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The *Brain Games* study: A randomised controlled trial of computerised cognitive training for preventing mental illness in adolescents with high-risk personality styles

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Abstract

Introduction: A broad range of mental disorders are now understood as aberrations of normal adolescent brain development. In both adolescents and adults, executive dysfunction has been implicated across a range of mental illnesses and enhancing executive functioning may prove to be a useful prevention strategy for adolescents at risk for a range of psychopathology. *Methods and analysis:* This study will consist of a double-blind, randomised controlled trial with a 12-month follow-up period. Participants will consist of 200 16-24 year olds who are at risk for a range of mental disorders based on personality risk factors, but have not experienced a lifetime mental illness as determined by a structured diagnostic interview. Participants will be randomly allocated to either an intervention group who complete an online cognitive training program specifically targeting executive functioning ability, or a control group who complete an online cognitive training program that has limited executive functioning training potential. Superiority of the executive functioning training program compared with the control training program will be assessed at baseline, post-training, and at 3-, 6- and 12-months follow-up. All assessments will be conducted online. The primary outcome of the study will be general psychopathology as measured by the Strengths and Difficulties Questionnaire (SDQ). Secondary outcomes will include executive functioning ability, day-to-day functioning and alcohol consumption. All analyses will be undertaken using mixed-model repeated measures ANOVA with planned contrasts. *Ethics and dissemination:* Ethics approval has been obtained from the University of New South Wales Human Research Ethics Committee (HC15094). Results of the trial immediately post-treatment and at 12-months follow-up will be submitted for publication in peer-reviewed journals. *Trial registration:* This trial is registered with the Australian and New Zealand Clinical Trials registry, ACTRN12616000127404. Registered 4 February 2016. Data collection ongoing 10 May 2017.

Key words: cognitive training, mental illness, adolescence, prevention, internet-delivered

Strengths and limitations of the study:

- This study has been designed to demonstrate genuine transfer of skills beyond task-specific learning, a limitation often identified within the cognitive training literature
- This study includes a rigorous active control condition meaning any differences between conditions can be confidently ascribed to improvements in executive functioning rather than other confounding factors
- This study will assess whether any effects are maintained over an extended 12-month follow-up period
- Participant contact will be limited and many processes will be automated, meaning that significant attrition is expected and has been accounted for in sample size calculations
- It may also be that the executive functioning intervention tasks are more engaging than the control tasks by virtue of their complexity and the mental process required for their completion, with subsequent differential attrition rates across the conditions

Introduction

Anxiety, depressive and substance use disorders frequently have the same risk factors, co-occur and interact in adolescence and young adulthood. Amongst young people (aged 15-24), the top ten causes of burden of disease are dominated by mental illness and substance use [1]. The US National Comorbidity Survey Adolescent Supplement (NCS-A) indicated that approximately 1 in 4 adolescents in the general population met criteria for an anxiety or affective disorder and 1 in 10 adolescents in the general population met criteria for a substance use disorder [2]. The same data indicated that almost a third (29%) of adolescents with one disorder in the general population also met criteria for another disorder, with a mean of 3 psychiatric disorders amongst those with comorbidity [3]. Mental illness is highly prevalent and comorbid in young people, and prevention programs need to be initiated early to reduce the occurrence, cost and significant functional impairment associated with these problems.

Given their typical age of onset, a broad range of mental disorders are increasingly being understood as the result of aberrations of developmental processes that normally occur in the adolescent brain [4-6]. Executive functioning, and its neurobiological substrate, the prefrontal cortex, matures during adolescence [5]. The relatively late maturation of executive functioning is adaptive in most cases, underpinning characteristic adolescent behaviours such as social interaction, risk-taking and sensation seeking which promote successful adult development and independence [6]. However, in some cases it appears that the delayed maturation of prefrontal regulatory regions leads to the development of mental illness, with neurobiological studies indicating a broad deficit in executive functioning which precedes and underpins a range of psychopathology [7]. A recent meta-analysis of neuroimaging studies focusing on a range of psychotic and nonpsychotic mental illnesses, found grey matter loss in the dorsal anterior cingulate, and left and right insula, was common across diagnoses [8]. In a healthy sample, this study also

demonstrated that lower grey matter in these regions was found to be associated with deficits in executive functioning performance. Similarly, another recent functional imaging study focused on 1,129 community youths (mean age 15.5 years) and investigated the relationship between psychopathology and activation of the executive system during a working memory task [9]. Overall psychopathology was associated with hypoactivation in the frontal pole, anterior cingulate, anterior insula and precuneas, implicating a network of executive regions across a range of psychiatric diagnoses. In both adolescents and adults, executive dysfunction has therefore been implicated across a range of mental illnesses.

Whilst the functional and structural organisation of the human brain was once considered static after critical developmental periods, it is now evident that neural changes are possible throughout the lifespan [10]. Experience-dependent neural reorganisation, or neuroplasticity, is apparent in response to repetitive and adaptive task engagement, disease, neglect and injury [11]. Cognitive training is one of many interventions (including brain stimulation, neuropharmacology, physical exercise and neurofeedback) that harnesses experience-dependent neuroplasticity with the aim of achieving durable behavioural and functional change [11]. Cognitive training generally consists of a program of exercises targeting specific cognitive skills, such as executive functioning, with the aim of achieving adaptive neural changes which underpin improvements in cognition and/or behaviour [12]. Cognitive training therapies, targeting a variety of cognitive processes, have demonstrated success in a range of clinical populations, including preliminary evidence of improvement in symptoms and cognition in those with affective, anxiety and substance use disorders [12]. The usefulness of cognitive training for schizophrenia has been studied extensively, with the research suggesting that such interventions can lead to enduring benefits for cognition and contribute to gains in overall functioning in individuals with both early [13, 14] and established [15, 16] symptoms.

Evidence therefore suggests that cognitive training may be a useful intervention strategy for those already showing symptoms of psychopathology, whether delivered during the early stages of mental illness or later in the course of disease progression. However, the effectiveness of cognitive training as a preventative strategy has not been thoroughly investigated. This is despite the evidence suggesting that cognitive impairments [4], and associated loss of day-to-day functioning [17, 18], frequently precede the onset of mental illness and may represent a non-specific prodromal phase for a broad range of mental illnesses. As such, for individuals identified as at high risk for developing a mental illness, cognitive training may therefore delay and, in some cases, prevent the onset of a clinical disorder. Given the evidence to suggest that deficits in executive functioning are associated with psychopathology across a range of mental illnesses [8, 9], this may be particularly the case for cognitive training using exercises focusing on this domain.

A small pilot study has demonstrated the feasibility of using cognitive training as a targeted prevention strategy during the critical adolescent period [19]. In this study, 15 adolescents (mean age ~13 years) experiencing social, emotional and behavioural difficulties, but without a clinical diagnosis, were randomised to a cognitive training intervention group (n=7) or a passive control group (n=8). The training group completed a 30-40 minute battery of visuospatial and verbal working memory tasks, five days a week, for five weeks. Compared with the passive control group, those in the intervention group showed significantly better post-training scores on measures of IQ, inhibition, test anxiety, and teacher-reported behaviour, attention and emotional symptoms. These findings provide encouraging support for the notion that cognitive training delivered to at risk adolescents may potentially prevent the onset of more serious social, emotional and behavioural problems.

Another study piloted a preventative cognitive training program; this time for those at clinical high risk for psychosis [20]. While there were encouraging results, particularly in respect to improvements in processing speed and prodromal symptoms, there was no comparison group used. However, the findings provide further evidence of the feasibility of an intensive cognitive training program for adolescents at risk for the development of mental illness. On the other hand, in another pilot study targeting individuals at clinical high risk for psychosis, there were no significant differences in cognition between the intervention and control groups immediately post-training [21]. Furthermore, high attrition rates led the authors to suggest that more engaging interventions should be trialled, especially for younger age groups.

Despite these promising findings in terms of both the treatment and prevention of mental illness, several limitations of the cognitive training literature have been noted [22]. The ultimate goal of cognitive training is to demonstrate that improvements in performing a particular task transfer to improvements in an underlying cognitive ability more generally (near transfer; i.e., training on a specific executive functioning task leads to improvements in overall executive functioning ability). This improvement in cognition generally would then be the basis for any improvements in behaviour (far transfer; i.e., improvements in overall executive functioning ability lead to decreases in psychopathology). However, the ways in which near transfer have been investigated in many previous studies has been flawed. Often only a single untrained task is used to measure near transfer to the underlying cognitive ability [22]. The capacity for a single task to accurately reflect multifaceted and complex cognitive abilities is questionable. Multiple tasks which measure different dimensions of the underlying cognitive ability are therefore required. Many previous studies have also used no control group or a "no contact" control group, which means that it is often not possible to rule out placebo effects [22]. Finally, the assessment of training effects rarely

extends beyond immediately post-training [22], meaning that the durability of any training effects has not been established.

The primary objective of the *Brain Games* study is to therefore investigate whether cognitive training delivered online within a "smart gaming" platform is a viable targeted prevention strategy by examining its ability to reduce psychopathology in young people at high risk for developing a mental illness. In order to identify those at risk for developing a mental illness, this study will target personality risk factors, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking, which have been shown to reliably predict substance misuse, anxiety, emotional and behavioural disorders in young people [23, 24]. It is hypothesised that the intervention cognitive training program (focusing on executive functioning) will be more effective than the active control cognitive training program (focusing on cognitive abilities other than executive functioning) in reducing psychopathology. Secondary aims include assessing the comparative effects of the intervention and control training programs on executive functioning ability, day-to-day functioning and alcohol consumption.

Methods and analysis

Study design

This study will consist of a parallel group randomised controlled trial with a 12-month follow-up period. The conduct and reporting of the trial will be in accordance with the CONSORT statement for non-pharmacological interventions. Participants will be randomly allocated to one of two cognitive training conditions: (1) the intervention group (cognitive training specifically focused on executive functioning), or (2) the control group (cognitive training focusing on other cognitive abilities). The allocation ratio will be 1:1. Superiority of the executive functioning training program compared with the control training program will be assessed at baseline, post-training, and at 3-, 6-

and 12-months follow-up. All assessments will be conducted online. The primary outcome of the study will be general psychopathology as measured by the Strengths and Difficulties Questionnaire (SDQ). Secondary outcomes will include executive functioning ability, day-to-day functioning and alcohol consumption.

Sample size calculations

The primary outcome measure will be scores on the self-report version of the Strengths and Difficulties Questionnaire (SDQ), a measure of psychopathology in young people with excellent psychometric properties [25] and test-retest reliability [26]. One previous pilot study has investigated the effect of cognitive training on psychopathology in at-risk young people using the SDQ [19]. According to this study, there was a between-group effect size of .36 for the SDQ. A similar effect size difference on the SDQ would therefore be expected in the current study. A total sample size of n = 140 (n=70 per group) is powered to have an 80% chance of detecting .36 effect size differences at $p < 0.5$. We will therefore aim to recruit n=200 (n=100 per group) in order to account for potential attrition.

Procedure

Participants and recruitment

Participants will be aged 16-24 years and at risk for a range of mental disorders. Participants will be included if they meet the following criteria: 1) at high risk for development of a mental illness based on elevated levels of personality risk factors, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking; 2) ability to access the internet via a computer; 4) residing within Australia; and 3) willingness to provide contact details. Exclusion criteria will be: 1) insufficient English comprehension; 2) a lifetime mental illness diagnosis; 3) current involvement in psychotherapy or taking medication for mental illness, pain, thyroid problems

and/or epilepsy; 4) intellectual disability; 5) a history of neurological or cardiovascular disorders, brain surgery, electroconvulsive or radiation treatment, thyroid disorders, brain haemorrhage or tumour, stroke, diabetes, seizures or epilepsy; and 6) significant previous experience with online cognitive training programs.

Community participants will be recruited through advertisements on social media platforms, and will indicate their interest by clicking on the advertisement, after which they will be taken to the study website (www.braingames.org) that provides more detailed information about the study. Online informed consent will be sought to complete online eligibility screening which will be conducted through the study website and assess for all exclusion and inclusion criteria, except for a prior diagnosis of a mental illness. If eligible, participants will be asked to provide written informed consent for a telephone-administered diagnostic interview conducted by a trained researcher from the University of New South Wales, Australia, as well as for participation in the study itself. Upon receipt of the signed informed consent, participants will be contacted by a member of the research team who will administer a diagnostic interview assessing for lifetime diagnoses of major depressive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, alcohol dependence, other substance dependence, attention deficit hyperactivity disorder, conduct disorder and oppositional defiant disorder. Those who do not meet eligibility criteria after completion of the online or telephone-administered interviews will be informed of their ineligibility, and given referrals and/or information for crisis care where necessary. After telephone screening, eligible participants will be sent a link to complete the baseline assessment through the study website. Following baseline assessment, participants will be given a unique code which will be randomly associated with one of the two cognitive training conditions. Randomisation of these codes to the intervention and control conditions will be conducted by an offsite technician who will allocate all unique codes to one of

the two conditions through the website random.org. Both the research team and participant will be blind to this allocation. Participants will be free to withdraw from the study at any time, and will not be prohibited from seeking concomitant care. Those participants who do withdraw will not complete any further assessments. Enrolment into the study will be rolling, with each participant starting their training the day after they have completed their baseline tasks.

Intervention and control conditions

Both the intervention and control conditions will complete cognitive training consisting of computerised tasks provided by *Lumosity* (http://www.lumosity.com/), and administered on a remote internet-connected computer owned by the participant. All tasks within the commercially available *Lumosity* package have "game-like" features making them visually engaging and motivating. The tasks are designed to be dynamic and adaptive, such that the difficulty increases as the participants' performance improves. Training for both conditions will consist of an intensive program of one hour per day, five days per week, over five weeks. Training compliance will be assessed during the active training phase, with reminder emails and text messages sent after one missed session, and telephone contact initiated after two missed sessions. Given the non-invasive nature of the intervention, adverse events are not anticipated. Spontaneous reporting of adverse events will be discussed with the study clinicians and responded to according to their recommendations. Training games for the intervention group will specifically focus on executive functioning, and will be based on classic paradigms used in cognitive neuroscience and executive functioning batteries. The control group will be administered cognitive training games that do not target executive functioning, and instead focus on field of view, verbal fluency and quantitative reasoning. The features of the control tasks will be matched to those of the intervention tasks in all other respects. Tasks included in both the intervention and control training programs were selected on the basis of consensus ratings with experienced clinicians.

Assessment Occasions

Both those assigned to the intervention and to the control group will be assessed at baseline, post-trial, and at 3-, 6- and 12- month follow-up intervals. All assessments at each occasion will be fully automated and conducted online using the participants' own computer.

Measures

Eligibility screening

Demographic data on gender, age, country of birth and rurality will be collected online before eligibility is assessed. Eligibility screening will consist of a 23-item self-report online questionnaire assessing personality risk factors [the Substance Use Risk Profile Scale (SURPS)] [27], with four subscales representing hopelessness, anxiety sensitivity, impulsivity, and sensation seeking. Participants scoring one or more standard deviations above the mean on any of the four SURPS subscales will be deemed eligible for the current study. Threshold means and standard deviations will be based on a previous validity study of the SURPS in Australian adolescents [23]. Scores on these subscales have been shown to reliably predict future substance use, as well as anxiety, emotional and behavioural disorders. The SURPS has been shown to have good concurrent and predictive validity, and the separate subscales display good specificity [28].

For those aged less than 18 years, the telephone-administered diagnostic interview for lifetime mental illnesses will be conducted using a lifetime version of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). The MINI-KID is a structured, lay-administered self-report diagnostic interview for children of ages 6 to 17 years old which is designed to assess DSM-IV psychiatric disorders. The MINI-KID has been shown to have excellent reliability and excellent concordance with clinician diagnoses [29]. For those aged 18

years and older, a lifetime version of the Mini International Neuropsychiatric Interview (MINI) will be administered. The MINI is also a structured, lay-administered self-report diagnostic interview designed to assess DSM-IV psychiatric disorders with excellent reliability and good concordance with a clinician-administered diagnostic interview [30, 31].

Baseline assessment

Psychopathology will be assessed using the SDQ, a 25-item self-report behavioural screening inventory for children and adolescents which measures positive and negative attributes of participants [32]. The SDQ has been used extensively and has strong psychometric properties [25]. An online version of this questionnaire will be developed for the current study in consultation with the original SDQ developers.

An online version of the WHODAS 2.0 12-item version (World Health Organisation, 2010) will be used to assess overall functioning and disability experienced as a result of health conditions (including mental illness or substance use) over the past 30 days. The WHODAS has been used extensively as a measure of functioning and disability and has been validated for use in youth populations [33].

Participants' recent and historical alcohol consumption will be assessed online by 14 questions adapted from the School Health and Alcohol Harm Reduction Project (SHAHRP) 'Patterns of Alcohol' index [34]. These questions ask responders about the frequency and quantity of different drinking behaviours, and age of first participation in these behaviours.

Online executive functioning assessment will be included as a measure of executive functioning improvement on untrained tasks. This assessment will consist of the N-Back Task [35] to evaluate

working memory, the Trail Making Test [36] to assess task shifting, and the Stroop Task [37] to evaluate inhibitory control. These tasks will be administered using Inquisit software (http://www.millisecond.com/download/library/).

Participants will also be asked to answer an online questionnaire about their satisfaction with the training program.

Follow-up assessments

Each of the assessments at post-training, 3-, 6- and 12-months follow-up will consist of the online versions of the SDQ, SURPS, WHODAS and alcohol consumption questionnaires, as well as the online executive functioning assessment. At the 12-month assessment, data will also be collected on service use and any use of the *Lumosity* program over the follow-up period.

All data collected in computerised format will be stored on password protected computers in databases using pre-defined codes. Rigorous data encryption will restrict external access to participant online content. The website uses industry leading encryption for all transmissions. The SSL certificate includes domain authentication and 256-bit SSL encryption. HTTPS (SSL) will be used for complete website including all sub domains. A data access layer (DAL) is used for all database functionality requirements within the site with the majority of database connections set up with stored procedures.

Statistical Analysis

Data will be analysed on an intention-to-treat basis. All analyses will be undertaken using mixed-model repeated measures (MMRM) ANOVA, with measurement occasion as a within-groups factor, and experimental group as a between-groups factor. These models are robust to missing data

under missing-at-random assumptions. Relationships between observations at different occasions will be modelled with an unstructured covariance matrix. For each experimental group, planned contrasts will be used to compare changes from baseline to post-test, 3-, 6- and 12- month follow-up intervals.

Ethics and dissemination

Ethical approval for the *Brain Games* study has been granted from the UNSW Human Research Ethics Committee (HC15094). Any protocol amendments will first be discussed by the team of investigators after which an ethics modification will be submitted.

Results of the trial immediately post-treatment and at 12-months follow-up will be submitted for publication in peer-reviewed journals. After all study data has been collected, all participants will receive a document outlining the main results of the study. All lead investigators will be listed as authors on all publications unless they opt out of authorship.

The de-identified dataset generated and analysed during the current study are available from the corresponding author on reasonable request.

Discussion

The present study protocol presents the design of a randomised controlled trial that assesses whether online executive functioning training is a viable strategy for the targeted prevention of mental illness and substance use in high-risk youth. The primary aim of the *Brain Games* trial is to investigate whether an executive functioning training program is more effective at preventing symptoms of psychopathology than cognitive training that has limited executive functioning training potential. By investigating a novel prevention strategy targeting executive functioning, the

Brain Games study will be the first full-scale trial conducted internationally that investigates the utility of cognitive training in the prevention of mental illness in high-risk adolescents. This study targets underlying executive functioning deficits that have been identified across the boundaries of traditional categorical psychiatric diagnoses. Novel universal prevention programs that cross diagnostic boundaries are currently being trialled in Australian schools [38]. For high-risk adolescents, however, universal prevention programs have been shown to have limited benefits [39]. It is envisaged that transdiagnostic prevention strategies that target high-risk adolescents, such as the present one, would eventually complement and augment a transdiagnostic approach to universal prevention. This stepped-care sequential prevention model has the potential to maximize outcomes for both high- and low-risk youth across a range of mental illnesses and reduce the considerable burden of disease associated with these illnesses in adolescence.

Declarations

Authors' contributions

LM is the Chief Investigator of the *Brain Games* study. AH and NG provide clinical and neuropsychological expertise and MT provides expertise in prevention research. LM, AH, NG and MT were all involved in the study design. LM and RV are involved in data collection. All authors will be involved in the reporting of the study results. LM and RV wrote the first draft of the manuscript. All authors provided feedback on subsequent drafts and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Murray, C.J., et al., *Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2013. **380**(9859): p. 2197-2223.
2. Merikangas, K.R., et al., *Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A).* Journal of the American Academy of Child & Adolescent Psychiatry, 2010. **49**(10): p. 980-989.
3. Kessler, R., et al., *Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A).* Psychological Medicine, 2012. **42**(09): p. 1997-2010.
4. Lewis, D.A., *Cortical circuit dysfunction and cognitive deficits in schizophrenia–implications for preemptive interventions.* European Journal of Neuroscience, 2012. **35**(12): p. 1871-1878.
5. Giedd, J.N., M. Keshavan, and T. Paus, *Why do many psychiatric disorders emerge during adolescence?* Nature Reviews Neuroscience, 2008. **9**(12): p. 947-957.
6. Crews, F., J. He, and C. Hodge, *Adolescent cortical development: a critical period of vulnerability for addiction.* Pharmacology, Biochemistry & Behavior, 2007. **86**(2): p. 189-99.
7. Vinogradov, S., M. Fisher, and E. de Villers-Sidani, *Cognitive training for impaired neural systems in neuropsychiatric illness.* Neuropsychopharmacology, 2011. **37**(1): p. 43-76.
8. Goodkind, M., et al., *Identification of a common neurobiological substrate for mental illness.* JAMA psychiatry, 2015. **72**(4): p. 305-315.

9. Shanmugan, S., et al., *Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth.* American journal of psychiatry, 2016. **173**(5): p. 517-526.

10. Valkanova, V., R.E. Rodriguez, and K.P. Ebmeier, *Mind over matter-what do we know about neuroplasticity in adults?* International Psychogeriatrics, 2014. **26**(6): p. 891.

11. Cramer, S.C., et al., *Harnessing neuroplasticity for clinical applications.* Brain, 2011. **134**(6): p. 1591-1609.

12. Keshavan, M.S., et al., *Cognitive training in mental disorders: update and future directions.* American Journal of Psychiatry, 2014. **171**(5): p. 510-522.

13. Revell, E.R., et al., *A systematic review and meta-analysis of cognitive remediation in early schizophrenia.* Schizophrenia research, 2015. **168**(1): p. 213-222.

14. Lee, R., et al., *Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients.* Psychological medicine, 2013. **43**(06): p. 1161-1173.

15. Wykes, T., et al., *A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes.* American Journal of Psychiatry, 2011. **168**(5): p. 472-485.

16. Medalia, A. and A.M. Saperstein, *Does cognitive remediation for schizophrenia improve functional outcomes?* Current Opinion in Psychiatry, 2013. **26**(2): p. 151-157.

17. Hetrick, S., et al., *Early identification and intervention in depressive disorders: towards a clinical staging model.* Psychotherapy and psychosomatics, 2008. **77**(5): p. 263-270.

18. McGorry, P.D., *Staging in neuropsychiatry: a heuristic model for understanding, prevention and treatment.* Neurotoxicity research, 2010. **18**(3-4): p. 244-255.

19. Roughan, L. and J.A. Hadwin, *The impact of working memory training in young people with social, emotional and behavioural difficulties.* Learning and Individual Differences, 2011. **21**(6): p. 759-764.

20. Hooker, C.I., et al., *A pilot study of cognitive training in clinical high risk for psychosis: initial evidence of cognitive benefit.* Schizophrenia research, 2014. **157**: p. 314.

21. Piskulic, D., et al., *Pilot study of cognitive remediation therapy on cognition in young people at clinical high risk of psychosis.* Psychiatry research, 2015. **225**(1): p. 93-98.

22. Shipstead, Z., T.S. Redick, and R.W. Engle, *Is working memory training effective?* Psychological bulletin, 2012. **138**(4): p. 628.

23. Newton, N.C., et al., *The validity of the Substance Use Risk Profile Scale (SURPS) among Australian adolescents.* Addictive behaviors, 2016. **53**: p. 23-30.

24. Castellanos, N. and P. Conrod, *Brief interventions targeting personality risk factors for adolescent substance misuse reduce depression, panic and risk-taking behaviours.* Journal of Mental Health, 2006. **15**(6): p. 645-658.

25. Goodman, R., *Psychometric properties of the strengths and difficulties questionnaire.* Journal of the American Academy of Child & Adolescent Psychiatry, 2001. **40**(11): p. 1337-1345.

26. Hawes, D.J. and M.R. Dadds, *Australian data and psychometric properties of the Strengths and Difficulties Questionnaire.* Australian and New Zealand Journal of Psychiatry, 2004. **38**(8): p. 644-651.

27. Woicik, P.A., et al., *The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles.* Addictive behaviors, 2009. **34**(12): p. 1042-1055.

28. Castellanos-Ryan, N., et al., *Sensitivity and specificity of a brief personality screening instrument in predicting future substance use, emotional, and behavioral problems: 18-month predictive validity of the substance use risk profile scale.* Alcoholism: Clinical and Experimental Research, 2013. **37**(s1): p. E281-E290.

29. Sheehan, D.V., et al., *Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID).* The Journal of clinical psychiatry, 2010. **71**(3): p. 313-326.

30. Lecrubier, Y., et al., *The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI.* European psychiatry, 1997. **12**(5): p. 224-231.

31. Sheehan, D., et al., *The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability.* European Psychiatry, 1997. **12**(5): p. 232-241.

32. Goodman, R., H. Meltzer, and V. Bailey, *The Strengths and Difficulties Questionnaire: A pilot study on the validity of the self-report version.* European child & adolescent psychiatry, 1998. **7**(3): p. 125-130.

33. Kimber, M., J. Rehm, and M.A. Ferro, *Measurement Invariance of the WHODAS 2.0 in a population-based sample of youth.* PloS one, 2015. **10**(11): p. e0142385.

34. McBride, N., et al., *Harm minimization in school drug education: final results of the School Health and Alcohol Harm Reduction Project (SHAHRP).* Addiction, 2004. **99**(3): p. 278-291.

35. Jaeggi, S.M., et al., *The concurrent validity of the N-back task as a working memory measure.* Memory, 2010. **18**(4): p. 394-412.

36. Reitan, R.M., *Validity of the Trail Making Test as an indicator of organic brain damage.* Perceptual and motor skills, 1958. **8**(3): p. 271-276.

37. Stroop, J.R., *Studies of interference in serial verbal reactions.* Journal of experimental psychology, 1935. **18**(6): p. 643.

38. Teesson, M., et al., *The CLIMATE schools combined study: a cluster randomised controlled trial of a universal Internet-based prevention program for youth substance misuse, depression and anxiety.* BMC psychiatry, 2014. **14**(1): p. 32.

39. Faggiano, F., et al., *School-based prevention for illicit drugs use: A systematic review.* Preventive medicine, 2008. **46**(5): p. 385-396.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (pg 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (pg 2)
	2b	All items from the World Health Organization Trial Registration Data Set (pg 2)
Protocol version	3	Date and version identifier (footer)
Funding	4	Sources and types of financial, material, and other support (pg 16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pg 1 & 15)
	5b	Name and contact information for the trial sponsor (N/A)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (pg 16)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (N/A)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (pg 4-8)
	6b	Explanation for choice of comparators (pg 11)
Objectives	7	Specific objectives or hypotheses (pg 8)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pg 8)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (10-11)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (pg 9-10)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (p 11)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (p 11)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (p 11)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (p 11)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (p 9)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (p 11-12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (p 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (p 10)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (pg 10-11)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (pg 10-11)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (pg 10-11)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (pg 10-11)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (pg 10-11)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (pg 12-14)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (pg 11)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (p. 14)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (pg 14-15)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pg 14-15)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (pg 14)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (pg 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (n/a)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (pg 11)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (n/a)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (pg 15)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (pg 15)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (pg 10)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (pg 14)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (pg 16-17)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (pg 15)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (n/a)

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (pg 15)
	31b	Authorship eligibility guidelines and any intended use of professional writers (pg 15)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (pg 15)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (see Appendix)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (n/a)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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UNSW AUSTRALIA

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The Brain Games Study
Dr Louise Mewton

The research study is being carried out by the following researchers:		
Role	**Name**	**Organisation**
Chief Investigator	Dr Louise Mewton	University of New South Wales
Co-Investigator/s	Dr Nicola Gates, Dr Antoinette Hodge & Professor Maree Teesson	Westmead Children's Hospital and University of New South Wales
Research Funder	This research is being funded by Australian Rotary Health and the Australian National Health and Medical Research Council.	

What is the research study about?
You are invited to take part in this online research study. You have been invited because of certain behaviours or emotions you reported in response to our questionnaire.

To participate in this research study you need to meet the following inclusion criteria:
1) the experience of risky behaviours, high anxiety or negative emotions; 2) be able to access the internet readily via a desktop or laptop computer (either in your home, or willingness to use public library/other suitable venue with internet access); 3) be willing to provide current email address and phone number. You will not be able to take part in this study if you meet criteria for an anxiety, mood or substance use disorder, if you take certain medications, or have certain medical conditions.

The research study is aiming to determine whether brain training in the form of online games ("Brain Games") can reduce risky behaviours, anxiety and negative emotions which may lead to mental illness in the future.

Do I have to take part in this research study?
This Participant Information Statement tells you about the research study. It explains the research tasks involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. If there is anything that you don't understand or want to know more about please feel free to contact the research team. Before deciding whether or not to take part, you might want to talk about it with a relative or friend.

If you decide you want to take part in the research study, you will be asked to:
- Type your name into the boxes at the bottom of this consent form ;
- Keep a copy of this Participant Information Statement;

What does participation in this research require, and are there any risks involved?
Before you begin any activities we need to do ask some more questions to understand whether it is ok for you to take part. In order to do this we will contact you by telephone and ask you to answer questions about your feelings and behaviours, including substance use. It is expected that these questions will take about half an hour for you to complete. If you are not suitable for the study, we will let you know over the telephone, provide you with information for services should you need them, and withdraw all your data from the study.

If you are suitable for the study, you will be randomly assigned to one of two different training groups. Both groups will be asked to complete an online Brain Games program. We will ask you to do the program for a maximum of one hour every weekday for a total of five weeks. In total, the program will take a maximum of 25 hours. The Brain Games program is like a computer game, and we expect that you will find the Brain Games sessions fun as well as challenging. Before and after you have completed your online Brain Games sessions we will ask you to complete online and telephone-

administered questionnaires about your feelings and behaviours, including substance use, as well as some tasks that will tell us about your different abilities. We will also ask you to complete these same questionnaires and tasks 3 months, 6 months and 12 months after you have finished the Brain Games program. We expect that each set of questionnaires and tasks will take up to an hour to complete so we expect you will spend a total of 5 hours doing these over the course of a year. At the end of the study we want to compare the two different Brain Games programs to see whether one is better than the other in terms improving any negative feelings or risky behaviours you might be experiencing. At the moment, we are not sure if one program is better than the other, or whether you will benefit from participating in this study.

We do not expect there to be any risks associated with completing the Brain Games program. It is possible you might experience some distress when answering the questionnaires that ask about sensitive topics. If you do experience distress you will be encouraged to contact the research team and you will be given contact information for services equipped to deal with any distress you might be experiencing.

Will I be paid to participate in this project?
You will be reimbursed $50 for taking the time to complete the Brain Games program. After you have completed all the questionnaires you will also go into a draw to win an iPad.

What are the possible benefits to participation?
We hope to use information we get from this research study to benefit others who might also behave in risky ways or experience anxiety or negative emotions.

What will happen to information about me?
By typing your name into this form, you consent to the research team collecting and using information from the questionnaire you complete for the research study. We will keep your confidential data for 7 years. Any information obtained in connection with this research study that can identify you will remain confidential. This project will use an external site to create, collect and analyse data collected in a questionnaire format. The site we are using is www.braingames.org.au. If you agree to participate in this study, the responses you provide to the questionnaire will be stored on a host server that is used by Indigo hosting. Once we have completed our data collection and analysis, we will import the data we collect to the UNSW server. The data on the Indigo hosting server will then be deleted.

It is anticipated that the results of this research study will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your research findings may be published, but you will not be individually identifiable in these publications.

How and when will I find out what the results of the research study are?
You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by emailing the study co-ordinator, Dr Louise Mewton (louisem@unsw.edu.au). This feedback will be in the form of a one page report. You will receive this feedback after the study is finished.

What if I want to withdraw from the research study?
If you do consent to participate, you may withdraw at any time. If you do withdraw, you will be asked to complete and sign the 'Withdrawal of Consent Form' which is provided at the end of this document. Alternatively you can contact the research team and tell them you no longer want to participate.

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The Brain Games Study
Dr Louise Mewton

If you decide to withdraw from the study, we will not collect any more information from you. Please let us know at the time when you withdraw what you would like us to do with the information we have collected about you up to that point. If you wish your information will be removed from our study records and will not be included in the study results, up to the point that we have analysed and published the results.

What should I do if I have further questions about my involvement in the research study?
The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the following member/s of the research team:

Research Team Contact

Name	Dr Louise Mewton
Position	Research Officer
Telephone	02 8936 1131
Email	louisem@unsw.edu.au

If at any stage during the project you become distressed or require additional support from someone not involved in the research please call:

Contact for feelings of distress

Name/Organisation	Kids Helpline
Telephone	1800 551 800
Email	www.kidshelp.com.au

What if I have a complaint or any concerns about the research study?
If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Complaints Contact

Position	Human Research Ethics Coordinator
Telephone	+ 61 2 9385 6222
Email	humanethics@unsw.edu.au
HC Reference Number	HC15094

Consent Form – Participant providing own consent

Declaration by the participant

☐I have read the Participant Information Sheet or someone has read it to me in a language that I understand;

☐I understand the purposes, study tasks and risks of the research described in the project;

☐I have had an opportunity to ask questions and I am satisfied with the answers I have received;

☐I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the project and withdrawal will not affect my relationship with any of the named organisations and/or research team members;

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The Brain Games Study
Dr Louise Mewton

☐I understand that I will be given a signed copy of this document to keep;

Participant Signature

Name of Participant (please type)	
Please type name again (this will be taken as your signature)	
Date	

Declaration by Researcher*

☐ I have given a verbal explanation of the research study, its study activities and risks and I believe that the participant has understood that explanation.

Researcher Signature*

Name of Participant (please print)	
Signature of Research Participant	
Date	

[+]An appropriately qualified member of the research team must provide the explanation of, and information concerning the research study.

Note: All parties signing the consent section must date their own signature.

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The Brain Games Study
Dr Louise Mewton

Form for Withdrawal of Participation

I wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** affect my relationship with The University of New South Wales.

Participant Signature

Name of Participant (please type)	
Signature of Research Participant (please type name)	
Date	

The section for Withdrawal of Participation should be forwarded to:

CI Name:	Louise Mewton
Email:	louisem@unsw.edu.au
Phone:	02 8936 1131

BMJ Open

The Brain Games study: Protocol for a randomised controlled trial of computerised cognitive training for preventing mental illness in adolescents with high-risk personality styles

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health
Keywords:	cognitive training, mental illness, adolescence, prevention, internet-delivered

The *Brain Games* study: Protocol for a randomised controlled trial of computerised cognitive training for preventing mental illness in adolescents with high-risk personality styles

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Abstract

Introduction: A broad range of mental disorders are now understood as aberrations of normal adolescent brain development. In both adolescents and adults, executive dysfunction has been implicated across a range of mental illnesses and enhancing executive functioning may prove to be a useful prevention strategy for adolescents at risk for a range of psychopathology. *Methods and analysis:* This study will consist of a double-blind, randomised controlled trial with a 12-month follow-up period. Participants will consist of 200 16-24 year olds who are at risk for a range of mental disorders based on personality risk factors, but have not experienced a lifetime mental illness as determined by a structured diagnostic interview. Participants will be randomly allocated to either an intervention group who complete an online cognitive training program specifically targeting executive functioning ability, or a control group who complete an online cognitive training program that has limited executive functioning training potential. Superiority of the executive functioning training program compared with the control training program will be assessed at baseline, post-training, and at 3-, 6- and 12-months follow-up. All assessments will be conducted online. The primary outcome of the study will be general psychopathology as measured by the Strengths and Difficulties Questionnaire (SDQ). Secondary outcomes will include executive functioning ability, day-to-day functioning and alcohol consumption. All analyses will be undertaken using mixed-model repeated measures ANOVA with planned contrasts. *Ethics and dissemination:* Ethics approval has been obtained from the University of New South Wales Human Research Ethics Committee (HC15094). Results of the trial immediately post-treatment and at 12-months follow-up will be submitted for publication in peer-reviewed journals. *Trial registration:* This trial is registered with the Australian and New Zealand Clinical Trials registry, ACTRN12616000127404. Registered 4 February 2016. Data collection ongoing 10 May 2017.

Key words: cognitive training, mental illness, adolescence, prevention, internet-delivered

Strengths and limitations of the study:

- This study has been designed to demonstrate genuine transfer of skills beyond task-specific learning, a limitation often identified within the cognitive training literature
- This study includes a rigorous active control condition meaning any differences between conditions can be confidently ascribed to improvements in executive functioning rather than other confounding factors
- This study will assess whether any effects are maintained over an extended 12-month follow-up period
- Participant contact will be limited and many processes will be automated, meaning that significant attrition is expected and has been accounted for in sample size calculations
- It may also be that the executive functioning intervention tasks are more engaging than the control tasks by virtue of their complexity and the mental process required for their completion, with subsequent differential attrition rates across the conditions

Introduction

Anxiety, depressive and substance use disorders frequently have the same risk factors, co-occur and interact in adolescence and young adulthood. Amongst young people (aged 15-24), the top ten causes of burden of disease are dominated by mental illness and substance use [1]. The US National Comorbidity Survey Adolescent Supplement (NCS-A) indicated that approximately 1 in 4 adolescents in the general population met criteria for an anxiety or affective disorder and 1 in 10 adolescents in the general population met criteria for a substance use disorder [2]. The same data indicated that almost a third (29%) of adolescents with one disorder in the general population also met criteria for another disorder, with a mean of 3 psychiatric disorders amongst those with comorbidity [3]. Mental illness is highly prevalent and comorbid in young people, and prevention programs need to be initiated early to reduce the occurrence, cost and significant functional impairment associated with these problems.

Given their typical age of onset, a broad range of mental disorders are increasingly being understood as the result of aberrations of developmental processes that normally occur in the adolescent brain [4-6]. Executive functioning, and its neurobiological substrate, the prefrontal cortex, matures during adolescence [5]. The relatively late maturation of executive functioning is adaptive in most cases, underpinning characteristic adolescent behaviours such as social interaction, risk-taking and sensation seeking which promote successful adult development and independence [6]. However, in some cases it appears that the delayed maturation of prefrontal regulatory regions leads to the development of mental illness, with neurobiological studies indicating a broad deficit in executive functioning which precedes and underpins a range of psychopathology [7]. A recent meta-analysis of neuroimaging studies focusing on a range of psychotic and nonpsychotic mental illnesses, found grey matter loss in the dorsal anterior cingulate, and left and right insula, was common across diagnoses [8]. In a healthy sample, this study also

demonstrated that lower grey matter in these regions was found to be associated with deficits in executive functioning performance. Similarly, another recent functional imaging study focused on 1,129 community youths (mean age 15.5 years) and investigated the relationship between psychopathology and activation of the executive system during a working memory task [9]. Overall psychopathology was associated with hypoactivation in the frontal pole, anterior cingulate, anterior insula and precuneas, implicating a network of executive regions across a range of psychiatric diagnoses. In both adolescents and adults, executive dysfunction has therefore been implicated across a range of mental illnesses.

Whilst the functional and structural organisation of the human brain was once considered static after critical developmental periods, it is now evident that neural changes are possible throughout the lifespan [10]. Experience-dependent neural reorganisation, or neuroplasticity, is apparent in response to repetitive and adaptive task engagement, disease, neglect and injury [11]. Cognitive training is one of many interventions (including brain stimulation, neuropharmacology, physical exercise and neurofeedback) that harnesses experience-dependent neuroplasticity with the aim of achieving durable behavioural and functional change [11]. Cognitive training generally consists of a program of exercises targeting specific cognitive skills, such as executive functioning, with the aim of achieving adaptive neural changes which underpin improvements in cognition and/or behaviour [12]. Cognitive training therapies, targeting a variety of cognitive processes, have demonstrated success in a range of clinical populations, including preliminary evidence of improvement in symptoms and cognition in those with affective, anxiety and substance use disorders [12]. The usefulness of cognitive training for schizophrenia has been studied extensively, with the research suggesting that such interventions can lead to enduring benefits for cognition and contribute to gains in overall functioning in individuals with both early [13, 14] and established [15, 16] symptoms.

Evidence therefore suggests that cognitive training may be a useful intervention strategy for those already showing symptoms of psychopathology, whether delivered during the early stages of mental illness or later in the course of disease progression. However, the effectiveness of cognitive training as a preventative strategy has not been thoroughly investigated. This is despite the evidence suggesting that cognitive impairments [4], and associated loss of day-to-day functioning [17, 18], frequently precede the onset of mental illness and may represent a non-specific prodromal phase for a broad range of mental illnesses. As such, for individuals identified as at high risk for developing a mental illness, cognitive training may therefore delay and, in some cases, prevent the onset of a clinical disorder. Given the evidence to suggest that deficits in executive functioning are associated with psychopathology across a range of mental illnesses [8, 9], this may be particularly the case for cognitive training using exercises focusing on this domain.

A small pilot study has demonstrated the feasibility of using cognitive training as a targeted prevention strategy during the critical adolescent period [19]. In this study, 15 adolescents (mean age ~13 years) experiencing social, emotional and behavioural difficulties, but without a clinical diagnosis, were randomised to a cognitive training intervention group (n=7) or a passive control group (n=8). The training group completed a 30-40 minute battery of visuospatial and verbal working memory tasks, five days a week, for five weeks. Compared with the passive control group, those in the intervention group showed significantly better post-training scores on measures of IQ, inhibition, test anxiety, and teacher-reported behaviour, attention and emotional symptoms. These findings provide encouraging support for the notion that cognitive training delivered to at risk adolescents may potentially prevent the onset of more serious social, emotional and behavioural problems.

Another study piloted a preventative cognitive training program; this time for those at clinical high risk for psychosis [20]. While there were encouraging results, particularly in respect to improvements in processing speed and prodromal symptoms, there was no comparison group used. However, the findings provide further evidence of the feasibility of an intensive cognitive training program for adolescents at risk for the development of mental illness. On the other hand, in another pilot study targeting individuals at clinical high risk for psychosis, there were no significant differences in cognition between the intervention and control groups immediately post-training [21]. Furthermore, high attrition rates led the authors to suggest that more engaging interventions should be trialled, especially for younger age groups.

Despite these promising findings in terms of both the treatment and prevention of mental illness, several limitations of the cognitive training literature have been noted [22]. The ultimate goal of cognitive training is to demonstrate that improvements in performing a particular task transfer to improvements in an underlying cognitive ability more generally (near transfer; i.e., training on a specific executive functioning task leads to improvements in overall executive functioning ability). This improvement in cognition generally would then be the basis for any improvements in behaviour (far transfer; i.e., improvements in overall executive functioning ability lead to decreases in psychopathology). However, the ways in which near transfer have been investigated in many previous studies has been flawed. Often only a single untrained task is used to measure near transfer to the underlying cognitive ability [22]. The capacity for a single task to accurately reflect multifaceted and complex cognitive abilities is questionable. Multiple tasks which measure different dimensions of the underlying cognitive ability are therefore required. Many previous studies have also used no control group or a "no contact" control group, which means that it is often not possible to rule out placebo effects [22]. Finally, the assessment of training effects rarely

extends beyond immediately post-training [22], meaning that the durability of any training effects has not been established.

The primary objective of the *Brain Games* study is to therefore investigate whether cognitive training delivered online within a "smart gaming" platform is a viable targeted prevention strategy by examining its ability to reduce psychopathology in young people at high risk for developing a mental illness. In order to identify those at risk for developing a mental illness, this study will target personality risk factors, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking, which have been shown to reliably predict substance misuse, anxiety, emotional and behavioural disorders in young people [23, 24]. It is hypothesised that the intervention cognitive training program (focusing on executive functioning) will be more effective than the active control cognitive training program (focusing on cognitive abilities other than executive functioning) in reducing psychopathology. Secondary aims include assessing the comparative effects of the intervention and control training programs on executive functioning ability, day-to-day functioning and alcohol consumption.

Methods and analysis

Study design

This study will consist of a parallel group randomised controlled trial with a 12-month follow-up period. The conduct and reporting of the trial will be in accordance with the CONSORT statement for non-pharmacological interventions. Participants will be randomly allocated to one of two cognitive training conditions: (1) the intervention group (cognitive training specifically focused on executive functioning), or (2) the control group (cognitive training focusing on other cognitive abilities). The allocation ratio will be 1:1. Superiority of the executive functioning training program compared with the control training program will be assessed at baseline, post-training, and at 3-, 6-

and 12-months follow-up. All assessments will be conducted online. The primary outcome of the study will be general psychopathology as measured by the Strengths and Difficulties Questionnaire (SDQ). Secondary outcomes will include executive functioning ability as measured by online neuropsychiatric tasks, as well as day-to-day functioning and alcohol consumption as measured by standardised measures listed below. See Figure 1 for enrolment, assigned intervention, intervention and follow-up scheme.

Sample size calculations

The primary outcome measure will be scores on the self-report version of the Strengths and Difficulties Questionnaire (SDQ), a measure of psychopathology in young people with excellent psychometric properties [25] and test-retest reliability [26]. One previous pilot study has investigated the effect of cognitive training on psychopathology in at-risk young people using the SDQ [19]. According to this study, there was a between-group effect size of .36 for the SDQ. A similar effect size difference on the SDQ would therefore be expected in the current study. A total sample size of n = 140 (n=70 per group) is powered to have an 80% chance of detecting .36 effect size differences at $p < 0.5$. We will therefore aim to recruit n=220 (n=110 per group) in order to account for potential attrition.

Procedure

Participants and recruitment

Participants will be aged 16-24 years and at risk for a range of mental disorders. Participants will be included if they meet the following criteria: 1) at high risk for development of a mental illness based on elevated levels of personality risk factors, including hopelessness, anxiety sensitivity, impulsivity, and sensation seeking [as measured by the Substance Use Risk Profile Scale (SURPS), described below] ; 2) ability to access the internet via a computer; 4) residing

within Australia; and 3) willingness to provide contact details. Exclusion criteria will be: 1) insufficient English comprehension; 2) a lifetime mental illness diagnosis; 3) current involvement in psychotherapy or taking medication for mental illness, pain, thyroid problems and/or epilepsy; 4) intellectual disability; 5) a history of neurological or cardiovascular disorders, brain surgery, electroconvulsive or radiation treatment, thyroid disorders, brain haemorrhage or tumour, stroke, diabetes, seizures or epilepsy; and 6) significant previous experience with online cognitive training programs.

Community participants will be recruited through advertisements on social media platforms. Recruitment through social media has been shown to be effective and cost efficient, with obtained samples of similar representativeness as those recruited via traditional methods [27] and will indicate their interest by clicking on the advertisement, after which they will be taken to the study website (www.braingames.org) that provides more detailed information about the study. After reading this information, the participant continues onto eligibility screening which will be conducted through the study website. Online eligibility screening will assess for all exclusion and inclusion criteria, except for a prior diagnosis of a mental illness. If eligible, participants will then be contacted by a trained researcher from the University of New South Wales, Australia, who will conduct a telephone-administered diagnostic interview to assess for a lifetime diagnosis of major depressive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, alcohol dependence, other substance dependence, attention deficit hyperactivity disorder, conduct disorder and oppositional defiant disorder. Those who do not meet eligibility criteria after completion of the online or telephone-administered interviews will be informed of their ineligibility, and given referrals and/or information for crisis care where necessary. After telephone screening, eligible participants will be sent a link to complete the baseline assessment through the study website. Following baseline

assessment, participants will be given a unique code which will be randomly associated with one of the two cognitive training conditions. Randomisation of these codes to the intervention and control conditions will be conducted by an offsite technician who will allocate all unique codes to one of the two conditions through the website random.org. Both the research team and participant will be blind to this allocation. Participants will be free to withdraw from the study at any time, and will not be prohibited from seeking concomitant care. Those participants who do withdraw will not complete any further assessments. Enrolment into the study will be rolling, with each participant starting their training the day after they have completed their baseline tasks.

Participants will provide online consent for the internet-administered eligibility screening, as well as formal written consent for the diagnostic interview and participation in the study itself. Online and written consent forms have been included in Supplementary Files 1 and 2.

Intervention and control conditions

Both the intervention and control conditions will complete cognitive training consisting of computerised tasks provided by *Lumosity* (http://www.lumosity.com/), and administered on a remote internet-connected computer owned by the participant. All tasks within the commercially available *Lumosity* package have "game-like" features making them visually engaging and motivating. The tasks are designed to be dynamic and adaptive, such that the difficulty increases as the participants' performance improves. Training for both conditions will consist of an intensive program of ten games per day (~30-40 minutes), five days per week, over five weeks. Training compliance will be assessed during the active training phase, with reminder emails sent after one missed session, and a further email sent after two missed sessions. Non-compliance to the training protocol will be recorded if a participant: 1) misses four or more consecutive days of training; 2) completes less than 20 full sessions of training; or 3) is unable to complete their program within 6

weeks (42 days). However, post-training and follow-up data will be collected for non-compliant participants unless they formally withdraw from the study or are unable to be contacted. Given the non-invasive nature of the intervention, adverse events are not anticipated. Spontaneous reporting of adverse events will be discussed with the study clinicians and responded to according to their recommendations. Training games for the intervention group will specifically focus on executive functioning, and will be based on classic paradigms used in cognitive neuroscience and executive functioning batteries. The control group will be administered cognitive training games that do not target executive functioning, and instead focus on field of view, verbal fluency and quantitative reasoning. The features of the control tasks will be matched to those of the intervention tasks in all other respects. Tasks included in both the intervention and control training programs were selected on the basis of consensus ratings with experienced clinicians.

Assessment Occasions

Both those assigned to the intervention and to the control group will be assessed at baseline, post-trial, and at 3-, 6- and 12- month follow-up intervals. All assessments at each occasion will be fully automated and conducted online using the participants' own computer.

Measures

Eligibility screening

Demographic data on gender, age, country of birth and rurality will be collected online before eligibility is assessed. Eligibility screening will consist of a 23-item self-report online questionnaire assessing personality risk factors [the Substance Use Risk Profile Scale (SURPS)] [28], with four subscales representing hopelessness, anxiety sensitivity, impulsivity, and sensation seeking. Participants scoring one or more standard deviations above the mean on any of the four SURPS subscales will be deemed eligible for the current study. Threshold means and standard deviations

will be based on a previous validity study of the SURPS in Australian adolescents [23]. Scores on these subscales have been shown to reliably predict future substance use, as well as anxiety, emotional and behavioural disorders. The SURPS has been shown to have good concurrent and predictive validity, and the separate subscales display good specificity [29].

For those aged less than 18 years, the telephone-administered diagnostic interview for lifetime mental illnesses will be conducted using a lifetime version of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). The MINI-KID is a structured, lay-administered self-report diagnostic interview for children of ages 6 to 17 years old which is designed to assess DSM-IV psychiatric disorders. The MINI-KID has been shown to have excellent reliability and excellent concordance with clinician diagnoses [30]. For those aged 18 years and older, a lifetime version of the Mini International Neuropsychiatric Interview (MINI) will be administered. The MINI is also a structured, lay-administered self-report diagnostic interview designed to assess DSM-IV psychiatric disorders with excellent reliability and good concordance with a clinician-administered diagnostic interview [31, 32].

Baseline assessment

Psychopathology will be assessed using the SDQ, a 25-item self-report behavioural screening inventory for children and adolescents which measures positive and negative attributes of participants [33]. The SDQ has been used extensively and has strong psychometric properties [25]. The SDQ is also brief and multidimensional, providing information across a wide range of psychopathology as required for the current study. An online version of this questionnaire will be developed for the current study in consultation with the original SDQ developers. Recently, a young adult version of the SDQ has also been developed, with minor changes to the wording and scoring of the adolescent instrument. According to the developers of this instrument, it has been

used extensively in practice but validation studies of this instrument have only been published in special populations at present [34, 35]. The young adult version will also be used to assess psychopathology in those aged 18 years and over in the current study to allow continuity of measurement across the full sample.

An online version of the WHODAS 2.0 12-item version (World Health Organisation, 2010) will be used to assess overall functioning and disability experienced as a result of health conditions (including mental illness or substance use) over the past 30 days. The WHODAS has been used extensively as a measure of functioning and disability and has been validated for both online use and in individuals aged 16 years and over in the Australian population [36, 37].

Participants' recent and historical alcohol consumption will be assessed online by 14 questions adapted from the School Health and Alcohol Harm Reduction Project (SHAHRP) 'Patterns of Alcohol' index [38]. These questions ask responders about the frequency and quantity of different drinking behaviours, and age of first participation in these behaviours.

Online executive functioning assessment will be included as a measure of executive functioning improvement on untrained tasks. This assessment will consist of the N-Back Task [39] to evaluate working memory, the Trail Making Test [40] to assess task shifting, and the Stroop Task [41] to evaluate inhibitory control. These tasks will be administered using Inquisit software (http://www.millisecond.com/download/library/).

Participants will also be asked to answer an online questionnaire about their satisfaction with the training program.

Follow-up assessments

Each of the assessments at post-training, 3-, 6- and 12-months follow-up will consist of the online versions of the SDQ, SURPS, WHODAS and alcohol consumption questionnaires, as well as the online executive functioning assessment. At the 12-month assessment, data will also be collected on service use and any use of the *Lumosity* program over the follow-up period.

All data collected in computerised format will be stored on password protected computers in databases using pre-defined codes. Rigorous data encryption will restrict external access to participant online content. The website uses industry leading encryption for all transmissions. The SSL certificate includes domain authentication and 256-bit SSL encryption. HTTPS (SSL) will be used for complete website including all sub domains. A data access layer (DAL) is used for all database functionality requirements within the site with the majority of database connections set up with stored procedures.

Statistical Analysis

Data will be analysed on an intention-to-treat basis. All analyses will be undertaken using mixed-model repeated measures (MMRM) ANOVA, with measurement occasion as a within-groups factor, and experimental group as a between-groups factor. These models are robust to missing data under missing-at-random assumptions. Relationships between observations at different occasions will be modelled with an unstructured covariance matrix. For each experimental group, planned contrasts will be used to compare changes from baseline to post-test, 3-, 6- and 12- month follow-up intervals. Given the high rates of attrition expected, secondary analyses will also be conducted for all outcome variables on a per-protocol basis.

Ethics and dissemination

Ethical approval for the *Brain Games* study has been granted from the UNSW Human Research Ethics Committee (HC15094). Any protocol amendments will first be discussed by the team of investigators after which an ethics modification will be submitted.

Results of the trial immediately post-treatment and at 12-months follow-up will be submitted for publication in peer-reviewed journals. After all study data has been collected, all participants will receive a document outlining the main results of the study. All lead investigators will be listed as authors on all publications unless they opt out of authorship.

The de-identified dataset generated and analysed during the current study are available from the corresponding author on reasonable request.

Discussion

The present study protocol presents the design of a randomised controlled trial that assesses whether online executive functioning training is a viable strategy for the targeted prevention of mental illness and substance use in high-risk youth. The primary aim of the *Brain Games* trial is to investigate whether an executive functioning training program is more effective at preventing symptoms of psychopathology than cognitive training that has limited executive functioning training potential. By investigating a novel prevention strategy targeting executive functioning, the *Brain Games* study will be the first full-scale trial conducted internationally that investigates the utility of cognitive training in the prevention of mental illness in high-risk adolescents. This study targets underlying executive functioning deficits that have been identified across the boundaries of traditional categorical psychiatric diagnoses.

Novel universal prevention programs that cross diagnostic boundaries are currently being trialled in Australian schools [42]. For high-risk adolescents, however, universal prevention programs have been shown to have limited benefits [43]. In terms of practical applications, it is envisaged that transdiagnostic prevention strategies that target high-risk adolescents, such as the present one, would eventually complement and augment a transdiagnostic approach to school-based universal prevention. This stepped-care sequential prevention model has the potential to maximize outcomes for both high- and low-risk students across a range of mental illnesses and reduce the considerable burden of disease associated with these illnesses in adolescence.

Declarations

Authors' contributions

LM is the Chief Investigator of the *Brain Games* study. AH and NG provide clinical and neuropsychological expertise and MT provides expertise in prevention research. LM, AH, NG and MT were all involved in the study design. LM and RV are involved in data collection. All authors will be involved in the reporting of the study results. LM and RV wrote the first draft of the manuscript. All authors provided feedback on subsequent drafts and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Figure 1 Flowchart of the randomised control trial: enrolment, assigned intervention, intervention and follow-up scheme

References

1. Murray, C.J., et al., *Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2013. **380**(9859): p. 2197-2223.
2. Merikangas, K.R., et al., *Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A).* Journal of the American Academy of Child & Adolescent Psychiatry, 2010. **49**(10): p. 980-989.
3. Kessler, R., et al., *Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A).* Psychological Medicine, 2012. **42**(09): p. 1997-2010.
4. Lewis, D.A., *Cortical circuit dysfunction and cognitive deficits in schizophrenia–implications for preemptive interventions.* European Journal of Neuroscience, 2012. **35**(12): p. 1871-1878.
5. Giedd, J.N., M. Keshavan, and T. Paus, *Why do many psychiatric disorders emerge during adolescence?* Nature Reviews Neuroscience, 2008. **9**(12): p. 947-957.
6. Crews, F., J. He, and C. Hodge, *Adolescent cortical development: a critical period of vulnerability for addiction.* Pharmacology, Biochemistry & Behavior, 2007. **86**(2): p. 189-99.
7. Vinogradov, S., M. Fisher, and E. de Villers-Sidani, *Cognitive training for impaired neural systems in neuropsychiatric illness.* Neuropsychopharmacology, 2011. **37**(1): p. 43-76.
8. Goodkind, M., et al., *Identification of a common neurobiological substrate for mental illness.* JAMA psychiatry, 2015. **72**(4): p. 305-315.
9. Shanmugan, S., et al., *Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth.* American journal of psychiatry, 2016. **173**(5): p. 517-526.
10. Valkanova, V., R.E. Rodriguez, and K.P. Ebmeier, *Mind over matter-what do we know about neuroplasticity in adults?* International Psychogeriatrics, 2014. **26**(6): p. 891.
11. Cramer, S.C., et al., *Harnessing neuroplasticity for clinical applications.* Brain, 2011. **134**(6): p. 1591-1609.
12. Keshavan, M.S., et al., *Cognitive training in mental disorders: update and future directions.* American Journal of Psychiatry, 2014. **171**(5): p. 510-522.
13. Revell, E.R., et al., *A systematic review and meta-analysis of cognitive remediation in early schizophrenia.* Schizophrenia research, 2015. **168**(1): p. 213-222.
14. Lee, R., et al., *Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients.* Psychological medicine, 2013. **43**(06): p. 1161-1173.
15. Wykes, T., et al., *A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes.* American Journal of Psychiatry, 2011. **168**(5): p. 472-485.
16. Medalia, A. and A.M. Saperstein, *Does cognitive remediation for schizophrenia improve functional outcomes?* Current Opinion in Psychiatry, 2013. **26**(2): p. 151-157.
17. Hetrick, S., et al., *Early identification and intervention in depressive disorders: towards a clinical staging model.* Psychotherapy and psychosomatics, 2008. **77**(5): p. 263-270.
18. McGorry, P.D., *Staging in neuropsychiatry: a heuristic model for understanding, prevention and treatment.* Neurotoxicity research, 2010. **18**(3-4): p. 244-255.
19. Roughan, L. and J.A. Hadwin, *The impact of working memory training in young people with social, emotional and behavioural difficulties.* Learning and Individual Differences, 2011. **21**(6): p. 759-764.
20. Hooker, C.I., et al., *A pilot study of cognitive training in clinical high risk for psychosis: initial evidence of cognitive benefit.* Schizophrenia research, 2014. **157**: p. 314.
21. Piskulic, D., et al., *Pilot study of cognitive remediation therapy on cognition in young people at clinical high risk of psychosis.* Psychiatry research, 2015. **225**(1): p. 93-98.
22. Shipstead, Z., T.S. Redick, and R.W. Engle, *Is working memory training effective?* Psychological bulletin, 2012. **138**(4): p. 628.
23. Newton, N.C., et al., *The validity of the Substance Use Risk Profile Scale (SURPS) among Australian adolescents.* Addictive behaviors, 2016. **53**: p. 23-30.
24. Castellanos, N. and P. Conrod, *Brief interventions targeting personality risk factors for adolescent substance misuse reduce depression, panic and risk-taking behaviours.* Journal of Mental Health, 2006. **15**(6): p. 645-658.
25. Goodman, R., *Psychometric properties of the strengths and difficulties questionnaire.* Journal of the American Academy of Child & Adolescent Psychiatry, 2001. **40**(11): p. 1337-1345.
26. Hawes, D.J. and M.R. Dadds, *Australian data and psychometric properties of the Strengths and Difficulties Questionnaire.* Australian and New Zealand Journal of Psychiatry, 2004. **38**(8): p. 644-651.
27. Thornton, L., et al., *Recruiting for health, medical or psychosocial research using Facebook: systematic review.* Internet Interventions, 2016. **4**: p. 72-81.

28. Woicik, P.A., et al., *The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles.* Addictive behaviors, 2009. **34**(12): p. 1042-1055.
29. Castellanos-Ryan, N., et al., *Sensitivity and specificity of a brief personality screening instrument in predicting future substance use, emotional, and behavioral problems: 18-month predictive validity of the substance use risk profile scale.* Alcoholism: Clinical and Experimental Research, 2013. **37**(s1): p. E281-E290.
30. Sheehan, D.V., et al., *Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID).* The Journal of clinical psychiatry, 2010. **71**(3): p. 313-326.
31. Lecrubier, Y., et al., *The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI.* European psychiatry, 1997. **12**(5): p. 224-231.
32. Sheehan, D., et al., *The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability.* European Psychiatry, 1997. **12**(5): p. 232-241.
33. Goodman, R., H. Meltzer, and V. Bailey, *The Strengths and Difficulties Questionnaire: A pilot study on the validity of the self-report version.* European child & adolescent psychiatry, 1998. **7**(3): p. 125-130.
34. Glenn, S., et al., *Using the strengths and difficulties questionnaire with adults with Down syndrome.* Research in developmental disabilities, 2013. **34**(10): p. 3343-3351.
35. Findon, J., et al., *Screening for co-occurring conditions in adults with autism spectrum disorder using the strengths and difficulties questionnaire: A pilot study.* Autism Research, 2016. **9**(12): p. 1353-1363.
36. Kimber, M., J. Rehm, and M.A. Ferro, *Measurement Invariance of the WHODAS 2.0 in a population-based sample of youth.* PloS one, 2015. **10**(11): p. e0142385.
37. Andrews, G., et al., *Normative data for the 12 item WHO Disability Assessment Schedule 2.0.* PloS one, 2009. **4**(12): p. e8343.
38. McBride, N., et al., *Harm minimization in school drug education: final results of the School Health and Alcohol Harm Reduction Project (SHAHRP).* Addiction, 2004. **99**(3): p. 278-291.
39. Jaeggi, S.M., et al., *The concurrent validity of the N-back task as a working memory measure.* Memory, 2010. **18**(4): p. 394-412.
40. Reitan, R.M., *Validity of the Trail Making Test as an indicator of organic brain damage.* Perceptual and motor skills, 1958. **8**(3): p. 271-276.
41. Stroop, J.R., *Studies of interference in serial verbal reactions.* Journal of experimental psychology, 1935. **18**(6): p. 643.
42. Teesson, M., et al., *The CLIMATE schools combined study: a cluster randomised controlled trial of a universal Internet-based prevention program for youth substance misuse, depression and anxiety.* BMC psychiatry, 2014. **14**(1): p. 32.
43. Faggiano, F., et al., *School-based prevention for illicit drugs use: A systematic review.* Preventive medicine, 2008. **46**(5): p. 385-396.

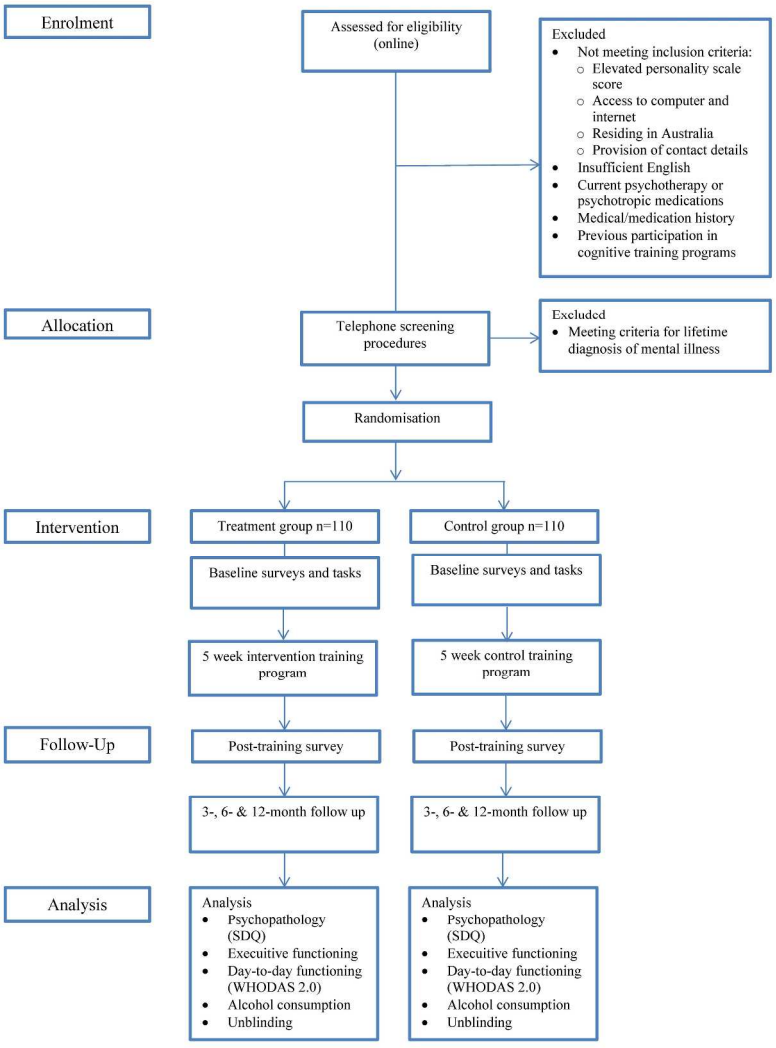

Figure 1 Flowchart of the randomised control trial: enrolment, assigned intervention, intervention and follow-up scheme

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ONLINE PARTICIPANT INFORMATION STATEMENT

The Brain Games Study

Dr Louise Mewton

The research study is being carried out by the following researchers:		
Role	**Name**	**Organisation**
Chief Investigator	Dr Louise Mewton	University of New South Wales
Co-Investigator/s	Dr Nicola Gates, Dr Antoinette Hodge & Professor Maree Teesson	Westmead Children's Hospital and University of New South Wales
Research Funder	This research is being funded by Australian Rotary Health and the Australian National Health and Medical Research Council.	

What is the research study about?

Thank you for your interest in the Brain Games study. Researchers at The University of New South Wales are seeking volunteer research participants to learn about whether brain training ("Brain Games") can reduce risky behaviours, anxiety and negative emotions which may lead to mental illness in the future.

Would the research project be a good fit for me?

The study might be a good fit for you if:

- You report risky behaviours, or experience high anxiety or negative emotions
- You have ready access to an internet computer
- You are willing to provide the researchers with a current phone number and email address

The study will not be a good fit for you if:

- You meet criteria for an anxiety, mood or substance use disorder, or report certain medical conditions

Do I have to take part in this research study?

This Participant Information Statement tells you about the research study. It explains the research tasks involved. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. Before deciding whether or not to take part, you might want to talk about it with a relative or friend. Participation in this research is voluntary. If you don't wish to take part, you don't have to. Your decision will not affect your relationship with The University of New South Wales.

What does participation in this research require, and are there any risks involved?

Before you begin any activities we need to do ask some more questions to understand whether it is ok for you to take part. Once you complete this consent form, you will be asked to complete an online questionnaire about yourself, your personality and any medical conditions you might have. This questionnaire will take about five minutes to complete and will be used to determine whether or not you are able to take part in the study. If you are able, we will ask you for your email address and contact number and a researcher will contact you and ask further eligibility questions over the telephone. If you are not able, we will provide you with the details of relevant healthcare professionals should you feel the need to speak with someone after the online or telephone administered questionnaires.

If you are able to participate in the study, you will be randomly assigned to one of two different training groups. Both groups will be asked to complete an online Brain Games program. We will ask you to do the program for a maximum of one hour every weekday for a total of five weeks. In total, the program will take a maximum of 25 hours. We will also ask you to complete some questionnaires and tasks before and after the Brain Games

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ONLINE PARTICIPANT INFORMATION STATEMENT
The Brain Games Study
Dr Louise Mewton

program, and then 3 months, 6 months and 12 months after you have finished the Brain Games program. We expect that each set of questionnaires and tasks will take up to an hour to complete so we expect you will spend a total of 5 hours doing these over the course of a year.

What will happen to information about me?

By clicking on the 'I agree' button you consent to the research team collecting and using information from the screening questionnaires you complete for the research study. If you are eligible for the study, we will keep your confidential data for 7 years. Any information obtained in connection with this research study that can identify you will remain confidential. If you are not eligible for the study, your data will be withdrawn.

What if I want to withdraw from the research study?

Submitting your completed questionnaire is an indication of your consent to participate in the study. You can withdraw your responses if you change your mind about having them included in the study, up to the point that we have analysed and published the results. You can do this by submitting the online Withdrawal of Participation form or contact Dr Louise Mewton any time by phone (02 8936 1131) or email (louisem@unsw.edu.au).

What should I do if I have further questions about my involvement in the research study?

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the following member/s of the research team:

Research Team Contact

Name	Dr Louise Mewton
Position	Research Officer
Telephone	02 8936 1131
Email	louisem@unsw.edu.au

If at any stage during the project you become distressed or require additional support from someone not involved in the research please call:

Contact for feelings of distress

Name/Organisation	Kids Helpline
Telephone	1800 551 800
Email	www.kidshelp.com.au

If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Complaints Contact

Position	Human Research Ethics Coordinator
Telephone	+ 61 2 9385 6222
Email	humanethics@unsw.edu.au
HC Reference Number	XXXX

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ONLINE PARTICIPANT INFORMATION STATEMENT

The Brain Games Study

Dr Louise Mewton

Consent Form – Participant providing own consent

Declaration by the participant

- ☐ I have read the Participant Information Sheet;
- ☐ I understand the purposes, study tasks and risks of the research described in the project;
- ☐ I have had an opportunity to ask questions and I am satisfied with the answers I have received;
- ☐ I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the project and withdrawal will not affect my relationship with any of the named organisations and/or research team members;
- ☐ I understand that I can download a copy of this consent form from www.braingames.org.au.

Participant Details

Name of Participant (please type)	
Participant email address (if applicable)	
Date	

I agree, start questionnaire

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ONLINE PARTICIPANT INFORMATION STATEMENT

The Brain Games Study

Dr Louise Mewton

Form for Withdrawal of Participation

I wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** affect my relationship with The University of New South Wales.

Participant Name

Name of Participant (please type)	
Date	

Submit withdrawal of consent

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

The Brain Games Study

Dr Louise Mewton

The research study is being carried out by the following researchers:		
Role	**Name**	**Organisation**
Chief Investigator	Dr Louise Mewton	University of New South Wales
Co-Investigator/s	Dr Nicola Gates, Dr Antoinette Hodge & Professor Maree Teesson	Westmead Children's Hospital and University of New South Wales
Research Funder	This research is being funded by Australian Rotary Health and the Australian National Health and Medical Research Council.	

What is the research study about?

You are invited to take part in this online research study. You have been invited because of certain behaviours or emotions you reported in response to our questionnaire.

To participate in this research study you need to meet the following inclusion criteria:
1) the experience of risky behaviours, high anxiety or negative emotions; 2) be able to access the internet readily via a desktop or laptop computer (either in your home, or willingness to use public library/other suitable venue with internet access); 3) be willing to provide current email address and phone number. You will not be able to take part in this study if you meet criteria for an anxiety, mood or substance use disorder, if you take certain medications, or have certain medical conditions.

The research study is aiming to determine whether brain training in the form of online games ("Brain Games") can reduce risky behaviours, anxiety and negative emotions which may lead to mental illness in the future.

Do I have to take part in this research study?

This Participant Information Statement tells you about the research study. It explains the research tasks involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. If there is anything that you don't understand or want to know more about please feel free to contact the research team. Before deciding whether or not to take part, you might want to talk about it with a relative or friend.

If you decide you want to take part in the research study, you will be asked to:

- Type your name into the boxes at the bottom of this consent form ;
- Keep a copy of this Participant Information Statement;

What does participation in this research require, and are there any risks involved?

Before you begin any activities we need to do ask some more questions to understand whether it is ok for you to take part. In order to do this we will contact you by telephone and ask you to answer questions about your feelings and behaviours, including substance use. It is expected that these questions will take about half an hour for you to complete. If you are not suitable for the study, we will let you know over the telephone, provide you with information for services should you need them, and withdraw all your data from the study.

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

The Brain Games Study
Dr Louise Mewton

If you are suitable for the study, you will be randomly assigned to one of two different training groups. Both groups will be asked to complete an online Brain Games program. We will ask you to do the program for a maximum of one hour every weekday for a total of five weeks. In total, the program will take a maximum of 25 hours. The Brain Games program is like a computer game, and we expect that you will find the Brain Games sessions fun as well as challenging. Before and after you have completed your online Brain Games sessions we will ask you to complete online and telephone-administered questionnaires about your feelings and behaviours, including substance use, as well as some tasks that will tell us about your different abilities. We will also ask you to complete these same questionnaires and tasks 3 months, 6 months and 12 months after you have finished the Brain Games program. We expect that each set of questionnaires and tasks will take up to an hour to complete so we expect you will spend a total of 5 hours doing these over the course of a year. At the end of the study we want to compare the two different Brain Games programs to see whether one is better than the other in terms improving any negative feelings or risky behaviours you might be experiencing. At the moment, we are not sure if one program is better than the other, or whether you will benefit from participating in this study.

We do not expect there to be any risks associated with completing the Brain Games program. It is possible you might experience some distress when answering the questionnaires that ask about sensitive topics. If you do experience distress you will be encouraged to contact the research team and you will be given contact information for services equipped to deal with any distress you might be experiencing.

Will I be paid to participate in this project?

You will be reimbursed $50 for taking the time to complete the Brain Games program. After you have completed all the questionnaires you will also go into a draw to win an iPad.

What are the possible benefits to participation?

We hope to use information we get from this research study to benefit others who might also behave in risky ways or experience anxiety or negative emotions.

What will happen to information about me?

By typing your name into this form, you consent to the research team collecting and using information from the questionnaire you complete for the research study. We will keep your confidential data for 7 years. Any information obtained in connection with this research study that can identify you will remain confidential. This project will use an external site to create, collect and analyse data collected in a questionnaire format. The site we are using is www.braingames.org.au. If you agree to participate in this study, the responses you provide to the questionnaire will be stored on a host server that is used by Indigo hosting. Once we have completed our data collection and analysis, we will import the data we collect to the UNSW server. The data on the Indigo hosting server will then be deleted.

It is anticipated that the results of this research study will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your research findings may be published, but you will not be individually identifiable in these publications.

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UNSW AUSTRALIA

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

The Brain Games Study

Dr Louise Mewton

How and when will I find out what the results of the research study are?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by emailing the study co-ordinator, Dr Louise Mewton (louisem@unsw.edu.au). This feedback will be in the form of a one page report. You will receive this feedback after the study is finished.

What if I want to withdraw from the research study?

If you do consent to participate, you may withdraw at any time. If you do withdraw, you will be asked to complete and sign the 'Withdrawal of Consent Form' which is provided at the end of this document. Alternatively you can contact the research team and tell them you no longer want to participate.

If you decide to withdraw from the study, we will not collect any more information from you. Please let us know at the time when you withdraw what you would like us to do with the information we have collected about you up to that point. If you wish your information will be removed from our study records and will not be included in the study results, up to the point that we have analysed and published the results.

What should I do if I have further questions about my involvement in the research study?

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the following member/s of the research team:

Research Team Contact

Name	Dr Louise Mewton
Position	Research Officer
Telephone	02 8936 1131
Email	louisem@unsw.edu.au

If at any stage during the project you become distressed or require additional support from someone not involved in the research please call:

Contact for feelings of distress

Name/Organisation	Kids Helpline
Telephone	1800 551 800
Email	www.kidshelp.com.au

What if I have a complaint or any concerns about the research study?

If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Complaints Contact

Position	Human Research Ethics Coordinator
Telephone	+ 61 2 9385 6222
Email	humanethics@unsw.edu.au
HC Reference Number	HC15094

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The Brain Games Study
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Consent Form – Participant providing own consent

Declaration by the participant

☐I have read the Participant Information Sheet or someone has read it to me in a language that I understand;

☐I understand the purposes, study tasks and risks of the research described in the project;

☐I have had an opportunity to ask questions and I am satisfied with the answers I have received;

☐I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the project and withdrawal will not affect my relationship with any of the named organisations and/or research team members;

☐I understand that I will be given a signed copy of this document to keep;

Participant Signature

Name of Participant (please type)	
Please type name again (this will be taken as your signature)	
Date	

Declaration by Researcher*

☐ I have given a verbal explanation of the research study, its study activities and risks and I believe that the participant has understood that explanation.

Researcher Signature*

Name of Participant (please print)	
Signature of Research Participant	
Date	

*An appropriately qualified member of the research team must provide the explanation of, and information concerning the research study.

Note: All parties signing the consent section must date their own signature.

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PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

The Brain Games Study

Dr Louise Mewton

Form for Withdrawal of Participation

I wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** affect my relationship with The University of New South Wales.

Participant Signature

Name of Participant (please type)	
Signature of Research Participant (please type name)	
Date	

The section for Withdrawal of Participation should be forwarded to:

CI Name:	Louise Mewton
Email:	louisem@unsw.edu.au
Phone:	02 8936 1131

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (pg 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (pg 2)
	2b	All items from the World Health Organization Trial Registration Data Set (pg 2)
Protocol version	3	Date and version identifier (footer)
Funding	4	Sources and types of financial, material, and other support (pg 16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pg 1 & 15)
	5b	Name and contact information for the trial sponsor (N/A)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (pg 16)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (N/A)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (pg 4-8)
	6b	Explanation for choice of comparators (pg 11)
Objectives	7	Specific objectives or hypotheses (pg 8)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pg 8)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (10-11)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (pg 9-10)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (p 11)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (p 11)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (p 11)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (p 11)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (p 9)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (p 11-12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (p 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (p 10)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (pg 10-11)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (pg 10-11)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (pg 10-11)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (pg 10-11)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (pg 10-11)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (pg 12-14)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (pg 11)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (p. 14)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (pg 14-15)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pg 14-15)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (pg 14)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (pg 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (n/a)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (pg 11)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (n/a)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (pg 15)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (pg 15)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (pg 10)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (pg 14)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (pg 16-17)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (pg 15)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (n/a)

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (pg 15)
	31b	Authorship eligibility guidelines and any intended use of professional writers (pg 15)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (pg 15)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (see Appendix)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (n/a)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.