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Electrophysiological assessment methodology of sensory processing dysfunction in schizophrenia and dementia of the Alzheimer type

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ABSTRACT

Schizophrenia and Alzheimer's disease impacts on various sensory processings are extensively reviewed in the present publication. This article describes aspects of a research project whose aim is to delineate the neurobiology that may underlie Social Withdrawal in Alzheimer's disease, Schizophrenia and Major Depression. This is a European-funded IMI 2 project, identified as PRISM (Psychiatric Ratings using Intermediate Stratified Markers). This paper focuses specifically on the selected electrophysiological paradigms chosen based on a comprehensive review of all relevant literature and practical constraints. The choice of the electrophysiological biomarkers were fundamentality based their metrics and capacity to discriminate between populations. The selected electrophysiological paradigms are resting state EEG, auditory mismatch negativity, auditory and visual based oddball paradigms, facial emotion processing ERP's and auditory steady-state response. The primary objective is to study the effect of social withdrawal on various biomarkers and endophenotypes found altered in the target populations. This has never been studied in relationship to social withdrawal, an important component of CNS diseases.

The PRISM project is attempting to identify the underlying neurobiological determinants of social withdrawal in selected psychiatric and neurodegenerative disorders utilizing a very novel transdiagnostic approach (Insel et al., 2010). Initially the project will focus solely on Alzheimer's disease (AD) and schizophrenia (SZ) but ultimately individuals with major depression (MDD) may also be recruited. The overarching aim of this project is to further our understanding of the underlying neurobiology behind these disorders so that subpopulations could be identified where personalized medicine approaches may be amenable. With this somewhat unusual transdiagnostic perspective the project engaged in a careful review of the possible approaches that encompassed all these variables. The output of this process is with respect to the electrophysiology and sensory processing work stream is presented here offering a novel slant on these literatures. For reference, it is worth noting that phenotypic characterization of schizophrenic, schizoaffective disorders and bipolar disorder patients or their first degree relatives using comprehensive electrophysiological and behavioral measurements has been conducted previously [please refer to Ethridge et al. (2015) and Clementz et al. (2016)] and that the overall quantitative approach is described in greater detail in the other articles within this special edition (Kas et al., 2017). Essentially, patients and age-matched healthy controls will undergo quantitative phenotyping assessment focused on four domains: (1) social withdrawal (van der Wee et al., 2018); (2) working memory and (3) attention (Gilmour et al., 2018) and (4) electrophysiological assessments of sensory processing (described in this article and Hornix et al., 2018). Social withdrawal will also be stratified according to a reference clinical scale (WODAS II) with cutoffs defining low and high withdrawal. This use of stratification allows the impact of these independent factors, on multiple quantitative measures, to be assessed and hence provide enhanced statistical sensitivity. This will allow the apparent similarities between populations, which may be based on very different constructs, to be disentangled.

The negative symptoms and cognitive impairment in schizophrenia

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Table 1
PRISM selected tests and properties of the various electrophysiological end points.

Paradigm Sensory modality	Key endpoints/ Key references	Test-Retest reliability of key endpoints	Age effect	Discriminating Schizophrenia patients from controls	Discriminating Mild-moderate AD patients from controls
Resting EEG	Bands definition, epochs and design (Jobert et al., 2012)	N/A in general Peak α frequency highly reliable trait (Grandy et al., 2013)	↑ Δ, ↑ θ, ↓: α-2 with age. ↑δ connectivity and ↑α connectivity (Vecchio et al., 2014a). Peak α frequency is reduced with age (Katada et al., 2000; Woodruff and Kramer, 1979). **Significant age effect**	Topographically limited ↓α (Clementz et al., 1994; Goldstein et al., 2015; Itil, 1978; Kim et al., 2015; Merrin and Floyd, 1996; Sponheim et al., 2000). ↓:α connectivity (Di Lorenzo et al., 2015; Hinkley et al., 2011). ↑α asymmetry (Gordon et al., 2010; Jetha et al., 2009). Spontaneous ϒ power in resting brain presents discrepancies between publications: -↓ϒ:(Giannitrapani and Kayton, 1974; Itil et al., 1972; Rutter et al., 2009; Winterer et al., 2004). -↑ϒ:(Andreou et al., 2015b; Kikuchi et al., 2011; Mitra et al., 2015; Tikka et al., 2014). ↑ϒ connectivity (Andreou et al., 2015a) Reviews on ϒ conclude that ↑ϒ is present and corresponds to endogenous activation of sensory pathways (in the absence of stimulus) (Uhlhaas and Singer, 2015[rev]; White and Siegel, 2016[rev]) ↑β (Miyauchi et al., 1990) α/θ ratio (left side) correlates with negative symptoms (Mitra et al., 2017) α asymmetry in withdrawn SCZ according to DSM5 personality domains (Papousek et al., 2018) **Sensitive to SZ**	↑Δ, ↑θ, ↓: α, ↓:β (Bhattacharya et al., 2011; Jelic et al., 2000; Jelles et al., 2008; Jeong, 2004; Koenig et al., 2005; Park et al., 2008). ↓: [α-2, β and ϒ] synchronization (Babiloni et al., 2004; Pijnenburg et al., 2004; Stam et al., 2007, 2003). MCI subjects: ↓:theta connectivity; AD: ↓:alpha connectivity (Vecchio et al., 2014b). Using MEG in a MCI group the DFN was functionally disrupted in the α band, no differences were found for, θ, beta β and ϒ -band (Garcés et al., 2014) **Sensitive to AD**
Mismatch Negativity (MMN) Auditory	N2 peak amplitude and latency: (Näätänen and Alho, 1995) [rev] (Frodl-Bauch et al., 1997) (Kathmann et al., 1999) (Duncan et al., 2009)	(Hall et al., 2006)[rev;ICC = 0.66-0.67] (Tervaniemi et al., 1999) [ICC = 0.78] (Pekkonen et al., 1995)	(A↓)(Bartha-Doering et al., 2015) [rev] (Pekkonen et al., 1996) (A↓)(Schiff et al., 2008) (A↓) (Chen et al., 2015)[rev] **Significant age effect**	(Braff and Light, 2004a) (Javitt and Sweet, 2015) [rev] (Gregory A. Light et al., 2015) [rev] (Näätänen and Kähkönen, 2009) [rev] (Light and Naatanen, 2013) 2013 [rev] (Umbricht and Krljes, 2005) [rev] (Rissling et al., 2012) (Light and Braff, 2005) (Braff and Light, 2004b) (Kärgel et al., 2014) (Näätänen et al., 2015) (Javitt and Sweet, 2015) (Haigh et al., 2017, 2016) **Sensitive to SZ**	(Lindín et al., 2013) (Baldeweg and Hirsch, 2015) (Pekkonen et al., 1994) (Pekkonen, 2000) **Sensitive to AD**
Oddball paradigm Auditory	Amplitude of P300 and latency: (Duncan et al., 2009)	(Perez et al., 2016)[ICC = 0.84] (Williams et al., 2005)[ICC = 0.78-0.81] (Mathalon et al., 2000) [SZ ICC = 0.82; NH ICC = 0.93]	(curvilinear) (van Dinteren et al., 2014) [rev] (Alperin et al., 2014) (greater compensatory frontal spread of P300 with ageing) (A↓ L↑) (Knott et al., 2003) **Significant age effect (curvilinear)**	(A↓) progressive over time (Turetsky et al., 2015) (A↓) (W.-H. Chang et al., 2014a) (A↓L↑) (Bramon et al., 2004) [rev] **Sensitive to SZ**	(L↑) (Tsolaki et al., 2017) (A↓) (Hedges et al., 2016) [rev] (L↑) (Howe et al., 2014)[rev] (A↓) (Polich and Corey-Bloom, 2005)[rev] (A↓) (Golob et al., 2009) (familial AD before onset) (A↓) (Holt et al., 1995) (greater frontal spread) (L↑)(Jackson and Snyder, 2008)[rev] **Sensitive to AD**

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Table 1 (*continued*)

Paradigm Sensory modality	Key endpoints/ Key references	Test-Retest reliability of key endpoints	Age effect	Discriminating Schizophrenia patients from controls	Discriminating Mild-moderate AD patients from controls
Oddball paradigm **Visual**	Amplitude of P300 and latency: (Duncan et al., 2009) (Antonakakis et al., 2016)	(Mathalon et al., 2000) [SZ ICC = 0.87; NH ICC = 0.86]	(Alperin et al., 2014) (greater compensatory frontal spread of P300 with ageing) (A↓) (O'Connell et al., 2012) (A↓ L↑) (Schiff et al., 2008) (A↓ L↑) (Knott et al., 2003) P300 L visual > L auditory (A↓ L↑) (Walhovd et al., 2008) **Significant age effect**	(A↓) (Oribe et al., 2013) (A↓)(Wynn et al., 2015) (A↓) (Mori et al., 2012) (emotional valence associated) (A↓) (Bestelmeyer et al., 2009) (twin study) **Sensitive to SZ**	(A↓) (Hedges et al., 2016)[rev] (A↓L↑) (Parra et al., 2012) **Sensitive to AD**
Auditory Steady-State Potentials	ASSR power calculated by PCA using all electrodes or gamma on Fz. (Tan et al., 2015) (Hamm et al., 2015)	(Legget et al., 2017)[r = 0.54-0.70 for evoked power] (McFadden et al., 2014) [r = 0.5-0.6 for evoked power]	(No age effect on ASSR intensity but Phase locking reduced) (Griskova-Bulanova et al., 2013) **No clear evidence**	(γ↓) (Brenner et al., 2009) (↓ SSR and γ and Phase locking)(O'Donnell et al., 2013a) (Mean Trial Power ↓)(Rass et al., 2012) (γ Phase Synchrony↓)(Lee et al., 2003) (γ phase locking↓) (Spencer et al., 2009) (evoked γ power ↓ and Phase locking)(Spencer et al., 2008) **Sensitive to SZ**	(↑) (Osipova et al., 2006) (↑) in AD but not MCI, (van Deursen et al., 2011) **Sensitive to AD (opposite to SZ)**
Facial Emotion induced ERPs	P100, N170, EPN and LPP (Sfärlea et al., 2016)	(Huffmeijer et al., 2014); all emotions N170 left ICC = 0.89; right ICC = 0.93	No data available	(Tempesta et al., 2014) (Kim et al., 2013) (Turetsky et al., 2007) **Sensitive to SZ**	(Asaumi et al., 2014) (limited to one component[P300]) **No clear evidence**

A: amplitude; AD: Alzheimer's disease; DFN: default network; EPN: early posterior negativity; ICC: intraclass coefficient; L: latency; LPP: late positive potential; MCI: mild cognitive impairment; MEG: magnetoencephalography; NH: Normal Healthy, N/A: not applicable; N170: negative wave centered on 170 ms after stimulus; N2: second negative wave in the 150–250 ms time domain; P100: positive wave centered on 100 ms after stimulus; PCA: principal component analysis; r: pearson's correlation coefficient; Rev: review; SZ: patients with schizophrenia; δθαβϒ: EEG bands as defined in (Jobert et al., 2012).

have been demonstrated to be independent components of schizophrenia (Bilder et al., 2000; Hughes et al., 2003; White et al., 1997). However social withdrawal, an important element of quality of life and a consequence of schizophrenia, is hypothetically related to negative symptoms and to the other dysfunctional processes, including sensory processing (Haigh et al., 2016). The question of what is the biological ground of social withdrawal is the main question that PRISM will analyse across the different domains, in Schizophrenia but also in other populations with negative symptoms and social withdrawal : Alzheimer's disease (Reichman et al., 1996; Reichman and Negron, 2001) and Major Depression (Galynker et al., 2000; Gerbaldo et al., 1995; Kulhara and Chadda, 1987). Processing of sensory modalities, predominately auditory and visual have been shown to be repeatedly altered in patients with AD and SZ (see Table 1). Morever, olfactory impairment has also been reported in both pathologies (Albers et al., 2015; Moberg et al., 2014; Zou et al., 2018). As a variety of approaches have been used to probe the different constructs of sensory processing, a comprehensive and detailed literature review was conducted to identify the most appropriate methodology for robust and consistent assessments. The key criteria employed for task selection were methodological standardization, test-retest reliability and discriminative sensitivity between disease pathologies and age effects. The later was considered important as the patient populations that will be recruited span a broad age range and it is well known that sensory capabilities are impacted with age (Musiek et al., 2005; Schadow et al., 2007).

Finally, it is important that the identified tasks are considered for their back-translational capabilities to facilitate inter-species assessments. For example, using geometric shapes in the visual oddball task rather than pictures would facilitate future assessment in non-human primates and potentially in rodents. It is important to note that an exception is made for the emotional processing task which although well established for functional magnetic resonance imaging (fMRI), is considerably less in its EEG modality and thus is identified as an exploratory endpoint only (Sfärlea et al., 2016). Finally, due to the limited amount of test time the patients may tolerate per session, during the electrophysiological, fMRI and behavioral testing, choices were made based on the intrinsic value of each task versus the time spent required to execute them. The selected electrophysiological tests are resting state EEG, auditory mismatch negativity, auditory and visual based oddball paradigms, facial emotion processing ERP's and auditory steady-state response. The selected tests, end points and key references are highlighted in Table 1. In order to verify that the parameters of each test were optimal, they (except FERT) were tested in healthy subjects in order to verify that outcome similar to the reference publications (indicated in the text) can be obtained. Two test populations were used for validation (Biotrial data on file): 124 recordings at baseline of a cross-over study conducted in 35 healthy male subjects aged 22–46 years (population A) and 21 healthy subjects (9 males and 12 females), aged 24–48 years and recruited later (population B). All were healthy and drug- free. The PRISM study itself is well on its way and is assessing quantitative biomarkers in schizophrenia (N = 72 SZ), Alzheimer's Disease (N = 72 AD) comparatively to healthy matched controls (N = 48).They will complete a series of fMRI, EEG, and behavioural paradigms, as well as contributing blood-derived (e.g. epigenetic) and a smartphone application collecting data related to social behavior (see Bilderebeck et al., 2018).

1. Objectives

These different dimensions used in phenotyping will be used in a multidimensional analysis using social withdrawal as a main grouping factor and analyze the links with the other dimensions with no underlying statistical hypothesis. For this purpose, the population is composed of half of patients with a high withdrawal level on a subscore of the World Health Organisation Disability Assessment Schedule (WHODAS-II) (Von Korff et al., 2008) and half with a low withdrawal level, with no overlap. In the present manuscript we will put forward the EEG endpoints of resting brain and several Evoked Related Potentials during Mismatch Negativity, Auditory and visual oddball paradigms and Facial emotion Processing as well as Auditory Steady State response to repeated stimuli.

2. Selected methods

2.1. Resting state EEG

The underlying neuronal circuitry involved in generating neuronal oscillations recorded by EEG are complex and diverse. All excitable membranes within the vicinity of the EEG electrodes, contribute at least in some part to the extracellular field potential recorded (Malmivuo, 2012). The electrical generators, from the very fast action potentials at the soma, axon or axonal terminals to the synaptic excitatory and inhibitory events associated with dendrites, superimpose at any given moment to elicit the recorded electrical potentials. Synchronized activity within or between any of these generators results in a measurable signal at the level of the EEG. The degree to which synchronization occurs at specific neuronal oscillation frequency bands is highly dependent on sensory input (for example, eyes open or closed), arousal levels (sleep versus awake) and cognitive load. To assist in classifying changes in these specific oscillations, frequency band definitions were defined (slow waves, delta, theta, alpha, beta and gamma; Jobert et al., 2012). These boundaries although based on prominent peaks in the power spectrum that occur during specific behaviors and in specific brain areas, are not often generalizable but do provide a somewhat robust framework from which to base comparative studies.

It is important to note that the EEG oscillations are inherently changeable, the most prominent is the classical alpha rhythm first described by Hans Berger (Berger, 1929) and originally termed Berger's wave. The alpha wave slowly oscillates when subjects have their eyes closed and are in a state of relaxed wakefulness, but it is immediately substituted with a faster and lower amplitude beta/gamma wave when eyes are opened. This is important to note as it highlights the critical importance of controlling a subject's behavioral state during EEG collection but also highlights that the non-stationary component of oscillatory amplitude, power and cross cortical synchrony also needs to be considered when collecting and analyzing data.

The most commonly reported changes in resting state EEG found in AD patients is a generalized EEG slowing. In both AD and Mild Cognitive Impairment (MCI) patients, the slowing is typically observed as a decrease in the mean frequency, alpha and beta band power with a corresponding increase in delta and theta band power when compared to healthy elderly (Bhattacharya et al., 2011; Jelic et al., 2000; Jelles et al., 2008; Jeong, 2004; Koenig et al., 2005; Park et al., 2008). Intriguingly, the increase in theta and delta band activity during wake contrasts with a reduction in slow wave activity that is observed during sleep in AD patients (Hassainia et al., 1997). One interpretation of this observation is that the disruption of the intrinsic circadian rhythms or sleep continuity leads to an abnormal increase in delta waves in awake AD patients, thus leading to a reduction during slow wave sleep. Others have argued that the enhanced slow wave and theta activity observed during wakefulness is a direct result of the cholinergic and/or other neurotransmitters deficits associated with AD (Adler et al., 2009; Babiloni et al., 2011). This hypothesis is also supported by studies showing that the acetylcholinesterase inhibitor rivastigmine in AD patients decreases power in both the delta and theta frequency bands and increases lower alpha frequency band power in those that show cognitive improvements (Gianotti et al., 2008). Moreover, muscarinic antagonists such as atropine and scopolamine have also been shown to produce a slowing like EEG phenotype in both cats and humans.

The circuits responsible for the generation of slow and delta EEG waves have been well described (Crunelli and Hughes, 2010; Destexhe et al., 2010) resulting from both the intrinsic bi-stability of cortico-

cortical synaptic neuronal networks (Steriade and Amzica, 1996) and the interplay with intrinsic oscillators within the thalamus (Crunelli and Hughes, 2010; Destexhe et al., 2010). The slow wave oscillations can be both large global network states as in deep slow wave sleep or more localized in specific cortical networks (Onisawa et al., 2017). It is therefore somewhat counter intuitive that slow wave power so dependent on synaptic connectivity is enhanced in a disease condition associated with such profound synaptic and neuronal loss (Busche et al., 2015). Thus, changes in neurotransmitter, hypometabolism (Babiloni et al., 2016a) may be involved as well as the reduction of activity of other generators like alpha which seems to correlate with hippocampus atrophy (Babiloni et al., 2009).

In contrast to AD, the commonly reported changes in the EEG signal observed in SZ patients are alterations in higher frequency bands (beta and gamma), but most notably task-evoked changes rather than resting state changes are usually reported more often. However, there are reports of changes in gamma oscillations in SZ patients either at rest or preceding a specific task. There is also evidence to suggest that the pattern of spontaneously occurring gamma-band activity may differ from the neural oscillations associated with cognitive processing. For example, Kikuchi and colleagues examined resting-state EEG-data in medication naïve, first-episode SZ patients versus healthy controls and found significantly elevated gamma-band power over the frontal electrode areas (Kikuchi et al., 2011). Interestingly, these changes were not seen in chronic SZ patients (Rutter et al., 2009). The interpretation and comparability of these findings is complicated by the fact that it is currently unclear whether the generating mechanisms underlying the high-frequency activity during rest are comparable to those seen during task-related oscillations. Classical gamma band oscillations emerge from the interactions of pyramidal cell excitation and inhibition from parvalbumin positive spiking interneurons within cortical networks (Buzsáki and Wang, 2012). These would however be expected to produce a clear and defined peak in the fast Fourier transform spectrum that can be seen during specific tasks and brain areas. In contrast, broadband power changes in the higher frequency bands are more likely explained by the sum of local synaptic events and action potentials and hence just the level of local cortical activation (Uhlhaas, 2011) rather than a specific oscillatory generator.

For the PRISM studies, EEG will be recorded in resting conditions with two sessions with eyes closed (5 min per session) separated by one 5-min session with eyes open. Both test conditions are required as spectral differences between AD and healthy controls are frequently seen in an eyes closed condition, but not in eyes open condition (Tartaglione et al., 2012). The comparison of spectral content (alpha band power) with eyes closed versus eyes open should discriminate between patients with SZ and healthy controls (Zaytseva et al., 2014). The power spectrum per electrode across 59 channels will be estimated and summarized using the reference International Pharmaco EEG Society (IPEG) frequency bands (Jobert et al., 2012), with delta: [1.5–6 Hz], theta [6–8.5 Hz], alpha 1 [8.5–10.5 Hz], alpha 2 [10.5–12.5 Hz], beta 1 [12.5–18.5 Hz], beta 2 [18.5–21 Hz], beta 3 [21–30 Hz] and gamma [30–40 Hz]. The area under the curve (AUC) of spectra segments will provide an estimation of power in each frequency band of interest. Absolute and relative powers will be analyzed for each band, both in eyes open and eyes closed conditions. For each band, the relative power will be the absolute power divided by the power on the total band.

With respect to data quality control, under both test conditions, all recordings will be visually inspected to reject artifact segments such as high frequency noise caused muscular activity, environmental noise, or eye blinks. In case of sleep episodes occurring during the recording period, these will be manually rejected from the analysis. The artifact free signal from each electrode will then be analyzed using a fast Fourier transform (FFT) to produce a power spectra. EEG flat maps will be created using absolute and relative powers estimated following IPEG definitions for frequency bands. To study resting brain circuitries, several electrode signals will be used simultaneously and additional computations will be conducted to assess potential relationships within or between specific brain regions. The correlations between an electrode and its neighbor (local properties) will be used with the cordance, that will ultimately provide data comparable with that obtained with brain imaging (Bell et al., 2012; Leuchter et al., 1994).

Connectivity at the scalp level can be quantified by several methods (Sakkalis et al., 2011), with coherence (Pascual-Marqui et al., 2014) as one of the most characterized thus permitting synchronization (Tan et al., 2013) or coupling quantification between electrodes (Babiloni et al., 2016b). Additional efforts derived at determining the cortical sources underlying the activities observed on the scalp (source localization) may also be implemented. Since the 1990's, low resolution brain electromagnetic tomography (Loreta) is widely used to estimate sources (Babiloni et al., 2011; Pascual-Marqui et al., 1994) which can also be the first step toward more complex methods targeting resting state networks (Aoki et al., 2015; Olbrich et al., 2014).

2.2. Auditory mismatch negativity

Mismatch Negativity (MMN) is passively evoked when a sequence of repetitive standard stimuli is occasionally interrupted by infrequent oddball or deviant stimuli that differ in some physical dimension (pitch, duration). The onset of MMN occurs within 50 ms of stimulus deviance and peaks after an additional 100–150 ms. MMN is thought to result from pre-attentive processes, since it is present when a subject is involved in tasks that are unrelated to a MMN stimuli (Garrido et al., 2009) and may even be modulated by attentional processing (Arnott and Alain, 2002). Two major hypotheses have been proposed to explain MMN, which can be unified within a predictive coding framework (Garrido et al., 2009). First, within the adaptation hypothesis (Jääskeläinen et al., 1999), the N1 response is modulated by similarities between the common tones and the novel tone and thus the MMN is generated locally at the auditory cortices. Second, within the model adjustment hypothesis (Näätänen et al., 2007), the incoming regular stimuli form a memory trace and the MMN is originated from circuitry comparing the novel stimuli with an internal representation. The inter stimulus intervals (ISI's) for which a MMN is elicited have been commonly associated as indicative measures of a memory trace duration. This is typically around 10 s for healthy young adults (Sams et al., 1993) and no more than 4.5 s in healthy older subjects (Pekkonen et al., 1996).

Both temporal and frontal circuitry have been identified underlying MMN. Although bilateral activation of the auditory cortices is known to be a primary contributor (Duncan et al., 2009), frontal components have also been described using EEG, MEG and fMRI (Fulham et al., 2014). Rinne et al. discovered that the frontal component of the MMN peaked later than the temporal component, lending support for the existence of a temporo-frontal network underlying MMN (Rinne et al., 2000). At the molecular level, the NMDA receptor has proven to be crucial for MMN in several cross-species studies and further support for this was generated when the NMDA receptor antagonist ketamine was shown to trigger a reduction in MMN amplitude in both the temporal and frontal generators in humans (Heekeren et al., 2008). Modulations of dopaminergic, GABAergic, serotonergic pathways have also been reported to alter the MMN response, although with less consistent effects (Garrido et al., 2009).

AD patients have been shown to present with a shorter MMN ISI from modulation, hypothesized to represent the memory trace, than their age-matched controls, whilst their MMN amplitudes in response to frequency deviants was found not to be altered at short ISIs of around 1 s, but decreased amplitudes were found for longer ISIs of 3 s (Pekkonen, 2000). In SZ patients, reduced MMN amplitude is a consistent finding for a wide range of ISI's (0.99 standard effect size across 32 studies with ISI's ranging from 0.25 to 4 s) (Umbricht and Krljes, 2005) and was found to correlate with global functional scores (Fulham

et al., 2014; Light and Braff, 2005). Duration deviants have been shown to be more sensitive than pitch deviants in SZ in MMN meta-analyses. Haigh et al. (2017) found no evidence of pitch MMN alteration in first episode SZ patients and whereas others authors (Umbricht et al., 2006) found stronger effects with changes in duration than pitch. At the early stages of AD, pitch deviants have shown little sensitivity while duration deviants elicit a more profound response (Pekkonen, 2000). Moreover, mimicking the cholinergic deficit of AD with scopolamine conversely produces a greater response on pitch deviants (Pekkonen et al., 2001).

The methodology that will be used in PRISM for MMN induction, recording and analyses will adhere to the guidelines derived from Duncan and colleagues (Duncan et al., 2009). Essentially, auditory MMN will be recorded in two test conditions: eyes closed and eyes open. Each test will last 6 min in the eyes closed condition and 12 min in the eyes open condition. The inter-stimuli interval will be 600 ms. For the eyes closed condition, subjects will be asked to keep their eyes closed and detract their attention from the sound. They will be randomly presented a series of two tones: frequent (85% probability) with standard tones (1000 Hz, 50 ms) and one infrequent (15%) pitch deviant tone (1100 Hz, 50 ms). All tones will have a 5 ms rise and fall time and will be played using headphones at 85 dB level. A total of 600 tones will be presented, with a total of 90 deviant and 510 frequent tones. For the eyes open condition, subjects will be asked to watch a short silent video to provide a visual distraction whilst a series of tones with identical properties as those used in the eyes closed test will be randomly presented. A total of 1500 tones will be played with 120 pitch deviants, 120 duration deviants (1000 Hz @ 100 ms) and 1260 frequent tones. The intensity of sounds used are similar to the one used by others authors (Chang et al., 2014a,b; Light et al., 2015).

Triggers synchronized with tone emission will be recorded on a channel of the EEG acquisition system. Artefact rejection will be conducted using an automatic rejection routine when EOG exceeds 75 μV within [−200; +1000 ms from the trigger] using Scan4.5 (Compumedics/neuroscan, Charlotte, USA) and then by exclusion of noisy segment performed visually by a trained technician. Then Mathlab will be used to perform the few tasks Scan4.5 cannot execute with a personal library or FieldTrip to estimate time-frequency representations and to generate figures. After the rejection process, responses to the frequent and rare sounds will be averaged. For each electrode, the average response will be defined by considering the difference between the average ERP induced by the frequent stimuli and the average ERP induced by the deviant stimuli. The parameters of interest will be the morphological descriptors of the wave of interest: amplitude, latency and area or average amplitude.

It is clear that MMN is altered in SZ and AD although the ISI impacts the degree of impairment in AD. Typically, longer intervals are required (greater than 1–1.5 s) to discriminate AD patients from controls (Pekkonen, 2000). In the planned studies, if these test parameters are not sufficient to discriminate between the two patient populations, additional analyses such as source localization performed with LORETA will first be used on the regions of interest, namely the auditory and prefrontal cortices. Complementary modelling methods such as dynamic causal modelling or functional connectivity can then be selected based on the regions of interest on the basis of an understanding of the network (Fulham et al., 2014; Garrido et al., 2009; Hughes and Rowe, 2013).

Preliminary data derived from twenty-one healthy subjects the MMN response produced similar patterns and amplitudes to that observed in the published literature (Duncan et al., 2009; Fulham et al., 2014; Todd et al., 2008).

2.3. Auditory oddball

The auditory oddball task is a commonly used paradigm that reliably produces a specific event-related potential across the parieto-central area of the skull that usually occurs around 300 ms after stimuli presentation termed the P300. The P300 is commonly interpreted within a context updating model (Polich, 2007). According to this model, incoming stimuli, such as tones are compared with a memory trace of the previously presented stimuli. If the novel stimulus matches this memory trace, sensory potentials such as N100, P200, N200 are evoked. If the stimulus is different, attentional processes are also engaged and the memory representation is updated. In line with this model, the P300 amplitude increases as the probability of deviant occurrence decreases (Polich, 1987). Additionally, the P300 latency is thought to reflect classification speed (Polich, 2007), as shorter P300 latencies are associated with higher cognitive performance in healthy subjects (Polich et al., 1983; Polich and Martin, 1992), and with increased memory function in the ageing population (Braverman and Blum, 2003).

The P300 latency has been repeatedly shown to increase from healthy controls to MCI and from MCI to AD (Howe et al., 2014). This increased P300 latency in AD-pathology is accompanied by a decreased amplitude (Hedges et al., 2016). P300 abnormalities have also been characterised in SZ across several studies. For example, Bramon et al. (2004) conducted a meta-analysis from forty-six auditory oddball studies in SZ and concluded that there is a decreased P300 amplitude and an increased latency with standardized effect sizes of 0.85 and 0.57, respectively (Bramon et al., 2004). Interestingly, the P300 amplitude seems to be related in SZ to verbal learning and memory capability (Kim et al., 2003).

The P300 can be recorded intracranially from widespread cortical and subcortical areas of the brain, including the frontal, parietal and occipital lobes, the thalamus and the hippocampus (Soltani and Knight, 2000). It can also be recorded via EEG at broad areas of the scalp, but it is strongest at the midline electrodes (Polich, 2007). Although the P300 has been hypothesized to arise from network activity (Duncan et al., 2009), lesions studies have described where the most important nodes for P300 generation are located. Whilst the P300 is conserved or minimally affected by a variety of cortical and subcortical lesions (Duncan et al., 2009), lesions in the temporo-parietal region dramatically impact the P300 potential (Knight et al., 1989; Kutas et al., 1990). From a neurochemical perspective, the glutamatergic system is thought to play a key role in the P300 wave (Frodl-Bauch et al., 1999) and pharmacological studies have shown that ketamine elicits a reduction of the P300 amplitude (Oranje et al., 2000). The GABAergic and cholinergic systems are also considered to have important contribution to the P300. Whilst acetylcholine increases the P300 amplitude and decreases its latency, GABA elicits the opposite effect (Soltani and Knight, 2000). The noradrenergic, dopaminergic (Huang et al., 2015) and serotonergic systems have also been shown to modulate P300, possibly indirectly by influencing the GABAergic and cholinergic systems (Soltani and Knight, 2000).

In the planned studies, the P300 wave will be assessed in response to an auditory oddball stimulus. Subjects with eyes closed will be asked to count the rare, high-pitched sounds (15% of the presentations @ 2000 Hz) that will be presented amongst the more frequent sounds (85%) using a lower frequency (500 Hz) tones. The interval ISI will randomly vary from 1200 to 1900 ms. The number of rare tones will be randomly determined but lie between 30 and 40. The volume for each stimulus will be 85 dB and they will each be 100 ms in duration. All stimuli will have a rise and fall times of 10 ms and the task will take between 4 to 9 min dependent of the number of rare tones and ISI. The participant will be asked at the end of the session how many tones were presented.

The P300 wave form will be quantified by its latency (duration between the stimulus onset and most positive peak within a 260–480 ms window), its amplitude (amplitude of the most positive peak within the 260–480 ms window) and its average amplitude at the 232–352 ms window. All parameters will be estimated using epochs related to rare sounds only. The epochs amplitudes will be corrected by subtraction of the average value from the pre-stimulus period (average

amplitude on the [−500; 0 ms] window). Artefact rejection: epochs with a signal amplitude exceeding 75μV within 500 ms to +500 ms of the trigger will be rejected from the averaging process. Time frequency representations of the ERP will also be analysed: evoked power, induced power and phase locking factor. The power will be averaged on the relevant epochs. As auditory and visual P300 have a very different time and circuit properties, they will be analysed separately (Katayama and Polich, 1999). The localisation of sources for P3a and P3b will be analysed using LORETA (Bachiller et al., 2015) as well as connectivity (Fujimoto et al., 2013). Auditory P300 previously obtained on a large database (n = 124) produced the expected pattern latency and magnitude.

2.4. Visual oddball

Visual oddball paradigms elicit both sensory processing and cognitive responses. The brain areas with activations over numerous repeats per acquisition were initially located using fMRI studies and found to be present in the supra-marginal gyrus, anterior cingulate cortex (Clark et al., 2000; Kiehl and Liddle, 2001), thalamus, insula (Clark et al., 2000; Linden, 2005), dorsolateral prefrontal cortex and medial frontal gyrus (Clark et al., 2000; Kiehl and Liddle, 2001; McCarthy et al., 1997; Yoshiura et al., 1999) as well as other cortical areas (Ardekani et al., 2002). Working memory contribution in the novel stimulus processing of the visual P300 is related to the frontal, parietal, inferior temporal areas and the insula (Bledowski et al., 2004). A reduced P300 amplitude has been localised to posterior and occipital areas (Oribe et al., 2013). The reduction in P300 amplitude has been shown to be a progressive decline throughout one year in SZ patients (Oribe et al., 2015). Reduced amplitudes were also observed in first episode SZ patients together with delayed P300 and N1 latencies. Furthermore, prodromal schizophrenics elicit a characteristic P300 deficit with amplitude reductions associated with increased severity of positive symptoms (Oribe et al., 2013). It is perhaps unsurprising that reduced P300 amplitudes are found in SZ, as volumetric abnormalities have been observed in the cortical grey matter of critical brain structures such as the frontal, temporal and parietal lobes as well as the left Heschl's gyrus (Kasai et al., 2003; Vita et al., 2012).

Over the course of AD, the P300 generators shift from frontal and occipital regions to be more located in the temporal lobe (Papadaniil et al., 2016). A reduction in frontal P300 amplitude was observed in MCI patients (Yener et al., 2014) and advanced AD patients have been shown to elicit reduced frontal theta (Caravaglios et al., 2010) as well as reduced frontal, parietal and central delta power (Caravaglios et al., 2008; Yener et al., 2008). Evidence also exists that cholinergic drugs modulate these responses with treated AD patients having similar phase locking and frontal theta power as healthy elderly controls (Yener et al., 2007). This highlights that cholinergic modulation of the cognitive processes contribute to the visual P300.

The P300 wave will be assessed in response to a visual oddball stimulus (circular line) presented randomly amongst another more frequent visual stimulus (square). The number of oddball stimuli will be randomly determined, but will lie between 25–30. All subjects will be asked to count the number of presented oddball stimuli during the task. ISI's will vary randomly from 1600 to 2100 ms and stimulus duration will be 100 ms. Stimulus intensity (85 dB) will be similar to Light et al. (2015). The task will take up to six minutes to complete. The P300 wave will be quantified by its latency (duration between stimulus onset and most positive peak within the 260–480 ms window), its amplitude (amplitude of the most positive peak within the 260–480 ms window) and its average amplitude in the 320–430 ms window. The window at which the average amplitude is estimated occurs later than the one employed for the auditory P300 as the visual P300 emerges later and has been well described (Bennington and Polich, 1999; Duncan et al., 2009).

All parameters will be estimated using epochs related to the rare visual presentations and epochs amplitudes will be corrected by subtraction of the average value from the pre-stimulus period (average amplitude of the −500 to −0 ms windows). Epochs with a signal amplitude exceeding 75μV within −500 ms to +500 ms of the trigger will be rejected from the averaging process. The analysis processing used for the auditory P300 data can also be used in the visual P300 task, but there may be a need to take into consideration the extended latency of the P300 peak (Biotrial data on file) and therefore the different time windows of interest to quantify P300 occurrence. As expected, the highest P300 amplitude is observed in centro-parietal area of the flat map. This area matches the region of interest commonly used to study P300 (Oribe et al., 2015).

2.5. Auditory steady state response

The ASSR is used to assess the capacity of auditory pathways to generate synchronous oscillations and the integrity of these pathways at given frequencies of an auditory stimulus. The source of the ASSR has been localised in the primary auditory cortex both in human (Herdman et al., 2002; Pantev et al., 1996) and animal (Conti et al., 1999; Dolphin and Mountain, 1992) studies. In contrast to amplitude modulated ASSR stimuli, click stimuli activate greater areas of the primary auditory cortex leading to higher amplitudes (O'Donnell et al., 2013b). The localisation of contributing brain structures is frequency specific. High synchronous oscillations elicited by frequencies modulated above 80 Hz are generated solely by the brainstem (Herdman et al., 2002) but frequencies in the low gamma range (30–40 Hz) also have components generated by the primary auditory cortex (Pantev et al., 1996).

Phase synchronicity of generated ERP's from a 40 Hz stimulus has been observed to be delayed in onset with delayed desynchronization in patients diagnosed with SZ (Hong et al., 2004). This appears unrelated to pharmacological treatment as these findings have been replicated in patients during first episodes (Spencer et al., 2008) and in first degree relatives (Rass et al., 2012). Phase locking of the ASSR is reduced in SZ in comparison to healthy controls for a 40 Hz frequency modulation whereas no differences were observed for 20 or 30 Hz frequency modulations (Hirano et al., 2015). There is some debate as to whether ASSR deficits are related to the presence of auditory hallucinations (Hirano et al., 2015; O'Donnell et al., 2013b) or not (Griskova-Bulanova et al., 2016). Observed ASSR SZ related deficits in frequency processing are likely to relate to the reduction in grey matter volume of the superior temporal gyrus where the auditory cortex is situated. Post-mortem tissue analysis of SZ patients has confirmed the reduction of temporal pyramidal neurons in the primary and secondary auditory cortices (Sweet et al., 2003). Furthermore, abnormalities in parvalbumin-expressing basket cells have also been proposed as source for the altered gamma oscillations observed in SZ (Lewis et al., 2012; Sohal et al., 2009).

Agonists for the GABAergic system have been observed to attenuate the 40 Hz ASSR indicating a role for GABA in auditory processing (Jääskeläinen et al., 1999; Plourde et al., 2008). Reduced amplitude ASSRs have also been associated with an upregulation of GABA, characteristic of SZ (Brambilla et al., 2003; Deng and Huang, 2006). The influence of GABA on the ASSR is a component in the reduction of phase locking (Griskova-Bulanova et al., 2013) and the decreasing synchronisation of high gamma with advancing age (Goossens et al., 2016). In contrast to healthy aging, AD is associated with enhanced ASSR in the low gamma range (Di Lazzaro et al., 2004; Osipova et al., 2006; van Deursen et al., 2011) and this is attributed to disinhibition of the GABAergic system (Limon et al., 2012). The changes measured in advanced AD patients appears to be related to temporal lobe neurodegeneration as the auditory processing deficit does not appear to be present at earlier stages of the illness when the temporal lobe is functional and largely unaffected (Villeneuve et al., 2017).

For the PRISM studies, EEG activity in the gamma range will be assessed in response to auditory oddball stimuli. Subjects will be asked

to fixate on a point on the monitor and asked to count the number of rare tones (10% @ 1000 Hz) that will be presented amongst more frequent stimuli (90% @ 1000 Hz modulated by a 40 Hz sinusoid). As we usually generate ASSR using clicks and as amplitude modulation was used instead, in order to limit hearing issues in the elderly the efficacy of this type of sound to generate ASSR was first verified in population B (Biotrial data on file). A total of 110 tones were presented, each tone lasting 2 s (Tan et al., 2015). The ISI varied randomly from 3.3 to 3.7 s with the sound level of each stimulus set at 78 dB. The duration of this task is approximately 7 min.

Artefact rejection will be performed by rejecting epochs for which the signal amplitude exceeds 75μV within the −500 to + 2000 ms of the trigger. By using this period, the time course of both the evoked and induced power in the gamma band will be estimated on a 35–45 Hz band of interest between a −450 to 1950 ms period. The evoked or induced power will be averaged on a 500–1950 ms period. The 1000 Hz carrier modulated at 40 Hz elicits a robust response in gamma band in healthy subjects (Biotrial data on file). Evoked gamma is more pronounced using click presentations rather than a modulated 1KHz sinusoid. As the clinical population under test will also contain elderly individuals, where hearing loss across high frequencies are common, it is preferred to use narrow spectrum sounds. ASSR will be analysed as inter-trial coherence per hemisphere with a source modelling approach according to a robust model previously developed (Edgar et al., 2017).

2.6. Facial emotions processing

Social cognition and social functioning are impaired in SZ (Barkhof et al., 2015; Langdon et al., 2014) and in AD (Belfort et al., 2017; Bora and Yener, 2017). These functions will be probed by the Facial Emotion Recognition Task that will be used with fMRI and repeated with EEG and recording ERPs on a separate session (see Table 2). At the end, the spatial resolution of fMRI and the time resolution of ERPs will be both used in the global analysis.

The networks involved in emotional processing include the amygdala, hypothalamus, meso-corticolimbic dopaminergic system, orbitofrontal, dorsolateral prefrontal and temporal cortices and parts of the parietal cortex (Adolphs et al., 1996; Breiter et al., 1996; LeDoux, 1995; Sprengelmeyer et al., 1998). From observations derived from CNS lesions, PET and functional MRI studies that have focused on the spatial dimension of the response, the temporal properties of the ERP's have been defined. An early and automatic processing stage (P100), corresponding to a perceptive stage peaks at the occipital electrodes and is modulated by attentional processing (Luck et al., 2000). This is closely followed by a vertex positive occiput-negative ERP component (N170) that corresponds to the structural encoding of the face (Eimer, 2000). The magnitude of this wave is increased with emotional faces when compared to neutral faces (Batty and Taylor, 2003; Holmes et al., 2008; Rellecke et al., 2012) and appears to involve the middle fusiform gyrus (Haxby et al., 2000).

Modulation of the magnitude of N170 has been replicated (Munk et al., 2016) and the later potentials involved in the affect recognition have also been reliably reproduced (Herbert et al., 2008; Rellecke et al., 2012; Schupp et al., 2006). The 200–300 ms domain represents a selective attentional surge (Schupp et al., 2006) and is associated with increased visual attention. Its maximal response occurs in temporo-occipital regions and is more pronounced for emotionally valenced faces either negatively or positively. The final component is the late posterior potential (LPP) which occurs under the centro-parietal electrodes around 300 ms from stimulus onset and corresponds to the later processing stages of emotionally salient material: stimulus representation in working memory and late cognitive emotional processing (Rellecke et al., 2012). Similar to the early posterior negativity (EPN), LPP waves are enhanced by valence stimuli and show a greater enhancement for fear, suggesting a two-step processing for facilitation and processing. A network analysis by MEG shows a right prefrontal cortex bottom-up and a top-down coupling bilateral to occipito-parietal cortices (Moradi et al., 2017; Moratti et al., 2011).

The face stimuli, provided by P1Vital (UK), comprises of one hundred and sixty coloured photographs with the faces of 40 different individuals (20 female and 20 male) displaying four expressions (neutral, happy, sad and afraid). A mask with an ellipsoid aperture is applied to all stimuli, so that only the facial areas are visibleand all stimuli are presented on the center of the screen on a black background. Each face stimuli will be presented twice. Subjects will be placed at a fixed position from the screen (150 cm) and instructed to direct their eyes and attention towards the computer screen to avoid movements and blinks during the task and to give answers as accurately and quickly as possible. During the test session, lasting approximately 15 min, each subject will view a total of 320 photographs and will have to decide if the person on each photograph is a male or a female by pressing on a relevant (left or right) button from a pad. Each trial will proceed in the following sequence: a fixation cross on a black background presented for a variable interval from 800 to 1200 ms, a face stimulus presented during 1500 ms and a black screen for 1000 ms. Answers given during the stimulus presentation or during the black screen will be recorded. Subjects will be presented a total of 320 trials, with 80 trials of each emotional face category. The order in which the faces will be presented will be pseudo randomly assigned.

The ERP time windows and ROI's were selected based on prior studies using emotional face stimuli (Batty and Taylor, 2003; Rellecke et al., 2013, 2012; Schupp et al., 2006; Sfärlea et al., 2016) and visual inspection of grand averages. The P100 and N170 peak amplitudes (mean peak amplitudes ± 20 ms around peak) and peak latencies, as well as EPN and LPP mean amplitudes, are exported from the averaged ERPs for all tasks and all emotional categories. The P100 positive peak amplitude are automatically detected between 80 ms and 130 ms after stimulus onset at the left electrode (Electrical Geodesics, Inc. Eugene, Oregon, 2018), reference (EGR: 65, 69, 70) and right (EGR: 83, 89, 90) occipital electrode clusters. The N170 negative peak amplitudes are automatically detected between 140 ms and 180 ms after stimulus onset at left (EGR: 50, 57, 58, 64) and right (EGR: 95, 96, 100, 101) parieto-occipital electrode clusters. The EPN mean amplitudes are measured from 220 ms to 300 ms post-stimulus at bilateral parieto-occipital electrode clusters (left EGR: 58, 59, 65, 69, 70; right EGR: 83, 89, 90, 91, 96).

After examination of grand averages, it was decided to quantify the LPP in two successive time windows (for a similar approach see Cuthbert et al., 2000; Solomon et al., 2012). Mean amplitudes of the LPP will be measured in an early time window from 400 ms to 600 ms

Table 2
Sequence of events and EEG duration per day during PRISM (note that first and second test day are not consecutive).

Day of assessment	Screening	First test day	Second test day
Events in sequential order	Demographics and medical history Rating scales MRI Tonal audiometry Behavioral assessments	Questionnaires MRI T1 structural fMRI (MSID and N-Back) Resting state EEG Passive auditory MMN eyes closed Auditory Steady State Response ERP-FEP	Questionnaires MRI T1 structural fMRI (FEP, DTI, Virtual Morris water maze, Arterial Spin Labeling) Passive auditory MMN eyes open Auditory oddball P300 P300 visual
Maximum duration of the EEG session (minutes)	–	50	35

MSID: Monetary and Social Incentive Delay; DTI: Diffusion Tensor Imaging.

post-stimulus, as well as in a later time window between 600 and 900 ms post-stimulus at a centro-parietal electrode cluster (EGR: 31, 37, 54, 55, 62, 79, 80, 87, 129). Within the EGRs, ERPs from single electrodes will be averaged. All groups should not differ significantly in the number of trials averaged across electrodes within the respective ROIs for each ERP component and each condition (all $p > 0.05$). EEG will be continuously recorded during the test sessions and analyses will be performed to obtain for each subject, averaged ERPs in response to each emotion category calculated from the 80 trials. As a basic analysis, four ERP components will be studied: P100, N170, EPN and LPP. For P100 and N170, peak amplitudes and peak latencies as well as for EPN mean amplitudes. LPP will be submitted to a similar analysis having shown reciprocal interactions between occipito-parietal and prefrontal cortices by using Granger causality, similarly to Moratti et al. (2011).

3. General operational aspects

An identical EEG acquisition system will be employed for all the testing at the multiple clinical sites. The system includes an EEG amplifier and a computerized stimulation module (for visual and auditory stimuli). Raw data will be recorded using an eego™ sports system (amplifier and software) from ANT neuro which provides amplification, filtering and sampling of the electrophysiological signal for up to 59 monopolar EEG channels and 2 bipolar EOG used for artefact rejection. The signal will be digitized on 24 bits. The sampling frequency will be set at 2048 Hz. Electromagnetic noise due to main power supply will be removed using a digital narrow 50 Hz centered notch filter. The EEG signal will be collected using Waveguard EEG caps from ANTneuro in which all electrodes are placed according to the International 10-10 electrode placement standard (Waveguard CA-202).

The computerized stimulation module was developed using E-prime software (Psychology Software Tools, Inc. USA). This module will deliver auditory (frequent and odd sounds for the auditory oddball P300, standard and deviant sounds for MMN, stimulation sound for auditory steady-state potentials) and visual (frequent and odd geometric figures for visual P300, face photographs expressing different emotions for FEP) stimuli. EEG acquisition system and stimulation module are linked and synchronized with 8-bit trigger input. All EEG data, including the start and stop times and the impedance check will be recorded digitally.

Evaluation of subjects hearing thresholds will be conducted during the screening phase using an automated pure tone audiometry test developed using E-prime. Hearing threshold determination will be conducted three times by alternatively increasing and decreasing sound pressures. The headset used (Sennheiser HD 25-1 II) and sound card (Edirol UA25) were previously calibrated with an artificial ear (Brüel & Kjær) and gain value measured on the same sound generator-headset employed in the study.

To reduce the burden of testing, the protocol is distributed across three days (screening, first day and second day of testing) during which the sequence of the tests was optimized to limit monotony and sleepiness as well as cognitive load by alternating passive and active tasks. The content and sequence of tests is described in Table 2.

4. Discussion

Although the approach of PRISM is complex, it reflects the heterogeneity of psychiatric and neurodegenerative diseases affecting multiple functions and brain circuitries. It also moves away from the clinical phenomenology to get closer to biolology (Kas et al., 2017). Indeed, progresses have been made in identifying the clinical features of schizophrenia, starting with acute symptoms, negative symptoms and then cognitive impairment which have lagged in time and so did therapies. The multidimensional approach used here is required to identify relationships between symptoms and to identify phenotypes possibly leading to individualized medicine. Many studies have compared various biomarkers of endophenotypes between affected and controls, sometimes relatives, but fewer have used multiple domains such as fMRI, behavior, scales and electrophysiology. Clementz et al. (2016) identified three neurobiologically distinct subtypes of schizophrenia (biotypes) in a study with 711 individuals with schizophrenia, 883 first degree relatives and 278 subjects combining clinical scoring, ERPs and voxel-based morphometry with MRI. These biologically distinct phenotypes did not respect the clinical boundaries and interestingly, the 3 biotypes had different levels of social functioning using the Birchwood Scale (Birchwood et al., 1990) which varied in an opposite manner when compared to the Positive and Negative Symptoms Subscale (PANSS) score. This may be suggestive of a relationship between biology and social functioning.

The biological substrate of social withdrawal is unclear. As there is no direct study, it is almost easier to define what social withdrawal is not. The overall cognitive impairment is present before the onset of SZ (Carrión et al., 2018) and in first degree relatives of the same age (Keshavan et al., 2009) progressing over time, while genetic studies have not identified one gene mutation but many of them (Smeland and Andreassen, 2018). Cluster analyses of SZ using clinical scales and cognitive testing have found evidences of four to five clusters in an inconclusive manner (Seaton et al., 2001) or in another study (Ahmed et al., 2018) three clusters from the pattern of negative symptoms.

There are numerous sensory processing abnormalities which correlate with the clinical diagnosis itself (see Table 1) that are present in different pathologies: SZ (Bilder et al., 2000; Hughes et al., 2003; White et al., 1997), AD (Reichman et al., 1996; Reichman and Negron, 2001) and MDD (Galynker et al., 2000; Gerbaldo et al., 1995; Kulhara and Chadda, 1987). The same reasoning would apply to the study of social withdrawal by broadening of the study population to distinct disorders and analyzing the relationships between all parameters and social withdrawal.

In this study, many biomarkers are obtained using electrophysiology and some with other methods. In a way, these have already been used for decades but improvements have either gone using multidimensional analyses of ERP or advanced analyses of signal-like source localization for MMN (Tsolaki et al., 2017), connectivity of spontaneous or induced gamma oscillations (Andreou et al., 2015b) or of any EEG band. Some authors (Ethridge et al., 2015) combined qEEG with oddball, collecting N1, P1 and P300. They found two principal components one shared and one not between 229 schizophrenics, 188 bipolar disorder patients and 284 controls. So, the same approach will be used with more advanced signal processing and a global approach bridging imaging with electrophysiology, cognitive and behavioral testing therefore learning from the latest evidences in the heterogeneity of pathologies.

5. Conclusions

The electrophysiologic techniques and sensory processing parameters outlined above will allow the proper exploration of the relationship between; social withdrawal, with and across current diagnostic classification, and the fundamental underlying biology. Contrasting the subpopulations of high and low social withdrawal may well point to domains closely associated with sensory processing abnormalities alone or interdependent with parameters derived in different areas of measurement elsewhere in the study. This in turn will allow biomarkers to be identified and explored that will inform as to these “construct” differences that underlie the apparent “face validity” apparent in the clinical similarities in the dimension of interest, social withdrawal. Further replications will be necessary to confirm the robustness of any such novel findings. Therefore the detailed methodology provided here will ease future comparisons and the replication in other cohorts and populations of interest. The results of this study will thus provide the framework with which to expand our understanding of what drives social withdrawal in a transnosographic manner, which so far is *terra incognita*.

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