**TITLE: Personalised treatment in depression: Improving cognitive, emotional and social function**

INVESTIGATOR DETAILS & QUALIFICATIONS

**Prof. Bernhard T Baune** PhD, MD, MPH, FRANZCP: extensive clinical and research experience in mood disorders and cognitive dysfunction disorders.

Clinical Interview: in both clinical and research practice Prof Baune has utilised clinical diagnostic interview protocols extensively over many years.

Neuropsychological Assessments: neuropsychological function is a key area of Prof Baune’s research focus and as such he has been involved in extensive use of a range of neuropsychological tests batteries including those being utilised in this study.

Specimen Collection: as a medically trained doctor Prof Baune has experience in blood collection and has extensive laboratory experience in blood preparation and analysis.

Self-Report Questionnaires: Prof Baune has utilised self-report psychometric assessments in research and clinical environments for many years. He is well versed in their use, scoring, interpretation, and statistical analysis.

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**Matthew Knight,** Bachelor of Psychology (Honours), Current PhD candidate: Mr Knight has submitted a PhD in experimental cognitive psychology and has experience with measurement of cognitive performance. Prior to his involvement in data collection Mr Knight will undergo additional training in the use of self-report measures, neuropsychological assessment, clinical diagnostic interviews and blood collection.

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**AIMS OF STUDY**

The primary aim of the study is

1. To evaluate the clinical effectiveness of a training program (CERT) intended to improve psychosocial functioning in individuals suffering from depression using a novel intervention. It is expected that cognitive, emotional and social cognitive treatment will result in improved psychosocial functioning at 8 weeks (i.e., end of RCT) relative to baseline, which will be maintained at 3 and 6 month post-RCT assessments.

The secondary aims of the study are

1. To test the overall effect of the intervention by comparing baseline psychosocial functioning to psychosocial functioning at 6 months post-RCT

2. To evaluate the effects of the intervention on subdomains of psychosocial functioning (e.g., autonomy, leisure and interpersonal relationships) (8 weeks relative to baseline).

3. To evaluate whether the intervention will lead to improvements in occupational functioning, resilience, and functional disability (e.g., home responsibilities).

4. To evaluate whether the intervention will lead to reduction in depression symptom severity and whether symptomatic recovery is maintained at 3 and 6 months post-RCT.

5. To determine whether a personalised treatment approach is beneficial relative to a standard battery of treatment tasks. We hypothesise that personalised treatment will lead to greater improvement in psychosocial functioning relative to standard treatment.

6. To associate blood serum concentration of the immune biomarkers (Il-1, Il-2, Il-6, Il-8, Il-10, TNF-alpha and CRP), neurotransmitters and stress biomarkers (5HT, DA, NE, BDNF, CRF) plus corresponding single nucleotide polymorphisms with psychosocial functional outcomes and cognitive, emotional and social cognitive functioning.

**BACKGROUND AND PRELIMINARY STUDIES**

**Introduction**

Depression is the leading cause of mental illness worldwide, affecting approximately 322 million individuals (WHO, 2017). The illness is characterised by prolonged negative mood, anhedonia and impaired cognition. Depressed individuals also demonstrate significantly impaired psychosocial function, indicated by diminished organisational, occupational and social ability (Baune & Renger, 2014; Godard, Baruch, Grondin, & Lafleur, 2012). In addition to the substantial burden of depression on the daily lives of individuals (Beblo, Kater, Baetge, Driessen, & Piefke, 2017) depression impacts on a societal level by reducing occupational productivity (Elgamal, McKinnin, Ramakrishnan, Joffe, & MacQueen, 2007). Established therapies (e.g., psychotherapy, CBT) and pharmaceutical treatments are costly and lead to high rates of recurrence in the long term (Nemeroff et al., 2003). As a consequence, there is a clear need to develop alternative and/or complimentary treatments for depression.

It is possible that existing treatments for depression underperform because they do not sufficiently address psychosocial functioning. Psychosocial function can be defined on a micro level as our day-to-day ability to contend with environmental and social tasks (e.g., maintaining work and relationships), and on a macro level as the pursuit of significant life outcomes (e.g., self-actualisation) (Ro & Clark, 2009). Previous work has operationalised these dimensions, such that quantitative and psychometrically valid assessments of psychosocial impairment have been established (Cacilhas et al., 2009; Ro & Clark; Rosa et al., 2007). For example, the Functioning Assessment Short Test (FAST) measures psychosocial disability in six domains; autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time.

Previous work has suggested that psychosocial functioning is related to a number of other functional outcomes (e.g., positive future outlook, ability to derive pleasure from life events), suggesting that psychosocial function may contribute to mental health in general (Goštautas, Pranckevičienė, Matonienė, 2006; Papakostas et al., 2004). Existing treatments for depression do not sufficiently address psychosocial dysfunction (Baune & Renger, 2014; Ro & Clark, 2009), as demonstrated by functional issues in symptomatically recovered patients (Godard et al., 2012). Ongoing psychosocial dysfunction may lead to recurrent episodes of depression, as impaired functioning negatively interacts with cognitive and emotional vulnerability in previously depressed individuals (Baune & Air, 2016; Baune & Renger, 2014; Jaeger et al., 2006; Raes, Williams, & Hermans, 2009).

In sum, current literature suggests that researchers developing new treatments for depression should consider psychosocial functioning as a primary outcome, and evaluate whether targeting psychosocial functioning leads to reduced symptomology and lasting remission. Existing evidence has indicated that cognitive, emotional and social cognitive factors underlie (i.e., cause) deficits in psychosocial functioning (Baune et al., 2010; Jaeger et al., 2006; Papakostas et al., 2004; Raes et al., 2009; Weightman, Air, & Baune, 2014). The proposed study follows this model, stipulating that improvements in cognitive, emotional and social cognitive functioning should flow on to improvements in psychosocial functioning, and hence improve treatment outcomes. The following paragraphs explore the cognitive, emotional and social cognitive domains in more details and provide explanations for their underlying roles in psychosocial functioning.

**Cognitive impairment**

According to DSM-5 criteria the cognitive symptoms of Major Depressive Disorder (MDD) are impaired decision making, management of attention, and coordination and maintenance of information in working memory (American Psychiatric Association, 2013). These deficits can be operationalised as functions of the central executive (Baddeley, 1983; Christopher & MacDonald, 2005; Westheide et al., 2008), which manages complex and multimodal working memory tasks. However, there is evidence that cognitive deficits in depressed persons are not restricted to executive functioning. Research has identified deficits in verbal ability (Garcia-Toro et al., 2003), visuospatial processing (Mondal, Sharma, Das, Goswami, & Ganshi, 2007), and psychomotor speed (Mondal et al., 2007). The finding that cognitive deficits occur across multiple domains suggests that depression interferes with underlying cognitive faculties, and with the coordination of cognitive subsystems, rather than interfering a specific modality of cognition. Underlying deficits in working memory and attention can be understood as features of “cold cognition”, as they describe mental impairment free of affective or personal information. Issues in cold cognition may flow on to impair functioning in “hot” cognitive tasks (i.e., those tasks affected by emotional state). For example, deficits in sustained attention may cause depressed individuals to miss positive affective information (e.g., a compliment from a co-worker), or focus on information which reaffirms an existing negative bias. Our ability to complete hot cognitive tasks is crucial to daily functioning, and to the severity of several cognitive difficulties associated with depression (e.g., over-reacting to negative feedback). Cognitive treatment targets improvement of cold cognition, with the rationale that increasing functioning will benefit performance in hot cognitive tasks, and hence improve experience of everyday life, psychosocial functioning and day-today functioning.

Current literature suggests that cognitive impairment is retained even after patients are remitted of depression diagnosis (Godard et al., 2012; Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007), suggesting that cognitive issues occur independently of depressive episodes (Baune & Air, 2016). The retention of cognitive impairment after diagnostic recovery may contribute to subsequent episodes of depression, as impaired cold cognitive functioning interacts in a negative feedback cycle with hot cognitive tasks eventually leading to recurrent depression. Training cognition may therefore be critical not only in symptom relief but also in reducing the rate of recurrent depression in recovered patients, which has traditionally been very high. In fact an analysis by Keller and Boland (1998) suggested that over 60% of recovered depression patients suffered subsequent episodes of depression in the decade following their initial treatment. These findings are consistent with the notion that alleviating the diagnostic dimensions of depression does not implicitly lead to improvement of cognition, and that separate cognitive treatment is needed.

Psychosocial and cognitive impairments in depression and in other illnesses are associated with elevated levels of several inflammatory cytokines (Hannestad, DellaGioia, & Bloch, 2011; McAfoose & Baune, 2009. Leading research by our team (Baune et al., 2008a) demonstrated that IL-8, IL-1beta and tumor necrosis factor (TNF) are associated with memory, processing speed and motor function in the elderly. In addition, inflammatory C-reactive protein (CRP) may also be associated with depression symptoms (Howren, Lamkin et al. 2009), and the neuro transmitters 5HT, DA and NE appear to be related to psychological stress (Wilson, Ebenezer, McLaughlin, & Francis, 2014). Investigating biomarkers for psychosocial functioning and cognitive dysfunction presents a valuable area for research, as there is potential for developing objective measurements of dysfunction predisposition, for improving our understanding of the neurological mechanisms of depression and associated poor psychosocial functioning (e.g., neurotrophic theory), and for improving pharmacological treatments that address not only symptoms of depression but also psychosocial functioning and workplace functioning. Existing evidence suggest that biomarkers of neuropsychological dysfunction are sensitive to antidepressant treatment (Hannestad et al., 2011; McAfoose & Baune, 2009), however there is much less research on the sensitivity of biomarkers to cognitive interventions in depression. One review suggested that inflammatory biomarkers are reduced by CBT (Lopresti, 2017), however the presence and magnitude of this effect was not consistent. As a result, the effect of cognitive treatment on biomarkers of stress and inflammation associated with mood, cognitive symptoms and psychosocial functioning is not well established. The current study provides an opportunity to expand our knowledge of this domain.

A large body of work has investigated the selective treatment of impaired cognition in depression with cognitive remediation programs (Baune & Renger, 2014; Elgamal, McKinnon, Ramakrishnan, Joffe, & MacQueen, 2007; Lee, Hermens, Porter, Redoblado-Hodge, 2011). Cognitive remediation typically involves repeated completion of cognitive tasks over several weeks with the aim of targeted improvement in the domain of the training task. The results of such programs generally reveal that patients improve on measures of executive, visuospatial and verbal function (Baune & Renger). These results support the theory that repeated activation of brain regions via cognitive treatment increases neuroplasticity and improves neural function (Maples & Velligan, 2008). Although cognitive gains following remediation programs are relatively consistent, the transfer of this benefit to occupational function, resilience and psychosocial functioning are not well established (Baune et al., 2010). Some research has suggested that cognitive remediation leads to broad improvement in psychosocial functioning and other functional domains (Jaeger et al., 2006), whereas other studies have not found generalisation of cognitive improvements (Kesler et al., 2013). Further research is needed to clarify this point. It is possible that transfer of cognitive skills does not reliably occur because remediation programs do not focus on improvement of impaired social cognitive skills and emotional processing, which mutually interact with general cognition in a detrimental manner on depression symptoms (Weightman et al., 2014). The following paragraphs discuss the role of emotion processing and social cognition in MDD, and highlight how an integrated and personalised treatment approach may be critical to maximising treatment outcomes.

**Emotion**

Our experience of emotion is fundamentally linked to cognition. Evidence for this link is demonstrated by neuroimaging research, which has found overlap in activation patterns of cognitive processes and emotional experience (Shackman et al., 2011; Raz et al., 2012, 2014). It is implied that cognition and emotion occur in shared neural networks, such that our cognitive functioning and affect are not dissociable entities. This conclusion is consistent with cognitive models of depression (Beck, 2008), which stipulate that interplay between cognitive vulnerability and negative emotion both lead to and sustain MDD. Specifically, cognitive models stipulate that attention and memory systems are biased to focus on negative information, suppress adaptive coping strategies (e.g., flexibility), and encourage maladaptive strategies (e.g., rumination) (Joorman & Vanderlin, 2014). The critical importance of emotion processing in coping and information processing supports the importance of this factor in determining overall psychosocial functioning (Baune et al., 2010)

The close overlap between emotion and cognition suggests that cognitive remediation should not neglect the role of emotion in treatment programs (Young et al., 2012). It stands to reason that efforts to improve function in only one of these domains will suffer negative feedback from the other domain in the long term. Remediation programs should therefore make efforts to address emotional deficits, as improving emotional function in conjunction with cognition may lead to more effective and longitudinal therapeutic benefit. Ideally, cognitive-emotional treatment should aim to use tasks which activate neural networks shared by the emotion of interest, to encourage mutual reinforcement of cognitive-emotional networks (Iacoviello & Charney, 2015).

Previous work in cognitive-emotional treatment has shown promising results in the implementation of working memory tasks with valenced stimuli (Iacoviello & Charney, 2015; Iacoviello et al., 2014). Iacoviello et al. (2014) conducted a study comparing the benefit of a cognitive-emotional task with that of a cold cognitive task for subjects with MDD. The cognitive-emotional task involved performing an emotional *n*-back task, which the authors named the Emotional Face Memory Task (EFMT). Specifically, subjects were presented with a series of faces which portrayed particular emotions (e.g., happiness, surprise, disgust). The task was to identify which emotion was portrayed on each face, and to state whether this emotion matched the emotion portrayed by a face earlier in the sequence. The cold cognition task was also an *n*-back, however shapes were used to ensure stimuli were neutral (i.e., non-emotional). The results showed that compared to the neutral *n*-back, the EFMT resulted in greater reduction in depression symptoms and reduced negative self-referential bias. In contrast, both tasks resulted in similar gains in attention and working memory performance. These findings are consistent with the notion that cognition and emotion are closely linked, and imply that integrating emotion processing tasks in cognitive remediation may improve treatment outcomes.

**Social Cognition**

Social cognition refers to the perception, identification and interpretation of social information in interpersonal interaction (Weightman et al., 2014). Maintaining function in this domain involves incorporating information from a range of social cues including prosody, facial expression, body language, verbal content and theory of mind. Research has identified that social cognition may be impaired in individuals with depression, though the social cognitive deficit is less severe than in other psychiatric illnesses (e.g., schizophrenia, autism spectrum disorder) (Kandalaft et al., 2012; Holdnack, Goldstein, & Drozdick, 2011). However, social cognition deficits in depression should not be overlooked, as issues with social interaction are associated with suicidality (Szanto et al., 2012), and with severity of depression symptoms (Donges et al., 2005; Lee, Harkness, Sabbagh, & Jacobson, 2005).

Social cognition is closely linked with both emotion processing and general cognition, such that impaired function may be mutually detrimental across with these domains (Raes et al., 2009). Given the complexity of social interactions, it stands to reason that cognitive functions (e.g., attention, processing speed, memory) are crucial in maintaining fluid and adaptive social ability. Likewise, emotional recognition and bias play an important role in identification and perception of social information. Impaired emotion recognition may cause incorrect or biased assessment of social interaction, which may exacerbate depressed mood and lead to further negative social interactions (Weightman et al., 2014). In turn, negative social experiences may lead to subsequent avoidance of interpersonal interactions, further enhancing feelings of isolation and impaired mood. The interplay between social cognition, emotion and general cognition further highlights the need for an integrated treatment approach. In addition, the broad and inter-related deficits associated with social cognitive issues suggest this factor contributes substantially to psychosocial functioning. This being said, the link between social cognition and psychosocial functioning has only recently been empirically investigated (Weightman et al.), and pilot data from the Baune group suggest this relationship; supporting the need for the current research.

The tasks used to gauge social cognitive ability typically involve reading facial emotions (Demenescu, Kortekaas, den Boer, & Aleman, 2010). Depressed persons are typically impaired in facial affect recognition, in part due to a tendency to negatively interpret facial emotions (Bourke, Douglas, & Porter, 2010). A plausible explanation is that impaired attention and emotional interpretation may cause depressed individuals to focus on mood-congruent (i.e., negative) features of facial affect. Other studies of social cognition employ videos of social interactions, which are intended to be more naturalistic and contain more dynamic social features (i.e., body language, prosody, verbal information) (Brewer, Young, & Barnett, 2017; Dziobek et al., 2006). Such videos typically display nuanced social interactions (e.g., sarcasm, bluffing) which require the subject to take the perspective of characters in order to correctly interpret the content of the interaction. These tasks emphasise theory of mind, as reliance on syntactic content and visual information alone is insufficient. Social cognition can also be measured with prosody tasks, in which several syntactically identical sentences are presented with different emotional intonations. Depressed persons appear to be impaired in prosody tasks (Kan, Mimura, Kamijima, & Kawamura), suggesting a verbal contribution to social cognitive deficits.

The research above suggests treatment programs should incorporate facial affect recognition, prosody detection and theory of mind. Ideally training should involve detection of subtle differences in emotion (e.g., the difference between neutral and sad), and synthesising all available information (e.g., body language, social context). Shortening reaction times to detect emotion should not be overlooked, as appropriate timing is crucial to successful social interaction.

**Personalisation**

Given the multifaceted nature of impairment in depression, it is reasonable to assume that deficits will not occur in a uniform nature within individuals. Certain individuals may be disadvantaged specifically in domains of emotional processing, while others are more disadvantaged in terms of cold cognitive ability or social cognition. Previous interventions may not have led to consistent improvements in psychosocial functioning because individual differences in domain-specific impairment were not addressed. Targeting baseline deficits enables subsequent treatment to focus on impaired domains while, also spending less time addressing more functional domains.

The current investigation will evaluate the personalised approach, by comparing psychosocial functioning following a personalised intervention and a standard (i.e., non-personalised) intervention. The personalised intervention will tailor treatment tasks around baseline individual deficits, such that the individual’s most impaired domains receive the greatest attention. It is expected that personalised treatment, relative to standard treatment, will result in greater improvements in psychosocial functioning, which are expected to be retained over a 6 month post-intervention period.

The personalisation process will involve measuring baseline cognitive, emotional and social cognitive functioning, and administering a greater proportion of treatment to participants’ most impaired domains. Previous work has identified that each of these domains (i.e., cognition, emotion processing, social cognition) is sensitive to treatment (Baune & Renger, 2014; Iacoviello et al., 2014; Tchanturia, Doris, & Fleming, 2015). However, it has not been established whether a personalised intervention approach is beneficial to cognitive, emotional and social cognitive function, nor whether personalisation of treatment by these domains is beneficial to overall psychosocial functioning.

**Participants**

Persons with mild-moderate intensity MDD will be eligible to participate, subject to the following inclusion/exclusion criteria. Severely depressed persons were not considered suitable for this intervention, as the complexity of treatment tasks would likely lead to high rates of deterrence.

**Inclusion Criteria**

1. Participants have current MDD, as confirmed by the MINI Neuropsychiatric Diagnostic Interview.

2. Depression symptom severity demonstrated as clinically significant (≥ 15) according to the Structured Interview Guide of the Hamilton Anxiety and Depression Scale (SIGH-AD).

3. Depression symptom severity demonstrated as mild (7-12), mild-moderate (13-19), or moderate (20-30) according the Montgomery Asberg Depression Rating Scale (MADRS) (Svanborg & Asberg, 2001).

4. Participants must be 18 years of age or older.

5. Participants must be willing and able to complete digital treatment tasks presented on a computer.

**Exclusion Criteria**

1. Current alcohol and / or substance use disorder.

2. Current diagnosis of Bipolar or Anxiety disorder.

3. Depression symptom severity demonstrated as severe (31+) according the Montgomery Asberg Depression Rating Scale (MADRS).

4. Previous diagnosis of or identified through screening with schizophrenia, a learning disorder, eating disorder, or a Pervasive Developmental Disorder (e.g., autism spectrum disorder).

5. Brain injury or impairment which could affect cognitive function (e.g., neurodevelopmental disorders, dementia)

6. Participants will be withdrawn from the study if they have subsequent severe brain/head injury; develop dementia; develop psychosis; or develop neurological conditions such as Multiple Sclerosis or Parkinson’s Disease.

7. Unable to complete questionnaires in written English

**Recruitment**

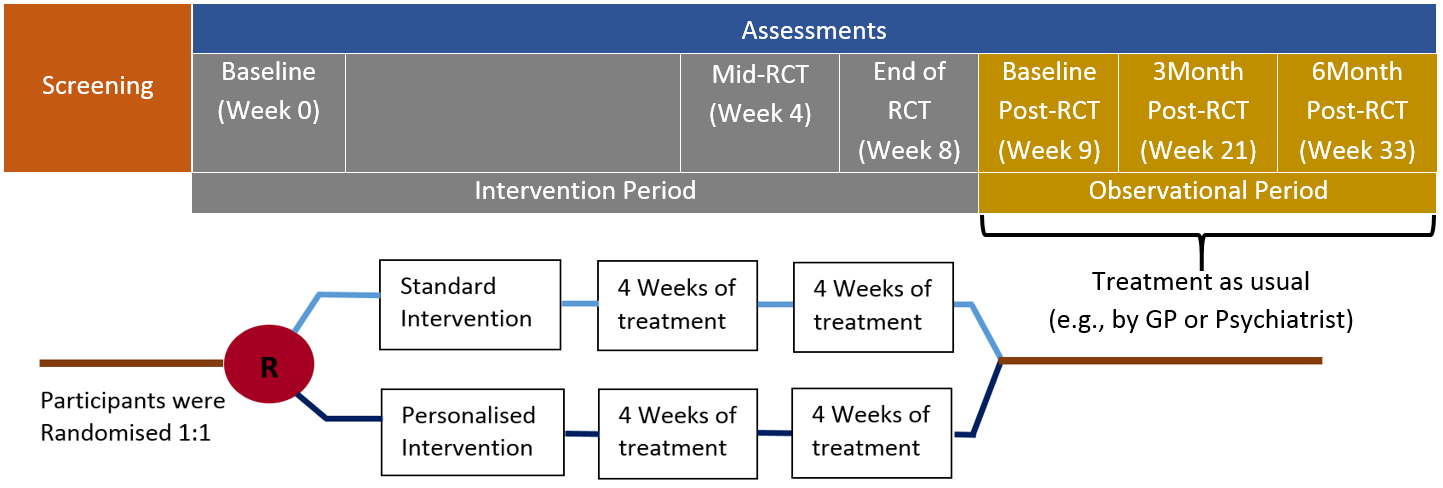
Participants are free to withdraw from the study at any time.

Recruitment will occur through research clinics of the Department of Psychiatry, University of Adelaide and the Eastern, Western, and Northern Mental Health Networks in Adelaide, South Australia. These facilities include 150 inpatients, with approximately 16000 patient contracts per year. Recruitment is also expected to occur via the new Royal Adelaide Hospital, which will take patients in mid-late 2017. Individuals in the general community may be recruited by advertisements and by invitation from independent private practitioners (e.g., psychiatrists, psychologists, GPs).

**STUDY PLAN AND DESIGN**

The study is a randomised controlled treatment (RCT) for individuals with current MDD. The intervention program will occur over 8 weeks, with 2x1hour intervention sessions per week (16hrs total). The intervention will involve training tasks targeting cognitive, emotional and social cognitive ability (See Appendix A). Measures of function in participants will be measured in 2 hour assessments at baseline, 4 weeks into treatment, after 8 weeks of treatment (end of RCT) and in the post-RCT phase at baseline, 3month and 6month post-RCT (12hrs total over 8 months). Assessments will measure cognitive, emotional and social cognitive functioning, as well as psychosocial functioning, occupational functioning, daily functional impairment and resilience. Figure 1 demonstrates the intended timeline for this study, Table 1 illustrates the tasks involved in assessments and Table 2 indicates the schedule of standard treatment sessions and appendices I, J and K illustrate the personalised treatment sessions.

The primary researcher will be aware of the allocation of subjects’ intervention group allocation (personalised, standard). Information about intervention group allocation will not be withheld from subjects, or from researchers administering clinical rating scales.



*Figure 1.* Clinical timeline for the CERT-D. Participants will complete 2 training sessions per week (16 sessions total) over the 8 week intervention period.

|  |  |  |  |  |  |  |  |  |  |  |
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| Table 1 | | | | | | | | | | |
|  |  | | | | | | | | | |
| *Schedule of Assessment Visits. The “X” symbol denotes that this measure / questionnaire will occur.* | | | | | | | | | | |
|  | | |  | | Timeline and assessments per visit | | | | | | |
|  | | Screening  Visit | | week 0  (Baseline)  Assessment  1 | | Week 4  (Mid-RCT)  Assessment2 | Week 8  (End of RCT)  Assessment  3 | Week 9  (Baseline  Post-RCT)  Assessment  4 | Week 21 (3 Month Post-RCT)  Assessment  5 | Week 33  (6 Month  Post-RCT)  Assessment  6 | |
| Measure / questionnaire | |
| MADRS | | **X** | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| MINI 600 | | **X** | |  | |  |  |  |  |  | |
| SIGH-AD | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| FAST | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Resilience Scale | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Disability Scale | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Work Productivity Scales | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Cognitive Failures Questionnaire | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| THINK-it Tool | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Verbal Fluency Test | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| PANAS | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| WAIS-IV SCT | |  | | **X** | | **X** | **X** | **X** | **X** | **X** | |
| Blood taking | |  | | **X** | |  | **X** |  |  | **X** | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 2 | | | | |
|  |  | | | |
| *Schedule of Standard Treatment Visits. The “X” symbol denotes that this modality of treatment will occur.* | | | | |
|  | | Cognition Tasks | Emotion Processing Tasks | Social Cognition Tasks | |
| Treatment Session # | |
| 1 | | **X** |  |  | |
| 2 | | **X** |  |  | |
| 3 | | **X** |  |  | |
| 4 | |  |  | **X** | |
| 5 | |  |  | **X** | |
| 6 | |  | **X** |  | |
| 7 | |  | **X** |  | |
| 8 | | **X** |  |  | |
| 9 | | **X** |  |  | |
| 10 | | **X** |  |  | |
| 11 | |  |  | **X** | |
| 12 | |  | **X** |  | |
| 13 | |  |  | **X** | |
| 14 | |  | **X** |  | |
| 15 | |  |  | **X** | |
| 16 | |  | **X** |  | |
| *Note: Broad impairment treatment uses the same schedule as above, but includes addition provisions (see personalised treatment pp. 12-13)* | | | | | |

**Randomisation process**

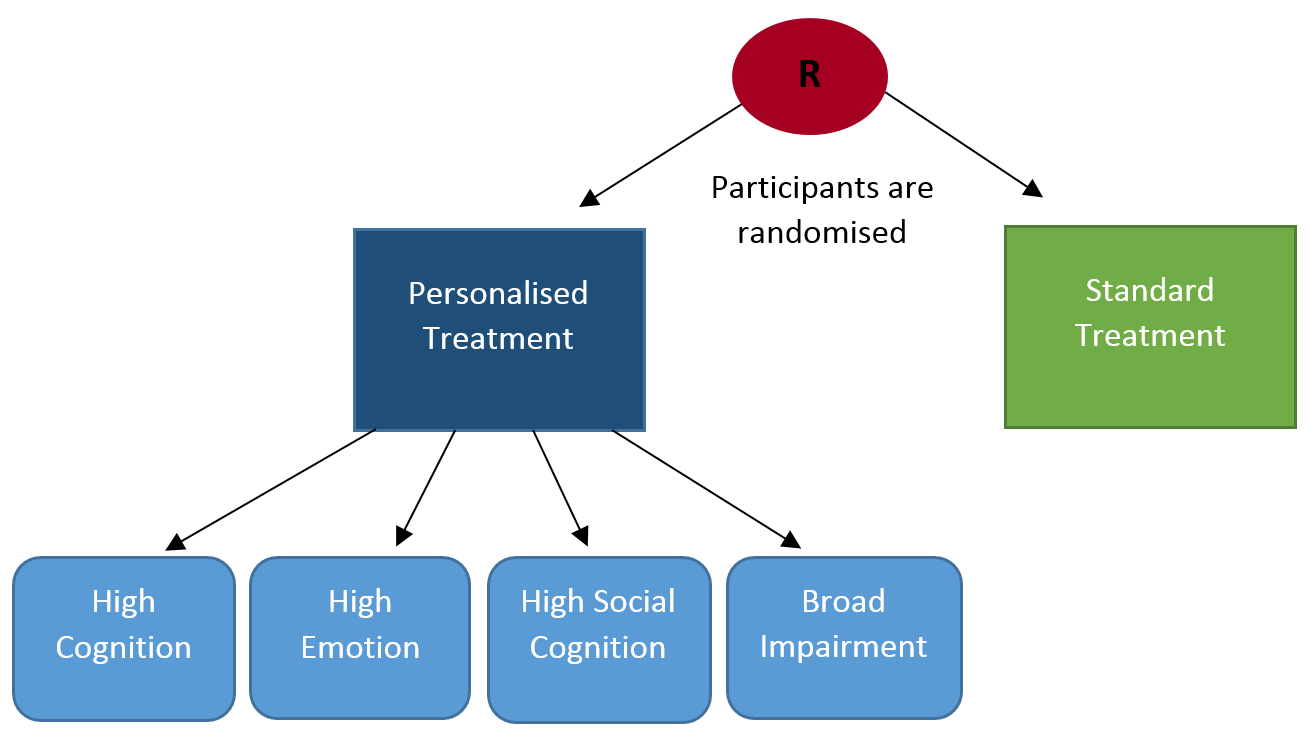
After screening subjects will be randomly allocated with digital randomisation software to receive either personalised or standard (non-personalised) treatment (See Figure 2). In both the standard and personalised intervention groups each treatment session will consist of domain-specific tasks. Every treatment session will be repeated at least once, to ensure that subjects have the opportunity to practice the treatment tasks. A list of the tasks used in domain-specific treatment sessions is presented in Appendix A. 

Figure 2. CERT-D randomisation process. Several streams of treatment are available for subjects in the personalised group (high cognition, high emotion, high social cognition, broad impairment), whereas treatment is the same for every participant in the standard treatment group.

* **Personalised treatment**

Personalised interventions will be tailored to address subjects’ most impaired domains. Baseline tests will determine impaired functioning by evaluating subjects’ performance with the THINC-it tool (cognition), the PANAS (emotion) and the WAIS-IV Social Cognition Test (social cognition). Significant impairment in these tests will be defined as performance at least .5 standard deviations below the norm.

On the basis of individual impairment, subjects allocated to personalised treatment will be delivered one of four potential treatment streams; (1) high cognition treatment, (2) high emotion treatment, (3) high social cognition treatment, and (4) broad impairment treatment (see Figure 2). Subjects will be allocated to streams 1, 2 or 3 if impairment is primarily represented in one of the 3 baseline domains. For example, if a subject demonstrates impaired performance on the THINC-it tool, but normal performance on the PANAS and WAIS-IV Social Cognition Test, then he would be allocated to the high cognition treatment stream. Subjects who are significantly impaired in two or more domains will be allocated to broad impairment treatment. Broad impairment treatments will be initiated more gradually (i.e., initial treatment sessions will be shorter in duration) and will use simpler tasks. The rationale for broad impairment treatment is that significant impairment across multiple domains may reduce subjects’ ability to cope with long or complex tasks, and hence simpler and more gradually applied treatment should be more suitable. It is expected that only a small minority of subjects within the personalised group will be allocated to the broad impairment stream, while most subjects should fit into treatment streams 1-3.

In personalised streams (1-3), 10 treatment sessions will be allocated to the domain of primary dysfunction, while 6 sessions will be allocated to the two remaining domains. For instance, a participant with impaired cognition would receive 10 sessions of cognition treatment, 3 sessions of emotion treatment and 3 sessions of social cognition treatment (see appendix I). Subjects allocated to broad impairment treatment will receive approximately equal number of sessions in each domain (i.e., 6 cognition, 5 emotion, 5 social cognition) (see table 2).

* **Standard treatment**

Subjects allocated to the standard (i.e., non-personalised) intervention will receive an identical intervention regardless of baseline impairment. The standard intervention will be comprised of approximately an equal number of treatment sessions in each domain (i.e., 6 cognition, 5 emotion, 5 social cognition). Unlike broad impairment treatment, standard treatment sessions will be the full duration (i.e., 1hr) from the outset and the difficulty curve of treatment tasks will be steeper.

**Schedule of visits:**

All components of the study will take place at the Clinical Research Facility in the Adelaide Health and Medical Sciences building, the University of Adelaide.

Before initiating the RCT phase, prospective participants will be screened to determine eligibility based on inclusion / exclusion criteria (see p. 8). Participants will then complete 20 visits comprised of treatment and/or assessment visits. Assessment visits are those devoted to taking measures of function (e.g., psychosocial function, cognition, depression severity). Treatment visits are those in which participants will complete cognitive, emotional or social cognitive treatment tasks. Participants will typically complete two visits per week, with a one day gap in between each visit (i.e., Monday (day1)/Wednesday (day2), Tuesday/Thursday, or Wednesday/Friday).

In week 4 and week 8 an assessment is conducted within the same visit as a treatment session. In week 4 the assessment will occur before treatment (day 1), while in week 8 the assessment will occur after treatment (day 2) (see table 3). The overlap of assessment/treatment sessions in weeks 4 and 8 is preferable because it will reduce the total number of visits required to complete the study.

The schedule description below outlines the standard intervention procedure, which will be completed by half the participant sample. For the sake of brevity, the 4 personalised treatment streams are not described here, however summary tables for these schedules are presented in the appendices (See appendices I, J and K).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Table 3 | | | | | |
|  |  |  | | | |
| *Schedule of Visits (treatments and assessments) by week and study phase.* | | | | | |
|  | Study Visit # | | Week of Study | First Weekly Visit  (Day 1) | Second Weekly Visit  (Day 2) |
| Study Phase |
| RCT Period | 1 | | 0 | Assessment 1 | No Visit |
| 2 & 3 | | 1 | Treatment 1 | Treatment 2 |
| 4 & 5 | | 2 | Treatment 3 | Treatment 4 |
| 6 & 7 | | 3 | Treatment 5 | Treatment 6 |
| 8 & 9 | | 4 | Assessment 2  Treatment 7 | Treatment 8 |
| 10 & 11 | | 5 | Treatment 9 | Treatment 10 |
| 12 & 13 | | 6 | Treatment 11 | Treatment 12 |
| 14 & 15 | | 7 | Treatment 13 | Treatment 14 |
| 16 & 17 | | 8 | Treatment 15 | Treatment 16  Assessment 3 |
| Observational  Period (Post-RCT) | 18 | | 9 | Assessment 4 | No Visit |
| 19 | | 21 | Assessment 5 | No Visit |
| 20 | | 33 | Assessment 6 | No Visit |
| *Note: In week 4 assessment will occur before treatment (day 1). In week 8 assessment will occur after treatment (day 2).* | | | | | |

**Study sample size:**

The effect size provided in the power calculation below refers to the primary outcome variable; psychosocial functioning (as measured by the “The Functioning Assessment Short Test” (FAST))

Given a sample size of 100 and an expected effect size of *d* = .5 for the effect of the intervention on FAST score at 8 weeks (i.e., end of RCT) relative to baseline, the study would achieve statistical power of approximately 89% (1-β = 89) (Faul, Erdfelder, Lang, & Buchner, 2007). The rationale for this “medium” effect size is that previous interventions have found positive outcomes approximate to this magnitude (Iacoviello et al., 2014; Elgamal et al., 2007), for example in cognitive functioning.

**Screening**

Detailed study information will be provided to participants, and written informed consent obtained. All subjects will be screened for psychiatric illness with the MINI600 Neuropsychiatric Diagnostic Interview (Sheehan et al., 1998, 2010). The MINI is well validated and has demonstrated high specificity and sensitivity, as well as close concordance with the American Psychiatric Association Diagnostic Criteria (SCID), and the Composite International Diagnostic Interview (ICD-10) (Sheehan et al., 1998, 2010).

The Montgomery Asberg Depression Rating Scale (MADRS) (see Appendix B) and the structured Interview Guide of the Hamilton Anxiety and Depression Scale (SIGH-AD) will be conducted together to establish depression symptom severity. The MADRS is a short rating scale for depression symptom severity designed to be sensitive to change over time (Montgomery and Asberg, 1979). The SIGH–AD is a 31-item structured interview that combines the Hamilton Depression Scale (HAM-D, 17 items) and the Hamilton Anxiety Scale (HAM-A, 14 items). Values over 15 represent clinically significant levels of anxiety or depression. Subjects will not be excluded on the basis of comorbid anxiety, however depression symptoms should be primary.

**Visit 1 (Week 0)**

**Assessment 1: Baseline**

Demographic information including date of birth, sex, and race will be recorded. The Functioning Assessment Short Test (FAST) questionnaire will be used to assess psychosocial function (see Appendix C). The FAST includes measures of independence in basic activities (e.g., dressing, toileting) and more complex tasks (e.g., shopping, managing money). Resilience will be assessed with the Resilience Scale (Wagnild, 2009), which comprises 26 statements indicating the subject’s perceived resilience (e.g., It’s ok if there are people who don’t like me). Subjects will indicate the degree to which resilience statements apply to him/herself on a 7 point Likert scale, with greater values indicating stronger agreement (see Appendix F). Occupational productivity and presentism will be measured with the Endicott Work Productivity Scale (EWPS) (Prasad, Wahlqvist, Shikiar, & Shih, 2004) and the Work Productivity and Activity Impairment Questionnaire (WPAI) (see Appendix D). Functional impairment will be measured with the Sheehan disability scale (Leon, Olfson, Portera, Farber, & Sheehan, 1997) (see Appendix E). Depression symptom severity will be measured with the MADRS (Montgomery and Asberg, 1979). Prevalence of cognitive failures will be measured with the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982). The CFQ asks subjects to rate the frequency of cognitive issues experienced in everyday life (e.g., forgetting names) (see Appendix H). With their consent, subjects will provide approximately 28ml of blood (5-6 teaspoons) for biomarker and genetic analysis

Cognitive function will be assessed with the THINC-it tool, which comprises four objective cognitive tests and 5 items from the Perceived Deficit Questionnaire (PDQ-5-D). The objective tests are digital versions of the *n*-back, digit symbol substitution, trail making, and choice reaction time tasks. Performance in trail making and choice reaction time tasks will be taken as indications of visuospatial ability, as these tasks involve visual attention spatial coordination to a greater extent than the other components of the THINC-it tool. Verbal functioning will be assessed with a separate verbal fluency task (Tombaugh, Kozak, & Rees, 1999), in which subjects have one minute to produce as many words as possible belonging to a particular category (e.g., starting with the letter “c”). Emotional functioning will be assessed with the Positive and Negative affect Schedule (PANAS), which requires subjects to indicate the intensity of current and recent emotions on a Likert scale. Scores are calculated separately for positive and negative emotions, with higher scores indicating greater intensity (see Appendix G). Social cognitive functioning will be measured with the WAIS-IV Advanced Clinical Solutions Social Cognition Test (Holdnack, Goldstein, & Drozdick, 2011). This task involves naming the emotions conveyed by presented images of faces, and completing prosody-face matching and prosody pair matching tasks.

Data from these tests will be collated and used as an indication of baseline functioning. This data will also be used to tailor subsequent intervention procedures for participants in the personalised intervention group. Specifically, appraisal of individual subjects’ descriptive data will reveal whether certain domains meet the criteria for significant impairment (≥.5 *SD*s below the norm), and therefore which domains require more sessions of treatment in the intervention program. Importantly, the intervention visits described below outline the standard intervention schedule, which is the same regardless of baseline performance.

**Visit 2 (Day 1, Week 1)**

**Treatment 1**

According to random allocation, subjects will begin personalised or standard interventions. Before initiating treatment, the researcher will explain the treatment program to the subject. Emphasis will be given to the transfer and application of skills obtained in treatment to psychosocial functioning (e.g., improved social relationships and problem solving). In addition, the researcher will explain the benefit of reinforcing neural connections by repeated treatment, and the function of this intervention in reduction of negative depression symptoms. The participants will be reassured that performance on these tasks does not predicate intelligence or ability. This statement is intended to prevent subjects engaging in negative self-evaluations or suffering decreased self-esteem from the perception of low task performance.

In both intervention groups, simpler and less demanding treatment tasks will be administered first in an effort to introduce treatment more gradually, and to minimise treatment deterrence. Notably, task complexity will increase more gradually for subjects allocated to the personalised “broad impairment” schedule. The standard treatment battery (presented below) will begin with treatment tasks centred on cognitive function, which resemble game-like activities. These tasks will be completed digitally with the Psychology Experiment Building Language (PEBL) software (Mueller & Piper, 2014).

In the first visit the subject will complete visuospatial tasks, beginning with a mental rotation task. Mental rotation requires the subject to hold a visual stimulus in working memory and make recognition judgments. A map learning task will be employed in which the subject studies a simple two-dimensional map for 60 seconds while conducting a simultaneous spatial tapping interference task. The subject will then attempt to sketch the map from memory (the original map will not be available). This map learning task is assumed to involve integration of several components of spatial learning and working memory (Coluccia, Bosco, & Brandimonte, 2007; Garden, Cornoldi & Logie, 2002; Knight & Tlauka, 2016), while simultaneous interference involves rapid switches of attention and spatial-executive control (Baddeley, 1983). A Corsi blocks task and a path memory task will then be completed digitally with the PEBL software. These tasks involve visuospatial attention, working memory and spatial updating (Vandierendonck, Kemps, Fastame, & Szmalec, 2004). Subjects will repeat these tasks (with different stimuli where appropriate) and receive encouragement from the researcher to gradually improve.

After completing the treatment tasks (here and in following weeks) participants will be asked questions about what they have learned. For example “what does this task tell you about your thinking style?” “How could you use the skills needed in this task in real life?” “In the future, how could these skills be applied?”. These questions are intended to facilitate the transfer of treatment to real life applications, and to encourage feelings of progress.

**Visit 3 (Day 3, Week 1)**

**Treatment 2**

In visit two subjects will complete executive tasks which focus on attention, inhibition, problem solving and updating. The sessions will begin with a random number generation task, in which subjects must inhibit the natural response of producing logical sequence (Artiges et al., 2000). Next, the subject will complete Berg’s Card sorting test (a variant of the Wisconsin Card Sorting Test), which requires problem solving, mental flexibility, and updating (Channon, 1996). Attention switching and executive control will then be trained with a symbol counter task. A Stroop task will then be completed, in which the subject must state the ink colour of a presented colour word (e.g., “green”), while ignoring the text of the word itself. Stroop tasks require set shifting, processing speed and attention (Stroop, 1935). The subject will repeat these tasks, receive encouragement to gradually improve and be asked the questions about real life application (see visit 3).

**Visit 4 (Day 8, Week 2)**

**Treatment 3**

Verbal working memory will be the focus in visit five. Subjects will begin verbal treatment with a Letter-number sequencing task, in which a series of letters and numbers is presented. The goal is to reproduce the letters in alphabetical order, and the numbers in ascending order. Letter-number sequencing involves coordination of verbal and executive memory and working memory span (Crowe, 2000). A reading span task will be employed which involves devoting a list of letters to memory, then reading and judging sentences for sensibility. This task involves processing linguistic information, which previous research has indicated is a function of verbal working memory (Cornwall, 1992). A backwards digit span task will be employed, which requires coordination of verbal memory span and executive processing (Conklin, Curtis, Katsanis, & Iacono, 2000).

**Visit 5 (Day 10, Week 2)**

**Treatment 4**

Social cognitive treatment will begin with a digital “reading the mind in the eyes” task. The subject will view a sequence of faces in which only the eyes are presented, and attempt to name the conveyed emotion (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Subjects will then complete the Adult Theory of Mind (A-ToM) task, which involves viewing multiple videos of social situations (Brewer et al., 2017). The subject is required to make judgements about the social situations taking place, including why certain actions occur and what emotions the characters are experiencing. The researcher will discuss responses with the subject, to encourage deeper thinking about interpersonal cues.

**Visit 6 (Day 15, Week 3)**

**Treatment 5**

The second social cognition treatment session will begin with the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006). This task is very similar to the A-ToM, presenting subjects with social situations and asking the subject to make theory of mind judgments. The subject will then complete an interpersonal word list exercise derived from the Cognitive Remediation and Emotional Skills Training (CREST) (Tchanturia, Doris, & Fleming, 2014). A number of emotionally salient words will be presented along with a prompt to provide further information about the words’ deeper communicative function. For example, “people experiencing happiness are communicating that they…”. The subject will be encouraged to think about the emotional communication outside the treatment session, and note any instances they wish to discuss in their next treatment session.

**Visit 7 (Day 17, Week 3)**

**Treatment 6**

Emotion processing treatment will begin with a brain storming task from the “Social Cognition and Interaction Training” (SCIT) intervention (Combs et al., 2007). The subject is asked to write as many emotions as he/she can. The researcher will emphasise that emotions are central to our experience of life, and therefore it is helpful to try and understand emotions. If the 7 basic emotions (i.e., happy, sad, angry, surprised, disgusted, afraid, ashamed) are not described, the subject will be prompted to include those which are missing. The researcher will discuss each emotion with the subject, such that more detail on the phenomenology of the emotion is provided. Subsequent emotion treatment sessions will revisit this task, and the subject will be encouraged to provide even greater detail (e.g., facial expressions associated with each emotion).

The subject will then complete an EFMT (i.e., emotional *n*-back) task (Iavoviello et al. (2014). This will involve viewing a series of faces, identifying the portrayed emotion and stating whether the current emotion matched or did not match the emotion portrayed by a previously viewed face. Task difficulty will be manipulated by increasing or decreasing the retention increment (i.e., the number of faces) in between each emotion matching judgement. If the participant answers correctly on three consecutive occasions, the retention increment will increase. Conversely, the retention increment will decrease following three incorrect answers.

**Visit 8 (Day 22, Week 4)**

**Assessment 2: Mid-RCT**

Assessment of outcome measures will occur at 50% treatment completion. This will include measurement of cognition using the THINC-it tool and of verbal function with the verbal fluency test. Emotional state will be measured with PANAS, while social cognition will be assessed with the WAIS-IV social cognition test.

Psychosocial functioning will be assessed with the FAST, while occupational productivity will be measured with the EWPS and WPAI. An indication of resilience will be obtained with the resilience scale (Wagnild, 2009) and functional impairment will be measured with the Sheehan Disability Scale. Prevalence of cognitive failures will be measured with the CFQ and depression symptom severity will be assessed with the MADRS.

**Treatment 7**

The second emotion processing session will begin with an exercise in emotion recognition derived from the CREST (Tchanturia et al., 2014). The subject will be asked to think of an emotion which is difficult to recognise (e.g., feeling “lost”), and then abstract this emotion to fit within a descriptive sentence (e.g., “If ‘lost’ were an animal, what would it be?”). This exercise in intended to encourage deeper emotion processing and facilitate more effective emotional recognition (Tchanturia et al., 2014).

A second emotional task from the CREST intervention will be employed in which the subject is presented with a two-dimensional anatomical model of the human body. The researcher will ask the subject to think of an emotion which he/she finds difficult to tolerate, and then to label how this emotion is represented in various parts of the body. For example, a subject could indicate that fear is felt in the heart, brain and stomach. The researcher will discuss this emotion with the subject to facilitate deeper thought about the link between emotion, cognition and physiological responses.

Secondly, subjects will complete an emotional word list task derived from the self-referential information processing (SRIP) task (Murray, 1999). The researcher will present a list of words which are either positive or negative. The subject is asked the extent to which this word “sounds like me”. A subsequent test of recall for the word list is then conducted, with the proportion of negative descriptive words used as an indication of negative bias. The researcher will talk through the results with the subject, with the intention of developing his/her understanding of emotional memory bias. The subject will be encouraged to think about instances in which the positive words could be ascribed to him/herself, or to imagine future scenarios in which this is the case.

**Visit 9 (Day 24, Week 4)**

**Treatment 8**

The central executive tasks completed in visit 4 will be repeated. The researcher will encourage the subject to try to recall how they approach these tasks initially, and think of any strategies which might increase their performance in this attempt. After completing the tasks the researcher will ask if the subject was able to use their previous experience to improve performance, and encourage transfer of any successful strategies to real life applications (e.g, organisational or mnemonic strategies).

**Visit 10 (Day 29, Week 5)**

**Treatment 9**

This session will repeat the visuospatial treatment tasks employed in visit 3. The researcher will encourage improvements and transfer of skills.

**Visit 11 (Day 31, Week 5)**

**Treatment 10**

The verbal tasks employed in visit 5 will be repeated. The researcher will encourage improvements and transfer of skills.

**Visit 12 (Day 36, Week 6)**

**Treatment 11**

This social cognition treatment session will repeat the social cognitive tasks used in visit 5 (i.e., the reading the mind in the eyes task, and the adult theory of mind video (A-ToM)). At the start of the session the researcher will summarise the main social cognition learning points from the previous social cognition session (e.g., attending to prosody and body language), and encourage the subject to apply these skills in the repeated tasks.

**Visit 13 (Day 38, Week 6)**

**Treatment 12**

The emotional treatment tasks used in visit 7 will be repeated. Before treatment tasks are completed the researcher will encourage transfer of learning in previous emotional processing sessions to the current tasks.

**Visit 14 (Day 43, Week 7)**

**Treatment 13**

The social cognition treatment tasks from visit 6 will be repeated.

**Visit 15 (Day 45, Week 7)**

**Treatment 14**

The emotional processing tasks used in visit 8 will be repeated.

**Visit 16 (Day 50, Week 8)**

**Treatment 15**

The social cognition treatment tasks from visit 5 will be repeated. However, time will be provided (approx. 15 mins) to synthesise the learning points from all previous social cognition tasks. The researcher will encourage the subject to retain and apply these social cognitive abilities (e.g., attending to prosody, body language, thinking about what others’ emotions communicate).

**Visit 17 (Day 52, Week 8)**

**Treatment 16**

The emotional processing tasks used in visit 7 will be repeated. Fifteen minutes will be allocated to the synthesis and transfer of emotional processing knowledge across the intervention.

**Assessment 3: End of RCT**

Post-treatment assessments of cognitive, emotional and social cognitive function will occur. Outcome measures of psychosocial functioning, occupational functioning and resilience will also be taken (see visit 8, Assessment 2). In addition to these measures, participants will also provide a blood sample for biomarker and genetic analysis. To avoid confounding the post-RCT follow up period (i.e., the following 6 months) with other factors, subjects will be asked to continue any extraneous treatments as normal.

**Visit 18 (Week 9)**

**Assessment 4: Post-RCT (Baseline)**

Measures of psychosocial function and depression/life outcomes will be measured (see visit 8).

**Visit 19 (Week 21)**

**Assessment 5: Post-RCT (3 months)**

Follow up measures of psychosocial function and depression/life outcomes will be measured (see visit 8).

**Visit 20 (Week 33)**

**Assessment 6: Post-RCT (6 months)**

Follow up measures of psychosocial function and depression/life outcomes will be measured (see visit 8). A final blood sample for biomarker and genetic analysis will also be taken.

**OUTCOMES**

Outcome measures will be taken at baseline, 4 weeks into treatment and after treatment completion (8 weeks). Post-RCT assessments of outcomes will be obtained at baseline (i.e., week 9) and at 3 and 6 months after treatment completion. The primary outcome, psychosocial functioning, will be measured with the FAST questionnaire. Secondary outcomes include occupational function (EWPS and WPAI), self-reported resilience (Wagnild, 2009), functional disability (Sheehan disability scale), cognitive failures (CFQ) and depression severity (MADRS).

Cognitive assessments will be conducted with the THINC-it tool and a verbal fluency test, emotional assessment with the PANAS and social cognition with the WAIS-IV Social Cognition Test. Biological outcome measures of inflammation, stress and neural activity will be obtained by blood tests. Biomarker levels will be entered into regression analyses with cognitive and psychosocial performance.

It is expected that the CERT intervention will lead to significant improvement in psychosocial functioning at 8 weeks in comparison to baseline, and that these benefits will be retained at 3 and 6 months post-RCT. Treatment effects of the CERT are also expected in the domains of occupational function, resilience, functional disability, depression symptom severity, as well as cognitive, emotional and social cognitive function.

**Primary outcome measure**

Primary Endpoint 1

Overall, subjects who took part in the intervention are expected to display improvement in psychosocial functioning (*d* ≈ .5) (measured by the FAST total score) at 8 weeks (i.e., end of RCT) relative to baseline. We hypothesise that psychosocial functioning status will be retained at follow up assessments (3 & 6 months post-RCT) relative to baseline post-RCT.

**Secondary outcome measures**

Secondary Endpoint 1

It is worthwhile evaluating the overall change in psychosocial function (i.e., FAST scores) over the entire study period. We predict that psychosocial functioning will be significantly greater at the 6 month post-RCT assessment relative to baseline (pre-intervention).

Secondary Endpoint 2

It is of interest which subdomains of psychosocial functioning as measured by the FAST (e.g., leisure, autonomy and interpersonal relationships) are sensitive to change over time (8 weeks compared to baseline) owing to the CERT intervention.

Secondary Endpoint 3

It is expected that the intervention will lead to improvements in occupational functioning (EWPS and WPAI), resilience (“The Resilience Scale”) and functional disability (Sheehan disability scale), and will reduce cognitive failures (CFQ) at 8 weeks relative to baseline. Improvements demonstrated at baseline post-RCT are not expected to change significantly at 3 and 6 months post-RCT assessments.

Secondary Endpoint 4

We hypothesise that the CERT intervention will reduce depression symptoms (i.e., MADRS score) at 8 weeks relative to baseline. Follow up assessments at baseline post-RCT and 3 and 6 months post-RCT will evaluate the longevity of expected symptomatic relief.

Secondary Endpoint 5

It is expected that subjects who receive a personalised intervention will display greater psychosocial functioning improvements 8 weeks relative to subjects who receive a standard intervention.

Secondary Endpoint 6

It is predicted that certain serum biomarkers (i.e., TNF, IL-1, Il-6, and IL-8, BDNF, other neurotrophic factors, Monoamines) will be related to psychosocial functioning and cognitive performance.

Mediation hypothesis

A secondary interest is the proposed mechanism for improvement in psychosocial functioning. Specifically, it is expected that cognitive, emotional and social cognitive performance will mediate the effect of the intervention on psychosocial functioning (FAST score).

**ETHICAL CONSIDERATIONS**

There are no significant physical, emotional, social or legal risks for participants. All participant processes are well established, valid and reliable and have been used clinically and in research to assess and collect data on many thousands of participants worldwide. However, if participants become distressed at any point during the study, the study will be interrupted for a break. If the distress continues, the study will be stopped. Distressed patients might be referred back to their treating psychiatrist during hospital treatment (inpatient and outpatient), or those with severe symptoms may be referred for emergency psychiatric care. Also, during the course of the study, participants with undiagnosed mental health issues (such as dementia or schizophrenia) may be identified at the time of assessment. In such cases, these participants will be withdrawn from the study and referred for psychiatric/psychological consultation. Participants with milder symptoms will be referred back either to their general practitioner or to their treating clinician, but those with severe symptoms may be referred for emergency psychiatric care. In the case of distress or undiagnosed psychiatric pathology, one of the following services would also be contacted:

* Assessment and Crisis Intervention Service (ACIS)/Mental Health Team South Australia – 13 14 65
* Health Direct Australia – 1800 022 222
* Mental Health Resource Centre – 8221 5166

Further, the study involves genetic analysis. The nature of the genetic analysis and the genes being investigated means that it is unlikely that definitive gene-disease associations will be found. It is more likely that possible “susceptibility” genetic variants will be identified. However, in the unlikely event that genetic information is identified that is medically significant for carriers of the genotype, notification will be made to all participants of the finding and its possible implications. The genetic variants under investigation have been used in a number of studies to date and no direct gene-disease relationships have been identified. Participants will be asked to contact the investigators if they wish to know their own individual result and will be provided appropriate referrals to counselling and support at the Clinical Genetics Unit, situated at the Women's and Children's Hospital.

Any harm or potentially harmful event will be immediately reported to the Principal Investigator, Principal Supervisor, Laboratory Manager (if relevant), Head of School of Medicine, Research Office, and the Royal Adelaide Hospital Ethics Committee within 72 hours. A written report of the event will be provided in accordance with each specific policy and procedure requirement (University of Adelaide, Royal Adelaide Hospital Ethics Committee, Health and Safety Officer, etc).

* Subjects are free to withdraw from the intervention at any time
* Subjects will be withdrawn from the intervention if symptom severity increases (≥ 20% MADRS score) at the mid-intervention assessment relative to baseline
* The purpose and design of the intervention and the study in general will be made clear to subjects at the outset (including risks and benefits).
* Subjects will be provided with an identification card with the contact number of the investigator in case of emergency.
* No payments will be made to participants for their participation or time. Reimbursements or the provision of bus/train/tram tickets or for parking may be made.
* If subjects experience a decline in mental state during the 6 month post-RCT trial period, the subjects would notify the study team as well as their treating GP / Psychiatrist. In addition, the study team would closely liaise with the treating GP/ Psychiatrist if this occurred.

**Adverse events**

In this study an adverse event (AE) is defined by any significant feelings of frustration, discomfort, confusion or negative self-evaluations owing to the intervention or outcome measures. Adverse events will be collected from screening to endpoint, and at the post-RCT visits. At each visit, study participants will be asked questions such as “how do you feel”, and if they have experienced any significant issues with the study procedures. To reduce the possibility of negative self-evaluations the researcher will emphasise at the outset of the study that individual performance in these tasks varies substantially, and does not indicate intelligence or ability. If subjects report distress regarding their experience with the study, they will be withdrawn from the intervention and referred to their treating psychiatrist or GP.

All AE’s will be recorded, whether or not considered related to the current intervention. This will include AE’s spontaneously reported by the study participant and/or observed by members of the research team, as well as AE’s reported in response to a direct question (e.g. “have you experienced any health problems since your last visit?”).

For each adverse event, the following parameters will be described:   
-start and stop date   
-outcome  
-if the adverse event caused the participant to withdraw from the study  
-the investigator’s assessment of the causal relationship between the event and the intervention  
-the intensity of the adverse event (mild – awareness of sign or symptom but easily tolerated; moderate – discomfort sufficient to cause interference with normal activities; or severe – incapacitating with inability to perform normal activities).

Follow-up of adverse events will be based upon the judgement of the investigator.

**Serious adverse events**

There are no serious adverse events expected to result from any phase of the current study. However if subjects respond negatively to treatment (i.e., show ≥ 20 increased symptom severity on the MADRS) they will be withdrawn from the study and referred to a treating psychiatrists or GP. If subjects indicate a heightened risk of suicide or other severe psychiatric issues then they will be referred to emergency psychiatric care.

**Data Safety Monitoring Board**

We will form an independent data monitoring committee. This committee will consist of local, national and international members, all with extensive experience with clinical trials. In addition, committee members will have experience with psychological therapies and cognitive treatments for depression.

**ANALYSIS AND REPORTING OF RESULTS**

**Data Collection Methods:**

Depression symptoms will be obtained with the previously described scales (i.e., MADRS, CGI-S and GAF). Scales and questionnaires will be paper-based, except for the THINC-It tool, which is computer based (https://www.thinccognition.com/thinc-cognition-tool).

**Data Management:**

The University of Adelaide will maintain ownership of all data and samples. Data will be stored securely, in locked cabinets within locked rooms at the University of Adelaide. Data from the THINC-It tool is stored electronically on a password protected computer. Access to the study data will be restricted to research personnel. All data reports will be prepared so that no individual study participant can be identified. Participant files will be kept for a period of 15 years after completion of the study.

Blood specimens are stored in de-identified, coded tubes and stored at -80c in a secure storage facility in the neurosciences laboratories of University of Adelaide’s Medical School.

**Statistical Methods:**

Primary Analyses

The primary outcome will be a within-subjects ANOVA with time (baseline, 8 weeks, baseline post-RCT, 3 month post-RCT, 6 month post-RCT) as the independent variable. The dependent variable will be psychosocial functioning (i.e., FAST score). It is expected that psychosocial functioning will be significantly greater at 8 weeks (end of RCT) relative to baseline. Three and 6 month post-RCT FAST scores are not expected to differ significantly from (baseline) post-RCT.

Secondary Analyses

A paired samples t-test will evaluate whether psychosocial function (i.e., FAST score) is significantly greater at 6 months post-RCT relative to baseline (pre-intervention).

A Within-subjects ANOVA with time (baseline, 8 weeks, baseline post-RCT, 3 month post-RCT, 6 month post-RCT) as the independent variable and FAST subdomain score as the dependent variable will be employed. These analyses will evaluate which domains of psychosocial functioning were significantly affected by the CERT intervention.

Within-subjects ANOVAs with time as the independent variable and secondary outcome measures (e.g., resilience score) as the dependent variable will be employed. These analyses will evaluate whether the intervention improved subjects’ resilience, functional disability, occupational productivity and rate of cognitive failures. This analysis will also test whether performance in these domains will be retained at 3 and 6 month post-RCT assessments (compared to baseline post-RCT).

Depression symptom severity will be assessed with a within-subjects ANOVA. Time will be the independent variable and MADRS score the dependent variable. It is expected that symptom severity will be significantly reduced at 8 weeks relative to baseline. It is further expected that symptom severity will not change significantly from baseline post-RCT to 3 and 6 months post-RCT.

A mixed ANOVA will be used with time as within subjects and intervention type (personalised, standard) as between-subjects. Psychosocial functioning (i.e., FAST score) will be the dependent variable. A between-within interaction is expected, such that that the personalised intervention group will display greater improvement in FAST scores (baseline-8 weeks) compared to the standard intervention group.

Regression analyses will be employed to evaluate whether biomarker expression is related to cognition (i.e., THINC-it performance) or psychosocial performance.

Mediation Analysis

Stepwise linear regression analyses will be used to evaluate a mediation hypothesis. The independent variable will be intervention (CERT, no-intervention (CoFaMS)), while FAST score at 8 weeks will be the dependent variable. Mediators for this relationship will be cognitive function (i.e., THINC-it), emotion processing (i.e., PANAS) and social cognitive function (i.e., WAIS-IV Social Cognition Test score) taken at 8 weeks.

It is expected that intervention (0 = no intervention, 1 = CERT intervention) will be positively related to FAST score. This relationship is expected to be mediated by the combination of cognitive, emotional and social cognitive performance. Whether any of these mediator variables will account for significant variance when entered as individual mediators is not known.

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**OTHER INFORMATION**

**Advertising**

An established recruitment network in Hospitals and Community Mental Health Services already exists. The study will be advertised to the general public in the form of a flyer.

**Publishing**  
Publications are planned in peer-reviewed journals. Upon completion of the study we will prepare a publication addressing the primary and secondary outcomes of the study.

**DATE OF PROPOSED COMMENCEMENT AND DURATION**

The total study period will be 2 years. We plan to commence the study in June-August 2017.

**SIGNATURES OF INVESTIGATORS**

Principal investigator: Bernhard Baune

Research Officer: Matthew Knight

|  |  |  |
| --- | --- | --- |
| Cognitive tasks  *Central Executive*   * Berg’s Card Sorting task * Digit Symbol Substitution * Iowa Gambling Task * Go/no-go task * Random number generation * DRM task * Continuous performance test * Neutral word list memory * Delayed alternation task * Stroop task * D2 letter cancellation test * Cognifit brain training tasks   *Verbal*   * Letter-number sequencing * Reading span * Backwards digit span * Ray verbal learning Test * Hopkins verbal learning test * Verbal route memory task * Auditory verbal learning test   *Visuospatial*   * Manual Dexterity task * Mental Rotation * Path Memory * Compensatory Tracker * Tower of London * Corsi Blocks * RBANS Figure Copy Test * Map learning task * Rey figure drawing |  | Emotion Processing Tasks   * SCIT emotional word list task * Emotional *n*-back (EFMT) * Emotion word brainstorming * CREST emotion recognition task * CREST emotion anatomy task * SRIP emotional bias word list task   Social Cognition Tasks   * Movie for the assessment of social cognition (MASC) * Adult theory of mind (A-TOM) task * Reading the mind in the eyes test * Happe strange stories test * CREST interpersonal word list task * Prosody sentence matching task * Ekman 60 emotional faces recognition test * Wechsler memory for faces subtest * MSCEIT-ME social vignette task * Triangles social perception task * Wilhelm facial affect battery |

**Appendix A**

Tasks by domain

**Appendix B**

**Montgomery-Åsberg Depression Rating Scale (MADRS)** *(Over last week; to be completed by trial psychiatrist)*

MADRS SCORE

INTERPRETATION

0-6 Normal/recovered

7-19 Mild depression

20-34 Moderate depression

35-60 Severe depression

1. **Apparent Sadness**

* 0 No sadness
* 1
* 2 Looks dispirited but does

brightens without difficulty

* 3
* 4 Appears sad and unhappy most

of the time

* 5
* 6 Looks miserable all the time;

extremely despondent

1. **Reported Sadness**

* 0 Occasional sadness in keeping  
   with the circumstances
* 1
* 2 Sad or low but brightens up

without difficulty

* 3
* 4 Pervasive feelings of sadness and

gloominess. The mood is still

influenced by external

circumstances

* 5
* 6 Continuous or unvarying

sadness, misery or despondency

1. **Inner tension**

* 0 Placid. Only fleeting inner

tension

* 1
* 2 Occasional feelings of edginess

and ill-defined discomfort

* 3
* 4 Continuous feelings of inner

tension or intermittent panic,

which the patient can master

only with some difficulty

* 5
* 6 Unrelenting dread or anguish,

overwhelming panic

1. **Reduced sleep**

* 0 Sleep as usual
* 1
* 2 Slight difficulty dropping off to

sleep or slightly reduced, light

or fitful sleep

* 3
* 4 Sleep reduced or broken by at

least 2 hours

* 5Id
* 6 Less than 2 or 3 hours sleep

1. **Reduced appetite**

* 0 Normal or increased appetite
* 1
* 2 Slightly reduced appetite
* 3
* 4 No appetite. Food is tasteless
* 5
* 6 Needs persuasion to eat at all

1. **Concentration difficulties**

* 0 No difficulties in concentrating
* 1
* 2 Occasional difficulties in

collecting one’s thoughts

* 3
* 4 Difficulties in concentrating and

sustaining thought, which

reduces ability to read or hold a

conversation

* 5
* 6 Unable to read or converse

without great difficulty

1. **Lassitude**

* 0 Hardly any difficulty in getting

started. No sluggishness

* 1
* 2 Difficulties in starting activities
* 3
* 4 Difficulties in starting simple

routine activities, which are

carried out with effort

* 5
* 6 Complete lassitude. Unable to do

anything without help

1. **Inability to feel**

* 0 Normal interest in

surroundings and in other

people

* 1
* 2 Reduced ability to enjoy

usual interests

* 3
* 4 Loss of interest in

surroundings. Loss of interest

for friends and acquaintances

* 5
* 6 The experience of being

emotionally paralysed.

Inability to feel anger or grief

and a complete or even painful

failure to feel for close

relatives or friends

1. **Pessimistic thought**

* 0 No pessimistic thoughts
* 1
* 2 Fluctuating idea of failure, self

reproach or self-deprecation

* 3
* 4 Persistent self-accusations, or

definite but still rational ideas

of guilt or sin. Increasingly

pessimistic about the future

* 5
* 6 Delusions of ruin, remorse, or

unredeemable sin. Self-

accusations which are absurd

and unshakeable

1. **Suicidal thoughts**

* 0 Enjoys life or takes it as it

comes

* 1
* 2 Weary of life. Only fleeting

suicidal thoughts

* 3
* 4 Probably better off dead.

Suicidal thoughts are common,

and suicide is considered as a

possible solution, but without

specific plans or intention

* 5
* 6 Explicit plans for suicide when

there is an opportunity. Active

preparations for suicide

**Appendix C**

**FUNCTIONING ASSESSMENT SHORT TEST (FAST)**

**To what extent is the patient experiencing difficulties in the following aspects?** Ask the patient about the areas of difficulty in functioning and score according to the following scale: (0): no difficulty, (1): mild difficulty, (2): moderate difficulty, (3): severe difficulty

|  |  |
| --- | --- |
| **AUTONOMY**  1. Taking responsibility for a household  2. Living on your own  3. Doing the shopping  4. Taking care of yourself (physical aspects, hygiene) | (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3) |
| **OCCUPATIONAL FUNCTIONING**  5. Holding down a paid job  6. Accomplishing tasks as quickly as necessary  7. Working in the field in which you were educated  8. Occupational earnings  9. Managing the expected work load | (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3) |
| **COGNITIVE FUNCTIONING**  10. Ability to concentrate on a book, film  11. Ability to make mental calculations  12. Ability to solve a problem adequately  13. Ability to remember newly-learned names  14. Ability to learn new information | (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3) |
| **FINANCIAL ISSUES**  15. Managing your own money  16. Spending money in a balanced way | (0) (1) (2) (3)  (0) (1) (2) (3) |
| **INTERPERSONAL RELATIONSHIPS**  17. Maintaining a friendship or friendships  18. Participating in social activities  19. Having good relationships with people close you  20. Living together with your family  21. Having satisfactory sexual relationships  22. Being able to defend your interests | (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3)  (0) (1) (2) (3) |
| **LEISURE TIME**  23. Doing exercise or participating in sport  24. Having hobbies or personal interests | (0) (1) (2) (3)  (0) (1) (2) (3) |

**Appendix D**

**Work Productivity Scales**

|  |  |  |
| --- | --- | --- |
| **ENDICOTT WORK PRODUCTIVITY SCALE (EWPS)** | | |
| Education: | |  |
| Occupation: | |  |
| Do you receive pay or other money for any type of work? | * No | * Yes |
| Do you do volunteer work? | * No | * Yes |
| **If you do not receive money for your work and do not do volunteer work, please indicate why you do not:** | | |
| I am physically ill |  |  |
| I am too upset, depressed, or nervous |  |  |
| I can’t find work |  |  |
| Other (Please describe) |  |  |
| **If you receive money for your work or do volunteer work, please complete the questionnaire, otherwise stop here.** | | |
| I am self-employed | * No | * Yes |
| I work for someone else | * No | * Yes |
| I have a boss/supervisor | * No | * Yes |
| I have co-workers with whom I must work | * No | * Yes |
| I supervise others at work | * No | * Yes |
| I deal with clients/customers/vendors | * No | * Yes |
| How many hours do you usually work or would you usually be expected to work? hours per week? | | |
| How many hours did you work last week? hours per week | | |
| If you missed time at work last week, please note all the reasons why: |  |  |
| I had a day off (holiday/vacation) |  |  |
| I was physically ill | |  |
| Too upset, depressed or nervous |  |  |
| Other | |  |
| PLEASE DESCRIBE |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| During the past week, how frequently did you--- | | | | | | |
|  |  | *NEVER* | *RARELY* | *SOME- TIMES* | *OFTEN* | *ALMOST ALWAYS* |
| 1 | Arrive at work late or leave work early? | 0 | 1 | 2 | 3 | 4 |
| 2 | Take longer lunch hours or coffee breaks? | 0 | 1 | 2 | 3 | 4 |
| 3 | Just do no work at times when you would be expected  to be working? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 4 | Find yourself daydreaming, worrying or staring into space when you should be working? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 5 | Have to do a job over because you made a mistake or your supervisor told you to do a job over? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 6 | Waste time looking for misplaced supplies, materials, papers, phone numbers, etc.? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 7 | Find you have forgotten to call someone? | 0 | 1 | 2 | 3 | 4 |
| 8 | Find you have forgotten to respond to a request? | 0 | 1 | 2 | 3 | 4 |
| 9 | Become annoyed with or irritated by co-workers  boss/supervisor, clients/customers/vendors or others? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 10 | Become impatient with others at work? | 0 | 1 | 2 | 3 | 4 |
| 11 | Avoid attending meetings? | 0 | 1 | 2 | 3 | 4 |
| 12 | Avoid interaction with co-workers, clients, vendors or supervisors? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 13 | Have co-worker redo something you had completed? | 0 | 1 | 2 | 3 | 4 |
| 14 | Find it difficult to concentrate on the task at hand? | 0 | 1 | 2 | 3 | 4 |
| 15 | Fall asleep unexpectedly or become very sleep while at  work? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 16 | Become restless while at work? | 0 | 1 | 2 | 3 | 4 |
| 17 | Notice that your productivity for the time spent is lower  than expected? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 18 | Notice that your efficiency for the time spent is lower than expected? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 19 | Lose interest or become bored with your work? | 0 | 1 | 2 | 3 | 4 |
| 20 | Work more slowly or take longer to complete tasks than expected? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 21 | Have your boss/co-workers remind you to do things? | 0 | 1 | 2 | 3 | 4 |
| 22 | Not want to return phone calls or put off returning calls? |  |  |  |  |  |
|  | 0 | 1 | 2 | 3 | 4 |
| 23 | Have trouble organizing work or setting priorities? | 0 | 1 | 2 | 3 | 4 |
| 24 | Fail to finish assigned tasks? | 0 | 1 | 2 | 3 | 4 |
| 25 | Feel too exhausted to do your work? | 0 | 1 | 2 | 3 | 4 |

**Work Productivity and Activity Impairment Questionnaire:**

**V2.0 (WPAI:D)**

The following questions ask about the effect of your depression on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_ NO \_\_\_ YES  
    *If NO, check “NO” and skip to question 6.*

The next questions are about the **past seven days**, not including today.

1. During the past seven days, how many hours did you miss from work because of problems associated with your depression? *Include hours you missed on sick days, times you went in late, left early, etc., because of your depression. Do not include time you missed to participate in this study.  
     
   \_\_\_\_\_* HOURS
2. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?  
     
   \_\_\_\_\_HOURS
3. During the past seven days, how many hours did you actually work?  
     
   \_\_\_\_\_HOURS  *(If “0”, skip to question 6.)*

1. During the past seven days, how much did your mood affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your mood affected your work only a little, choose a low number. Choose a high number if your mood affected your work a great deal.

Consider only how much your mood affected   
productivity while you were working.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My mood had no effect on my work |  |  |  |  |  |  |  |  |  |  |  | My mood completely prevented me from working |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE A NUMBER

1. During the past seven days, how much did your mood affect your ability to do your regular daily activities, other than work at a job?   
     
   *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your mood affected your activities only a little, choose a low number. Choose a high number if your mood affected your activities a great deal.*

Consider only how much your mood affected your ability   
to do your regular daily activities, other than work at a job.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My mood had no effect on my daily activities |  |  |  |  |  |  |  |  |  |  |  | My mood completely prevented me from doing my daily activities |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE A NUMBER

1. During the past seven days, how much did your cognitive function affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your cognitive function affected your work only a little, choose a low number. Choose a high number if your cognitive function affected your work a great deal.

Consider only how much your cognitive function affected   
productivity while you were working.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My cognitive function had no effect on my work |  |  |  |  |  |  |  |  |  |  |  | My cognitive function completely prevented me from working |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE A NUMBER

1. During the past seven days, how much did your cognitive function affect your ability to do your regular daily activities, other than work at a job?   
     
   *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your* cognitive function *affected your activities only a little, choose a low number. Choose a high number if your* cognitive function *affected your activities a great deal.*

Consider only how much your cognitive function affected your ability   
to do your regular daily activities, other than work at a job.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My cognitive function had no effect on my daily activities |  |  |  |  |  |  |  |  |  |  |  | My cognitive function prevented me from doing my daily activities |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE A NUMBER

1. During the past seven days, how much did your social abilities affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your social abilities affected your work only a little, choose a low number. Choose a high number if your social abilities affected your work a great deal.

Consider only how much your social abilities affected   
productivity while you were working.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My social abilities had no effect on my work |  |  |  |  |  |  |  |  |  |  |  | My social abilities completely prevented me from working |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

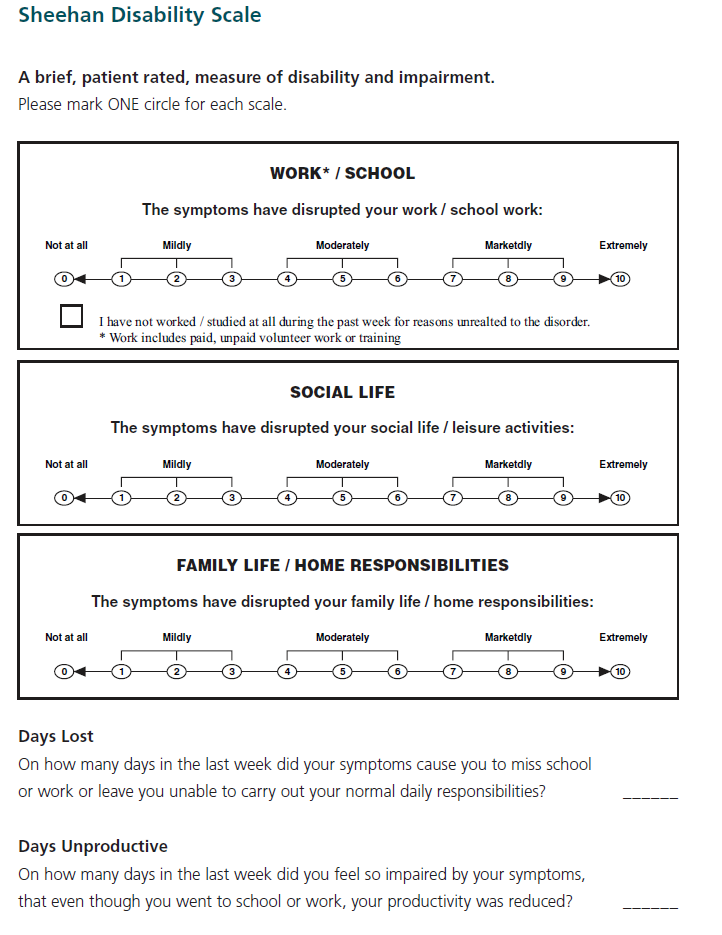
CIRCLE A NUMBER

1. During the past seven days, how much did your social abilities affect your ability to do your regular daily activities, other than work at a job?   
     
   *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your* social abilities *affected your activities only a little, choose a low number. Choose a high number if your* social abilities *affected your activities a great deal.*

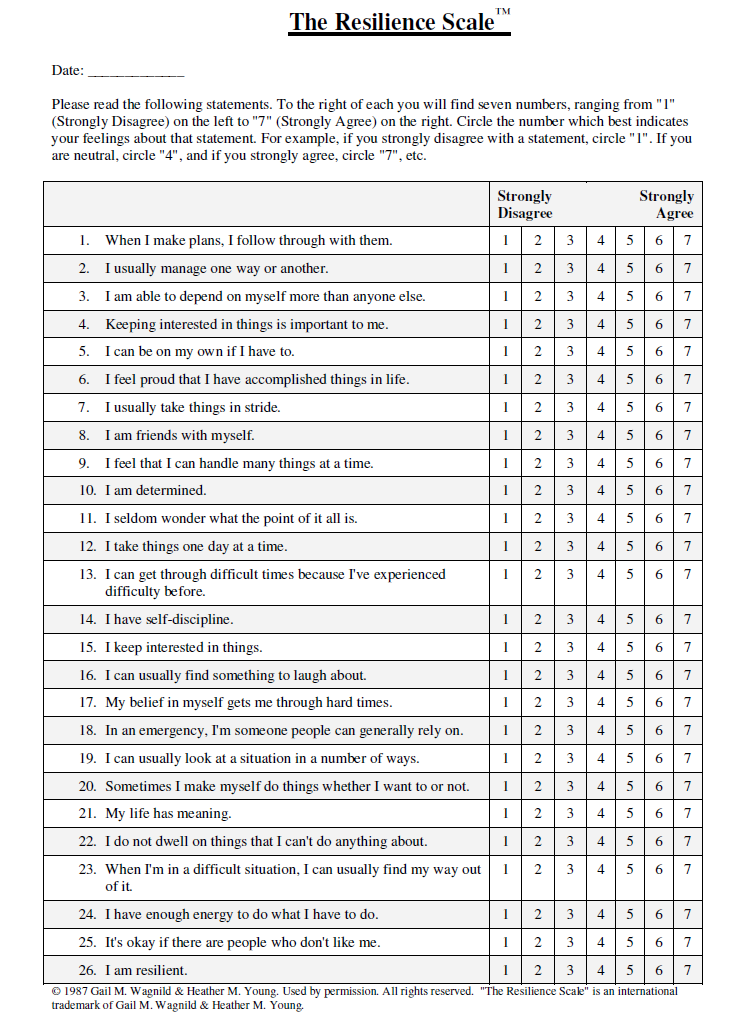
Consider only how much your social abilities affected your ability   
to do your regular daily activities, other than work at a job.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| My social abilities had no effect on my daily activities |  |  |  |  |  |  |  |  |  |  |  | My social abilities prevented me from doing my daily activities |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

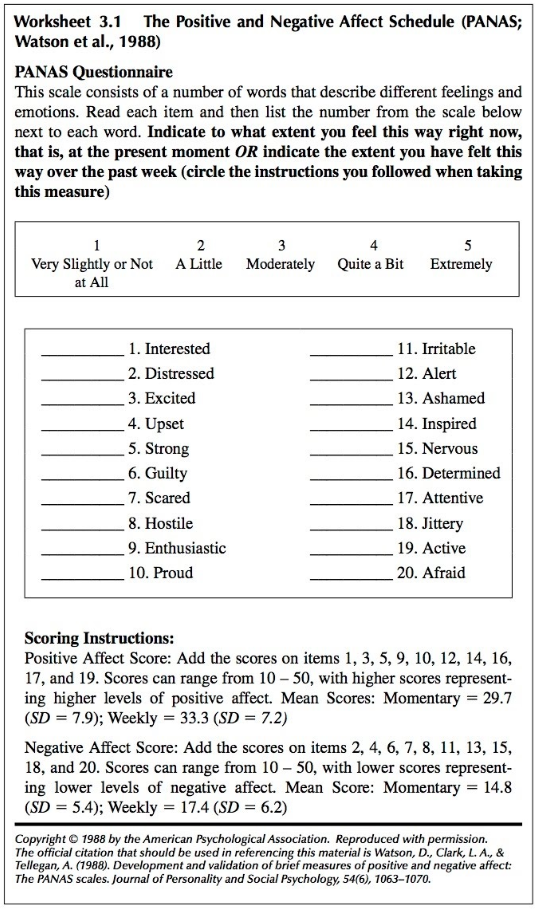
CIRCLE A NUMBER

**Appendix E**

**Appendix F**

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**Appendix G**

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**Appendix H**

**The Cognitive Failures Questionnaire** (Broadbent, Cooper, FitzGerald & Parkes, 1982)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to your in the past 6 months. Please circle the appropriate number.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Very  often | Quite often | Occasion- ally | Very  rarely | Never |
| 1. | Do you read something and find you haven’t been thinking about it and must read it again? | 4 | 3 | 2 | 1 | 0 |
| 2. | Do you find you forget why you went from one part of the house to the other? | 4 | 3 | 2 | 1 | 0 |
| 3. | Do you fail to notice signposts on the road? | 4 | 3 | 2 | 1 | 0 |
| 4. | Do you find you confuse right and left when giving directions? | 4 | 3 | 2 | 1 | 0 |
| 5. | Do you bump into people? | 4 | 3 | 2 | 1 | 0 |
| 6. | Do you find you forget whether you’ve turned off a light or a fire or locked the door? | 4 | 3 | 2 | 1 | 0 |
| 7. | Do you fail to listen to people’s names when you are meeting them? | 4 | 3 | 2 | 1 | 0 |
| 8. | Do you say something and realize afterwards that it might be taken as insulting? | 4 | 3 | 2 | 1 | 0 |
| 9. | Do you fail to hear people speaking to you when you are doing something else? | 4 | 3 | 2 | 1 | 0 |
| 10. | Do you lose your temper and regret it? | 4 | 3 | 2 | 1 | 0 |
| 11. | Do you leave important letters unanswered for days? | 4 | 3 | 2 | 1 | 0 |
| 12. | Do you find you forget which way to turn on a road you know well but rarely use? | 4 | 3 | 2 | 1 | 0 |
| 13. | Do you fail to see what you want in a supermarket (although it’s there)? | 4 | 3 | 2 | 1 | 0 |
| 14. | Do you find yourself suddenly wondering whether you’ve used a word correctly? | 4 | 3 | 2 | 1 | 0 |
|  |  | Very  often | Quite often | Occasion- ally | Very  rarely | Never |
| 15. | Do you have trouble making up your mind? | 4 | 3 | 2 | 1 | 0 |
| 16. | Do you find you forget appointments? | 4 | 3 | 2 | 1 | 0 |
| 17. | Do you forget where you put something like a newspaper or a book? | 4 | 3 | 2 | 1 | 0 |
| 18. | Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket? | 4 | 3 | 2 | 1 | 0 |
| 19. | Do you daydream when you ought to be listening to something? | 4 | 3 | 2 | 1 | 0 |
| 20. | Do you find you forget people’s names? | 4 | 3 | 2 | 1 | 0 |
| 21. | Do you start doing one thing at home and get distracted into doing something else (unintentionally)? | 4 | 3 | 2 | 1 | 0 |
| 22. | Do you find you can’t quite remember something although it’s “on the tip of your tongue”? | 4 | 3 | 2 | 1 | 0 |
| 23. | Do you find you forget what you came to the shops to buy? | 4 | 3 | 2 | 1 | 0 |
| 24. | Do you drop things? | 4 | 3 | 2 | 1 | 0 |
| 25. | Do you find you can’t think of anything to say? | 4 | 3 | 2 | 1 | 0 |

**Appendix I**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 4 | | | | |
|  |  | | | |
| *Schedule of High Cognition Treatment Visits. The “X” symbol denotes that this modality of treatment will occur.* | | | | |
|  | | Cognition Tasks | Emotion Processing Tasks | Social Cognition Tasks | |
| Treatment Session # | |
| 1 | | **X** |  |  | |
| 2 | | **X** |  |  | |
| 3 | | **X** |  |  | |
| 4 | |  |  | **X** | |
| 5 | |  |  | **X** | |
| 6 | |  | **X** |  | |
| 7 | |  | **X** |  | |
| 8 | | **X** |  |  | |
| 9 | | **X** |  |  | |
| 10 | | **X** |  |  | |
| 11 | |  | **X** |  | |
| 12 | |  |  | **X** | |
| 13 | | **X** |  |  | |
| 14 | | **X** |  |  | |
| 15 | | **X** |  |  | |
| 16 | | **X** |  |  | |
|  | | | | | |

**Appendix J**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 5 | | | | |
|  |  | | | |
| *Schedule of High Emotion Treatment Visits. The “X” symbol denotes that this modality of treatment will occur.* | | | | |
|  | | Cognition Tasks | Emotion Processing Tasks | Social Cognition Tasks | |
| Treatment Session # | |
| 1 | |  | **X** |  | |
| 2 | |  | **X** |  | |
| 3 | |  | **X** |  | |
| 4 | | **X** |  |  | |
| 5 | | **X** |  |  | |
| 6 | |  |  | **X** | |
| 7 | |  |  | **X** | |
| 8 | |  | **X** |  | |
| 9 | |  | **X** |  | |
| 10 | |  | **X** |  | |
| 11 | |  |  | **X** | |
| 12 | | **X** |  |  | |
| 13 | |  | **X** |  | |
| 14 | |  | **X** |  | |
| 15 | |  | **X** |  | |
| 16 | |  | **X** |  | |
|  | | | | | |

**Appendix K**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 6 | | | | |
|  |  | | | |
| *Schedule of High Social Cognition Treatment Visits. The “X” symbol denotes that this modality of treatment will occur.* | | | | |
|  | | Cognition Tasks | Emotion Processing Tasks | Social Cognition Tasks | |
| Treatment Session # | |
| 1 | |  |  | **X** | |
| 2 | |  |  | **X** | |
| 3 | |  |  | **X** | |
| 4 | | **X** |  |  | |
| 5 | | **X** |  |  | |
| 6 | |  | **X** |  | |
| 7 | |  | **X** |  | |
| 8 | |  |  | **X** | |
| 9 | |  |  | **X** | |
| 10 | |  |  | **X** | |
| 11 | |  | **X** |  | |
| 12 | | **X** |  |  | |
| 13 | |  |  | **X** | |
| 14 | |  |  | **X** | |
| 15 | |  |  | **X** | |
| 16 | |  |  | **X** | |
|  | | | | | |