



## Higher-order language dysfunctions as a possible neurolinguistic endophenotype for schizophrenia: Evidence from patients and their unaffected first degree relatives.



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### ABSTRACT

The purpose of the study was to examine the presence of pragmatic dysfunctions in first episode (FE) subjects and their healthy first degree relatives as a potential endophenotype for schizophrenia. Thirty-four FE patients, 34 parents of the patients (REL) and 32 healthy controls (HC) took part in the study. Pragmatic language functions were evaluated with the Right Hemisphere Language Battery, attention and executive functions were controlled, as well as age and education level. The parents differed from HC but not from their FE offspring with regard to overall level of language and communication and the general knowledge component of language processing. The FE participants differed from HC in comprehension of inferred meaning, emotional prosody, discourse dimensions, overall level of language and communication, language processing with regard to general knowledge and communication competences. The FE participants differed from REL regarding discourse dimensions. Our findings suggest that pragmatic dysfunctions may act as vulnerability markers of schizophrenia; their assessment may help in the diagnosis of early stages of the illness and in understanding its pathophysiology. In future research the adoptive and biological parents of schizophrenia patients should be compared to elucidate which language failures reflect genetic vulnerability and which ones environmental factors.

### 1. Introduction

Schizophrenia is considered to be a heritable disease acting via a polygenetic mechanism, but the complex nature of its phenotype hinders discovery of the genes responsible (Cannon, 2005; Harrison and Law, 2006; Harrison and Owen, 2003; Liu et al., 2017; Misiak et al., 2016; Rutkowski et al., 2017). In order to simplify the genetic analysis and to identify susceptibility genes, an effort has been made to identify the endophenotypes of the susceptibility genes (Braff et al., 2007; Gould and Gottesman, 2006). These measures are hypothesized to act in the chain between genes and clinical disorders, and are hence used to identify the genes associated with the disorder. Endophenotypes should be heritable and co-segregate with a psychiatric illness, they ought to be state independent (be present even when the disease is not), and should be found in non-affected family members at a higher rate than in the general population (Flint and Munafò, 2007; Glahn et al., 2012; Gould and Gottesman, 2006; Ritsner and Gottesman, 2009). Endophenotype

identification plays a vital role in understanding the genetic epidemiology, molecular genetics and pathophysiology of schizophrenia, and in elucidating its etiology. In addition, it may facilitate the early detection of individuals at risk of developing schizophrenia for the purposes of prevention and early intervention (McGorry, 2015; Nelson et al., 2016).

Studies of schizophrenia have used structural and functional magnetic resonance images, sensory processing measures, neuromotor abilities, physical examination and neuropsychological testing to identify vulnerability markers associated with the disease, based on variation in schizophrenia patients, their first-degree relatives and healthy controls (Allen et al., 2009; Chahine et al., 2017; Liu et al., 2017; Mackowick et al., 2014; Simons et al., 2013). A review by Allen et al. (2009) found very few papers that analyzed and compared the vulnerability markers present in the three groups: schizophrenia patients, first-degree relatives and healthy controls. In addition, most of the studies examining first degree relatives evaluated the children of

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patients (Cornblatt and Keilp, 1994; de la Serna et al., 2017; Harvey et al., 1982), their siblings (Cannon et al., 1994; Condray et al., 1992; Ordóñez et al., 2016; Zalesky et al., 2015), or a combination of first-degree relatives, including parents, siblings or offspring (Allott et al., 2015; Elvevag et al., 2010; Hain et al., 1995; Kendler et al., 1995). This led to the inclusion of mentally-ill or potentially preschizophrenia subjects, making it difficult to determine whether the findings were endophenotypes or traits of the illness state. Additionally, the greater part of neuropsychological research addresses working memory, attention, and executive functions (Chan et al., 2011; Tuulio-Henriksson et al., 2011); only a few studies have evaluated communication and language.

Communication and language skills refer to higher level (pragmatic) abilities related to the use of language in a certain context, as well as the communication of intentions, goals, thoughts and emotions, and to the symbolic aspects of communication (Balconi, 2010; Cummings, 2009, 2014). In particular, these skills may be described as lexical-semantic processes, discourse production and comprehension, indirect speech act processing (humor, metaphor, irony), comprehension and appreciation of shared reflection and knowledge, as well as vocal non-verbal speech acts (prosody) (Balconi, 2010; Bryan, 1995; Łojek, 2009). These pragmatic functions, as suggested by various studies (Apperly et al., 2009; Cummings, 2013, 2015; Newton and de Villiers, 2007; Pluta et al., 2017) are associated with the theory of mind (ToM): an ability that allows people to make inferences about the thoughts, intentions and emotions of others to predict and explain their behavior (Baron-Cohen et al., 1985; Cummings, 2013; Muller et al., 2010). Disturbances in higher order language skills can cause dysfunctions in social communication by obscuring understanding and preventing the recognition of communicative failures (Bosco et al., 2012), misunderstanding the emotions and intentions of other people (Cummings, 2015; Heaton et al., 2012), making it difficult to understand inferred meanings (Dennis et al., 2001) and keeping track of the conversation topic (Bogart et al., 2012; Marini et al., 2011). In addition, they make it difficult to convey a message or an intention, and can result in the omission of significant information, the speaker focusing on details or interjecting inappropriate remarks (Joanette et al., 2008; Jodzio et al., 2005; Myers, 2001). Therefore, when present, language difficulties cause major obstacles which interfere with everyday life. Ruben (1999) reports an association between communication disorders and higher rates of unemployment and lower income. The association between communication impairment and quality of life, interactions with others, daily functioning and satisfaction with life in people with schizophrenia have also been described (Bambini et al., 2016; Bowie and Harvey, 2008; Tan et al., 2014) as well as disturbances in comprehending sarcasm, affecting recreational functioning (Sparks et al., 2010).

Language and communication abnormalities have been described in schizophrenia patients (Bryan, 2014; Colle et al., 2013; Cummings, 2014; McKenna and Oh, 2005; Pawełczyk et al., 2017a), particularly with regard to anomalies in lexical-semantic processing (Salisbury et al., 2000; Salisbury et al., 2002; Sitnikova et al., 2002; Titone et al., 2000), humor understanding (Corcoran et al., 1997; Polimeni et al., 2010; Rosin and Cerbus, 1984), metaphors (Brune and Bodenstern, 2005; Chapman, 1960; de Bonis et al., 1997; Kiang et al., 2007; Thoma et al., 2009), discourse comprehension (Andreasen et al., 1995; McKenna and Oh, 2005; Noel-Jorand et al., 1997; Perlina et al., 2012) and prosody (Edwards et al., 2001; Martinez et al., 2015; Murphy and Cutting, 1990). Patients with schizophrenia have also displayed reduced context processing (Schenkel et al., 2005), impaired recognizing and repairing communicative failures (Bosco et al., 2012) and difficulties in referential communication (Champagne-Lavau et al., 2009). Studies describing language dysfunctions in first episode schizophrenia patients, although rather limited in number, suggest the presence of language abnormalities (Fuller et al., 2002; Hoff et al., 1999; Pawełczyk et al., 2017b; Perlina et al., 2017). Also, children at risk of schizophrenia have been reported to demonstrate dysfunctions in receptive language

(Cannon et al., 2002), reading (Fuller et al., 2002; Ott et al., 2001) and pragmatic use of language (Done and Leinonen, 2013; Pawełczyk et al., 2017b; Sullivan et al., 2016). Some studies with schizophrenia patients have linked pragmatic language disturbances to impairments associated with theory of mind and cognitive dysfunctions (Bosco et al., 2012; Cummings, 2013, 2015); however, no stable significant relationship was reported between ToM or executive dysfunctions and pragmatic impairment in a recent study (Parola et al., 2017).

Language abnormalities have also been found in a mixed sample of first-degree relatives (Elvevag et al., 2010; Kendler et al., 1995; Kendler and Walsh, 1995), siblings (Cannon et al., 1994; Condray et al., 1992; Docherty et al., 2004), children (Asarnow et al., 1978; Cornblatt and Keilp, 1994; Harvey et al., 1982) and parents (Docherty, 1993, 1995; Docherty et al., 1998a; Docherty et al., 1998b; Singer and Wynne, 1965). The parents of patients communicated in a more confusing way; in their speech, “attention and meaning were diffused, and there was a deep pessimism about ever establishing meaningful, affective interactions.” (Singer and Wynne, 1965). They also used more allusive thinking defined as having loose associations (Catts et al., 1993), incorporated more disordered elements of formal thought (Hain et al., 1995), were more likely to use references which were unclear (Docherty, 1995), demonstrated examples of ambiguity in speech, such as language structure breakdown, and used overinclusive words, vague words, and words with ambiguous meanings (Docherty et al., 1999). Even though studies have examined communication and language disturbances in patients with first episode schizophrenia and their parents, it is rarely assumed that cognitive and executive functions contribute to these language disorders (Docherty, 2012; Gavilan and Garcia-Albea, 2011; Parola et al., 2017), and the results of the studies are inconsistent: some suggesting that cognitive functions influence language (Docherty, 2005; Gavilan and Garcia-Albea, 2011) while others do not (Parola et al., 2017).

Although patients with schizophrenia demonstrate impairments in language and communication functions, no study has yet examined a wide range of these skills in first episode (FE) of schizophrenia and their healthy parents. Also, most research on pragmatic language in schizophrenia would not control the influence of working memory and executive function dysfunctions. Executive functions, conceptualized as planning, volition or effective performance, and working memory are the intrinsic bases of cognitive, emotional and social skills (Lezak et al., 2004a). They allow effective organization of activity, self-regulation and self-direction and concentration on certain activity. Therefore, disturbances in these functions may influence the results in language evaluation (Docherty, 2005, 2012; Gavilan and Garcia-Albea, 2011) and should be controlled in the study.

As it is vital to distinguish variables associated with the vulnerability for schizophrenia from those concerned with prodromal conditions and the illness itself, the present study examines both patients in the first episode of schizophrenia and their parents without schizophrenia who are beyond the usual age of risk. The aim of this study was to examine higher order language functions as a potential endophenotype when confounding attention and executive functions are controlled for. Our hypothesis is that language and communication abilities will be impaired in FE patients, and milder disorders will also be present in their parents. We expect that the language and communication skills of the parents will be higher than those of the FE patients, but lower than those of healthy controls (HC).

## 2. Methods

### 2.1. Participants

Three samples of participants provided data for the study: a group experiencing their first episode of schizophrenia (FE), a group who were first-degree relatives of first episode schizophrenia patients (REL) and a healthy control group (HC). The FE sample consisted of 34

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