Exploring biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in Alzheimer*s disease, schizophrenia, and major depression: replication and generalisability of the Psychiatric Ratings using Intermediate Stratified Markers (PRISM)1 study

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The overall goal of the PRISM programme of research is to develop a quantitative, transdiagnostic, neurobiological approach to the understanding of neuropsychiatric disorders in order to accelerate the discovery and development of better treatments...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Psychiatric disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON53842

Source
ToetsingOnline

Brief title
PRISM2

Condition

- Psychiatric disorders NEC

Synonym
Alzheimer's disease and Major Depressive Disorder; psychotic disorder, dementia and depression, Schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Gregorio Marañón Hospital
Source(s) of monetary or material Support: Innovative Medicines Initiative (IMI) 2 Joint Undertaking;under grant agreement number 101034377. The IMI Joint Undertaking receives support from the European Union's Horizon 2020 research;the pharmaceutical industry association EFPIA (European Federation of Pharmaceutical Industries and Associations);and Cohen Veterans Bioscience Inc.

Intervention

Keyword: Alzheimer's disease, neurobiology, psychiatric disorders, social withdrawal

Outcome measures

Primary outcome

Each objective for this clinical study is associated with specific endpoints.

This will enable us to achieve the study objectives and overall goal, to show

the reproducibility and generalizability of the quantitative biological

parameters which were identified in the original PRISM clinical study (Protocol

number ABR59359) as having significant relationships with social dysfunction,

in a transdiagnostic manner.

Replication Endpoints:

1. To replicate, in a separate cohort, the finding that DMN functional

connectivity in the rostromedial prefrontal cortex (rmPFC) on rsfMRI is

negatively associated with social functioning in patients with schizophrenia

(SZ), Alzheimer*s Disease (AD) and in Healthy Control (HC) participants.

Associated endpoints:

I. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower social functioning score (SFS) total scores measured on the same day in patients with AD, SCZ, and in HC, independent of their diagnostic labels.

II. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower De Jong-Gierveld Loneliness Scale (LON) scores measured on the same day in patients with AD, SCZ, and in HC, independent of their diagnostic labels.

III. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower mean cumulative total SFS and LON scores measured on the same day in patients with AD, SCZ, and in HC, independent of their diagnostic labels.

2. To replicate, in a separate cohort, the correlation of SFS self-report social functioning scales with the objective BeHapp measurement of social functioning. Associated endpoints:

I. Composite BeHapp scores correlate with SFS total scores across the full range of the scale, independent of study participants* diagnostic labels. The composite BeHapp scores will also be correlated to the total scores from the De Jong-Gierveld Loneliness Scale (LON) for discriminant validity purposes.

3. To replicate, in a separate cohort, the finding that high Behapp social functioning scores are associated with high DTI fractional anisotropy (FA) in the Inferior Frontotemporal Fasiculus (IFF) and forceps minor (FM). Associated endpoints:

I. High Social Functioning BeHapp scores predicts high FA scores in the IFF measured on the same day in patients with AD, SCZ, and in HC, independent of their diagnostic labels.
II. High Social Functioning BeHapp scores predicts high FA scores in the FM measured on the same day in patients with AD, SCZ, and in HC, independent of their diagnostic labels.

4. To replicate, in a separate cohort, the finding that high Behapp social functioning scores are associated with high resting state EEG connectivity index scores in the DMN of patients with AD, SCZ, and in HC, independent of their diagnostic labels. Associated endpoints:
I. High Social Functioning BeHapp scores predicts high EEG DMN connectivity index scores in patients with AD, SCZ, and in HC, independent of their diagnostic labels.

5. To replicate in a separate cohort, the finding that reduced connectivity in response to emotional valent faces between the mPFC and amygdala is associated with lower social functioning in patients with SZ, AD, and in HC independent of diagnostic labels. Associated endpoints:
I. Reduced connectivity between the mPFC and amygdala (based on fMRI BOLD in response to emotional valent faces) predicts low social functioning as assessed by the total SFS.

Generalisation Endpoints:

1. To demonstrate that the relationship of comparatively lower DMN functional connectivity in the rmPFC predicts worse social functioning in SZ, AD, and HC applies to patients with Major Depressive Disorder (MDD). Associated endpoints:
I. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower social functioning score (SFS) total scores measured on the same day in MDD patients.
II. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower De Jong-Gierveld Loneliness Scale (LON) scores measured on the same day in MDD patients.
III. Lower rsfMRI DMN functional connectivity in the rmPFC predicts lower mean cumulative total SFS and LON scores measured on the same day in MDD patients.

2. To demonstrate that the finding of high BeHapp social functioning scores predicts high DTI FA in the Inferior Frontotemporal Fasiculus (IFF) and forceps minor (FM) in SZ, AD, and HC applies to patients with MDD. Associated endpoints:
I. High BeHapp composite scores predict high FA scores in the IFF measured on the same day in patients with MDD.
II. High BeHapp composite scores predicts high FA scores in the FM measured on the same day in patients with MDD.

3. To demonstrate that the finding of higher Behapp social functioning scores predicts higher resting state EEG functional connectivity in the DMN applies to patients with MDD. Associated endpoints:
I. High Social Functioning BeHapp scores predicts high EEG DMN connectivity index scores in patients with MDD.

4. To demonstrate that reduced connectivity in response to emotional valent faces between the mPFC and amygdala is associated with lower social functioning in patients with MDD. Associated endpoints:

II. Reduced connectivity between the mPFC and amygdala (based on fMRI BOLD in response to emotional valent faces) predicts low social functioning as assessed by the total SFS.

Discovery Endpoints:

1. To determine whether speech-based endpoints measured from a variety of speech elicitation tasks are related to social dysfunction in participants with SZ, AD, MDD and HC participants. The speech-based endpoints measure various aspects of cognitive-linguistics and speech motor control. Associated endpoints:

I. Social dysfunction endpoints: Total SFS, BeHapp sociability score and LON

2. To determine whether EEG DMN connectivity index scores (in response to emotional valent faces) are associated with social dysfunction in patients with SZ, AD, MDD and in HC participants independent of diagnostic labels. Associated endpoints:

I. Associations between EEG source and network connectivity scores in response to emotional valent faces (FEP) and social dysfunction based on the total SFS and the BeHapp sociability score.

3. To discover multimodal biomarkers that predict social functioning outcomes

using data-driven machine learning

4. To explore population subtyping and the relationships between these subtypes and outcomes through application of unsupervised clustering techniques.

5. To determine multivariate relationships between biomarkers and demographic characteristics that predict social functioning outcomes.

6. To determine multivariate relationships between biomarker and demographic characteristics that predict social functioning outcomes.

7. To determine multivariate relationships between biomarkers and demographic characteristics that predict social functioning outcomes

8. To discover candidate biomarkers informed by diagnostic labels or symptom severity.

9. To discover biologically interpretable biotypes described by the epigenome and/or the transcriptome through the application of unsupervised methods

10. To identify candidate and discovery inflammation, synaptic integrity, and neurodegeneration gene expression in peripheral blood samples as biomarkers of disease using transcriptome and proteome profiling

11. To support verification of the identified genes and pathways using more

focused approaches such as RT-qPCR, mass spectrometry, and immunoassay.

12. To explore the correlation between the identified peripheral gene

expression and social functioning in AD, SZ, MDD, and HC.

Secondary outcome

Not applicable

Study description

Background summary

The development of treatments for neuropsychiatric conditions forms one of the major challenges of our time in public health and in pharmaceutical industry. According to the World Health Organisation (WHO) report on priority medicines for Europe and the World (Update Report, 2013), neuropsychiatric conditions rank third on mortality for the EU (5.4% of total) and rank second on burden of disease as measured in disability, adjusted for life years (DALYs) (19.6% of total DALYs).
The current pharmacopeia for the treatment of neuropsychiatric disorders amounts to over 100 compounds. However, most of them were discovered by serendipity and have the same mechanisms of action. There is still a high, unmet clinical need because of issues including insufficient efficacy, limited tolerability, as well as the existence of domains that have no single approved therapeutic yet. Since the 1950*s, very few new therapeutic concepts and Mechanisms of Action (MoAs) have been identified, and no new relevant treatment options have emerged for either neuropsychiatric or neurodegenerative disorders. One reason for this lack of meaningful progress may be that the diagnostic classification system of neuropsychiatric disorders (be it International Classification of Diseases-11 (ICD-11) or Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)) separates such disorders into non-overlapping diagnostic categories, such as schizophrenia (SZ), Major Depressive Disorder (MDD), or Alzheimer*s disease (AD). This separation is not based on any underlying aetiologies, but on convention-based, qualitative clustering of clinical symptoms. While these current diagnostic categories are helpful to provide a basis for general clinical management, they fail to consider the underlying neurobiology that often gives rise to variations in symptoms between patients. The ability to link symptoms to the underlying

neurobiology would be expected to facilitate the development of better (personalised) treatments and could also allow physicians to provide patients with a better understanding of the complexities and management of their illness. The original PRISM (Psychiatric Ratings Using Intermediate Stratified Markers) project, conducted between 2016 and 2020, sought to determine whether similar symptomatologies, that are assumed to result from different pathological processes, could be associated using quantitative parameters. The PRISM project selected social dysfunction as the *symptom* of interest. AD and SZ, two disorders of different origin (one being neurodegenerative, the other neurodevelopmental) and with a different age-profile, but both partly characterised by social dysfunction, were used as the prototype disorders. Choosing social dysfunction as the phenotypic transnosological domain for PRISM was motivated by the fact that this provides a major burden to patients and their families, and this area has no approved approach for clinical intervention yet.

As anticipated, PRISM has generated a wide variety of interesting new data and insights, including links between social dysfunction and functional integrity of the Default Mode Network (DMN). The DMN is a network of brain regions, characterised by high functional connectivity, that generally exhibits higher activity during rest than during performance of many attention-demanding tasks. The PRISM 2 refined test battery will include only the most relevant paradigms to test for the reproducibility and generalizability of the identified relationships between social dysfunction and DMN integrity, including functional magnetic resonance imaging (fMRI) and electroencephalography (EEG)) and connectional (diffusion tensor imaging (DTI) & resting state-fMRI (RS-fMRI)) paradigms, as well as social dysfunction measures (total social functioning scale (SFS) score and BeHapp smartphone data). This refined and optimized test battery will be deployed in SZ/AD patients and age-matched healthy controls. In addition, to further attest the generalisability and therefore transdiagnostic utilty of DMN social-dysfunction interactions, we will add MDD patients to our sample, given the substantial social deficits documented in this patient population that previous research has linked to altered DMN integrity. In addition to the effort to determine the reproducibility and generalizability of the identified quantitative, transdiagnostic, biological parameters which have significant relationships with social dysfunction, PRISM 2 will also include the assessment of novel biomarkers. It is well understood that there is a neurobiological basis to SZ, MDD and AZ which is present at the DNA, RNA, and epigenome level (Khavari & Cairns, 2020; Lozupone et al., 2019; Qazi et al., 2018; Smigielski et al., 2020). Therefore, a blood draw and subsequent analysis will also allow the exploration of biological and epigenetic biomarkers. Analysis of peripheral blood samples with subsequent transcriptome and proteome profiling may aid the discovery of novel biomarkers that predict social functioning outcomes or identify new therapeutic targets. In addition, spoken language contains several measurable biomarkers that can indicate various aspects of cognitive health and social skills.

Study objective

The overall goal of the PRISM programme of research is to develop a quantitative, transdiagnostic, neurobiological approach to the understanding of neuropsychiatric disorders in order to accelerate the discovery and development of better treatments for patients with those disorders.
The main goal of PRISM 2 is to show the reproducibility and generalizability of quantitative biological parameters which were identified in the original PRISM clinical study (Protocol number ABR59359) as having significant relationships with social dysfunction, in a transdiagnostic manner. Namely,
1. SFS total score and rostromedial prefrontal cortex (PFC) activity
2. SFS and BeHapp composite score
3. BeHapp composite score and DTI fractional anisotropy (FA)
4. BeHapp composite score and EEG
5. SFS and connectivity between the medial PFC (mPFC) and amygdala

We aim to work towards this goal in the current study by having a set of distinct objectives. Objectives are defined as either replication objectives, generalisation objectives, or discovery objectives, with clearly defined end-points

Replication Objectives:
1. To replicate, in a separate cohort, the finding that DMN functional connectivity in the rostromedial prefrontal cortex (rmPFC) on rsfMRI is negatively associated with social functioning in patients with schizophrenia, Alzheimer*s Disease and in Healthy Control participants.
2. To replicate in a separate cohort, the correlation of SFS self-report social functioning scales with the objective BeHapp measurement of social functioning.
3. To replicate in a separate cohort, the finding that high BeHapp social functioning scores are associated with high DTI fractional anisotropy (FA) in the Inferior Frontotemporal Fasciculus (IFF) and forceps minor (FM)
4. To replicate in a separate cohort, the finding that high BeHapp social functioning scores are associated with high resting state EEG connectivity index scores in the DMN of patients with AD, SCZ, and in HC, independent of their diagnostic labels.
5. To replicate in a separate cohort, the finding that reduced connectivity in response to emotional valent faces between the mPFC and amygdala is associated with lower social functioning in patients with SZ, AD, and in HC independent of diagnostic labels.

Generalisation Objectives:
1. To demonstrate that the relationship of comparatively lower DMN functional connectivity in the rmPFC predicts worse social functioning in SZ, AD, and HC applies to patients with Major Depressive Disorder (MDD).
2. To demonstrate that the finding of high BeHapp social functioning scores

predicts high DTI FA in the Inferior Frontotemporal Fasciculus (IFF) and forceps minor (FM) in SZ, AD, and HC applies to patients with MDD.
3. To demonstrate that the finding of higher BeHapp social functioning scores predicts higher resting state EEG functional connectivity in the DMN applies to patients with MDD.
4. To demonstrate that reduced connectivity in response to emotional valent faces between the mPFC and amygdala is associated with lower social functioning in patients with MDD.

Discovery Objectives:
1. To determine whether speech-based endpoints measured from a variety of speech elicitation tasks are related to social dysfunction in participants with SZ, AD, MDD and HC participants. The speech-based endpoints measure various aspects of cognitive-linguistics and speech motor control.
2. To determine whether EEG DMN connectivity index scores (in response to emotional valent faces) are associated with social dysfunction in patients with SZ, AD, MDD and in HC participants independent of diagnostic labels.
3. To discover multimodal biomarkers that predict social functioning outcomes using data-driven machine learning
4. To explore population subtyping and the relationships between these subtypes and outcomes through application of unsupervised clustering techniques.
5. To determine multivariate relationships between biomarkers and demographic characteristics that predict social functioning outcomes.
6. To discover candidate biomarkers informed by diagnostic labels or symptom severity.
7. To discover biologically interpretable biotypes described by the epigenome and/or the transcriptome through the application of unsupervised methods
8. To identify candidate and discovery inflammation, synaptic integrity, and neurodegeneration gene expression in peripheral blood samples as biomarkers of disease using transcriptome and proteome profiling
9. To support verification of the identified genes and pathways using more focused approaches such as RT-qPCR, mass spectrometry, and immunoassay.
10. To explore the correlation between the identified peripheral gene expression and social functioning in AD, SZ, MDD, and HC.

Study design

The study comprises a naturalistic, cross-sectional study of four groups. Three patient cohorts, 1) patients with probable AD, 2) patients with SZ, and 3) patients with MDD will be studied, together with 4) a healthy control group, approximately matched in age distribution and gender proportion to the SZ, AD, and MDD groups.
Approximately 40 participants will be recruited into each of the AD, SZ, and MDD groups, together with approximately 60 healthy controls, resulting in a total of approximately 180 participants.
First, a pre-screening is performed. The purpose of the pre-screening email correspondence or telephone call is to discuss the study and answer questions

that potential participants might have, and to ascertain the likelihood that participants will be eligible (i.e. satisfying inclusion/exclusion criteria).
By performing a telephone or email pre-screening we intend to reduce the burden for potential candidates, by preventing them for as much as possible to visit the study center only to find out they are not eligible for participation, for example, determining any obvious MRI contraindications, such as claustrophobia.
Typically, participants will attend the study centre for a single assessment day. This assessment day includes screening, the collection of questionnaire measures, behavioural testing, a blood draw, the installation of BeHapp on participants* phones, and a short MRI and EEG neuroimaging session.
In some cases, participants may indicate fatigue during assessments days, or due to restrictions in their availability may not be able to complete all the required activities for a given assessment day. In these cases, the participant will be invited, if they prefer, to attend a greater number of assessment visits (e.g., a separate visit for the EEG and MRI scan) to complete all the study activities. The number of assessment visits required to complete all the study activities will be determined by the participant*s capacity and left to the judgement of the clinician. All study activities will preferably be collected within a single week. No assessment day will have a duration of greater than 6 hours, and, as far as possible, the order of study events will be held constant across participants.
Follow-up, during which time remote data collection with BeHapp will be collected, will continue for a maximum total follow-up period of up to 42 days (6 weeks) from the screening/assessment day. Participants will be encouraged to engage in follow-up for at least 28 days (4 weeks) to allow for the collection sufficient data for meaningful analysis, but they can choose to discontinue BeHapp data collection at any time whilst continuing with other aspects of the study. Therefore, the maximum duration of the study, if a participant consents to BeHapp installation, is 42 days.

Study burden and risks

Potential benefits to participating in the study are low on the short term. Participants may value contributing to research that may lead to new treatment approaches in the future. However, risks associated with participating in the study are also low. Some risk is associated with the blood-draw procedure, such as bruising. Risks associated with MRI scanning are minimized by screening of research participants prior to each scan. Although there are no associated risks with the EEG, it may cause minor discomfort.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria (MDD, SZ and AD populations)
- Provision of signed and dated informed consent form (ICF) from patient prior to any study-specific procedures being performed.
- The patient should have a reliable study partner with whom he/she cohabits or has regular contact with, who gives consent to participate in the study and provide study data (limited to the Neuropsychiatric Inventory for AD patients and the WHO Disability Asessment Schedule (WHODAS) for AD, SZ and MDD patients).
- Not socially withdrawn due to external circumstances (e.g. lack of access to transport, rural location) or comorbid medical disorder or disability (e.g., hearing loss, lack of mobility, facial disfigurement).
- Patient and study partner must be able to read, write, and speak the language in which assessments are provided.
- Unless otherwise stated central nervous system (CNS) medications to treat cognitive impairment due to AD, symptoms of SZ or MDD, and other stable CNS conditions requiring such medication, are permitted provided the patient has been maintained on a stable dose regimen for at least 8 weeks before start of the study, and they are expected to continue this treatment in a stable manner during the current study. Similarly, psychological treatments (e.g., Cognitive

Behaviour Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc.) are all permitted in this study regardless of frequency and duration, so long as this treatment is expected to remain stable during the duration of the study.
- Patient is right-handed or ambidextrous. In the case of ambiguity the Edinburgh Handedness Inventory will be used to determine handedness.

Additional inclusion Criteria - AD participants
- Men and women aged 50 to 80 years (inclusive).
- Probable AD, meeting the National Institute on Aging (NIA) and the Alzheimer*s Association (AA) (NIA-AA) criteria for probable AD
- Mini-Mental State Examination (MMSE) score of 20 to 26, inclusive.

Additional inclusion Criteria - SZ participants
- Patients are male or female, 18-45 years of age (inclusive) with an established diagnosis of schizophrenia according to medical history.
- If the patient uses any antipsychotic, anticholinergic or antidepressant medication, dosage needs to be stable for at least 8 weeks prior to the study start.
- A DSM-IV diagnosis of SZ with at least one confirmed psychotic episode but not longer than 15 years of disease duration (since first date of established SZ clinical diagnosis). It is, however, preferred and actively encouraged to include patients with a maximum disease duration of 10 years.

Additional inclusion Criteria - MDD participants
- Male or female, aged 18-55 years of age, inclusive. It is, however, preferred and actively encouraged to include patients aged 45 years and under.
- Have a primary Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) diagnosis of MDD without psychotic features, as confirmed by medical history. Subjects with a diagnosis of comorbid Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), Panic Disorder, insomnia or specific phobia may be included.
- Meet the DSM-IV criteria for a current Major Depressive Episode.

Additional inclusion Criteria - HC participants
- Men and women, aged 18-80, inclusive (of similar age distribution and gender proportion to AD, SZ and MDD groups).
- Provision of signed and dated informed consent form (ICF) prior to any study-specific procedures being performed.
- Participant must be able to read, write, and speak the language in which psychometric tests are provided
- Considered reliable and be willing to perform all study procedures.
- Younger and older healthy controls will, as far as possible, be recruited from similar geographical locations to those participants in the SZ and AD groups, respectively (*zip-code matching*), to help address differences in objective social engagement data (via the BeHapp App) driven by residential location.

- Participant is right-handed or ambidextrous. In the case of ambiguity the Edinburgh Handedness Inventory will be used to determine handedness.
- Participant scores approximately average in the MMSE according to their age and years of education, as compared with normative data (specifically, no more than 1 mark below the average that would be expected).

Exclusion criteria

Exclusion criteria (MDD, SZ and AD populations)
Patients cannot enter the study if any of the following exclusion criteria are fulfilled:
- Significant neurological disease affecting the CNS, other than AD, SZ, or MDD (e.g. other dementias, serious infection of the brain, Parkinson*s disease, epilepsy) as documented in the patient*s medical file which in the judgement of the investigator may affect the patient's ability to complete the study assessments.
- Any other current psychiatric diagnosis, including personality disorders, requiring intervention other than AD, SZ, and MDD according to medical history that in the judgement of the investigator may affect the patient's ability to complete the study assessments.
- Current serious or unstable clinically important systemic illness (e.g. hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, hematologic, or ocular disorders) that in the judgement of the investigator may affect the patient's ability to complete the study assessments.
- History of chronic alcohol or drug abuse or dependence within the previous 3 years.
- Participated in any investigational study to treat either AD, SZ, or MDD symptoms or has taken an investigational drug within 90 days (or 5 times the half-life of the investigational drug, whichever is longer). In addition, if they have participated in two or more studies with an experimental drug within 5 months prior to screening.
- In the investigator*s judgement is medically non-compliant in the management of their disease.
- Has within 6 weeks prior to the first assessment visit been prescribed a medication that may affect the CNS that in the judgment of the investigator may interfere with the patient's ability to complete the study assessments.
- Has any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, pregnancy, or cardiac pacemaker that is not compatible with MRI scanning.
- Are, in the opinion of the investigator, likely to present a danger to themselves or others or where the severity of the illness precludes them from completing the study procedures. In the case of high suicidality scores on the QIDS, the study researcher will contact the person who referred the participant to the study.

Additional exclusion Criteria - AD participants
- Multiple strokes based on history and/or imaging results
- A score of 4 or greater on the global Parkinsonism item of the Extrapyramidal Symptom Rating Scale (ESRS) (only relevant to those patients currently taking an antipsychotic medication).
- QIDS-SR16 score of >= 16

Additional exclusion Criteria - SZ participants
Patients will be excluded from the study if they meet any of the following criteria:
- A score of 22 or more on the sum of the 7 PANSS (The Positive and Negative Syndrome Scale) positive symptom factor items. The score of the items of P1 (delusions), P3 (hallucinatory behaviour), P6 (suspiciousness) and G9 (unusual thought content) meet the following requirements:
- No more than 2 of the above items have a score of 4.
- All of the above items score less than 5.
- In the clinician*s judgment, patients who, for any reason, are considered to be a danger to themselves.
- QIDS-SR16 score of >= 16
- A score of 4 or greater on the global Parkinsonism item of the ESRS (only relevant to those SZ patients currently taking antipsychotic medication).

Additional exclusion Critera - MDD participants
- Currently receiving or waitlisted for third line treatments; for example, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or ketamine treatment.

Additonal exclusion Criteria - HC participants
- Current, or history of, Axis-I psychiatric disorder according to medical history at the Screening Visit.
- Participant scores >5 on the QIDS-SR16 (indicative of mild or more severe depression)
- Is currently, or has ever, required antidepressant or anxiolytic medication, including benzodiazepines (with the exception of the intermittent use of medications such as zolpidem, zopiclone, and eszopiclone which can for example be used in treatment for transient sleep disturbances provided that they are not taken the night before an assessment day).
- Significant neurological disease or psychiatric condition affecting the CNS, which is associated with cognitive impairment or in the judgement of the investigator may affect the patient's ability to complete the study assessments.
- Participated in any investigational study involving investigational drug within 90 days (or 5 times the half-life of the investigational drug, whichever is longer). In addition, if they have participated in two or more studies with an experimental drug within 5 months prior to screening.
- Has within 6 weeks prior to the first assessment visit been prescribed a medication that may affect the CNS that in the judgment of the investigator may interfere with the participant's ability to complete the study assessments.

- Current serious or unstable clinically important systemic illness (e.g. hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, hematologic, or occular disorders) that in the judgment of the investigator may affect the participant's ability to complete the study assessments.
- Has any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, pregnancy, or cardiac pacemaker this is not compatible with MRI, or other contraindications due to local requirements.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-06-2022
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	21-03-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL79569.029.21