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Working definitions, subjective and objective assessments and experimental paradigms in a study exploring social withdrawal in schizophrenia and Alzheimer's disease

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ABSTRACT

Social withdrawal is one of the first and common signs of early social dysfunction in a number of important neuropsychiatric disorders, likely because of the enormous amount and complexity of brain processes required to initiate and maintain social relationships (Adolphs, 2009). The Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project focusses on the shared and unique neurobiological basis of social withdrawal in schizophrenia, Alzheimer and depression. In this paper, we discuss the working definition of social withdrawal for this study and the selection of objective and subjective rating scales to assess social withdrawal chosen or adapted for this project. We also discuss the MRI and EEG paradigms selected to study the systems and neural circuitry thought to underlie social functioning and more particularly to be involved in social withdrawal in humans, such as the social perception and the social affiliation networks. A number of behavioral paradigms were selected to assess complementary aspects of social cognition. Also, a digital phenotyping method (a smartphone application) was chosen to obtain real-life data.

1. Background

A recently EU-funded project aims to develop a quantitative biological approach to the understanding and classification of neuropsychiatric diseases in order to accelerate the discovery and development of better treatments, amongst others via new preclinical animal models By combining already existing clinical cohort data and by applying innovative deep-phenotyping technologies to newly recruited patient groups, the project aims to define a set of quantifiable biological parameters for social withdrawal and related cognitive deficits in Schizophrenia, Major Depression, and Alzheimer's disease. Patient participants, stratified for social withdrawal, will complete a series of fMRI, EEG, and behavioural paradigms, contribute blood-derived (e.g. epigenetic) data, and smartphone data related to social behaviour. Normative data will also be collected from a group of healthy controls. The project is called Psychiatric Ratings using Intermediate Stratified Markers (PRISM) (http://prism-project.eu/en/prism-study/). The different papers in this issue of Neuroscience and BioBehavioral Reviews describe the various aspects of this project, with the first paper detailing the aims and expectations for the project.

In the present paper, we describe the development of a working definition of social withdrawal, the selection of appropriate rating scales, and the selection of experimental and behavioral paradigms for the assessment and deep phenotyping of social withdrawal for this

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project.

PRISM focuses on social withdrawal, probably one of the first signs of social dysfunction in a number of important neuropsychiatric disorders, likely because of the enormous amount and complexity of brain processes required to initiate and maintain social relationships (see Porcelli et al. in this issue and (Adolphs, 2009). Social withdrawal and isolation can potentially be observed and measured in an objective way both in human and in animal models, putatively representing a real-world indicator of social dysfunction, in contrast to experimental measures of impairments in social cognition. (Torralva et al., 2013).

In humans, the complexity of social living is enormous and requires the coordinate functioning of several processes, such as the detection and processing of social stimuli, mentalising, bond formation and maintenance, social learning, etc. (Cacioppo et al., 2014; Dunbar, 2009; Dunbar and Shultz, 2007). Indeed, the human brain shows a marked specialization for social functioning and it probably evolved specifically to sustain our complex social interactions (Dunbar and Shultz, 2007). This specialization comprises, for example in the cognitive domain, functions such as: 1) emotional processing, 2) social perception and knowledge, 3) theory of mind (mentalising), and 4) attributional bias (Fett et al., 2011), which are globally known as "social cognition". The so-called social brain, i.e. the circuitry and processes underlying these functions, is sophisticated but also fragile, since difficulties in social functioning may arise from even small deficits in any one of the involved processes and circuitry.

Beyond the neuropsychiatric disorders primarily associated with impairments in social functioning, such as Schizophrenia (SZ) (Addington and Addington, 2008; Green et al., 2015), Autism Spectrum Disorders, and Hikikomori (Barak and Feng, 2016; Li and Wong, 2015), deficits in social functioning have also been demonstrated in Alzheimer's Disease (AD) and other dementias (Dickerson, 2015; Havins et al., 2012), Major Depressive Disorder (MDD) (Bora and Berk, 2016; Kupferberg et al., 2016), Anxiety disorders (Plana et al., 2014), and Borderline and Antisocial Personality Disorders (Beeney et al., 2015; Jeung and Herpertz, 2014; Patin and Hurlemann, 2015a, 2015b). Social dysfunction represents a common, often severe and deleterious, symptom of all these disorders, which is likely partially independent from the other psychopathological core features of the disorders (Bowie et al., 2008; Dickerson, 2015; Fett et al., 2011; Puig et al., 2008; Shinagawa et al., 2015).

Taken together, although social functioning as a whole is clearly influenced by a variety of socio-demographic and environmental features, a growing body of evidence suggests that across psychiatric disorders disturbances in social functioning are also related to disturbances at the level the of the social brain (Bickart et al., 2014; Hampton et al., 2016).

1.1. Working definition of social withdrawal

Social withdrawal is a complex deviation from normal behaviour and may be defined in several ways, which could be a reason for a lack of specific investigations of this phenomenon in the past. It is a complex phenotype, influenced by a variety of socio-demographic features, such as age, culture, economic status, availability of transports, mobility impairment, etc., which are hard to completely capture. Moreover, social network size varies greatly among healthy individuals, ranging from very small to very large networks (Hill and Dunbar, 2003). Thus, variability in social behaviour due to socio-demographic and personal features has to be taken into account in research on disturbances of social functioning.

Since the current project aims to investigate in a cross-sectional way the neurobiological basis of social withdrawal manifesting in a set of specific neuropsychiatric disorders, the researchers decided to focus on reduced social interaction that had become evident at or after disease onset and was likely associated with the target disease, and not to other factors such as pure economical or environmental ones (for details on the PRISM clinical study, see the paper by Dawson et al. in this issue). Consequently, the first part of working definition of Social Withdrawal was: "**Reduced social interaction associated with the target disease".**

A problem with the assessment of social functioning when having to rely on self-report in a cross-sectional design, is the poor insight often observed in patients with SZ and AD. To address this possible bias, we decided to add: "**as confirmed by the patient and/or significant other**". The term "significant other" is used to specify that this should be a person who knows the patients' social habits and their changes after the disease onset, but not necessarily a family member or care taker.

Finally, the difference between objective social withdrawal and subjective feelings of loneliness had to be taken into account. Feelings of loneliness can be defined as 'the distressing feelings that accompany the perception that one's social needs are not being met by the quantity or the quality of the one's social relationships' (Hawkley and Cacioppo, 2010). Loneliness and objective social withdrawal might have, at least partially, different neurobiological substrates (Cacioppo et al., 2015), thus the concomitant evaluation of both these aspects was thought to provide more comprehensive information about the social functioning of subjects (Cacioppo et al., 2014). Therefore, it was decided to include also an evaluation of the subjective feeling of loneliness.

Since social withdrawal as a specific construct and phenotype has never been investigated extensively before, one would ideally develop a specific assessment scale. The development and validation of such a specific scale, however, would require considerable time and efforts which was not compatible with the IMI 2 call directives. Instead a comprehensive literature review was done to identify already available instruments that could be used to assess (proxies of) social withdrawal. In particular, two sets of tools have been selected: one for the psychometric assessment of social withdrawal (i.e. scales and questionnaires) and one for the assessment of key elements of social cognition under experimental conditions (i.e. MRI, EEG and behavioral paradigms). Finally, PRISM will try to integrate these assessments with a single objective measure of social withdrawal, derived from a Smartphone application developed for this aim (Eskes et al., 2016). The Smartphone application will also provide an objective measure of telephone and social media use, which is complementary information to the ones measured by rating scales and instrumental paradigms.

1.2. Criteria for rating scales and experimental paradigms

In order to select the rating scales and experimental paradigms for the assessment of social withdrawal in a pragmatic way, given the specificaims and time constraints of the project, the following set of criteria was chosen:

1 Robustness and feasibility of implementation
2 Applicability to the population under investigation (i.e. AD, SZ, and MDD)
3 Allowing the integration of EEG and fMRI analyses
4 Possible alignment with measures used in the already available clinical cohorts
5 Potential for reverse translation into animal models

More in detail, the arguments for this specific set of criteria were the following. Choosing instruments which already had demonstrated their reliability and robustness would avoid bias due to assessment weakness. Also, due to the time schedule foreseen for a project in the IMI 2 Call, the selected tools need to be implemented in the clinical recruitment centres as soon as possible. As the time schedule did not allow a preliminary phase for validation of tools in clinical populations, applicability to the specific clinical samples (i.e. SZ, AD and MDD) was another criterion. Further, we chose in to investigate as much as feasible both the fMRI and EEG correlates of specific neurocognitive domains putatively involved in social withdrawal, in order to obtain a

comprehensive picture of the psychobiological correlates. Since PRISM has access to several large clinical, but not deep-phenotyped, cohorts which will be used for preliminary studies of social withdrawal, alignment with measures used in these cohorts will increase data comparability. Finally, a key point of the project is the back-translational intent, i.e. to develop novel preclinical testing paradigms derived from studies in humans. Therefore, the selected measures should ideally have characteristics which can be translated in preclinical paradigms.

2. Rating scales selected for PRISM

2.1. Screening scale: WHO disability assessment schedule - domain 4 - adapted for PRISM

For the cross-sectional clinical study (see paper by Bilderbeck et al. in this issue) in which newly recruited patients will be deep phenotyped, we first had to decide on a screening tool which would allow to identify within populations currently followed by the clinical centres, patients with probable low and high levels of social withdrawal who could be included in this study. After reviewing the literature, we deemed as most promising scale the WHO Disability Assessment Schedule (WHODAS) (Ustün et al., 2010), which assesses different domains of functioning, including social functioning. The reasons for this selection were 1) the WHODAS extensive prior use in both clinical (including SZ, AD and MDD) and in general populations; 2) the open access availability of 3) multiple language translations; 4) the time needed to administer, particularly for a single WHODAS domain (i.e. 2–5 minutes); 5) the availability of a self- and a caregiver-report version; 6) the already validated possibility to administer only the questions for a single domain.

Two WHODAS domains appeared particularly suitable for a screening purpose: the domain 4 ("Getting along ") and the domain 6 ("Participation"). WHODAS domain 4 assesses getting along with other people and difficulties that might be encountered with this due to a health condition, while WHODAS domain 6 assesses what restrictions to participate, subjects experience from other people, laws and other features of their environment.

To verify the suitability and the distribution of these two domains for PRISM, we performed an exploratory analysis in the already available cohorts in which the WHODAS was administered. We were able to perform this analysis for all three disorders, i.e. AD, SZ, and MDD. The results showed a good distribution of the scores for domains 4 and 6, suggesting their suitability for screening purposes. However, some adaptations to the original questions were suggested to increase the usefulness of these domains for screening. In particular, item 5 of domain 4 (i.e. "Sexual activities") was thought to introduce a potential bias, as PRISM will focus on clinical populations which differ greatly in age (i.e. AD, SZ, and MDD) and partner status (e.g. SZ patients often without partner). Therefore, it was decided to not include this item in the screening tool. Further, among the items of domain 6, the first item (i.e. "Problems in joining in community activities") was deemed relevant for social withdrawal, while the other items assess other consequences of disabilities not relevant for studying social withdrawal (e.g. financial aspects, emotional impact, laws etc.). So, the final screening tool included the first four items of WHODAS domain 4 and the first item of WHODAS domain 6, resulting in an adapted scale of five items. This adapted scale was tested in subsamples of the already available cohorts (Netherlands Study Depression and Anxiety (636 healthy controls, 1024 patients with MD) and CIBERSAM (55 patients with AD, 282 patients with SZ and 102 healthy controls) showing a good distribution and good discriminatory capacity for high and low levels of social withdrawal.

2.2. Evaluation of social functioning: social functioning scale (Birchwood et al., 1990)

Based on the literature review, we selected for the deep phenotyping clinical study a psychometric instrument providing an assessment of social withdrawal as well as a more comprehensive assessment of social functioning: The Social Functioning Scale (SFS). As recently emphasized by Green et al., 2017, a better understanding of social disability in neuropsychiatric disorders, such as schizophrenia, requires to disentangle its constituent components. Importantly, although the SFS was not specifically designed to exam social withdrawal, the SFS contains three sections assessing aspects of social withdrawal, i.e. the sections on 1) social withdrawal/engagement, 2) interpersonal behaviour and 3) pro-social engagement. The main other reasons for the selection of the SFS were that 1) it has been extensively used, particularly in SZ (e.g. (Simons et al., 2016)) but also in AD (e.g. (Torralva et al., 2000)) and MDD (De Silva et al., 2013). 2) Its validity and reliability have been extensively demonstrated (De Silva et al., 2013). 3) Its administration time (i.e. 15 min) and its self-report and caregiver-report versions made this scale very suitable for PRISM's aims and timeline. 4) Normative data on healthy controls are available, allowing the comparison of populations differing by age (e.g. SZ and AD populations). 5) The SFS allows to discriminate patients with social functioning deficits from those without any impairments in social functioning. 6) It is available both in Spanish and Dutch (the two languages used in the PRISM clinical centres). 7) Finally, the SFS provides, next to an assessment of social withdrawal, a detailed and comprehensive picture of social functioning, assessing functioning in several areas of social life such as the marital role, the household role, social/recreational activities, interpersonal relationships, independence/self-care. A main concern with regard to the SFS with regard to the more comprehensive assessment, was its section about work activities, since AD patients are usually retired. However, normative data were available for both employed and unemployed populations, allowing its use also in retired population. The SFS contains information about the quality of behaviours, but also objective measures can be extracted, such as social network size. This may be an important asset, since it potentially permits to better separate objective and subjective aspects of social withdrawal, which are likely sustained by partially different biological substrates (Cacioppo and Hawkley, 2009).

2.3. Subjective feeling of loneliness and affiliation: the De Jong Gierveld loneliness and affiliation scale

Although PRISM focuses mainly on objective measures of social withdrawal, it was decided that feelings of loneliness should also be taken into account. To this end, we selected the De Jong Gierveld Loneliness and Affiliation Scale (de Jong-Gierveld, 1987). It measures the subjective feeling of isolation, explained as the discrepancy between one's desired and actual relationships. The main reasons for this choice were: 1) its validation in clinical and healthy populations; 2) the availability of normative data for both clinical and healthy populations; 3) its use in several of the already available cohorts ; 4) its self-report structure; 5) the short time needed for administering (i.e. 5 min); 6) the detailed assessment of the subjective feeling of perceived isolation.

2.4. Overview of rating scales considered for use in this specific project on social withdrawal

Apart from the scales that were selected, several other scales were evaluated during the literature review. The table below summarizes per evaluated scale the reasons for selecting or not selecting it for use in this project. Of note, none of the evaluated scales provides an adequate assessment of internet and social network use. This must be considered an important limitation, given the increasing importance of this type of social interactions in today's societies. However, since the Smartphone

Table 1
Rating Scale.

Rating Scales	Pro	Cons	Ref.
WHO Disability Assessment Schedule Domain 4 (Getting along) and 6 (participation)	1. Specifically assesses social interaction 2. Extensive prior use in SZ, AD and MDD 3. Used in already available cohorts in PRISM 4. Administration time of 2-5 minutes 5. Availability of self- and caregiver versions in Spanish and Dutch 6. Possibility to administer only a single Domain	1. Adaptation needed as some items were not relevant or could introduce potential bias	(Ustün et al., 2010)
The Social Functioning Scale	1. Comprehensive evaluation of social withdrawal with focus on objective measures. 2. Used in SZ, AD and MDD 3. Robust, normative data on healthy controls available 4. Administration time 15 minutes 5. Self- and caregiver versions in Spanish and Dutch		(Birchwood et al.,1990)
De Jong Gierveld Loneliness and Affiliation Scale	1. Validated in SX, AD, MDD and healthy populations 2. Normative data available for clinical and healthy populations 3. Used in available PRISM cohorts 4. Self-report structure 5. Administration time 5 minutes		(de Jong-Gierveld, 1987)
Social Withdrawal Scale	1. Specifically assesses social withdrawal (in Motor Neuron Disease) 2. Provides info about objective and subjective aspects of social withdrawal	1. Mainly used in motor neurons disease, few data from other populations 2. Too much focus on physical disability	(Rigby et al., 1999)
Social Isolation Index	1. Includes the evaluation of marital status, frequency of contacts with friend, family, children, the participation in social activities	1. Validity and robustness are still to be confirmed 2. There are not studies on AD, SZ, and MDD	(Shankar et al., 2011)
Social Disconnectedness Scale	1. Developed to assess social disconnectedness specifically 2. Provides an objective evaluation of social withdrawal	1. Validity and robustness are still to be confirmed 2. Mainly used in studies on elderly (reliability in SZ, AD, and MDD to be confirmed)	(Cornwell and Waite, 2009)
Social Support Network Inventory	1. Provides an objective evaluation of social network size	1. Does not assess other aspects of social withdrawal	(Sarason et al., 1987)
Duke Social Support and Stress Scale	1. Assesses both objective and subjective aspects of social functioning	1. Complexity of administration 2. Too much focus on stress related issues	(Parkerson et al., 1991)
Objective Social Outcome Index	1. Assesses employment, accommodation and living situation	1. Validity and robustness are still to be confirmed 2. Provides little information, on social withdrawal	(Priebe et al., 2008)
Lubben Social Network Scale - Revised	1. Provides an objective evaluation of social network size 2. Widely used in AD, SZ, and MDD 3. Assesses also some subjective aspects of social withdrawal	1. Provides too limited information for deep phenotype purposes 2. Assesses mainly the quantity/quality of family and friend relationships, not taking into account other aspects of social behaviors	(Lubben et al., 2006)
Multidimensional Observation Scale for Elderly Subjects	1. Provides a measure of psychosocial functioning, covering five domains, including withdrawal 2. Used in a variety of descriptive studies 3. Does not require the cooperation of the person rated	1. Was developed for diverse purposes in the elderly, in residential care; 2. Should be substantially modified for PRISM	(Helmes et al., 1987)
Assessment of subjective feelings associated with Social Withdrawal			
Perceived Isolation Scale	1. Developed to specifically assess perceived social isolation 2. Provides an objective evaluation of social withdrawal	1. Validity and robustness are still to be confirmed 2. Mainly used in elderly so far 3. Problems with the reliability in SZ, AD, and MDD	(Hughes et al., 2004)
UCLA loneliness scale	1. Extensively used, also in AD, SZ, and MDD 2. Normative data are available 3. Easy to be administered (> short versions)	1. Too much oriented toward concerns of the young (scale was originally developed for college students)	(Russell, 1996)
The Social Support Questionnaire	1. Quite extensively used, although it was developed to assess social support in the general population	1. There are likely differences between sexes 2. Short version may lack reliability 3. Focuses only on perceived social support and does not assess feeling of loneliness	(Sarason et al., 1987)
The Multidimensional Scale of Perceived Social Support	1. Quite extensively used 2. Assesses social support from family, friends and significant others 3. Easy to administer	1. Focuses only on perceived social support perceived and does not assess feelings of loneliness	(Zimet et al., 1990

application included in this project's protocol (see below) will provide an objective measure of telephone and social media use, we judged that this limitation could be partially overcome through data integration (Table 1)

3. Selection of experimental neurobiological and behavioral paradigms

Based on several in-depth discussions on the goals, background and future applicability of potential results from this specific project, the

choice of experimental paradigms to examine social withdrawal in PRISM was limited to structural and functional MRI measures, EEG measures and additional behavioral paradigms. Furthermore, we had to prioritize because of constraints with regards to the participants burden and the time path. Within the context of this specific project, general criteria for paradigm selection for the deep phenotyping were specificity, robustness, feasibility, prior use across SZ and AD patients (and preferably also MDD), applicability in cross-methodological tasks (functional MRI, EEG, behavioral) and the availability of (potential) rodent homologues designed to meet a wider, reverse and forward translational objective of the project. Finally, the selected paradigms should probe the systems and neural circuitry thought to underlie social functioning and more particularly to be involved in social withdrawal in humans (see review by Porcelli et al in this issue)

3.1. Structural MRI, resting state and task related MRI and EEG paradigms

MRI examinations in the current project comprise both structural and functional scan sequences. For the structural MRI part, we chose to acquire routine 3D structuralT1 weighed scans to allow the investigation of volumetric and shape correlates of measures of social withdrawal. We additionally chose to acquire Diffusion Tensor Imaging (DTI) scans to examine parameters of structural connectivity.

Resting state and task related functional MRI (fMRI) and EEG cover partially different spatial and temporal domains and may in this way be considered complementary in assessing neural circuitry at rest and during task related activation.

3.2. Probing the social perception network

3.2.1. Facial emotion processing paradigms

Our literature review of available MRI and EEG paradigms focused on, but was not limited to studies in patients with SZ, patients with early AD and to a lesser degree patient with MDD. An obvious candidate for both a fMRI and a EEG paradigm was a Facial Emotion Processing (FEP) Task. In this task with a duration of about 10 min, subjects typically are presented faces with different emotional valence, usually neutral, sad, angry and happy, but other expressions like disgust might be added.

The FEP was considered as an obvious candidate because of the importance of the processing of facial expressions in social interaction, and because of the wide use of the FEP in fMRI and EEG studies across disorders, as described below. With the FEP task it would be possible to probe the brain's Social Perception network and to some extent also the Aversion network (with more negatively valenced pictures) (see Porcelli et al in this issue).

Impairments in processing of facial emotions and their association with social and functional outcome, have been explored in several studies of SZ patients (Edwards et al., 2001; Marwick and Hall, 2008; Pinkham et al., 2011). Overall, individuals with SZ show an impairment in facial emotion recognition compared with healthy controls (Marwick and Hall, 2008), but this deficit appears to be more pronounced in the case of negatively-valenced emotional expressions such as fear and sadness (Edwards et al., 2001). Since the amygdala-based Perception Network is thought to play an important role in the processing of negative emotions such as fear (Adolphs, 2002), these findings are consistent with the reduced amygdala volume (Wright et al., 2000) and amygdala hypoactivation observed in SZ patients, especially when comparing BOLD signal changes elicited by fearful versus neutral faces (Aleman and Kahn, 2005). Of special relevance to the current project, Bark et al. found in a recent review and meta-analysis that facial emotion identification was already impaired in patients with early-onset and first-episode psychosis (Barkl et al., 2014), with a generalized effect of poorer accuracy of identifying expressions.

Results from EEG studes using a FEP paradigm corroborate with the observation that processing of emotional facial expressions is aberrant in SZ. The N170 evoked response potential (ERP), thought to be face-sensitive, is generally observed to be of reduced amplitude in response to facial stimuli in SZ (Tsunoda et al., 2012; Turetsky et al., 2007). Altered theta power and N170 ERPs following presentation of emotional faces may signal difficulties in the integration of socio-emotional processing and sustained attention in SZ (Brenner et al., 2016). In a recent meta-analysis of face processing ERPs in SX, the amplitude of both the N170 ERP and the N250 ERP in response to facial stimuli was smaller in patients, with comparable effect sizes (McCleery et al., 2015). Notwithstanding the results of this meta-analysis, there is heterogeneity in research findings from individual studies, some of which may be accounted for by variability in social withdrawal between SZ patients. For example, a study by Pinkham et al. (2011) found no significant differences between overall performance on a facial emotion processing (FEP) task between SZ and control participants, but a specific tendency in the SZ group to misattribute anger to neutral faces. Their sample of SZ patients were experiencing prominent paranoid symptoms, which itself is likely to be linked to increased social withdrawal. Thus, it is possible that different levels of social withdrawal are associated with different information processing patterns and biases in SZ patients, and that the FEP task is sensitive to those differences. Supporting this idea, N170 ERPs have been linked to social functioning in patients with SZ (McCleery et al., 2015). Furthermore, a study combining three measures of emotion recognition (Facial Emotion Identification Test, Voice Emotion Identification Test and Videotape Affect Perception Test) found that the total score on these measures at baseline predicted improvement in functional outcomes following a 12-month community-based psychosocial rehabilitation for patient with SZ (Brekke et al., 2007). Difficulty in facial affect processing and especially recognition has also been documented in relation to AD and MCI. For instance, compared to healthy elderly controls, elderly individuals with MCI tend to perform significantly worse on FEP tasks, regardless of the affective valence of the facial expression, but with better performance when intensity is increased (Sarabia-Cobo et al., 2015). A more pronounced deficit was suggested, however, in terms of recognising disgust. Of interest, several studies report a recognition impairments in patients with early-stage Alzheimer's disease (Hot et al., 2013; Sapey-Triomphe et al., 2015)

In conclusion, impairments related to facial emotion identification and processing are evident in both SZ and AD patients. However, as conceptualised in the RDOC approach, diagnostic groups may differ both behaviorally and by neural substrates across the processing of emotional facial expressions or valence. The specific profiles of deficits are likely to have a relationship with social behaviour, and in particular social withdrawal.

A relative wealth of previous data exists to compare our findings with, although no previous study has directly compared findings from SZ and AD patients. The FEP tasks were well-tolerated in these patient groups, and indeed these pardigms are of relatively short duration (10–15 min). By collecting both fMRI and EEG data during FEP we will gather data with these methodologies' higher spatial and temporal resolution, respectively, allowing a more comprehensive understanding of implicated neural processes. Of relevance for the potential later stages of the current project, an extensive body of literature also documents abnormalities in the processing of facial emotional expressions in patients with MDD as examined with fMRI and EEG, also in remitted and early stages of the disease (Delle-Vigne et al., 2014; Groenewold et al., 2013; Cusi et al., 2013). A relative disadvantage of the use of FEP paradigms in the current project may be the lack of comparable robust paradigms in animals other than non-human primates, especially rodents, limiting reverse and forward translation.

3.2.2. Affective prosody

The working group also considered paradigms focused on the detection of affective prosody (i.e. the emotional modulation of voices) as potential tools to probe the social perception network. Deficits in

auditory emotion recognition have been demonstrated in patients with SX and impairments were shown to be related to levels of social functioning (Hoertnagl CM et al. 2014). Some studies have also shown altered processing of affective prosody in patients with AD (Lee et al., 2014). However, given that this paradigm overlaps with the FEP in probing the social perception network, and that for the FEP paradigm a lager body of data existed and ample experience was available in the PRISM consortium, preference was given to the FEP.

3.3. Probing the social affiliation network

3.3.1. Monetary and social incentive delayed task

There was a discussion in the working group, also inspired by comments from the projects reviewers' panel, that within the social cognition domain one should next to the basic processing of the socially-relevant stimuli (such as facial expression) also consider the rewarding or punishing properties of these social stimuli as assessed by elements of the brain's Social Affiliation system. Reduced or altered reward processing associated with social stimuli is likely to be associated with reduced motivation or capacity to interact socially (Gossen et al., 2014).

The working group identified a number of paradigms focused on the processing of monetary like reward, but also a relatively novel task combining this with probing the processing of social incentives. This Monetary and Social Incentive Delayed task (MSID) allows collection of neural data relevant to the processing of both non-social (monetary) and social (facial expression) rewards. The MSID is based on the Monetary Incentive Delay Task (MID), a well-replicated and validated paradigm that measures both the receipt of rewards as well as reward anticipation, and which robustly activates areas of the brain associated with reward processing including the ventral striatum (Knutson et al., 2001; Rademacher et al., 2014). Using this task, it has been shown that in SZ reward anticipation is directly impaired and associated with reduced activation of the ventral striatum: impaired reward anticipation has been observed in both unmedicated patients with SZ and those treated with typical antipsychotics (Kirsch et al., 2007; Schlagenhauf et al., 2008). A negative correlation has also been found between ventral striatum activation and overall level of negative symptoms, suggesting that it may be a biomarker of negative symptoms in SZ (Juckel et al., 2006; Waltz et al., 2007). The MID is therefore a biomarker model for reward anticipation that is independent of learning, and is thought to be sensitive to negative symptomatology in SZ.

The MSID is an extension of the MID, including blocks of trials that examine both monetary as well as social reward, with a total duration of around 20 min. Social rewards can, for example, be comprised of pictures showing happy facial expressions (signalling social cohesion, shared enjoyment, and/or social approval) at different levels of reward (i.e. faces at different intensities of happy/smiling expressions). Studies show that both monetary and social rewards activate the ventral striatum in healthy controls (Rademacher et al., 2010; Spreckelmeyer et al., 2009).

Of note, a behavioral-only version of the MSID has been recently used to explore reward and loss processing in AD and frontotemporal dementia, although healthy control data was not collected (Perry et al., 2015). The MSID therefore provides a measure of both reward processing more broadly – as may be relevant to symptoms of general apathy and anhedonia experienced by patients with SZ, AD and MDD – as well as allowing a direct comparison between reward processing associated with monetary vs. social rewards. In addition, EEG, behavioral and rodent homologues are available to support future translational studies. As such, the MSID task was viewed as relevant and valuable in achieving PRISM's goals.

3.3.2. Approach-avoidance paradigms

The workgroup also discussed the potential of a novel elegant approach-avoidance paradigm to probe the brain's social affiliation and social aversion networks. In this paradigm subjects have to move a joystick towards or away from a stimulus with a specific valence. The paradigm has been used in some ERP and fMRI studies in healthy controls (Roelofs et al., 2007, 2009). The paradigm has also been used in a fMRI study examining the rewarding properties of social interactions in relation to approach motivation traits (Radke et al. 2016). So far, however, this approach-avoidance paradigm has not been used in combination with fMRI in patient populations and comparable paradigms in animals do not exist yet

3.4. Probing the mentalising and mirror networks

Problems in more complex social functioning, involving aspects like Theory of Mind (ToM) or empathy, have been demonstrated in both SX and early AD. A review by Sandoz et al. (2014) showed a decrease in ToM performance in patients with AD, more pronounced in more complex task. Healey et al. (2016) reviewed the literature on amongst others ToM performance in patients with first-episode psychosis and concluded that these patients consistently show a reduced performance.

We therefore reviewed several paradigms developed to study (aspects of) more complex social functioning, putatively relying on the mentalising or mirror network. A variety of these paradigms is available, but frequently used to study disorders like autism spectrum disorders and sociopathy. More importantly, we considered the fact that ToM and similar paradigms typically rely on intact executive functions and may therefore sensitive to the influence of reduced cognitive abilities as an important limitation for use in the current project (Sandoz et al., 2014). Furthermore, the potential for more direct reverse translation of these constructs to animal models, especially in rodents, is limited. We therefore decided at this stage, also based on the earlier mentioned restraints for PRISM, not to include a ToM paradigm in our set of fMRI and EEG paradigms, but to examine this construct in a behavioral paradigm.

3.5. Behavioral paradigms assessing complementary aspects of social cognition

The selection of additional behavioral tasks was predominantly secondary to the selection of imaging and EEG tasks described above. Behavioral tasks were selected according to the same criteria as imaging and EEG tasks (e.g. sensitivity, feasibility, applicability to patient with SZ and AD, and potentially MD, and potential for reverse translation into animal models), but with an emphasis on selection of tasks that tested aspects of relatively independent, or complementary, domains to those measured during neuroimaging or EEG. In addition, these tasks could be of a more exploratory nature.

In total six behavioral tests were selected for the study protocol, of which four tasks to examine additional aspects of social cognition, two other task examined aspect of other cognitive domains such as attention. The four additional social cognition tasks were: a task of Facial Expression Recognition (FERT), two effort-based decision-making tasks (Deck Choice Effort Task, DCET, and Effort Expenditure for Rewards Task, EEfRT) to examine motivational aspects and complement the MSID, and a vignette "Hinting" task probing higher level cognition.

3.5.1. Facial expression recognition task

As a homologue and extension of FEP fMRI and EEG paradigms probing the social perception network, we selected the Facial Expression Recognition Task (FERT). It requires participants to view photos of faces with various expressions, presented very briefly (typically around 0.5 s), followed by indicating whether the expression was happy, sad, fearful, disgusted, surprised, angry, or neutral. Faces vary in the 'intensity' of the presented emotion, allowing more detailed exploration of sensitivity to different facial expressions, as well as bias in processing (i.e. systematic errors in expression classification). The FERT and similar tasks have been used widely as a measure of socially-

relevant emotional information processing across disorders including SZ, AD and major depressive disorder (MDD). Both SZ and AD groups seem to be impaired on this task. In SZ, it appears that recognition of fear (Okada et al., 2015) and sadness (Huang et al., 2011) is more impaired than the recognition of positive facial expressions of emotion, and that this impairment is related to the severity of patients' negative symptoms (Turetsky et al., 2007). In AD, research suggests that all facial expressions emotions are affected to the same degree, and impairments in recognition are shown when the emotions presented are relatively subtle (Torres et al., 2015). Nevertheless, impairments in facial expression recognition seem to be more noticeable in other forms of dementia (e.g. frontotemporal dementia (FTD); indeed FERT tasks are often used in research to differentiate between AD and FTD patients (Goodkind et al., 2015). The task therefore shows potential both as a tool for diagnostic differentiation, and in providing behavioral markers related to symptoms.

The 10 min FERT task is easy to implement and the inclusion of a behavioral version of an emotional face processing task in addition to the fMRI and EEG version will allow for measurement of responses to a broader range of facial expressions, as imaging protocols typically only include four emotional expressions (happy, fearful, sad and neutral), and at a range of emotional intensities, allowing for more in-depth analysis of sensitivity curves that are characteristically associated with emotional expression recognition.

3.5.2. Effort-based decision making paradigms examining motivation

As described in the section on MRI and EEG paradigms, the MSID task probes neural circuitry putatively involved in sensitivity to (social) reward and anticipation of (social) reward. A further important aspect of reward processing is the evaluation of the "cost" of the effort involved in pursuing rewards, i.e. motivation. In SZ and early AD, this effort-cost computation may be altered in general or in the case of social reward. Effort-based decision-making tasks aim to assess the degree to which costs and benefits are incorporated into choice behaviour. These tasks measure how willing participants are to engage in effortful responding as a function of the probability and magnitude of potential rewards or monetary compensation. Healthy participants typically exert more effort when the probability of a reward is high and monotonically increasing with the value of that reward. Moreover, anhedonia has been found to correlate with increased effort-cost computations in healthy volunteers. The willingness to expend effort for low probability outcomes has been directly related to differences in striatal dopamine activity (Treadway et al., 2012). In SZ, negative symptoms were found to relate to reduced willingness to invest effort for larger rewards (Gold et al., 2013). This suggests a possible role for impaired effort-cost computations in SZ that are related to negative symptom severity and may impact on social interaction. We selected for inclusion in the protocol two short tasks (15 min each) for effortful decision-making: the Deck Choice Effort Task (DCET) and the Effort Expenditure for Rewards Task (EEfRT). Both these tasks require participants to make a series of choices between an easier or a more difficult task, for different levels of reward, but the kind of effort required differs between tasks. The DCET provides a measure of willingness to expend cognitive effort for reward, whilst the EEfRT measures willingness to expend motor/physical effort. Expending effort within these different domains is likely to involve or recruit partially different brain networks, with cognitive effort associated more with prefrontal cortex activity, and motor/physical effort more linked with motor and premotor cortex function. Both tasks show good external validity (with performance related to negative symptoms in SZ) and psychometric properties in SZ populations (Horan et al., 2015; Reddy et al., 2015). Less is known about the validity of the task in AD patients. However, it is noteworthy that apathy, one of the most common psychological symptoms of dementia - if not the most common (Craig et al., 2005; Guimaraes et al., 2008; Landes et al., 2001; Lyketsos et al., 2002; Onyike et al., 2007) - is likely to be related to motivational deficits that are detectable in effort-based decision-making tasks. Furthermore, tasks of comparable cognitive demand involving computations of reward and risk have been used in AD (Sinz et al., 2008), suggesting that the paradigm is feasible in this patient group.

3.5.3. The hinting task

The working group decided not to include a MRI or EEG paradigm probing higher-level social functioning because of the possible confound by cognitive impairments, but to examine this more exploratory in a behavioral paradigm. We selected the Hinting task as a strong candidate measure of higher-level social cognition (e.g. ToM), to complement other tasks of lower-level social cognition (such as facial emotion processing and tasks of simple social reward processing). The Hinting task has a duration of 10 min and measures the ability to infer the true intent of indirect speech. Participants are read 10 short passages presenting an interaction between two characters, and each passage ends with one of the characters dropping a hint. Participants are then asked what the character truly meant. Participants can earn partial credit for that passage if they require additional hints. The task shows notably good psychometric properties, particularly in SZ (Pinkham et al., 2016). Although vignette tasks such as the Hinting Task may be viewed as problematic for use in groups with more pronounced cognitive impairments, such as the AD group in the current study, challenging theory-of-mind tasks have previously been used successfully in AD (Rowse et al., 2013).

4. Social withdrawal: passive remote monitoring

Clearly, a key challenge in studying a construct like social withdrawal is to obtain objective measures of social interaction over time and not to solely having to rely on subjective measures derived from self-reporting, especially in disorders were self-monitoring may be compromised, or on the reporting by the significant others of patients.

For the current project, we have therefore chosen to use a smartphone application (BeHapp) that has been developed to provide a remote, unobtrusive and objective measure of sociability and social exploration in a longitudinal daily-life manner using different data modalities collected through an Android based smartphone (www.Behapp.com) (Eskes et al., 2016a,b). Once installed, the application continuously monitors communication and exploration patterns in participants as a function of social acts (e.g. number of text messages sent and received, number and duration of phone calls), environment social density measurements (e.g. blue tooth devices and WiFi in direct vicinity), GPS location updates and general smartphone usage. The BeHapp is currently used in ongoing studies in patients with SX, in at-risk populations and in a large longitudinal study in youth.

A key goal of using BeHapp in the current project is to develop and validate an objective measure of social withdrawal/sociability, with the future goal of harmonizing objective and subjective social withdrawal measures across cohorts and diseases, to allow more focused and effective research into this construct and its clinical relevance. Of relevance, gathering objective patters of social interaction over time in humans will be also important for back-translation of findings to animal experimental settings were elaborate methods for objectively tracking and characterizing social interactions already exist.

Installation of the BeHapp app and submission of the associated data is optional. When participants do not have an Android smartphone, one can be provided by the research team for the duration of the study. Where participants agree to providing data through BeHapp, the app will be activated with a unique "key" on each participant's phone, and this key will expire after six weeks, so that data collection stops automatically. Participants will be given instructions and guidance on how to uninstall the app if it has been installed on a personal phone, and on how to return the device to the research team if it has been provided for the duration of the study

No directly identifiable information about any participant is stored

within any system that is part of the BeHapp service. Also, BeHapp monitoring data is encrypted before being stored locally on the participant's device and cleared after each successful upload to the secured server. Furthermore, in no instance any information with regard to the content of any spoken or written messages is recorded through BeHapp. In addition, BeHapp irretrievably obfuscates any information related to any individual interacting with the participant before sending it to the research database.

In this manuscript, we discussed the working definition of social withdrawal and the selection of rating scales and experimental and complementing behavioral paradigms, including a digital phenotyping approach, for a project investigating the psychoneurobiology of social withdrawal across three neuropsychiatric disorders. Clearly, although this project will employ a fairly comprehensive set of assessments, it should be taken into account that choices were limited by the specific time constraints and requirements, as well as by the availability and reliability of currently available instruments and paradigms.

Disclaimer

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