Metacognitive Training for Negative Symptoms (MCT Minus)

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1. Purpose and aims

There is a clear rationale for developing interventions targeting negative symptoms of schizophrenia as negative symptoms are a stronger indicator of current and future functioning than positive symptoms (Velligan et al., 2015) and because they respond poorly to medication (Veerman et al., 2017) and existing psychological interventions (Fusar-Poli et al., 2015). This is reflected in the National Institute of Mental Health (NIMH)- Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus statement (Kirkpatrick, Fenton, Carpenter, & Marder, 2006) that emphasised that persistent negative symptoms represent an unmet therapeutic need for patients suffering from schizophrenia.

The purpose of this study is to evaluate, in a scientific manner, the intervention developed by Swanson et al. 2021: Metacognitive Training (MCT) Minus. This intervention adapted MCT to target negative symptoms in psychotic disorders (e.g. schizophrenia, schizoaffective or non-affective functional psychosis) as the original version of MCT (Moritz & Woodward, 2007) focused exclusively on positive symptoms. The specific aim is to study whether MCT Minus is a promising treatment for the intended population in terms of:

- Reductions in negative symptoms as measured by the Clinical Assessment Interview for Negative Symptoms (CAINS) (Forbes et al., 2011), the Motivation and Pleasure Scale- Self-Report (MAP-SR) (Llerena et al., 2013) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987)

- Reductions in severity of defeatist attitudes as measured by the Dysfunctional Attitudes Scale (DAS) (Weissman & Beck, 1978)

- Improvements in reflective ability as measured by the Reflective Functioning Questionnaire (RFQ-8) (Fonagy et al., 2016)

- Reduction in internalised stigma as measured by the Internalized Stigma of Mental Illness Scale-9 (ISMI-9) (Hammer & Toland, 2017)

- Reductions in depression as measured by the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Schissel, 1990)

- Improved functioning as measured by the World Health Organization (WHO) Disability Assessment Schedule (WHODAS) 2.0 (WHO, 2010)

The research will add to existing research by identifying and measuring potential mechanisms of change for negative symptoms (i.e., defeatist attitudes, reflective functioning, stigma and depression). It will also add to the existing evidence base by measuring whether the cognitive biases addressed in MCT lead to changes in the wider conceptualisation of metacognition used elsewhere and whether the promising results seen in the feasibility study of MCT Minus (Swanson et al., 2021) can be replicated in a randomised controlled trial (RCT) with a control group and a blinded assessor. We also hope to replicate the findings of a previous study by Shan et al. 2020, where MCT was found to be related to the modulation of default-mode network (DMN) homogeneity in schizophrenia, an area thought to be involved in self- and other-reflectivity.

2. State-of-the-art: Introduction

While clinicians tend to focus on positive symptoms as primary treatment targets in schizophrenia, patients prioritize the treatment of depressive and negative symptoms (Moritz et al., 2017). Persistent negative symptoms are experienced by approximately 20%–40% of individuals diagnosed with schizophrenia (Sarkar et al., 2015). Current research indicates that negative symptoms are independent from positive symptoms, depression, cognitive dysfunctions, and disorganization (Galderisi et al., 2018). However, neither medication nor existing psychosocial interventions have proven to be efficacious in reducing negative symptoms (e.g., Correll & Schooler, 2020; Fusar-Poli et al., 2014; Veerman et al., 2017). Consequently, Lutgens et al. (2017) highlighted the need for better understanding of treatment mechanisms underpinning psychological interventions that directly target negative symptoms.

Psychological conceptualizations suggest that negative symptom expression can, in some cases, be understood as a response to adverse experiences (Aleman et al., 2017). For example, Beck et al.'s (2009) cognitive model suggests that negative symptoms emerge from a process where individuals adopt coping strategies of ‘shutting down’ the cognitive–affective experience. This allows individuals to cope with overwhelming or aversive situations in the short term but leads to a reliance on negative symptoms (including social withdrawal, avolition, and diminished expression) to reduce exposure to, and impact of, negative experiences in the longer term. From an attachment framework, Griffiths and McLeod (2019) suggest that negative symptoms may be seen ‘as responses involving emotional and social withdrawal that emerge from threats to self-security’ (p. 62). If negative symptoms can be understood within cognitive and developmental frameworks, it may be possible to develop theoretically driven interventions for their treatment.

2.1. A cognitive model of negative symptoms

Negative symptoms are associated with low expectations of future success (Cox et al., 2016), asocial beliefs (Grant & Beck, 2009), a reduced sense of self-efficacy (Bentall et al., 2010), negative self-concepts (Lincoln et al., 2011), defeatist performance beliefs (Campellone et al., 2016) and self-stigma (Horsselenberg et al., 2016). The cognitive model therefore proposes that negative symptoms might be caused and maintained by dysfunctional beliefs arising as a consequence of repeated failures and setbacks. These appraisals might include negative beliefs about social affiliations; low expectations of pleasure, success and acceptance; defeatist beliefs about performance; and a perception of limited resources (see Beck et al., 2019). The self-perception, and perceived self-efficacy, of individuals diagnosed with schizophrenia may also be influenced by self-stigmatizing views of their mental illness. It might be that these factors result in hypervigilance to perceived criticism (Rector et al., 2005). Longitudinal studies have shown support for the cognitive model as defeatist performance attitudes and asocial beliefs are found to predict future negative symptoms (Granholm et al., 2018; Luther et al., 2015; Thomas et al., 2017).

2.2. Metacognition and psychosis

Metacognition was initially referred to as the capacity to think about and monitor one's mental processes (Flavell, 1979). However, the definition has broadened in contemporary research (Moritz & Lysaker, 2018), ranging ‘from discrete processes involving noticing specific thoughts and feelings to more synthetic acts in which information is integrated into complex representations of the self and others’ (García-Mieres et al., 2020, p. 170). This has given rise to interventions targeting metacognitive processes, some of which have been specifically developed for psychosis (e.g., metacognitive training (MCT), Moritz & Woodward, 2007; metacognitive reflection and insight therapy (MERIT), Lysaker & Klion, 2017) while others have been modified for this population (see Lysaker, Gagen, et al., 2020; Moritz et al., 2019;

Weijers et al., 2020). MCT is based on the premise that cognitive biases play a role in the development and maintenance of psychotic symptoms which can be alleviated by targeting underlying cognitive processes (Pos et al., 2018). The aims are to gain insight and to learn practical strategies to manage distressing symptoms (Schneider & Andreou, 2014). MCT has been shown to reduce delusions (Liu et al., 2018) and positive symptoms (Philipp et al., 2019) and improve cognitive insight (Birulés et al., 2020) and biases (Sauvé et al., 2020). Preliminary evidence also suggests effects on quality of life (Moritz, Andreou, et al., 2014) and illness insight (Lopez-Morinigo et al., 2020).

Several authors highlight the links between negative symptoms and compromised capacity for self/others mental state processing (Griffiths & McLeod, 2019; Gumley et al., 2014; Harder, 2014). There is evidence that suggests a link between metacognition and negative symptoms as limitations in complex metacognitive processes predict negative symptoms in first episode psychosis (Austin et al., 2019) and in more chronic samples, even after controlling for defeatist beliefs, affect recognition and neurocognitive functioning (Lysaker et al., 2015). Metacognitive deficits are also associated with concurrent and future negative symptoms when controlling for verbal memory and education (Faith et al., 2020; Lysaker, et al., 2020). Interestingly, self-reflection in itself has been found to mediate the relationship between neurocognition and negative symptoms (especially for deficits in capacity to communicate about internal states, so called diminished expression) while interpersonal cognitive differentiation (i.e., the ability to construe one's experiences as either similar or different from others' experiences) has been found to mediate the pathway between self-reflectivity and negative symptoms (García-Mieres et al., 2019, 2020). This suggests that negative symptom reduction may at least partially depend on improved metacognitive capacity and that a metacognitive intervention specifically targeting negative symptoms may be beneficial.

Swanson et al. (2021) therefore adapted MCT for negative symptoms to assess the acceptability and feasibility of the intervention, examine variable change over the course of the intervention and carry out a preliminary investigation of putative mechanisms of change. The current project is a further evaluation of this, where we hope to achieve similarly encouraging results in a randomised controlled trial (RCT) with a control group and blinding. We also hope to replicate the findings of a previous study by Shan et al. 2020, where MCT was found to be related to the modulation of default-mode network (DMN) homogeneity in schizophrenia, an area thought to be involved in self- and other-reflectivity. Importantly, it was found that high network homogeneity levels at baseline in the bilateral superior medial prefrontal cortex could predict symptomatic improvement after 8 weeks of drug plus psychotherapy treatment; this illustrates that a more developed understanding of the biological mechanisms underlying negative symptoms would allow us to identify patients that would benefit from each type of treatment and, through that, change the prognosis and treatment outcomes of the condition.

3. Significance and scientific novelty

Research funding would facilitate a RCT to evaluate the intervention trialled by Swanson et al, 2021 in a more rigorous and scientific manner. Given our limited understanding of negative symptoms and how to treat them (see Galderisi et al., 2021), the study would be of both significance and scientific novelty. To fully understand the biological mechanisms behind negative symptoms is essential to be able to develop future treatment options and to identify patients that would benefit from each type of treatment. A more thorough understanding of schizophrenia would decrease the heterogeneity of the condition which would have vast implications for how individuals diagnosed with schizophrenia are treated both in society and in the healthcare setting.

4. Previous results

Two articles (which were based on the main researcher's doctoral thesis at Edinburgh University with funding from National Health Service (NHS) Lothian) have been published in Clinical Psychology and Psychotherapy (Swanson et al., 2022; Swanson et al. 2022) and a poster has been presented at "The 2022 Congress of the Schizophrenia International, Research Society (SIRS)" (6-10 April 2022 in Florence). The project will also be covered in several articles in "Empati" which is the Schizophrenia Association's paper for members which is also distributed to politicians on local, regional and national level.

5. Project description

5.1. Participants, sample size, settings and ethics

Eligible participants will be over the age of 18 with a diagnosis of schizophrenia, delusional disorder or non-affective psychosis in Region Sörmland, Region Västmanland and Region Uppland. Exclusion criteria will be evidence of severe organic brain dysfunction or a learning disability, difficulty with the Swedish language, visual and/or hearing impairment, or being unable or unwilling to provide written informed consent. Clinical teams will be approached by L.S. or a research assistant and asked to inform suitable patients about the study. The research assistant will then meet the subjects and inform them (both orally and written) prior to gaining written consent. Subjects who have been allocated to the control group (i.e. supportive counselling) will be offered metacognitive training after the trial has finished if they request this. We have used t/z-test, with a power of 0,85, and a significance level of 0,05, to calculate sample size. In order to find a difference of 4 units on CAINS (as a change in total score of 4 points has been found to show a true change at a 95% confidence level in previous research (Laraki et al., 2022)), 41 participants in each arm will be needed. We will aim to recruit 45 in each arm to allow for drop-out, group heterogeneity and to make future analysis (e.g. on. the effect of medication) possible. Ethical approval will be applied for at the Etikprövningsmyndigheten.

5.2. Intervention

The original MCT intervention was adapted to negative symptoms by incorporating psychoeducation and strategies to target the cognitions suggested by the cognitive model (Beck et al., 2009) to be implicated in the development and/or maintenance of negative symptoms (see Table 1). Although some of the strategies have traditionally been used to target positive symptoms, it is assumed that the same reasoning styles lead to negative symptoms through the dysfunctional cognitions discussed previously (e.g., jumping to conclusions in regard to social rejection and a dysfunctional attribution style reinforcing social withdrawal). Metacognitive training for negative symptoms consists of eight sessions, delivered individually as there is evidence indicating that this approach may lead to stronger effect sizes than delivery in a group format (Liu et al., 2018). The developer of MCT (Professor Steffen Moritz) approved the modification.

5.3. Outcome measures

This study will use a combination of interviews and self-rated questionnaires to assess negative symptoms. The primary outcome measures will be the Clinical Assessment Interview for Negative Symptoms (CAINS) (Forbes et al., 2011), the Motivation and Pleasure Scale–Self-Report (MAP-SR) (Llerena et al., 2013), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (with the PANSS negative factor proposed by Wallwork et al. (2012)). The CAINS was chosen as it has been developed to measure negative symptoms as defined by the NIMH consensus development conference (i.e., blunted affect, alogia, anhedonia, asociality and avolition) (Kumari et al., 2017). (We replaced the Brief

Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2010) with CAINS as the BNSS has not been validated or translated into Swedish).

To identify and measure mechanisms of change, four measures will be used: the Dysfunctional Attitudes Scale (DAS) (Weissman & Beck, 1978) to measure the severity of defeatist attitudes; the Reflective Functioning Questionnaire (RFQ-8) (Fonagy et al., 2016) to assess metacognitive capacity; the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) to measure depression; and the Internalized Stigma of Mental Illness Scale-9 (ISMI-9) (Hammer & Toland, 2017) to measure stigma. Finally, the World Health Organization (WHO) Disability Assessment Schedule (WHODAS) 2.0 (WHO, 2010) will be used as this has been suggested to be a more reliable measure than the Global Assessment of Functioning (GAF) (American Psychiatric Association (APA), 1987) for assessing a person's overall functioning (Gspandl et al., 2018).

5.4. Procedure

Written informed consent, relevant demographic information and baseline measures will be completed before beginning the intervention. The Motivation and Pleasure Scale–Self-Report (MAP-SR) (Llerena et al., 2013) will be used to certify that some level of negative symptoms exist prior to the intervention. The patients will be randomised to either MCT Minus and treatment as usual or supportive counselling combined with treatment as usual using an online calculator. Pre-, post-, and follow-up assessments will be conducted by a research assistant who is blind to group allocation. Exit interviews will be held after completing the intervention where a standardized interview schedule (with open-ended questions) will be applied to minimize variations in questions asked while retaining enough flexibility to assess individual experiences (Patton, 1987). The head of the division psychiatry in the regional health board (Region Sörmland) has approved the study and there are structures (e.g. funding, research time, support from clinicians and managers) that would facilitate recruitment and feasibility.
During the pre and post assessment visits, the patients will also undergo a magnetic resonance imaging (MRI) investigation, including anatomical (T1-weighted) imaging, resting-state functional MRI to assess changes in default mode network connectivity after the active compared to control intervention, and additionally diffusion weighted imaging (DWI) and MR spectroscopy (MRS) to relate the functional connectivity findings to structural connectivity and prefrontal glutamate levels.

5.5. Contributors and collaborators

Participants will be recruited by research assistants who the main researcher will train in the intervention. The main researcher (L.S.) will analyse transcripts with thematic analysis (which will then be discussed with other research collaborators), undertake the statistical analysis (potentially with support from a statistician) and write the manuscript (potentially with the assistance of others). Associate Professor Persson will assist with the analysis of the brain scans. Professor Cervenka and Doctor Tyrberg will help with recruitment as they work clinically in Region Uppland and Region Västmanland and together with Professor Moritz, Professor Boden and Associate Professor Persson comment on the final article.

6. Data analysis and statistics

6.1. Quantitative data

Repeated measures ANCOVA will be used to evaluate changes at pre, post and follow-up analysis due to the repeated-measure nature of the data whilst regression analysis will be used for identifying and measuring potential mechanisms of change for negative symptoms. Missing data on questionnaires will be replaced with case-mean substitution if fewer than 20% of the items were missing as this has been found to be a robust way of handling data missing on an item level (Fox-Wasylyshyn & El-Masri, 2005).

Preprocessing and analysis of fMRI data will be performed in the conn toolbox in Matlab, preprocessing of DWI and MRS data in FSL and LCModel, respectively, or equivalent software.

6.2. Qualitative data

Thematic analysis (Braun & Clarke, 2006) will be used to analyse the qualitative data. The interviews will be transcribed and transcripts will be read multiple times for familiarity with the material and to generate an overview of the responses (Mairs et al., 2011). The recordings will then be analysed with thematic analysis conducted according to a standard format (i.e., exploring the feasibility of the intervention and potential mechanisms of change). Themes will be developed, labelled and reviewed to assure that they are representative of the data set. This analysis will be undertaken by the primary researcher and discussed with other research collaborators.

7. International and national collaboration

There is a high level of national collaboration in the project as the main researcher (employed by Region Sörmland) is collaborating with Professor Simon Cervenka, Associate Professor Jonas Persson, and Professor Robert Boden at Region Uppsala/Uppsala University and Dr Tyrberg at Region Västmanland/Uppsala University through this research. There is also a longstanding collaboration with Professor Moritz at University Medical Center Hamburg-Eppendorf Department of Psychiatry and Psychotherapy, Hamburg, Germany.

8. Clinical significance and implications of the project

The project is of high importance for individuals with psychosis but also for clinicians as there is a lack of treatment options and knowledge about negative symptoms. This has immense financial implications as schizophrenia, which affects approximately one percent of the population, has been estimated to cost Europe €93,9 billion per year (Marcellusi et al., 2018). The intervention, when it has been fully translated and edited, will be available at the official website for MCT (https://clinical-neuropsychology.de/metacognitive_training-psychosis/) and hence be available free of charge for clinicians all over the world. The articles will be published with open access agreements.

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