Neurofeedback training to improve prefrontal functioning in older adults with subclinical depression and anxiety: a randomised control trial

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a) Project title: Neurofeedback training to improve prefrontal functioning in older adults with subclinical depression and anxiety: a randomised control trial

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c) Proposed Commencement and End Date: 1 January 2023–31 March 2024 (15 months)

d) Project Summary: Symptoms of depression and anxiety are common in older adults and are associated with poor outcomes and the risk of dementia. The prefrontal cortex (PFC) is crucial for emotion regulation. Poor PFC function may underlie subclinical depression and anxiety symptoms in older people, which could progress to clinical conditions. Neurofeedback training based on electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS) teaches individuals to self-regulate different aspects of brain activity and induce neurocognitive improvements. This proposed project will examine whether prefrontal EEG and fNIRS neurofeedback training programmes can enhance the mood and cognition of older adults with subclinical depression and anxiety.

e) Keywords: depression, anxiety, neurofeedback, prefrontal cortex

f) Introduction/Background:

Subclinical symptoms of depression and anxiety are common in older adults, with some estimates indicating that these symptoms are present in 10–52% of community-dwelling older adults (Bryant et al., 2008; Meeks et al., 2011). These symptoms strongly correlate with each other and frequently co-occur in older adults (Beekman et al., 2000; Yochim et al., 2010). In older adults without any psychiatric disorder, subclinical depression and anxiety are associated with a poor quality of life, adverse health outcomes, cognitive deficits, and self-reported functional impairments similar to those seen in patients with mood and anxiety disorders (Beaudreau & O'Hara, 2008; Haigh et al., 2018; Laborde-Lahoz et al., 2015; Meeks et al., 2011). Most concerningly, studies have shown that older adults with subclinical depression and anxiety are more likely than those with low levels of relevant symptoms to be diagnosed with affective disorders and mild cognitive impairment or dementia later in life (Richard et al., 2013; Steenland et al., 2012). Thus, interventions for older people with elevated subclinical symptoms of depression and anxiety are crucial for preventing affective disorders and dementia late in life. **Although the public is highly aware of measures to prevent physical illnesses (e.g., vaccination, medication), prevention of mental illnesses in the context of geriatric care has been neglected, and effective interventions for subclinical depression and anxiety in older adults remain elusive.** For example, a meta-analysis of six psychotherapy studies on subclinical depression in older adults identified only a small effect-size improvement from psychotherapies relative to control interventions (Cuijpers et al., 2014).

During negative emotional experiences, the prefrontal cortex (PFC) plays a pivotal role in downregulating activity in the amygdala and other limbic regions (Etkin et al., 2015; Wager et

al., 2008). PFC dysfunction may cause the amygdala to become overactivated and dysregulated, resulting in mood and anxiety symptoms. This prefrontal–subcortical model has received extensive support from neuropsychological and neuroimaging studies of mood and anxiety disorders (Grahek et al., 2019; Mochcovitch et al., 2014; Snyder, 2013; Snyder et al., 2015). **Our and others' work also supports the utility of this model for studying subclinical depression and anxiety (Mathersul et al., 2008; Szymkowicz et al., 2019; Yeung et al., 2021a, b).** For example, our recent study showed similar negative relationships between PFC functioning and symptoms of depression and anxiety in non-psychiatric older adults (Yeung et al., 2021a).

In humans, emotion is addressed by the frontal asymmetry model, which posits that the left and right frontal lobes mediate positive emotion/approach behaviour and negative emotion/ withdrawal behaviour, respectively. In keeping with this model, converging evidence indicates that mood and anxiety symptoms are primarily associated with reduced left frontal activity and increased right frontal activity, respectively, and both are related to a reduction in left-asymmetric frontal activity in resting and task states in both clinical and general populations (Adoph & Margraf, 2017; Bruder et al., 2017; Mathersul et al., 2008). **Therefore, improving PFC function, particularly restoring frontal asymmetry, represents a promising trajectory for enhancing the mental health and cognitive function of older adults with subclinical depression and anxiety.** To date, this has remained an unexplored area in neuroscience research on ageing.

Neurofeedback training is a non-pharmaceutical neurorehabilitation technique that can potentially improve prefrontal function and enhance mental health and cognitive functions. This technique uses sensory feedback to teach individuals to self-regulate specific brain activities, with the goal of inducing long-term neuroplasticity and functional improvements (Hammond, 2011; Sitaram et al., 2017). Traditionally, neurofeedback training has been conducted using EEG, and much research has applied such training interventions for the treatment of a variety of psychiatric disorders (Hammond, 2005; Marzbani et al., 2016). Randomised controlled trials have shown that compared with placebo, approximately eight sessions of EEG neurofeedback training, often intended to increase the symmetry of frontal alpha power, can significantly reduce symptoms across mood and anxiety disorders (Trambaiolli et al., 2021). According to two meta-analyses, the estimated effect sizes of the improvement in symptoms of depression or anxiety ranged from large to very large (Fernández-Álvarez et al., 2020; Steingrimsson et al., 2020), which are similar to, if not greater than, the medium-size effects for pharmacological treatment vs. placebo controls (Kirsch et al., 2008). In older adults, a recent systematic review showed that most studies (N = 14) reported positive immediate effects of regimens comprising approximately 8 sessions of EEG neurofeedback training in at least one cognitive domain (Laborda-Sánchez & Cansino, 2021). **However, the literature is limited by the lack of randomised controlled trials with follow-up. The effect of EEG neurofeedback training on negative affective symptoms in older adults also remains unclear.**

In recent years, interest in using fNIRS (in which our team has expertise, e.g., Yeung et al., 2016a, b, 2019a, b, 2021a, b) to deliver neurofeedback training has grown (Ehlis et al., 2018; Kohl et al., 2020). The underlying mechanism of such training with fNIRS is different from that of training with EEG. Whereas EEG neurofeedback training involves self-regulation of the

synchronous activity of neuronal populations, fNIRS neurofeedback training focuses on self-regulation of the haemodynamic response elicited by neuronal activity. Compared with EEG, fNIRS has a lower temporal resolution but a higher spatial resolution and is more resilient to movement artifacts. **As such, fNIRS can increase the convenience of neurofeedback training and allow for the regulation of brain activity at more localised sites (e.g., the dorsolateral PFC).** Some studies have observed successful regulation of frontal haemodynamics after only one fNIRS neurofeedback session in young and/or older adults (Kober et al., 2019; Li et al., 2019). Hence, fNIRS neurofeedback training may increase the pace of learning and require fewer sessions than its EEG counterpart (Kohl et al., 2020). In addition, one recent study showed that patients with social anxiety disorder had reduced anxiety symptoms after fNIRS neurofeedback training (Kimmig et al., 2019). Nevertheless, **whether and to what extent fNIRS neurofeedback training improves mental health and cognitive functions in older adults with subclinical depression and anxiety remain to be demonstrated.**

g) Objectives:

The aim of this proposed project will be to compare the mood- and cognitive-enhancing effects of 8 sessions of prefrontal EEG and fNIRS neurofeedback training programmes in older adults with subclinical depression and anxiety through a randomised controlled trial. We planned to compare EEG and fNIRS neurofeedback because in principle they act on two different aspects of brain function. Because electrical activity and hemodynamic activity in the brain have a non-perfect relationship (Shibasaki, 2008), the two neurofeedback methods may yield varying effects. In addition, we chose EEG and fNIRS because they are the only two existing neuroimaging methods that allow for real-time human-computer interactions conducted through a wearable system. The findings will provide crucial knowledge about whether prefrontal neurofeedback training can reduce the risks of affective disorders and accelerated cognitive decline in old age (Steenland et al., 2012; Richard et al., 2013).

Three objectives are set, as follows:

1) To elucidate whether EEG and fNIRS neurofeedback training programmes improve the mental health of older adults with subclinical depression and anxiety;
2) To determine whether EEG and fNIRS neurofeedback training programmes enhance the frontal cognitive functions of older adults with subclinical depression and anxiety; and
3) To compare the relative effectiveness of these two programmes based on different neural mechanisms in enhancing the mental health and cognitive functions of older adults with subclinical depression and anxiety.

h) Research Plan and Methodology:

Design: This proposed project has been designed in accordance with current consensus on the reporting and experimental design of clinical and cognitive–behavioural neurofeedback studies (CRED-nf; Ros et al., 2020). The participants will be randomly and equally assigned to one of three neurofeedback training groups: (1) sham, (2) EEG, and (3) fNIRS. Each participant will

complete a neurophysiological assessment (1) before, (2) immediately after, and (3) 1 month after the intervention (see Appendix I).

Participants: Ninety older adults without dementia will be recruited via advertisements at PolyU and community centres for older adults. The inclusion criteria will be as follows: (i) age of 60–79 years; (ii) right-handedness as assessed using the short form of the Edinburgh Handedness Inventory (Veale, 2014); (iii) a moderate or higher score on at least one of the depression and anxiety subscales (but not necessarily both) of the Depression Anxiety Stress Scale-21 (DASS-21), which has been shown to yield reliable and valid scores (Gomez, Summers, Summers, Wolf, & Summers, 2014; Norton, 2007); (iv) no history of neurological or psychiatric disorder; (iv) no history of traumatic brain injury requiring hospitalisation; (vi) not currently using psychotropic medication; (vii) ability to read Traditional Chinese text; (viii) normal or corrected-to-normal vision; and (ix) a score of at least 19 on the Hong Kong Montreal Cognitive Assessment (HK-MoCA; Wong et al., 2009).

The inclusion criteria that we planned to use were based on those employed by prefrontal neurofeedback studies in mood or anxiety disorders (e.g., Kimmig et al., 2019; Peeters et al., 2014). Conventionally, participants are selected based on a certain threshold of depressive or anxiety symptoms, or the clinical diagnosis; neither cognitive nor brain dysfunction constitutes an inclusion criterion. Nevertheless, since variation in cognitive and PFC functioning levels may affect the treatment response, subsequent analyses will consider baseline cognitive and PFC functioning levels.

The proposed sample size was determined based on randomised controlled trials on neurofeedback training for mood/anxiety disorders, which collectively reported a weighted mean Cohen's *f* of 0.59 for the group × time interaction on the scores for depression, anxiety, and/or post-traumatic stress [(0.37 × 90 + 0.88 × 24 + 0.89 × 44 + 0.63 × 18)/(90 + 24 + 44 + 18)] (Lee et al., 2019; van der Kolk et al., 2016; Wang et al., 2019; Zilverstand et al., 2015). Accordingly, a power analysis (G*Power v3.1.9.4) indicated that 14 participants per group will be required to detect any significant differences between the three groups based on a power of 0.80 and an alpha level of 0.017 (three outcome measures per data type). We expect a smaller effect size for subclinical populations and a loss of participant data due to dropouts and unusable data. As such, **we will recruit 30 individuals per group.**

Study Procedures: Potential participants will first be subjected to a screening evaluation to assess eligibility. Eligible individuals will be invited to PolyU for assessment and training. The training will comprise 8 60-min sessions conducted within 4 weeks. Each session will include 25-min effective training time, for a total training time of 250 min, in keeping with recent recommendations (Kohl et al., 2020). In addition, the participants will undertake several experimental tasks under simultaneous EEG–fNIRS recording and complete several questionnaires at three time points, as described in the 'Neurophysiological Assessment' section. Multiple studies have demonstrated that EEG, fNIRS, and neurofeedback training can be applied to older adults over 70, and even to individuals with dementia (Laborda-Sánchez & Cansino, 2021; Trambaiolli et al., 2021; Yeung & Chan, 2021). Therefore, we expect that older adults who are screened for dementia by the HK-MoCA will be able to follow both the assessment and training protocols.

Neurofeedback Training: During training, participants will be asked to follow the instructions on a computer screen. **They will complete five rounds of training task. Each round starts with a 30-s rest phase followed by 4.5 min of self-regulation phase.** During the rest phase, a fixation cross will appear onscreen, and the participants will be instructed to sit still and relax. During the regulation period, the participants will be asked to make the square change from white to black (i.e., an intrinsic social reward) but will not be given specific strategies. The darkness of colour will represent the increase in either frontal alpha asymmetry or frontal oxyhaemoglobin (HbO) asymmetry. The values at the moment will be compared against the 25-s pre-regulation baseline. In the sham condition, participants will receive visual feedback based on pre-recordings and/or other participants' recordings. Participants will undergo a 3-min rest period before and after each training session to track changes in resting-state brain activity within and across sessions.

During each training session, a cap adjusted to the participant's head size will be used to mount the EEG and fNIRS sensors. The hardware setup will be the same for all groups to ensure that both the participant and the experimenter are blinded to the training group. For EEG to be recorded by the ANT eego rt8 amplifier (ANT Neuro, Hengelo, The Netherlands), electrodes will be placed at Fp1, F3, F4, Fz, Fpz, Cz, GND (ground), lower VEOG, and on the two earlobes (references). Data will be collected at 2,048 Hz. For fNIRS to be recorded by the wearable OctaMon+ system (Artinis Medical Systems, Gelderland, The Netherlands), two sources, each surrounded by four detectors positioned approximately 3 cm apart, will be placed on the scalp such that the two channels near the cerebral fissure on each side of the hemispheres are surrounded F3 and F4. Data will be sampled at 50 Hz. **Depending on the training group, frontal asymmetry in terms of the difference in alpha power (8–13 Hz) between F3 and F4 and the mean change in HbO concentration between the left and right PFC will be chosen as the target objective.** For both real training groups, real-time data streaming will be performed using the Lab Streaming Layer (Kothe, 2014) and OpenVibe (Renard et al., 2010) according to published guidelines (Kohl et al., 2020) (see the Appendix I for the detailed signal processing pipelines).

Neurophysiological Assessment: A 1.5-h neurophysiological assessment will be administered at each of three time points (pre, post, and 1-month follow-up) to evaluate the effects of neurofeedback training. The participants will complete the DASS-21 (Chinese version) to measure their depressive and anxiety symptoms over the last week (Gomez et al., 2014; Norton, 2007); the Hospital Anxiety and Depression Scale (HADS; Chinese version) to measure their signs of anxiousness and depression during the previous week (Flint & Rifat, 2002); the Pittsburgh Sleep Quality Index to measure their sleep quality over the last month (Buysse et al., 1989); the Satisfaction with Life Scale (Chinese version) to quantify their general life satisfaction (Wu & Yao, 2006); and Lawton Instrumental Activities of Daily Living Scale (IADL; Chinese version) to assess independent living skills (Tong & Man, 2002). The participants will also complete three computerised tasks to assess different components of frontal cognitive function (see below) under simultaneous EEG–fNIRS measurements, using the same setup described for neurofeedback training. At the first visit, the participants will also complete the HK-MoCA to screen for dementia (Wong et al., 2009). Immediately after the intervention, they will be asked whether they know their treatment group assignment to check the strength of blinding.

Each assessment task (eyes open, Emotional Stroop, *n*-back) proposed for this research will comprise a difficult and an easy condition. The eyes open test is used to let the machine measure the activation baseline when the participants open their eyes (Barry & De Blasio, 2017). It requires participants to maintain their eyes open for 3 minutes. The Emotional Stroop task is used to assess inhibitory control (Imbir et al., 2022). Participants are shown photos of different emotions with unrelated traditional Chinese emotion names. They are asked to name the photos by emotion. It requires participants to inhibit their emotions lead by the wordings and react to the content of the photo. Differences in accuracy and mean RT and changes in the prefrontal HbO concentration and theta power between the two conditions will be the dependent variables. The *n*-back task is used to assess working memory (Yeung et al., 2016b, 2019b). During the task, participants are shown a sequence of digits and asked to judge via button press whether the digit they are seeing is zero (0-back; easy) or the same as the digit they saw two trials before (2-back; difficult). Differences in accuracy and mean reaction time (RT) and changes in the prefrontal HbO concentration and theta power between the two conditions will be the dependent variables.

Data Analysis: In this project, the primary outcome measures are mood and anxiety measures (i.e., DASS-21 and HADS scores), and the secondary outcome measures are task performance and PFC measures, as well as other mental health measures. The outcome measures will be analysed according to the CRED-nf checklist (Ros et al., 2020). Linear mixed models with group (sham, EEG, fNIRS), time (baseline, post, follow-up), and condition (easy, difficult) as the fixed factors; age and education years as covariates; and the subject as a random factor will be used to analyse the behavioural, fNIRS, and EEG data. We expect that participants in the two real neurofeedback training groups will demonstrate significant improvements in mental health, cognitive function, and frontal lobe function at the post and follow-up assessments relative to the sham group participants. In addition, we will evaluate differences in pre–post changes in mental health and cognitive functions between the two real training groups to address Objective 3. Moreover, we will examine the correlation between baseline cognitive and PFC functioning levels and the pre-post changes in DASS-21 scores to elucidate individual differences in the treatment response for each neurofeedback group.

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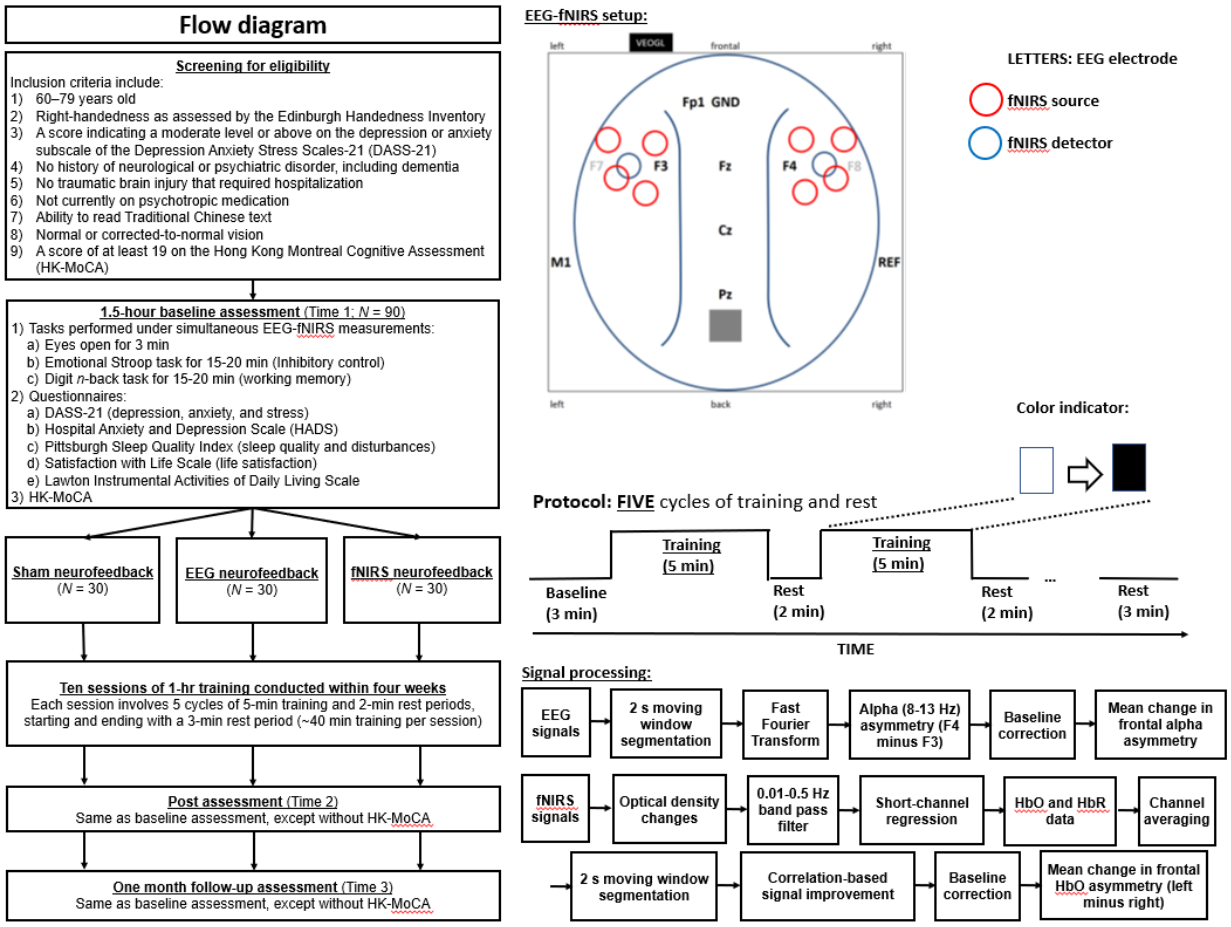
Appendix:

Appendix I: Experimental design.



For both modalities, features will be extracted online using a Hamming window function applied to 2-s moving window epochs (with 0.2-s sliding windows). For EEG groups, the automated subspace reconstruction (ASR) method will first be applied to the 3-minute baseline EEG recording to derive a filter for artifact correction for the rest of the session. Before calibrating the ASR filter, a 0.5-Hz highpass filter will be applied for zero-centreing, and data will be re-referenced to the average of the two earlobes. During training, the ASR filter will be used to remove ocular and muscle artifacts. To yield the target index, an 8–13-Hz bandpass filter will be applied to extract EEG power in the alpha band, and after log transformation, the alpha power at F4 will be subtracted from that at F3 to yield the frontal alpha asymmetry index.

For fNIRS, raw signals will be converted to optical density changes and then to changes in HbO and deoxyhaemoglobin concentration (Delpy et al., 1988). Correlation-based signal improvement that considers both HbO and HbR changes will be used to remove movement artifacts (Cui et al., 2010). Short-separation channels will be subtracted from long-separation channels to remove global physiological confounders, and the CBSI-HbO signals will be averaged across long-

separation channels for each hemisphere. The difference in mean changes in frontal CBSI-HbO between hemispheres will be generated.