks are most relevant to at-risk populations and the development of new early intervention-style services. In these cohorts, traditional diagnostic concepts are less useful and choice of optimal interventions remains highly controversial.

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