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Brain correlates of verbal fluency in subthreshold psychosis assessed by functional near-infrared spectroscopy

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ABSTRACT

The prevalence of subthreshold psychotic symptoms in the general population has gained increasing interest as a possible precursor of psychotic disorders. The goal of the present study was to evaluate whether neurobiological features of subthreshold psychotic symptoms can be detected using verbal fluency tasks and functional near-infrared spectroscopy (fNIRS).

A large data set was obtained from the Zurich Program for Sustainable Development of Mental Health Services (ZInEP). Based on the SCL-90-R subscales 'Paranoid Ideation' and 'Psychoticism' a total sample of 188 subjects was assigned to four groups with different levels of subthreshold psychotic symptoms. All subjects completed a phonemic and semantic verbal fluency task while fNIRS was recorded over the prefrontal and temporal cortices. Results revealed larger hemodynamic (oxy-hemoglobin) responses to the phonemic and semantic conditions compared to the control condition over prefrontal and temporal cortices. Subjects with high subthreshold psychotic symptoms exhibited significantly reduced hemodynamic responses in both conditions compared to the control group. Further, connectivity between prefrontal and temporal cortices revealed significantly weaker patterns in subjects with high subthreshold psychotic symptoms compared to the control group, possibly indicating less incisive network connections associated with subthreshold psychotic symptoms.

The present findings provide evidence that subthreshold forms of psychotic symptoms are associated with reduced hemodynamic responses and connectivity in prefrontal and temporal cortices during verbal fluency that can be identified using fNIRS.

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1. Introduction

Current research proposes that there is a continuum from mental health, to subthreshold and clinical forms of psychosis (Rössler et al., 2011b). The present study focused on the assessment of subthreshold psychotic symptoms in the general population. Symptoms of psychosis (e.g., Paranoid Ideation, Psychoticism) may not exclusively experienced by people with psychiatric disorders, such as schizophrenia. Subthreshold psychotic symptoms also occur in otherwise healthy people, but are less severe and may not necessarily have clinical relevance. Investigating people with subthreshold psychotic symptoms has therefore gained

increasing interest to evaluate whether there exist behavioral and neural correlates of subthreshold psychosis.

Subthreshold psychotic symptoms can be identified with standardized scales (e.g., Rössler et al., 2007, 2013), providing an index of psychosis proneness. A high score of psychosis proneness has been reported to represent a 10% increased risk to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen et al., 2005; Meehl, 1990). Subthreshold psychotic symptoms also represent risk factors for subsequent other common mental disorders (Rössler et al., 2011a).

On the behavioral level, studies in individuals with subthreshold psychotic symptoms (Allen et al., 2012; Becker et al., 2010; Bodatsch et al., 2013; Krabbendam et al., 2005) demonstrated that performance on verbal fluency tasks (VFTs) provides a possible predictor for prospective identification of future clinical psychosis. Verbal fluency deficits have been reported to precede psychosis onset up to 30 months (Lencz et al., 2006). Letter and category VFT are common tests to investigate phonemic and semantic processes central to word retrieval.

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Previous neuroimaging studies applying VFT implicated both frontal and temporal lobe areas, suggesting that letter fluency (phonemic-based word retrieval) is mediated primarily by the frontal cortex, while category fluency (semantic-based word retrieval) is mediated primarily by the temporal cortex (Baldo et al., 2006). Accordingly, pathologies affecting these areas produce behavioral impairments (typically a reduction in the number of items generated) in one or both versions of the task (Ardila et al., 2006). In persons with subthreshold psychotic symptoms and subsequent conversion to schizophrenia, reduced activation in prefrontal brain regions and reduced prefrontal–temporal functional connectivity have been reported during verbal fluency performance (Allen et al., 2012; Fu et al., 2002; Fusar-Poli et al., 2011; Jung et al., 2012; Sabb et al., 2010; Spence et al., 2000).

The present study was conducted in a large community sample. This aspect differentiates the study from other studies conducted in selected populations (Allen et al., 2012; Brent et al., 2014; Fusar-Poli et al., 2010, 2011; Jacobson et al., 2010; Jung et al., 2012; Modinos et al., 2011; Sabb et al., 2010). To assess the brain correlates of this community sample, the present study applied functional near-infrared spectroscopy (fNIRS). fNIRS is an optical brain imaging method that measures cortical activity via concentration changes of cortical hemoglobin (Obrig and Villringer, 2003). An advantage of fNIRS over functional magnetic resonance imaging (fMRI) is its low susceptibility to movement artifacts, especially artifacts due to overt speech (Fallgatter et al., 2004; Okamoto et al., 2004; Suto et al., 2004). This fact led to a multitude of studies investigating overt verbal fluency assessed by fNIRS (Ehliis et al., 2007; Herrmann et al., 2003, 2004, 2005, 2006; Kameyama et al., 2006; Matsuo et al., 2000, 2002, 2004, 2005; Schecklmann et al., 2007, 2008a,b; Suto et al., 2004), revealing comparable results to fMRI literature (Basho et al., 2007; Fu et al., 2002). Moreover, fNIRS offers ease of administration, a more convenient setting compared to an fMRI scanner, and a less expensive technology than fMRI. These advantages render fNIRS as a neuroimaging method that allows for the screening of neuropsychological deficits in large samples such as in the context of early diagnostic assessments in psychiatry (Ehliis et al., 2014; Fallgatter et al., 2004).

The first objective of the present study was to examine in this community sample, how VFT performance would differ in subjects with high subthreshold psychotic symptoms compared to a control group. Based on the described previous behavioral studies, we hypothesized that subjects with high compared to low subthreshold psychotic symptoms would exhibit a reduction in the number of items generated in response to the phonemic and semantic VFT.

The second objective was to examine whether there exist differences in cortical correlates of VFT performance, in terms of both hemodynamic responses and connectivity patterns, in subjects with high subthreshold psychotic symptoms compared to a control group. According to previous literature, we hypothesized that subjects with high subthreshold psychotic symptoms would show reduced prefrontal and temporal responses to the phonemic and semantic VFT compared to the control group.

2. Materials and methods

2.1. Subjects

Data were obtained from the Epidemiology Survey of the Zurich Program for Sustainable Development of Mental Health Services (ZInEP) (Ajdacic-Gross et al., 2014). The total subsample undergoing fNIRS examination consisted of 188 subjects, who were recruited out of a representative sample of 20–41 years old adults restricted to Swiss residents. The catchment area, the canton of Zurich, is a mixed urban–rural area with a population of 1.35 million, which comprises about one sixth of the total Swiss population. All subjects gave written informed consent. The study was approved by the ethics committee of the Canton Zurich and conducted in accordance with the Declaration of Helsinki.

Subjects were assigned to four groups based on the subscales 'Schizophrenia Nuclear Symptoms' (SNS) and 'Schizotypal Signs' (STS) (Rössler et al., 2007) derived from the Symptom Checklist-90-R (SCL-90-R) (Derogatis, 1977). While the SNS scale subsumes four items of the original 'Psychoticism' scale of the SCL-90-R (thought broadcasting, hearing voices), the STS scale corresponds mostly to the original 'Paranoid Ideation' scale. The two subscales correlated moderately positively ($r = 0.301$, $p < 0.001$). Group CO (control) consisted of subjects below the fifth quintiles of the two subscales ($N = 28$, 14.5%). Group PA (Paranoia) represented subjects within the fifth quintile of the STS subscale but below the fifth quintile of the SNS scale ($N = 66$, 34.2%). Group PS (Psychoticism) represented subjects within the fifth quintile of the SNS subscale but below the fifth quintile of the STS scale ($N = 39$, 20.2%). Group PA–PS (Paranoia–Psychoticism) represented subjects from both the fifth quintile of the SNS and STS subscales ($N = 55$, 28.5%). There were no significant differences between groups regarding gender, marital status, number of children, and professional education or occupation (Table 1).

2.2. VFT design

All subjects were asked to perform a phonemic and a semantic VFT. In the phonemic fluency task, subjects were instructed to name words that began with a given letter (A, F, S) within 30 s. In the semantic fluency task, subjects were instructed to generate words belonging to a given category (animals, fruits, flowers) within 30 s. Both fluency conditions were repeated three times. The order of the fluency conditions was fixed across all subjects. In both the phonemic and semantic fluency conditions, subjects were told to avoid repetitions. Performance of both fluency tasks was assessed by the total production of words and the number of correct words generated in response to the cues. Items were scored as correct if they belonged to the letter or the category and were not repetitions. As a common control task, subjects were asked to recite weekdays within 30 s (Schecklmann et al., 2010), which is assumed to be an automatic cognitive process not associated with a significant activation of frontal and temporal brain regions. All

Table 1

Demographic data. Data were obtained from the Epidemiology Survey of the Zurich Program for Sustainable Development of Mental Health Services (ZInEP) (Ajdacic-Gross et al., 2014). The total sample consisted of 188 subjects was assigned to four groups based on the subscales 'Schizophrenia Nuclear Symptoms' (SNS) and 'Schizotypal Signs' (STS) (Rössler et al., 2007) (correlation $r = 0.301$, $p < 0.001$) derived from the Symptom Checklist-90-R (SCL-90-R) (Derogatis, 1977). Group CO ($N = 28$, 14.5%), group PA ($N = 66$, 34.2%), group PS ($N = 39$, 20.2%), and group PA–PS ($N = 55$, 28.5%).

	Group			
	CO	PA	PS	PA–PS
Gender				
Female	17	22	23	29
Male	11	44	16	26
Age	30 (± 5.952)	31 (± 6.985)	31 (± 6.243)	31 (± 6.757)
Material status				
Single	20	50	23	43
Married	6	12	15	11
Divorced	2	4	1	1
Children				
Yes	5	14	13	10
No	23	52	26	45
Professional education				
Yes	28	66	39	55
Professional occupation				
Yes, >30 h/week	13	38	22	30
Yes, <30 h/week	6	21	11	12
No	9	7	5	12
No answer	0	0	1	1

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