Providing quantitative biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in Alzheimer*s disease and schizophrenia.

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The overall objective of this exploratory study is to develop a quantitative biological approach to the understanding and classification of the endophenotypes that contribute to neuropsychiatric diseases, to accelerate the discovery and development...

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

Summary

ID

NL-OMON49237

Source
ToetsingOnline

Brief title
PRISM

Condition

- Psychiatric disorders NEC

Synonym
Schizophrenia and Alzheimer's disease; psychotic illness and dementia.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Europese Commissie;via IMI (innovative medicines initiative);Pfizer,Pfizer

Intervention

Keyword: cognitive deficits, fMRI, psychiatric disorders, social deficits

Outcome measures

Primary outcome

The primary endpoint is based on the fMRI analysis of the N-back fMRI task:

whether high or low social withdrawal in patients with AD or SZ is associated

with differences in the blood oxygen level dependent (BOLD) signal in brain

areas associated with executive function (working memory) during performance of

the N-Back task, after controlling for the effects of normal aging. The key

region of interest is the dorsolateral prefrontal cortex (dlPFC).

Secondary outcome

1. To assess differences or overlap in the underpinnings of social withdrawal

for AD and SZ patients as indexed by BOLD signals in key Regions of Interest

(ROIs) while performing the N-back, Virtual Morris Water Maze, MSID, and FEP

tasks.

Key fMRI endpoints and ROIs for each task include:

* BOLD fMRI activity (%signal change) within the ventral striatum, including

the nucleus accumbens while performing win, neutral and lose trials in the MSID

task at different levels of reward, and for monetary or social rewards.

* BOLD fMRI signal within the hippocampus and ventral striatum while performing

the encoding, retrieval and control trials of the Virtual Morris Water Maze Task.

* BOLD fMRI signal whilst viewing different facial expressions (happy, sad or fearful) in the FEP. The regions of interest are the amygdala, subgenual cingulate and prefrontal cortex.

2. To assess differences or overlap in the underpinnings of social withdrawal for AD and SZ patients in the electrical activity of the brain associated with basic sensory processing and captured by EEG.

3. To assess differences or overlap in the underpinnings of social withdrawal for AD and SZ patients as behavioural outcomes measured in behavioural testing with the Conner*s CPT-III, EEfRT, FERT, DSST, and Hinting Task.

Study description

Background summary

Withdrawal from friends, family, and colleagues is a common feature of both schizophrenia (SZ) and Alzheimer*s disease (AD) and it is one of the symptoms that is particularly burdensome for relatives of those affected. Interestingly, it is also one of the earliest signs of disease in both groups of patients (Cullen et al., 2011; Nelis et al., 2011; Reichman & Negron, 2001). The aim of this study is to determine the biological substrates that correlate with social withdrawal and determine whether they are similar in both groups. The study will also investigate whether the biological substrates of social withdrawal are linked to the impaired cognitive processes observed in both patient populations.
The link between social withdrawal and cognition has been established in both animal and human studies. Animal studies show that social isolation might be related to fundamental aspects of cognition (Schrijver, Pallier, Brown, & Wurbel, 2004). Moreover, a number of studies have shown that loneliness in

humans is a risk factor for cognitive decline (Gow, Pattie, Whiteman, Whalley, & Deary, 2007; Tilvis et al., 2004; Wilson et al., 2007). Loneliness has been associated with amyloid burden, itself one of the most promising biomarkers of AD (Donovan et al., 2016). Furthermore, Gow and colleagues (Gow et al., 2007) investigated the cognitive abilities of 488 individuals from the Lothian Birth Cohort Study who were assessed at age 11 and age 79. Loneliness, social support and living arrangement were most consistently associated with aspects of cognitive ability in older people. Thus, we will explore areas of overlapping and distinct neurobiological underpinnings for social withdrawal in the two diagnoses. If biological markers associated with social withdrawal are found, we will ascertain whether and how this is associated with cognitive deficits that might also be common between the groups.

This study is influenced by the Research Domain Criteria (RDoC) framework proposed by the National Institute of Mental Health (NIMH) and the adaptations and recommendations formulated in the EU Roadmap for Mental Health in Europe (ROAMER) initiative. This approach attempts to identify behavioural phenotypes across different psychiatric conditions, and to further identify specific neurobiological pathways underlying those behaviours. This phenotype-driven approach is different from the predominant treatment approach in which patients with neuropsychiatric disorders are grouped into non-overlapping diagnostic categories, e.g. 'schizophrenia' and *Alzheimer*s Disease', and are then treated according to their diagnosis rather than the symptoms they present with. While these diagnostic categories are sufficient to provide the basis for general clinical management, they do not describe the underlying neurobiology that gives rise to individual symptoms. The ability to precisely link these symptoms to underlying neurobiology would not only facilitate the development of better treatments, it would also allow physicians to provide patients and relatives with a better understanding of the complexities and management of their illness. Moreover, there is a growing realisation that psychiatric and neurodegenerative disorders overlap by much more than previously thought, and that they may better be described as domains of trans-diagnostic traits rather than separable categories (Insel & Cuthbert, 2015; Kas, Fernandes, Schalkwyk, & Collier, 2007). Recently the conclusions from the ROAMER project were published and it identified six priorities for mental health research in Europe. The EU-funded ROAMER project, developed by over 1000 scientists, patients, families and professional groups from across Europe, identified as its second priority a focus on causal mechanisms of mental disorders and identifying factors underlying co- and multi-morbidity and extending research on single disorders to examine common psychopathology across disorders. In line with this priority, this study aims to develop a quantitative biological approach to identify common symptoms that may have the same biological construct in patients with early SZ and probable AD. If they do, then is it possible that similar symptoms observed in other psychiatric and neurological diseases are the result of impairments in the same biological constructs. This possibility will be directly assessed in a follow up study in patients with Major Depressive Disorder (MDD), a psychiatric condition also associated with social withdrawal.

Study objective

The overall objective of this exploratory study is to develop a quantitative biological approach to the understanding and classification of the endophenotypes that contribute to neuropsychiatric diseases, to accelerate the discovery and development of better treatments for patients with AD and SZ.

We aim to work towards this objective in the current study by:
I. Exploring differences and overlap between SZ and AD patients, on the basis of quantitative biological parameters extracted primarily from fMRI and EEG data, but also behavioural data.
II. Exploring dimensional relationships between pathology (e.g., cognitive deficits) and social withdrawal, with social withdrawal indexed by:
a. Self-report questionnaire measures (e.g. the WHODAS)
b. And remote monitoring of social activity (via the BeHapp App)
III. Clustering patients based on endpoint data extracted as part of objectives (I) and (II) to identify specifically data-driven groups of patients that share a common feature or features.

Study design

The study comprises an exploratory study of three groups. Two patient cohorts, 1) patients with probable AD and 2) patients with SZ, will be studied, together with 3) a healthy control group, approximately matched in age distribution and gender proportion to the SZ and AD groups.
Patient participants (SZ and AD) will differ by level of social withdrawal (high vs. low). Thus, for patient participants, the study takes a 2 x 2 (diagnostic group x social withdrawal status) factorial group design. A total of up to 192 participants will complete the study.

Approximately 160 patient participants (80 SZ, 80 AD) will be enrolled with the expectation that 144 (72 SZ, 72 AD) will complete the study. Half of each patient group will be classified as high in social withdrawal, and half as low in social withdrawal, according to items extracted from the WHODAS.

Approximately 72 healthy control participants, with age distributions and gender proportions similar to the (younger) SZ and (older) AD group, will be recruited, with the expectation that up to 64 healthy controls (32 younger, 32 older) will complete the study.

Participants will attend the study centre on three assessment days. The first assessment day will include screening, collection of questionnaire measures, behavioural testing, an blood draw, and optional installation of BeHapp on participants* phones. The second and third assessment days will each include an fMRI and EEG neuroimaging session.

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Provision of signed and dated informed consent form (ICF) from patient and consent from

study partner (if this person contributes data to the study) prior to any study-specific procedures being performed.
2. Half of each patient group (AD and SZ) must have a score <=<10 on a subset of items from the WHODAS-2 (social withdrawal) scale, and half must have a score of ><=11. In this way patients are characterised as lower or higher in social withdrawal, respectively.
3. Not socially withdrawn due to external circumstances (e.g. lack of access to transport, e.g. rural location) or comorbid medical disorder or disability (e.g., hearing loss, lack of mobility, facial disfigurement).
4. Patient and study partner must be able to read, write, and speak the language in which psychometric tests are provided, with acceptable visual and auditory acuity (corrected if necessary with MRI compatible materials e.g. plastic lens for sight correction).
5. Patients must be considered reliable and have a level of understanding sufficient to perform all tests and examinations required by the protocol, and be willing to perform all study procedures.
6. Unless otherwise stated CNS medications to treat cognitive impairment, due to AD or symptoms of SZ and other stable CNS conditions requiring such medication, is 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.
7. Patients must have an adequate hearing of the 1000Hz frequency with no greater loss than 40dB at screening using an automated audiometric assessment.
8. Patient is right-handed or ambidextrous.;Inclusion Criteria * AD participants
1. Men and women aged 50 to 80 years (inclusive).
2. Probable AD, meeting the National Institute on Aging (NIA) and the Alzheimer*s Association (AA) (NIA-AA) criteria for probable AD, and
3. MMSE score of 20 to 26, inclusive. ;Inclusion Criteria * SZ participants
1. Patients are male or female, 18-45 years of age (inclusive) with an established diagnosis of schizophrenia according to medical history.
2. If the patient uses any antipsychotic, anticholinergic or antidepressant (see below) medication, dosage needs to be stable for at least 8 weeks prior to the study start.
3. Based on the screening MINI, a DSM-4 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).;Inclusion Criteria * HC participants
1. Men and women, aged 18-45 inclusive (of similar age distribution and gender proportion to SZ group) or 50-80 inclusive (of similar age distribution and gender proportion to AD group)
2. Provision of signed and dated informed consent form (ICF) from participant prior to any study-specific procedures being performed.
3. Participant must be able to read, write, and speak the language in which psychometric tests are provided, with acceptable visual and auditory acuity (corrected if necessary with MRI compatible materials e.g. plastic lens for sight correction).
4. Participants must be considered reliable and be willing to perform all study procedures.
5. Participants must have an adequate hearing of the 1000Hz frequency with no greater loss than 40dB at screening using an automated audiometric assessment
6. 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. Recruitment strategies for HC participants will target the

relevant geographical regions. However, as the BeHapp data is not linked to the primary objective, this criteria will be evaluated for feasibility several months into the project and may be retracted.
7. Participant is right-handed or ambidextrous.
8. 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 (both SZ and AD populations):;1. Significant neurological disease affecting the CNS, other than AD and SZ, (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.
2. Patients with a current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) diagnosis of Major Depressive Disorder (MDD) as assessed by the MINI, and with a QIDS-SR16 score of * 16
3. Patients with or any other current primary psychiatric diagnosis requiring intervention other than AD (as per DSM-4) or SZ (as per DSM-4) using the MINI that in the judgement of the investigator may affect the patient's ability to complete the study assessments.
4. Current serious or unstable clinically important systemic illness (e.g. hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, hematologic, or ocular disorders) that in the judgment of the investigator may affect the patient's ability to complete the study assessments.
5. Has history of chronic alcohol or drug abuse or dependence within the previous 3 years.;Medication
1. Participated in any investigational study to treat either AD or SZ 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.
2. Is currently requiring antidepressant or anxiolytic medication, unless treatment is stable as indicated in the inclusion criteria.
3. In the investigator*s judgement is medically non-compliant in the management of their disease.
4. 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.;Procedural
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.;Exclusion Criteria * AD participants:
1. Multiple strokes based on history and/or previous imaging results
2. A score of 4 or greater on the global Parkinsonism item of the ESRS-A (only relevant to those patients currently taking an antipsychotic medication).;Exclusion Criteria * SZ participants:

1. A score of 22 or more on the sum of the 7 PANSS 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:
1.1. No more than 2 of the above items have a score of 4.
1.2. All of the above items score less than 5.
2. In the clinician*s judgment, patients who, for any reason, are considered to be a danger to themselves.
3. A score of 4 or greater on the global Parkinsonism item of the ESRS-A.;Exclusion Criteria * HC participants
1. Current, or history of, Axis-I psychiatric disorder as determined by the MINI at the Screening Visit.
2. Participant scores >5 on the QIDS (indicative of mild or more severe depression)
3. 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).
4. 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.
5. 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.
6. 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.
7. 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 patient's ability to complete the study assessments.
8. 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):	02-08-2017
Enrollment:	138
Type:	Actual

Ethics review

Approved WMO Date:	15-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-09-2018
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL59359.041.16