BMJ Open Neurobiology Youth Follow-up Study: protocol to establish a longitudinal and prospective research database using multimodal assessments for current and past mental health treatment-seeking young people within an early intervention service

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ABSTRACT

Introduction Approximately 75% of major mental illness occurs before the age of 25 years. Despite this, our capacity to provide effective, early and personalised interventions is limited by insufficient evidence for characterising early-stage, and less specific, presentations of major mental disorders in youth populations. This article describes the protocol for setting up a large-scale database that will collect longitudinal, prospective data that incorporate clinical, social and occupational function, neuropsychological, circadian, metabolic, family history and genetic metrics. By collecting data in a research-purposed, standardised manner, the 'Neurobiology Youth Follow-up Study' should improve identification, characterisation and profiling of youth attending mental healthcare, to better inform diagnosis and treatment at critical time points. The overall goal is enhanced long-term clinical and functional outcomes.

Methods and analysis This longitudinal clinical cohort study will invite participation from youth (12–30 years) who seek help for mental health-related issues at an early intervention service (headspace Camperdown) and linked services. Participants will be prospectively tracked over 3 years with a series of standardised multimodal assessments at baseline, 6, 12, 24 and 36 months. Evaluations will include: (1) clinician-administered and self-report assessments determining clinical stage, pathophysiological pathways to illness, diagnosis, symptomatology, social and occupational function; (2) neuropsychological profile; (3) sleep–wake patterns and circadian rhythms; (4) metabolic markers and (5) genetics. These data will be used to: (1) model the impact of demographic, phenomenological and treatment variables, on clinical and functional outcomes;

Strengths and limitations of this study

- Broad eligibility criteria with minimal exclusions will allow for the establishment of a transdiagnostic longitudinal and prospective research database that is representative of all youth in contact with mental health services.
- The use of standardised multimodal assessments with known psychometrics and clinimetrics will ensure the development of a comprehensive database.
- The cohort size will ensure adequate statistical power for all planned analyses and modelling. We aim to track approximately 4000 young people (aged 12–30 years) over 3 years.
- This study is part of a structured research framework including evaluations of the utility of the transdiagnostic clinical staging and pathophysiological mechanisms framework.

(2) map neurobiological profiles and changes onto a transdiagnostic clinical stage and pathophysiological mechanisms framework.

Ethics and dissemination This study protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (2020/ETH01272, protocol V.1.3, 14 October 2020). Research findings will be disseminated through peer-reviewed journals and presentations at scientific conferences and to user and advocacy groups. Participant data will be de-identified.

INTRODUCTION

Approximately 75% of major mental illness occurs before the age of 25 years.¹ Moreover,

in those aged 10–24 years, neuropsychiatric disorders contribute more than any other cause to the global burden of disease.^{1 2} Despite the profound burden of mental illness in young people, our capacity to provide effective early personalised interventions is limited by insufficient evidence for characterising early-stage, and often less specific, presentations of major mental disorders in youth populations.³ Contributing significantly to poor characterisation of early presentations of mental illness is the current adult-based thresholds for diagnosis which often map weakly onto earlier non-specific patterns of illness in young people.⁴ It is therefore of significant value to characterise and longitudinally track specific clinical phenotypes of young mental health treatment-seeking patients, to help inform treatment. Identification of these phenotypes will enable the implementation of effective personalised early interventions at critical time points and thus ultimately give young people maximal opportunity for full recovery.^{3 5}

As part of the ongoing Youth Mental Health Research Programme (YMHRP; 2008–present) run at The University of Sydney's Brain and Mind Centre (BMC), a number of cross-sectional, longitudinal and intervention studies on mental health treatment-seeking young people aged 12–30 years have been conducted. Outcomes from this programme have included the development of a transdiagnostic framework consisting of the clinical staging model^{6–8} and a pathophysiological model based on pathways of illness in mental disorders.^{8 9} Moreover, a number of studies have examined specific neurobiological features of mental illness that have contributed to the understanding of how these features may present in youth populations and progress over the course of illness. Specifically, these studies include neuroimaging,^{10–13} sleep–wake patterns and circadian rhythms,^{14–16} and neuropsychological function.^{17–19}

Our transdiagnostic framework that integrates clinical staging and a novel pathophysiological mechanisms pathway model are described in detail by Carpenter *et al.*⁸ In summary, the clinical staging model characterises mental illness on a continuum from stage 1a (non-specific symptoms accompanied by mild to moderate functional impairment) through to stage 4 (severe, persistent and unremitting illness with clear evidence of marked functional deterioration). Clinical stage is assigned based on the severity and persistence of symptoms assessed together with the degree of functional impairment experienced by individuals as a result of symptomatology. Importantly, clinical stage is not based on traditional diagnostic categories, which map weakly onto earlier non-specific patterns of illness in young people.⁴

Our research group has proposed a pathophysiological mechanisms model that identifies at least three possible pathways of illness in mental disorders.^{8 9 20} We hypothesise that these pathways can be distinguished by different underlying pathophysiological mechanisms: (1) neurodevelopmental impairments (neurodevelopmental psychosis); (2) heightened arousal and stress sensitivity

(hyperarousal-anxious depression); and (3) circadian rhythm dysregulation (circadian–bipolar spectrum). Individuals may shift between pathways over time as their illness progresses from non-specific-type symptomatology through to a possible full-threshold syndrome. Understanding these underlying pathophysiological mechanisms in broad transdiagnostic populations, and being aware of how they present phenomenologically in youth populations, will advance our understanding of how disorders develop and progress, and guide treatment options that explicitly target these underlying mechanisms and thus aid improved clinical outcomes.⁸

Combining clinical staging with the pathophysiological mechanisms into one transdiagnostic framework may assist in clinical decisions regarding most effective care and treatment of the youth mental health population. Of particular importance is tracking movement within this framework longitudinally to gain a greater understanding of individual illness trajectories and thus being able to personalise treatment at critical time points.⁸

To utilise this transdiagnostic framework to personalise treatment at critical time points, it is necessary to explore how neurobiological factors, such as neuropsychological and circadian rhythm profiles, map onto and move within this framework over time. Research has demonstrated neuropsychological differences in young people with attenuated syndromes as compared with those with discrete and persistent mental health disorders.¹⁷ While both groups are impaired across neuropsychological measures compared with controls, there are greater impairments in patients with discrete and persistent disorders compared with those with attenuated syndromes.^{17 18} The greatest impairments in those with discrete and persistent disorders are found in tests of verbal memory and executive functioning.^{17 18} Interestingly, verbal memory improved over time in those with attenuated syndromes relative to those with discrete and persistent disorders.¹⁸ While these studies have provided important findings, there is a significant need for further research in this area. Increasing sample sizes within such studies and tracking neuropsychological movement longitudinally to gain a greater understanding of illness trajectories are vital. This can in turn better inform diagnosis and further personalise treatment at critical time points.

As with neuropsychological profiling, tracking sleep–wake behaviours and circadian rhythms may also better inform personalised treatment at critical time points. Research to date shows 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.¹⁴ Moreover, delayed sleep–wake timing is more pronounced in those who have bipolar-type illness (supporting a circadian–bipolar spectrum pathway) compared with those who have unipolar mood disorders and controls.^{21 22} Despite these important findings, there is a need for more robust longitudinal studies in this area. This will enable the translation of research findings

into targeted personalised treatment that considers the importance of circadian and sleep–wake rhythms.

In addition to the above, several other important domains clinically impact young people with emerging mental disorders. For young people in the early stages of illness, significant contributors to disability and mortality include social and economic disability,²³ suicide and self-harm behaviours,^{23–25} risky alcohol and substance use,²⁶ cardiometabolic illness^{27 28} and family history of mental disorders.^{29–31} Given the clinical impact of these factors for young people with emerging mental disorders, we have identified them as key domains that should also be a focus of targeted assessment and intervention. These factors all have significant (often concomitant) impacts on levels of functioning in young people. Early interventions that aim to address these domains may prove to be particularly valuable because they span across traditional diagnostic categories, and target specific outcomes associated with illness persistence and greater disability.³²

The current study will be conducted as part of the ongoing YMHRP and will further expand and build on the significant clinical, circadian, neuropsychological, metabolic and functional research to date. The aim of the Neurobiology Youth Follow-up Study will be to establish a longitudinal database, incorporating clinical, neuropsychological, sleep–wake and circadian rhythm, metabolic, social and occupational function, family history of mental illness and genetic measures in a standardised manner for research purposes. The establishment of the Neurobiology Youth Follow-up Database will enable improved identification, characterisation and profiling of the youth mental health population over time, to better inform diagnosis and treatment at critical time points, with the aim of establishing enhanced long-term clinical and functional outcomes.

METHODS AND ANALYSIS

The Neurobiology Study will be a longitudinal and prospective clinical cohort study at the BMC youth mental health clinic, ‘headspace’, located in the inner-city Sydney suburb of Camperdown. Headspace Camperdown is an early intervention service consisting of an integrated mix of primary-level psychological support and more specialised services including psychiatry, drug and alcohol support, and occupational therapy.³³ Young people aged 12–30 years will be invited to participate. All participants invited into the study will be current or past treatment-seeking youth for mental health-related issues at headspace Camperdown. Recruitment will be based on either past (previous 5 years) or current presentation for care at headspace Camperdown and linked services. These linked services include the Early Intervention in Psychosis team and headspace Early Intervention Team. These specialist teams provide more intensive psychiatry and care coordination to young people who require an increased level of care. Recruitment is not limited by specific diagnostic criteria. Therefore, young

people presenting with non-specific anxiety or depressive symptoms, attenuated syndromes or full-threshold syndromes will be included. Additionally, past mental health treatment-seeking youth, who may or may not be currently symptomatic, will also be included. This broad inclusion criteria will enable a robust and representative sample of the youth mental health population. Moreover, this diagnosis-independent approach is consistent with the US National Institute of Mental Health recommendations to conduct more inclusive clinical research in cohorts from service settings, without excluding subjects outside a specific diagnostic category.³⁴ Young people who are not proficient in the English language or who have a clinically evident intellectual disability will be excluded due to the difficulty for these young people to accurately complete multimodal assessments.

Study procedures

The study will start in early 2021. Participants will be tracked over a 3-year period with a series of standardised multimodal assessments occurring at baseline and 6, 12, 24 and 36 months. Recruitment will continue for a minimum of 5 years.

Current help-seeking young people presenting to headspace Camperdown will be assessed at intake (as per standard clinical care) by a headspace clinician not associated with the Neurobiology Youth Follow-up Study. At the completion of this assessment, the clinician will provide a brief overview about the study. If the young person is interested in learning more about the study, a research assistant associated with the study will provide written and oral information and answer any questions prior to obtaining consent.

Past treatment-seeking youth, who are no longer actively engaged in treatment at headspace Camperdown, will be identified via the Brain and Mind Research Institute Patient Research Register (BPRR). The BPRR was established by the University of Sydney (ethics application 2012/1626). The BPRR recruited 7000 young people aged 12–30 years presenting to the BMC’s youth mental health clinics. The BPRR consists of patients who consented to having their de-identified clinical information used for research purposes. This information includes routinely collected coded information that forms part of the patient’s standard clinical care.³⁵ In addition, a proportion of young people on this register consented to be contacted for up to 5 years from their time of consent, to be informed about relevant research studies at the BMC. These young people will be contacted and invited to participate in the Neurobiology Youth Follow-up Study. A research assistant will provide written and oral information and answer any questions prior to obtaining consent.

Young people under the age of 16 years will undergo the standard consent process outlined above. However, both the parent/guardian and the young person will be required to undergo the informed consent process and sign the consent form if it is agreed that the young person wishes to take part in the study. Participants will be

reimbursed for their time commitment to the study and any out-of-pocket expenses incurred by them. Reimbursement will be in the form of a shopping voucher up to an amount of \$100 per time point.

Assessments

To establish improved identification, characterisation and profiling of the youth mental health population over time, a series of repeated multimodal assessments (outlined below) will be administered. All assessments have been carefully selected based on their relevance to the study outcomes and their validity for use in the youth population.

Clinical assessments

A series of clinical assessments will be administered by a trained clinical researcher at baseline, 6, 12, 24 and 36 months. The clinical assessments will collect information regarding diagnosis, symptomatology, mental health and treatment history, family history of mental illness, physical health, social and occupational function, clinical stage and possible underlying pathophysiological illness trajectories. These will be evaluated as follows:

1. Clinical staging^{6–8}: based on the transdiagnostic clinical staging model,^{6–8} participants will be identified as either those in the earliest phases with non-specific clinical presentations (stages 1a ‘seeking help’), those at greater risk with more specific, subthreshold presentations (stage 1b ‘attenuated syndromes’), or those who have already reached a threshold for a progressive or recurrent disorder meeting diagnostic criteria (stage 2, 3 or 4).^{6 36–38}
2. Diagnostic assessment: the presence of any DSM-5 Axis I Disorders will be evaluated using the Structured Clinical Interview for DSM-5 Axis I Disorders.³⁹
3. Mental health and treatment history: a detailed assessment of participants’ past and present mental health and treatment history will be assessed via a clinical interview and recorded by a trained clinical research staff member.
4. Family history of mental illness: brief screening for family psychiatric history—the Family History Screen (FHS).^{40 41} The FHS collects information on 15 psychiatric disorders and suicidal behaviour in first-degree relatives. An adapted version of this questionnaire will be used to include the addition of the presence of psychiatric disorders in second-degree relatives and to capture information on treatment level.
5. Pathophysiological mechanisms^{8 9 42}: three pathways (and their respective clinical phenotype labels), which may reflect underlying pathophysiological mechanisms have been proposed: (1) neurodevelopmental impairments (neurodevelopmental psychosis); (2) heightened arousal and stress sensitivity (hyperarousal-anxious depression); and (3) circadian rhythm dysregulation (circadian–bipolar spectrum). Each participant will be assigned to one of these three pathways based on their clinical presentation as described in detail by Carpenter *et al.*⁸ In summary, participants with significant manic-like symptoms or significant atypical features (eg, reduced activation and energy or prolonged fatigue) will be allocated to the ‘circadian–bipolar spectrum’ subtype. Participants with a current primary psychotic disorder or a history of childhood-onset developmental difficulties (such as an autism spectrum disorder or learning disability) will be allocated to the ‘neurodevelopmental psychosis’ subtype. It is important to note that any participants with manic-like symptoms are preferentially allocated to the ‘circadian–bipolar spectrum’ subtype irrespective of current or past evidence of psychotic phenomena. Participants reporting anxiety symptoms and evolving depressive disorder symptoms are allocated to the ‘hyperarousal-anxious depression’ subtype. This subtype is also the default subtype for those without clear evidence of a circadian–bipolar spectrum or neurodevelopmental psychosis subtype. The allocation of participants to an illness pathway will be conducted by trained clinical research staff who have received specific training and who are familiar with the pathophysiological mechanisms model.
6. Clinical Global Impression (CGI)⁴³: CGI comprises two one-item measures evaluating the severity of psychopathology from 1 to 7 (CGI-Severity) and the change from the initiation of treatment on a similar 7-point scale (CGI-Improvement).
7. Social and Occupational Functioning Assessment Scale (SOFAS)⁴⁴: The SOFAS is a global rating of current functioning with a good construct validity, inter-rater reliability and predictive validity.^{45 46} The scale ranges from 0 to 100, with lower scores representing lower functioning. It focuses exclusively on the individual’s level of social and occupational functioning and is not directly influenced by the overall severity of the individual’s psychological symptoms. Notably, the SOFAS is used to rate functioning for the current period (ie, the level of functioning at the time of the evaluation).
8. The Brief Psychiatric Rating Scale (BPRS)⁴⁷: The BPRS is a clinician-rated scale measuring type and severity of psychiatric symptoms such as depression, anxiety, hallucinations and unusual behaviour.
9. Quick Inventory of Depressive Symptomatology–Clinician Rated⁴⁸: assesses the nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/decision-making, self-view, thoughts of death or suicide, general interest, energy level and restlessness/agitation) designated by the DSM to diagnose a major depressive episode.
10. The Young Mania Rating Scale⁴⁹: an 11-item, multiple-choice diagnostic questionnaire which psychiatrists use to measure the severity of manic episodes in patients based on patient subjective report and clinical observations during the clinical interview.

Table 1 Self-report assessments

Domain	Tool
Demographics	► Work and education, ethnicity, living circumstances, relationship status
Pregnancy and menstrual cycle	► Menstrual cycle, presence/diagnosis of PCOS and pregnancy
Physical health	► International Physical Activity Questionnaire-short version ^{57 58} ► Height, weight and waist circumference
Alcohol and other substance use	► WHO Alcohol, Smoking and Substance Involvement Screening Test ⁵⁹ ► Alcohol Use Disorders Identification Test-Consumption ⁶⁰
Suicidal ideation and behaviour	► Suicidal Ideation Attributes Scale ⁶¹ ► Columbia-Suicide Severity Rating Scale ⁶² : a self-rating adaptation of this questionnaire will be used
Self-harm	► Brief Non-suicidal Self-injury Assessment Tool; modules A-F ⁶³
Distress	► Kessler Psychological Distress Scale ^{64 65}
Depressive symptomatology	► Quick Inventory of Depressive Symptomatology-self-report ⁴⁸
Anxiety	► Overall Anxiety Severity Impairment Scale ^{66 67} ► Generalised Anxiety Disorder-7 ⁶⁸
Mania	► Altman Self-Rating Mania Scale ⁶⁹
Post-traumatic stress	► Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) ⁷⁰
Psychosis risk	► Prodromal Questionnaire ⁷¹
Disordered eating	► Eating Disorder Examination ^{72 73} ; an adapted brief self-report version of this scale will be used
Sleep-wake cycle and chronotype	► Sleep timing items are based on the Pittsburgh Sleep Quality Index ⁷⁴ , the Munich Chrono Type Questionnaire ^{75 76} and the Insomnia Severity Index ⁷⁷ ; sleep quality items are based on expert consensus in the literature
Social and occupational functioning	► Work and Social Adjustment Scale (Work and Social Life Scale) ⁷⁸
Social support	► Schuster Social Support Scale ⁷⁹
Childhood trauma	► Childhood Trauma Questionnaire ⁸⁰
Parental bonding	► Parental Bonding Instrument ⁸¹
Personality traits	► Behavioural Inhibition System/Behavioural Activation System ⁸²

PCOS, polycystic ovary syndrome; PTSD, post-traumatic stress disorder.

- Anthropometric assessment: a trained clinical researcher will assess blood pressure, pulse, height and weight (to determine body mass index), and waist circumferences.

Self-report assessments

The self-report questionnaires (see [table 1](#)) will be hosted online and will be individually tailored using skip logic questions. Participants will complete the self-report questionnaire at baseline, 6, 12, 24 and 36 months.

Actigraphy assessment

The 24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings (ambulatory measurement of motor activity using a wrist-worn device). Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate sleep and circadian patterns based on validated algorithms. Participants will be asked to wear an actigraph (GENEActiv Sleep device; Activinsights, Kimbolton, UK) for at least 14 consecutive days from the start of each time point, that is, baseline, 6, 12, 24 and 36 months. The devices will be worn on the non-dominant wrist, and will continuously record motor activity, wrist temperature and light exposure. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors^{50–53} as well as for sleep-wake scoring.^{54 55}

Neuropsychological testing

Participants will complete subtests from the Cambridge Neuropsychological Test Automated Battery,⁵⁶ to assess a series of neuropsychological domains. These domains and associated tests include: (1) sustained attention and processing speed measured via the Rapid Visual Information Processing task; (2) working memory measured via the Spatial Span task; (3) spatial planning and problem-solving measured via the One Touch Stockings of Cambridge; (4) visual memory and learning measured via the Paired Associate Learning task; (5) attention measured via the Intra-Extra Dimensional (IED) task; (6) decision-making and risk-taking measured via the Cambridge Gambling Task; (7) social cognition measured via the Emotional Recognition task; (8) verbal memory measured via the Verbal Recognition Memory task. These measures (excluding the IED task) are suitable for retesting over time. The IED task will be administered at baseline only.

Blood markers and genomics

Participants will be invited to undergo blood sample collection after informed consent, at baseline, 6, 12, 24 and 36 months to assess metabolic, inflammatory and a series of standard clinical blood markers. Blood samples will be collected in a fasting state by a trained phlebotomist. Participants will also be invited to undergo saliva sample collection after informed consent. Saliva samples will be collected at baseline only, for the assessment of genomic risk markers.

Sample size calculation

There is no set sample size for this study. The average annual number of young people accessing mental health treatment at headspace Camperdown ranges from 1200 to 1500 young people per year (headspace Q1–Q4 annual data report, 2019–2020, headspace National Commonwealth of Australia). Given recruitment is based on present or past presentation to care at headspace Camperdown and linked services, and is not limited by specific diagnostic criteria, we believe the number of young

people enrolled in the study will be a minimum of 800 participants annually. Recruitment will continue for a minimum of 5 years.

Data analysis plan

This Neurobiology Youth Follow-up Study will track key functional, clinical, neuropsychological, circadian, metabolic and genetic outcomes over a 3-year period in the youth mental health population.

1. Modelling the impacts of demographic, phenomenological and treatment variables, on clinical and functional outcomes.
2. Map neurobiological profiles onto the transdiagnostic clinical stage and pathophysiological mechanisms framework, to track the associated neurobiological changes over time.

Statistical techniques well suited to complex longitudinal data will be used, including mixed-effects modelling, Bayesian modelling and structural equation modelling. Moreover, we will use data-driven techniques (eg, cluster analysis, latent profile analysis, group-based trajectory modelling) to attempt to define homogeneous and treatment relevant subgroups with potentially greater utility than current diagnostic systems.

Patient and public involvement

Young people were not invited to participate in the study design. Study participants will however be invited to provide feedback on their experience of participating in the research project. Research findings will be disseminated through presentations to user and advocacy groups.

ETHICS AND DISSEMINATION

This study has been reviewed and approved by the Human Research Ethics Committee (HREC) of the Sydney Local Health District (2020/ETH01272, protocol V.1.3, 14 October 2020). Protocol modifications will only be implemented after HREC approval. All procedures contributing to this work will comply with ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Research findings will be disseminated through peer-reviewed journals and presentations at scientific conferences and to user and advocacy groups. Participant data will be de-identified.

CONCLUSION

The establishment of the Neurobiology Youth Follow-up Database should enable improved identification, characterisation and profiling of youth attending mental health-care. Importantly, the study aims to gain greater insight into individual illness trajectories, enabling more personalised treatment at critical time points and ultimately leading to enhanced long-term clinical and functional outcomes.

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Contributors IBH conceived the research idea, designed the study and is the principal investigator. AN, YJCS and NZ contributed to the study conception. AN wrote the study protocol with input from IBH, YJCS, NZ, CW, CM, BH, JC, JSC, NW, KRM, JS, NH, FI, SLN, AJG, EMS, FML and DK. AN wrote the manuscript with input from IBH, NZ, YJCS, CW, CM, BH, JC, CR, DFH, JS and KRM.

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Competing interests IBH was an inaugural Commissioner on Australia's National Mental Health Commission (2012–2018). He is the co-director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates early-intervention youth services at Camperdown under contract to headspace. He is the chief scientific advisor to, and a 5% equity shareholder in, InnoWell. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the \$30 million Australian government-funded Project Synergy (2017–2020; a 3-year programme for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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