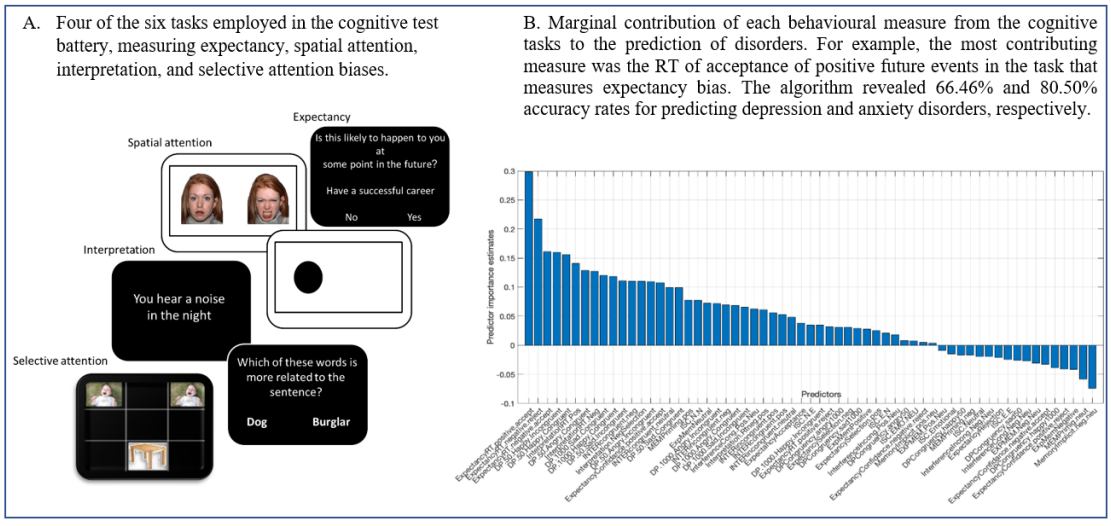
Aims and deliverables.

We propose a novel stratification and intervention approach across anxiety and depression based on a cognitive mechanistic framework[1] of antidepressant treatment effects. Selective serotonin reuptake inhibitors (SSRIs) are known to improve cognition *before* symptom alleviation[2], offering the opportunity to optimise treatment in the early stages of antidepressant administration. The research aims to: (1) characterise altered cognitions associated with symptoms severity using a comprehensive cognitive test battery; (2) capitalise on early cognitive change following SSRI treatment onset to predict treatment responsiveness, using advanced machine learning (ML)-based analysis; and (3) develop timely individually-tailored cognitive interventions aimed to potentiate responsiveness to SSRI treatment.

Background and justification

The prevalent psychiatric evaluation of anxiety and depression, which is based on self-reported symptoms and classification to discrete disorders, is faced with vast overlap between disorders and within-disorder heterogeneity, which may explain the medium success rates of treatments[3]. The suggested research proposes a new framework for stratification, which is based on alterations in the underlying cognitive mechanisms early in antidepressant treatment, rather than on subjective symptomatology. Distinct patterns of processing affect the way individuals with anxiety and depression pay attention to, interpret, expect, learn and remember information[4]. Employing advanced ML-based analysis and a comprehensive cognitive test battery (Fig 1A), the PI Okon-Singer and co-applicant Fishbain accurately predicted symptoms of anxiety and depression based solely on cognitive performance[5-6] (Fig 1B).

Figure 1: Predicting anxiety and depression using cognitive test battery and ML-based analysis[5,6]



Assessing early cognitive change following treatment onset offers the opportunity to predict treatment outcome. Currently, SSRIs serve as the first line of treatment for anxiety and depression. Many individuals do not profit from the first administered drug and antidepressants have a slow onset in their therapeutic effects, which can lead to a long delay until treatment is optimised. Recently, collaborator Harmer found early changes in cognitive processes can predict response to SSRIs in depression[2]. The proposed research builds on this knowledge to develop early cognitive intervention for those individuals, who are not likely to respond to SSRIs alone.

Using a cognitive intervention targeting similar mechanisms to those affected by SSRIs, may offer an effective approach to potentiate treatment effects. For example, encouraging participants to choose benign over negative interpretations for ambiguous situations reduces interpretation bias, which mediates symptoms reduction[8]. Specific altered cognitions, identified by the cognitive test battery[5-6], will enable development of personalized-intervention expected to enhance positive affective processing.

Details of the planned activities

WP1- Optimisation of cognitive measures with Lived Experience Advisory Group:

Building on the expertise of co-applicant Murphy in using participatory research practice and lived experience involvement[7], we will form a Lived Experience Advisory Group (LEAG). The LEAG will meet at least every 6 months during the project and will be actively involved in all aspects of the research cycle, from planning, to delivery and dissemination. We will work with the LEAG to optimize the cognitive measures and ensure the measures are relevant to their own experience and treatment. Members of the LEAG will be recruited from Murphy's existing networks and through outreach activities to include underrepresented groups and will be compensated for their time and expenses. The LEAG will be represented on the steering committee and provide input on all core decisions. Importantly, this collaborative research will offer the Israeli PI and her team an opportunity to learn how to involve lived experience in research, and to pioneer the involvement of lived experience in Israel.

The cognitive measures used in WP2 and WP3 will be based on those used by the PI's group previously (see Figure 1) and will be adapted together with the LEAG to ensure relevance, feasibility and acceptability. These will include interpretation of ambiguous situations, expectancy of positive and negative future events, selective and spatial attention biases, reward learning, and processing of emotional facial expressions.

WP2: Identifying cognitive patterns and predict treatment responsiveness.

240 (including 20% dropout) individuals with anxiety and/or depression who have been prescribed SSRIs by their GP, but who have not yet started treatment will be included in the study. The study will run in the UK with the support of UCL Priment Clinical Trials Unit (3-4 participants per week).

At baseline and before the onset of SSRI treatment, symptoms of anxiety and depression will be assessed using questionnaires and semi-structured clinical evaluation. Participants will perform a battery of cognitive tasks to establish baseline cognitive patterns associated with symptom severity. Participants will complete the same assessments on day 7-9 post-SSRI treatment onset. After 8 weeks of SSRI treatment, symptoms of anxiety and depression will be re-assessed.

ML-based prediction of responsiveness to treatment in week 8 will involve clustering participants to responders and non-responders based on the reduction of symptoms in week 8, and predicting it from cognitive task performance change from baseline to day 7-9. The predictive model will be validated using K-fold cross-validation. Larger affective processing change is expected to predict responsiveness to treatment[7].

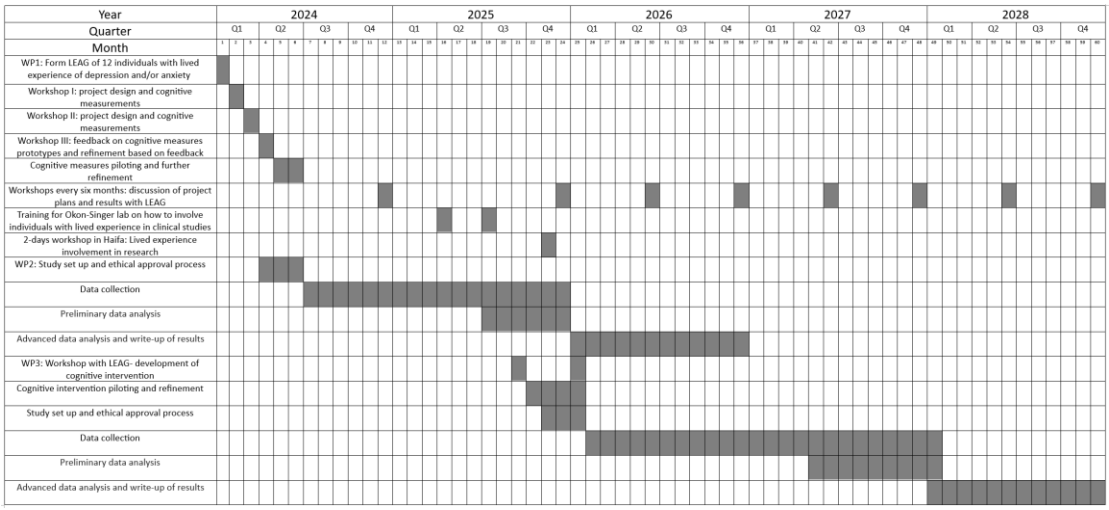
WP3: Individually-tailored cognitive intervention to increase responsiveness to SSRIs.

360 (including 20% dropout) individuals with anxiety and/or depression that were recommended by their GP to start SSRI treatment will be recruited in Israel in collaboration with community clinics at three large hospitals (3-4 participants per week).

The same cognitive measures as used in WP2 will be administered to participants at baseline and on day 7-9 post-SSRI treatment onset. Following the day 7-9 assessment, participants will be randomly assigned to two groups: 100 participants will continue to receive SSRI treatment as usual. The remaining 200 participants will be classified using the predictive model developed in WP2 into responders/non-responders to SSRIs. About half of these participants (n=100) are expected to be classified into each group. Responders and non-responders will also continue SSRI treatment; Half of the non-responders will be randomised to receive adjunct personalized cognitive intervention and the other half will receive a dummy-intervention. After 8 weeks, anxiety and depression symptoms will be re-assessed among all participants.

Among non-responders, personalized-intervention is expected to alleviate symptoms compared to the dummy-intervention. Both prediction groups (i.e., responders+ non-responders) are expected to show greater improvement in symptoms compared to the treatment as usual group.

Timetable and milestones



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