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Full title: Can youth at high risk of illness progression be identified by measures of rumination and sleep-wake disturbance

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Short title: Can youth at high risk of illness progression be identified by rumination and sleep-wake disturbance

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ABG and JS, with the assistance of NG, identified the hypotheses and methodology for the current study. ABG carried out the literature review and drafted the main sections of the manuscript. ABG and JS undertook the statistical analyses and interpretation of findings. ABG wrote the initial draft manuscript and all authors read, redrafted, and approved the final manuscript.

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Abstract

Aim: Clinical staging models offer a useful framework for understanding illness trajectories, where individuals are located on a continuum of illness progression from stage 0 (at-risk but asymptomatic) through to stage 4 (end-stage disease). Importantly, clinical staging allows investigation of risk factors for illness progression with the potential to target trans-diagnostic mechanisms at an early stage, especially in help-seeking youth who often present with sub-threshold syndromes. Whilst depressive symptoms, rumination, and sleep-wake disturbances may worsen syndrome outcomes, the role of these related phenomena has yet to be examined as risk factors for trans-diagnostic illness progression in at-risk youth.

Methods: Prospective follow-up of 248 individuals aged 12-25 years presenting to *headspace* services with sub-threshold syndromes (stage 1) classified under the clinical staging model to determine transition to threshold syndromes (stage 2). Factor analysis of depression, rumination, and sleep-wake patterns was used to identify key dimensions and any associations between factors and transition to stage 2 at follow-up.

Results: At one year, 9% of cases met criteria for stage 2 (n=22). One of three identified factors, namely the factor reflecting the commonalities shared between rumination and sleep-wake disturbance, significantly differentiated cases that transitioned to stage 2 versus those that did not demonstrate transition. Items loading onto this factor, labelled Anergia, included depression severity and aspects of rumination and sleep-wake disturbance that were characterised as introceptive.

Conclusions: Common dimensions between rumination and sleep-wake disturbance present a detectable trans-diagnostic marker of illness progression in youth, and may represent a target for early intervention.

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Key words: clinical staging, rumination, sleep-wake disturbance, trans-diagnostic, youth

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Introduction

Mental disorders are a critical health issue for young people in the developed world (Insel & Fenton, 2005). Manifestations of mental disorders in youth are distinguished by mixed symptom patterns and comorbid diagnoses (Sawyer et al., 2000; Scott et al., 2012), and most likely reflect sub-threshold syndromes that emerge before any more distinct disorder can be diagnosed (Van Os et al., 2009). Clinical staging models offer a useful framework for understanding the emergence and progression of mental disorders in this group (McGorry et al., 2006; 2014; Hickie et al., 2013; Scott et al., 2013), where individuals are located on a continuum of disorder from stage 0 (an at-risk but asymptomatic state) through to stage 4 (late or end-stage disease). In young people presenting to early intervention youth mental health services, such as *headspace* in Australia, stage 1 (attenuated or sub-threshold forms of major mental disorder) and stage 2 (first episode of a major mental disorder that meets recognised diagnostic criteria) are the most commonly observed problems (Purcell et al., 2015).

A benefit of using a staging approach is that it allows clinicians and researchers to investigate risk factors for illness progression with the potential to target shared, trans-diagnostic mechanisms at an early stage. This strategy has been implemented recently in Australia with the Transitions Study (Purcell et al., 2013) as a large longitudinal investigation of a range of illness markers in over 802 young people. Previous examinations of the Transitions Study have identified such markers as delayed sleep onset for chronic psychological ill health (Glozier et al., 2014), as well as alcohol, tobacco, and cannabis use for those at greatest risk for psychosis (Carney et al., 2017).

Two additional factors that may be associated with onset, maintenance or worsening of mental health problems in youth are rumination and sleep-wake disturbance. Rumination is defined as a tendency to repetitively and passively focus on one's symptoms of distress (Nolen-Hoeksema, 2000) and can be

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broadly categorised as adaptive, labelled reflective pondering, or maladaptive, labelled toxic brooding (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). Toxic brooding has been found to be a predictor for a range of disorders among youth, most notably for depression, where brooding has been shown to be a robust predictor of depression onset, maintenance, and relapse, but also adversely affects the early course of psychotic, bipolar and alcohol and substance use disorders (see Grierson et al., 2016 for a review).

Similarly, previous research of sleep-wake disturbance has demonstrated strong associations with depression (Glozier et al., 2014), anxiety (Mooney, Allen & Trinder, 2016), and problematic alcohol and substance use (Negriff et al., 2011). Disturbed sleep-wake cycles have been shown to predict subsequent depressive episode in at-risk adolescents (Goodyer et al., 2009), as well as recurrence of major depressive disorder (MDD) in recovered adolescents (Emslie et al., 2001).

Youth studies also support bidirectional associations between rumination and sleep-wake disturbance. For example, young people with higher levels of rumination show increased sleep-wake disturbance, including prolonged sleep-wake latency and reduced sleep quality (Thomsen et al., 2003; Takano, Iijima, & Tanno, 2012; Pillai et al., 2014). It is suggested that rumination (which is known to increase anxiety in adolescents) may lead to hyperarousal (Fernandez-Mendoza et al., 2016), with subsequent disruption of sleep onset (Yeh, Wung & Ling, 2015). Additionally, adults with poor sleep are more likely to ruminate, particularly focusing on symptoms such as dysphoria and fatigue (Carney et al., 2006).

Whilst rumination and sleep-wake disturbances may worsen symptom and syndrome outcomes, especially depression as a recognised precursor state to many threshold syndromes (McGorry et al.,

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2006), the role of these related phenomena has yet to be examined as risk factors for trans-diagnostic illness progression under the clinical staging model. Studies assessing rumination and sleep-disturbances rarely include young people with attenuated syndromes or individuals without a formal diagnosis, limiting sensitivity to mechanisms operating trans-diagnostically. There is also a lack of research clarifying the link between the two phenomena in terms of potential commonalities or shared dimensions in young people, and whether these shared and separate dimensions operate differently in predicting illness progression. In adults, symptom-specific rumination is associated with poor sleep in general (Carney et al., 2006), so it might be expected that sleep-wake related ruminations (i.e. about fatigue and achiness) would be linked to the physical symptoms of sleep-wake disturbance. Furthermore, given that these linked phenomena are known predictors of illness onset and adversely affect the early course of a range of disorders, commonalities between rumination and sleep-wake disturbance could represent an important marker for illness progression in at-risk youth.

This study examined the characteristics of young people participating in the Transitions Study who presented to clinical services with sub-threshold syndromes (stage 1) and explored the proportion of cases that met criteria for transition to threshold syndromes (stage 2) at one year follow-up. Specifically, we aimed to identify separate and common dimensions of rumination, sleep-wake patterns, and depressive symptom severity as a recognised precursor state to other threshold syndromes in young people classified as clinical stage 1, and whether any of these dimensions were associated with disease progression to stage 2.

Methods

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The Human Research Ethics Committees at the University of Melbourne and The University of Sydney, Australia approved the protocol for the Transitions Study. Full details of the sampling, methodology, and measures employed in the Transitions Study are available elsewhere (Purcell et al., 2013). The key elements relevant to the current study are briefly outlined below.

Sample

From January 2011 to August 2012, individuals aged 12-25 attending four *headspace* clinical services centres in Melbourne and Sydney were invited to participate in a prospective longitudinal outcome study. The exclusion criteria for the Transitions study were: (i) unable or unwilling to give written informed consent (for those aged 12–14 years, written informed consent provided by a parent or guardian), (ii) significant intellectual disability (clinically assessed IQ < 65), and (iii) being non-English speaking and/or unable to complete English language assessments. Study entry was deferred for youth who were acutely suicidal until the treating clinician confirmed that any risk had resolved.

From the total sample (n=802), we identified 248 cases who presented with a sub-threshold syndrome at baseline and were classified as clinical stage 1b (attenuated or sub-threshold forms of major mental disorder).

Assessment

1. Baseline assessments

Structured interviews were conducted by trained research assistants with a minimum 4-year graduate degree in psychology. Participants were re-contacted after 12 months to complete follow-up interviews and questionnaires. Data used in the current study were:

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a) *Demographics*- Age at baseline interview and gender were recorded.

b) *Depressive symptom severity*- Depression was measured at baseline using the Quick Inventory of Depressive Symptomatology (QIDS; Rush et al., 2003), 16-item adolescent version. Symptoms are rated on a 4-point Likert scale and combined to provide total scores ranging from 0 to 27; scores of 10-15 indicate mild-moderate depression, whilst > 21 indicates severe depression.

c) *Ruminative response style*- Rumination was assessed at baseline using the 10-item version of the ruminative response style questionnaire (RRS-10; Treynor, Gonzalez & Nolen-Hoeksema, 2003; Nolen-Hoeksema & Morrow, 1991). The short version is highly correlated to the full version of the scale (r = .90) and has a high level of internal reliability (Cronbach's a = .85). Each item is scored on a 4-point Likert scale, ranging from 1 ("almost never") to 4 ("almost always"). The total score ranges from 10 to 44, with higher scores indicating higher degrees of ruminative symptoms.

d) *Sleep-wake patterns*- Sleep-wake cycles were assessed at baseline using four items selected from the Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989) that have been used in previous investigations by the Transitions Study group (Glozier et al., 2014). We focused on four key, easily interpretable parameters of sleep-wake patterns, including: *Sleep onset latency (SOL):* minutes taken to fall asleep; *Self-reported total sleep time (TST):* self-estimate of hours of sleep per night; *Sleep quality:* categorised as 'good' or 'bad'; *Daytime disturbance:* frequency of difficulties staying awake during certain daytime activities during the past month (categorised as persistent or non-persistent).

2. Baseline and follow-up assessment

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Clinical stage was assessed at baseline and again at 12-months using information gathered via a structured interview. Information regarding the participant's current and past history of symptoms (type, severity, frequency, self-harm etc.), treatments, and functioning were used by expert consensus to determine clinical stage according to established criteria (Hickie et al. 2013; McGorry et al. 2006). Transition was considered to have occurred if the individual was assigned to stage 1 at baseline, and stage 2 at follow-up.

Statistical Analyses

Statistical analyses were performed using SPSS version 22 (IBM SPSS Statistics, 2014). Statistical significance was set a priori at $p < 0.05$. The analysis proceeded in three steps:

1) Sample description: means (with standard deviations: S.D.) or frequencies (numbers and percentages) are reported for baseline demographic and clinical characteristics of the total sample. Univariate comparisons of any gender differences employed $Ç^2$, Fisher's exact tests, and analysis of variance (ANOVA) as appropriate.
2) Factor analysis: Principal Component Analysis (PCA) with a VARIMAX rotation was undertaken to explore the factor structure of the RRS-10 and sleep-wake parameters. The QIDS total score was included in the analysis to explore whether overall depression severity (a known precursor state to many potential stage 2 outcomes; McGorry et al., 2006) loaded separately from or with different sub-components of ruminative response style and/or sleep-wake patterns. We first determined the appropriateness of PCA by assessing the Kaiser-Mayer-Olkin (KMO) index and Bartlett's test of sphericity (KMO: 0.88; Bartlett's: $p < .001$). The number of factors to retain was determined by identifying factors with an Eigenvalue e 1.0 combined with Catell's Scree Plot (to determine the point of inflexion). Items with

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loadings e 0.35 on any factor were retained; any item loading on e 2 factors was allocated to the factor for which it had the highest loading.

3) Multivariate analysis of variance (MANOVA): the association between PCA factors and clinical stage at follow-up was analysed controlling for age and gender (as RRS-10 and sleep-wake patterns may vary with these characteristics).

Results

As shown in Table 1, the mean age of the sample was 19 years and majority of cases were female (n=178; 72%). At baseline, the sample mean QIDS score was 11.37 (*SD* = 5.38), and mean RRS-10 was 30.28 (*SD* = 6.44). The selected PSQI ratings revealed that the sample mean TST was 432.36 mins (*SD* = 128.86) and mean SOL was 61.22 mins (*SD* = 60.57); just over half of the sample (51%) reported poor sleep quality and 18% reported persistent daytime disturbance. Males scored significantly lower on the QIDS than females ({ = 9.19 *vs*. { = 12.24) and RRS-10 ({ = 27.84 *vs.* { = 31.26), but had a significantly longer TST ({ = 467.08 *vs*. { = 418.93).

Factor analysis demonstrated that a three-factor solution accounted for 59% of the explained variance. Factor 1 explained 37% of the variance (Eigenvalue = 5.67). As shown in Table 2, it appeared to reflect Toxic Brooding with maladaptive rumination about one's depressive state and situation (thinking about loneliness, sadness, an inability to handle things better).

Factor 2 explained 13% of the variance (Eigenvalue = 1.94), with significant loadings for depression severity and for rumination and sleep-wake measures. Specifically, Factor 2 (labelled Anergia) included the RRS-10 items regarding thoughts and feelings thinking about fatigue and achiness, (e.g.

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low motivation, inability to get going, and not feeling up to anything), as well as the sleep parameter of daytime disturbance.

Factor 3 (labelled Sleeplessness) explained 9% of the variance (Eigenvalue = 1.29), with positive significant loadings for self-reported SOL, and significant negative loadings for self-reported TST and sleep quality.

At 12-month follow-up, 22 individuals (9%) met criteria for a threshold syndrome (i.e. stage 2), while 226 individuals were classified as sub-syndromal (i.e. stage 1).

As shown in Table 3, only Factor 2 (Anergia) significantly differentiated those who met criteria for threshold syndrome (M = .861, SD = 1.71) from those that did not (M = -.124, SD = 1.11) (F(1,223) = 6.62, p=.009).

Discussion

The aim of this study was to explore the shared and separate components of rumination and sleep-wake disturbance in youth presenting with sub-threshold syndromes, and their relationship to syndrome trajectories and disease progression. Factor analysis demonstrated that rumination and sleep-wake disturbance exhibit both shared and separate components, where a three-factor solution accounted for over half of the explained variance. The first factor, which we labelled as Toxic Brooding, represented the unique sub-component of rumination, and exclusively contained RRS-10 items, including those relating to negative repeated thinking about loneliness, shortcomings, and past situations. This factor resembled the maladaptive component of rumination (toxic brooding) found in previous empirical investigations (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). Likewise, the third

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factor, which we labelled Sleeplessness, resembled insomniac sleep patterns and represented the unique sub-component of sleep-wake disturbance, including SOL, TST, and sleep quality exclusively.

In contrast, the second factor, labelled as Anergia, reflected the hypothesised commonalities shared between rumination and sleep-wake disturbance. This factor contained cognitive and emotional items from both the RRS-10 related to fatigue (i.e. thinking about lethargy, achiness, inability to get motivated or concentrate) and the sleep-wake parameter of daytime disturbance, and could be best characterised by fatigue and considered as interoceptive (a sense of the physiological condition of the body). Interestingly, compared to Toxic Brooding and Sleeplessness, Anergia had significantly stronger loadings onto measures of depression severity. Although literature examining rumination and sleep-wake disturbance tends to focus on toxic brooding and insomniac complaints as markers of depression in youth, this finding may indicate that Anergia is a more informative symptom because of the greater diagnostic specificity of fatigue, where toxic brooding and insomnia are non-specific symptoms of a range of illnesses in youth.

Furthermore, using multivariate analyses, we demonstrated that Anergia was the only factor that significantly differentiated cases that met threshold criteria (stage 2) at 12-months from those that did not report transition, controlling for age and gender. Taken together, this finding indicates that the cognitive, affective, and somatic elements of Anergia are a key marker of vulnerability to developing threshold syndromes in young people. Furthermore, Anergia may reflect the early manifestation of illness in which brief presentations of rumination and sleep-wake disturbance (in the form of cognitive and behavioural responses to bodily senses) could be a precursor state to more distinct, prolonged, or diagnosable disorders like depression. It is noteworthy that although Toxic Brooding and Sleeplessness did not significantly predict transition to threshold syndromes, for sub-threshold

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states, they may have moderated the effects of Anergia on transition risk (i.e. insomnia-like patterns related to increased daytime disturbance), and therefore both the separate and shared dimensions of rumination and sleep-wake disturbance may be important in indexing future risk.

We note that the current study has several limitations. Firstly, for sleep-wake cycles, a number of other objective measures and assessment tools are possible, for example actigraphy, which may illuminate further relationships with rumination shown in previous adolescent research (Thomsen et al., 2003; Takano, Iijima, & Tanno, 2012; Pillai et al., 2014). Additionally, the high proportion of females in this sample (72%) may suggest that our results exhibit gender bias and are not necessarily consistent with population prevalence of sub-threshold syndromes. Finally, although we did report factor loadings for depressive symptom severity, we did not report on all conventional diagnostic criteria such as psychotic or manic symptoms collected in the Transition Study. Although these measures were found to be highly skewed in the sample, as can be expected, and therefore unlikely to impact our results (Purcell et al., 2015), future studies may benefit from an investigation of factor loadings of other diagnostic measures.

Despite the limitations, this investigation has several strengths. The use of a longitudinal design and prospective follow-up of a well-defined cohort offered insights into the specific associations between sleep-wake and rumination in youth and illness progression. Additionally, the focus on clinical staging rather than unspecified or diffuse clinical presentations offers a novel approach to exploring risk factors for the trans-diagnostic evolution of syndromal mental disorders. Clinical staging permits sensitivity to mechanisms operating in patients with undifferentiated syndromes or mixed symptom patterns that would be difficult to examine using traditional diagnostic criteria, particularly in youth with subthreshold syndromes that fall below the usual symptomatic 'cut-offs' for specific diagnoses.

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As such, this research strategy may be especially useful for understanding and identifying the best candidate variables and factors for early intervention.

Clinically, the findings on Anergia may represent a useful target for early intervention. Further investigations of Anergia in youth with sub-threshold syndromes might also include the development and testing of a unified assessment tool to measure all elements of Anergia simultaneously. This study shows that novel conceptualisations of rumination and sleep-wake disturbance, and youth mental health (i.e. clinical staging models), may help refine and validate models of mental illness in at-risk youth and enhance treatment options.

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Table 1. Baseline characteristics of 248 individuals presenting with sub-threshold syndromes

	N (%)
Gender	
Males	70 (28)
Females	178 (72)
	M (SD)
Age	19.18 (3.24)
Depression (*QIDS Total Score*) [a]	11.37 (5.38)
Rumination (*RRS-10 Total Score*) [b]	30.28 (6.44)
Sleep pattern (selected PSQI items) [c]	
TST (minutes) [d]	432.36 (128.86)

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SOL (minutes) [e]	61.22 (60.57)
	N (%)
Sleep quality	
Poor sleep quality	124 (51)
Good sleep quality	121 (49)
Daytime Disturbance	
Persistent disturbance	43 (18)
Non-persistent disturbance	202 (82)

N = number of cases; M = mean; S.D. = standard deviation
[a] QIDS = Quick Inventory of Depression Symptomology
[b] RRS-10 = Ruminative Response Style Brief 10-Item Questionnaire
[c] PSQI = Pittsburgh Sleep Quality Index
[d] SOL = sleep onset latency
[e] TST = total sleep time
percentages are given as the nearest whole number

Table 2. Item loadings for the 3 factors extracted from the Principal Component Analysis (see text for details)

Component	**Factor**		
	1	**2**	**3**
QIDS Total score		.550	
RRS item 1: I think about how alone I feel	.614		
RRS item 2: I think about my feelings of fatigue and achiness		.746	
RRS item 3: I think about how hard it is to concentrate		.655	
RRS item 4: I think about how passive and unmotivated I feel		.680	
RRS item 5: I think 'Why can't I get going?'		.712	
RRS item 6: I think about a recent situation, wishing it had gone better	.782		
RRS item 7: I think about how sad I feel	.692		
RRS item 8: I think about my shortcoming, failings, faults, and mistakes	.835		
RRS item 9: I think about how I don't feel up to doing anything		.651	
RRS item 10: I think 'Why can't I handle things better?'	.745		
Self-reported SOL			.747
Sleep quality			-.760
Self-reported TST			-.800
Daytime disturbance		.437	

QIDS = Quick Inventory for Depression Symptomology; RRS = Ruminative Response Style; Sleep items derived from the Pittsburgh Sleep Quality Index: SOL = sleep onset latency, TST = total sleep time

Table 3. Comparison of baseline factor scores and outcome at follow-up (i.e. groups that did or did not meet criteria for a threshold syndrome at 12 months).

	12 month follow-up	Statistics

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	Threshold syndrome N = 22		Sub-threshold syndrome N = 226			
Factor	*Mean*	*SD*	*Mean*	*SD*	*F(df=1,223)*	*p value*
Toxic Brooding	-.144	1.75	-.067	1.14	0.02	p =.902
Anergia	.861	1.71	-.124	1.11	6.62	p =.009**
Sleeplessness	-.158	1.74	-.081	1.14	0.04	p =.839

N = number of cases; M = mean; S.D. = standard deviation

**p < 0.01

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Full title: Can youth at high risk of illness progression be identified by measures of rumination and sleep-wake disturbance

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Short title: Can youth at high risk of illness progression be identified by rumination and sleep-wake disturbance

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