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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.

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 (Ehlis 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 (Ehlis 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

blocks of the VFT and the control condition were separated by an inter-stimulus interval of 30 s.

2.3. fNIRS instrumentation

Oxy- [O_2Hb] and deoxy- [HHb] hemoglobin concentration changes were measured using an ETG-4000 Optical Topography System (Hitachi, Medical Corporation, Tokyo, Japan) with a 52-channel probe setup consisting of 17 laser diodes and 16 photo-detectors. The probe setup covered large parts of the prefrontal and temporal cortex (Fig. 1), all of which were included in the data analysis.

fNIRS data were recorded with a sampling frequency of 10 Hz, and transformed by the modified Beer–Lambert law and prepossessed using NIRS-SPM (Ye et al., 2009). Calculation of the hemodynamic concentration changes of [O_2Hb] and [HHb] was done by use of the Beer–Lambert Law (absorption coefficients (μ_a) for O_2Hb: μ_a(760 nm) = 1486, μ_a(850 nm) = 2526, for HHb: μ_a(760 nm) = 3843, μ_a(850 nm) = 1798; differential pathlength factor (DPF): DPF(760 nm) = 7.25, DPF(850 nm) = 6.38). Data were visually inspected for motion artifacts; the removal of motion artifacts (in particular, “steps” and “spikes”) was finally done in 21 subjects. We employed the wavelet minimum description length algorithm (Jang et al., 2009) to remove systemic confounds, and the precoloring method for estimating temporal correlation (Worsley and Friston, 1995).

For statistical analysis, dependent variables were derived by extracting the entire hemodynamic response to each verbal fluency condition using a fixed impulse response model that estimated the response at each time point time-locked to intervals 5–10 s after stimulus onset. Average Δ[O_2Hb] and Δ[HHb] hemodynamic responses were then calculated per subject, trial, and condition and baseline corrected.

2.4. Statistical analysis

Statistical analysis was performed using MATLAB (Version R2014a, The Math Works, MA). Data were tested for normal distribution using the Kolmogorov–Smirnov test. The behavioral VFT parameters (production, number) were entered into repeated measures analyses of variance (ANOVA) with the within-subject factor ‘condition’ (control vs. phonemic vs. semantic) and the between-subject factor ‘group’ (CO, PA, PS, PA–PS). The Bonferroni correction was used to counteract the problem of multiple comparisons and the results were reported at a significance level of $p < 0.05$.

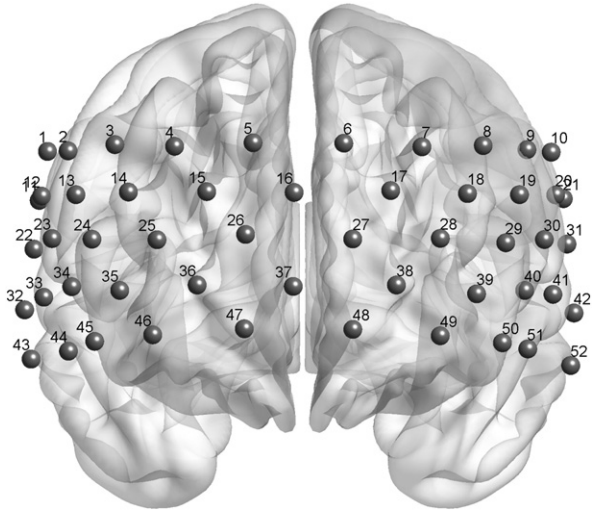

Fig. 1. fNIRS probe setup. Schematic front view of the fNIRS probe setup. Channels 1–52 between light emitters and detectors are depicted by filled circles. The MATLAB toolbox NFRI (Singh et al., 2005) was used to estimate the MNI coordinates of the used EEG 10–20 positions. Brain networks were visualized using BrainNet Viewer (Xia et al., 2013).

The fNIRS parameters (Δ[O_2Hb], Δ[HHb]) were entered into linear regression analysis with the factors ‘condition’ (control vs. phonemic vs. semantic), ‘group’ (CO, PA, PS, PA–PS), and ‘VFT production/number’. Results were reported based on ANOVA assessing the differences between regression slopes at a significance level of $p < 0.001$.

3. Results

3.1. VFT data

Repeated measures ANOVA of the behavioral VFT data revealed significant main effects of the between-subject factor ‘group’ (CO, PA, PS, PA–PS) and the within-subject factor ‘condition’ (control vs. phonemic vs. semantic) (Fig. 2). Poorest performance was observed in the group PA–PS as indicated by less ‘production’ compared to the control group (phonemic: $F_3 = 2.879$, $p = 0.037$, control condition: $F_3 = 3.419$, $p = 0.019$). No significant group-differences were found in response to the semantic VFT.

3.2. Hemodynamic responses

The factor ‘group’ revealed significant main effects over large parts of the bilateral (primarily left) prefrontal and temporal cortices (Fig. 3). Linear regression analysis showed significantly reduced Δ[O_2Hb] hemodynamic responses for the groups PA, PS, and PA–PS, compared to group CO (representative channel: $F_3 = 12.147$, $p < 0.0001$).

The factor ‘condition’ revealed significant main effects only over dorsolateral and temporal cortices (Fig. 3). Linear regression analysis showed significantly increased Δ[O_2Hb] hemodynamic responses for the phonemic and the semantic conditions compared to the control condition (representative channel: $F_2 = 16.778$, $p < 0.0001$).

There were no significant interaction effects between the factors ‘group’ and ‘condition’. No relevant significant effects were observed for the Δ[HHb] hemodynamic responses.

3.3. Connectivity

To assess the connectivity between cortical areas, i.e., the relationship between the hemodynamic responses of channels 1–52, linear regression analysis was performed between each channel-pair regressed with the factors ‘group’ and ‘condition’.

The factor ‘group’ revealed significant effects on Δ[O_2Hb] connectivity primarily between the left prefrontal and temporal cortices (Fig. 4). Linear regression analysis showed significantly reduced Δ[O_2Hb] connectivity for the groups PA, PS, and PA–PS, compared to group CO (representative channel: $F_3 = 34.384$, $p < 0.0001$).

There were no significant effect on connectivity of the factor ‘condition’, or significant interaction effects between the factors ‘group’ and ‘condition’. No significant effects were observed for the Δ[HHb] connectivity.

3.4. Effects of VFT performance on hemodynamics and connectivity

To assess the effect of the behavioral VFT performance on fNIRS hemodynamic and connectivity data, linear regression analysis was computed for the Δ[O_2Hb] hemodynamic and connectivity data with the factors ‘VFT production/number’ and ‘group’ (CO, PA, PS, PA–PS) (Fig. 5).

Results revealed a significant interaction effect of the factors ‘group’ and ‘VFT number’ on Δ[O_2Hb] hemodynamics over the temporal cortex (representative channel: $F_3 = 4.406$, $p = 0.0045$). Besides the already known negative effect of groups PA, PS, and PA–PS on Δ[O_2Hb] hemodynamic responses compared to group CO, this finding showed that Δ[O_2Hb] hemodynamic responses increased with an increasing number of correct VFT performance.

In accordance, the same analysis for the connectivity data revealed a significant effect of the factor ‘VFT number’ on Δ[O_2Hb] connectivity

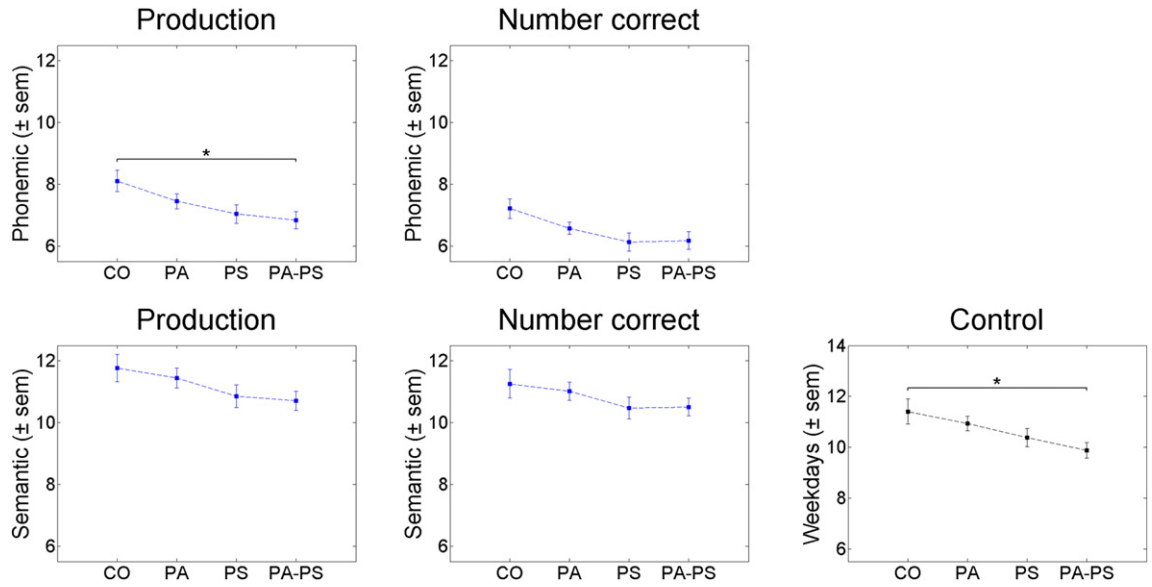

Fig. 2. VFT data. Bar plots of the VFT parameters (production, number) using the within-subject factor 'condition' (control vs. phonemic vs. semantic) and the between-subject factor 'group' (CO, PA, PS, PA–PS). Error bars indicate standard error of the mean.

over the prefrontal cortex (representative channel: $F_1 = 16.583$, $p < 0.0001$). This finding showed that connectivity increased with an increasing number of correct VFT performance. There was, however, no significant interaction effect of the factors 'group' and 'VFT number' on connectivity.

4. Discussion

Neuroimaging studies have reported a number of abnormalities in brain function and structure of people with subthreshold psychotic symptoms (Brent et al., 2014; Jacobson et al., 2010; Lagioia et al., 2010; Modinos et al., 2010, 2011, 2013), and suggested that subthreshold psychotic symptoms may be a confounding factor for neuroimaging studies in other clinical populations, such as subclinical depression (Modinos et al., 2013).

Verbal fluency paradigms have been widely used to test cognitive functions during the early phases of psychosis (Fusar-Poli et al., 2007). Verbal fluency tasks can assess the intrinsic generation of a verbal response, suppression of inappropriate responses, and the holding of information about previous responses online (Broome et al., 2009). Particularly, the functionality of prefrontal and temporal cortices, contributing to executive and working memory functions, may provide

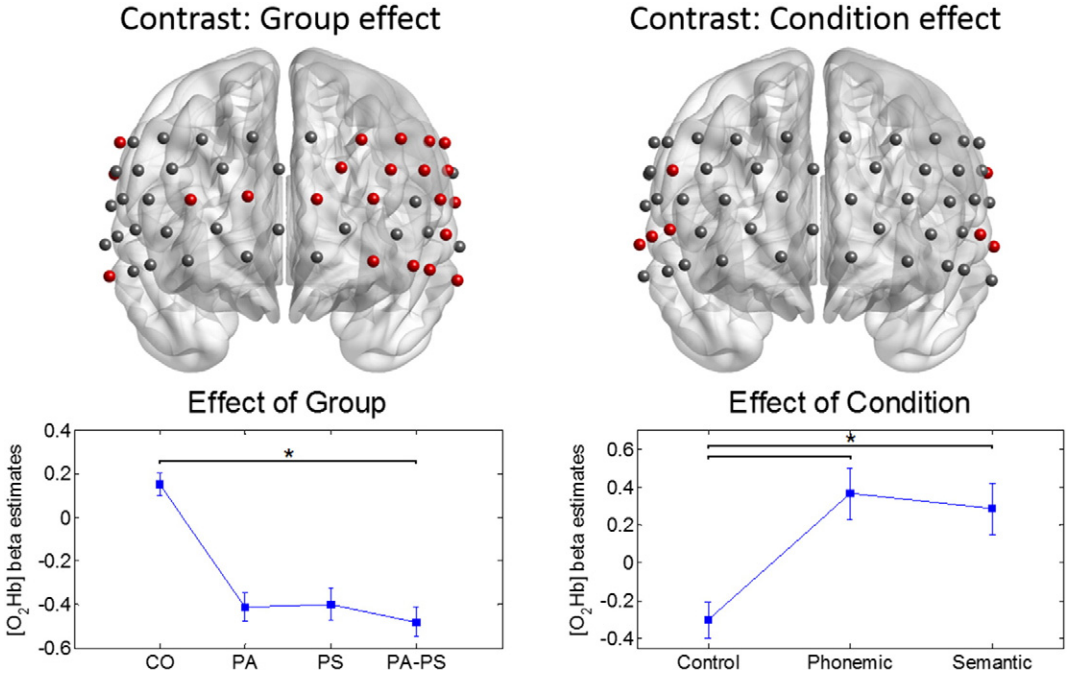

Fig. 3. Hemodynamics. (Right) Effect of Group. Illustration of significant effect of the factor 'group' (CO, PA, PS, PA–PS) on $\Delta[O_2Hb]$ hemodynamic responses over channels 1–52; below is an example of a representative channel (CH 17) illustrating the group effect ($F_3 = 12.147$, $p < 0.0001$). (Left) Effect of Condition. Illustration of significant effect of the factor 'condition' (phonemic, control, semantic) on $\Delta[O_2Hb]$ hemodynamic responses over channels 1–52; below is an example of a representative channel (CH 51) illustrating the condition effect ($F_2 = 16.778$, $p < 0.0001$). Error bars indicate standard error of the regression beta estimate.

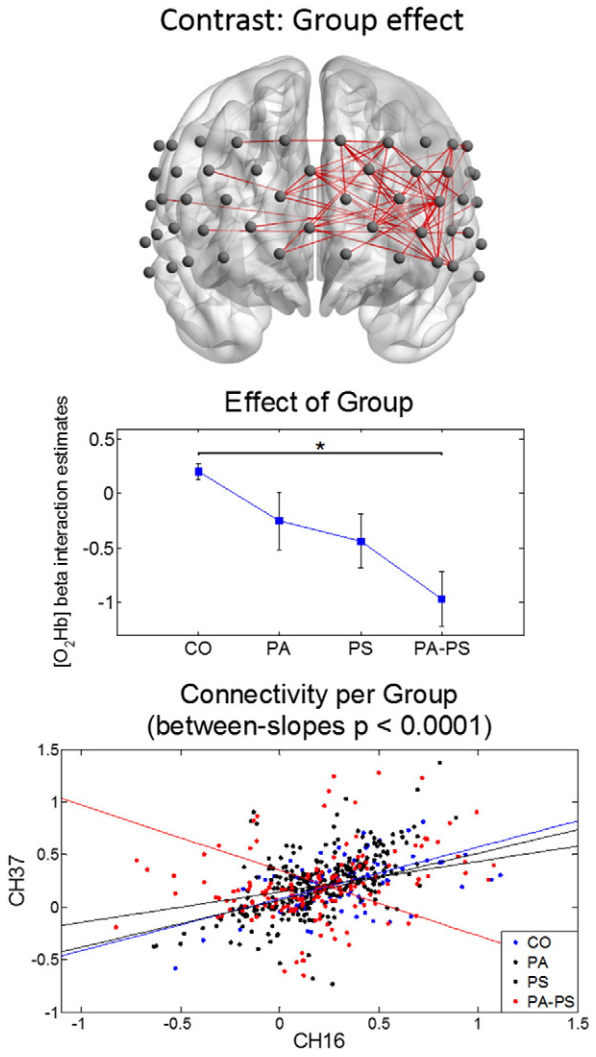

Fig. 4. Connectivity. (Top) Effect of Group. Illustration of significant effect of the factor 'group' (CO, PA, PS, PA–PS) on $\Delta[O_2Hb]$ connectivity over channels 1–52, and in a representative channel (CH 16–CH 37) ($F_3 = 34.384$, $p < 0.0001$). Error bars indicate standard error of the regression beta interaction estimate. (Bottom) Channel example. Representative channel illustrating the group effect with group-specific regression slopes (significance between-slopes $p < 0.0001$). There was no significant effect of the factor 'condition'.

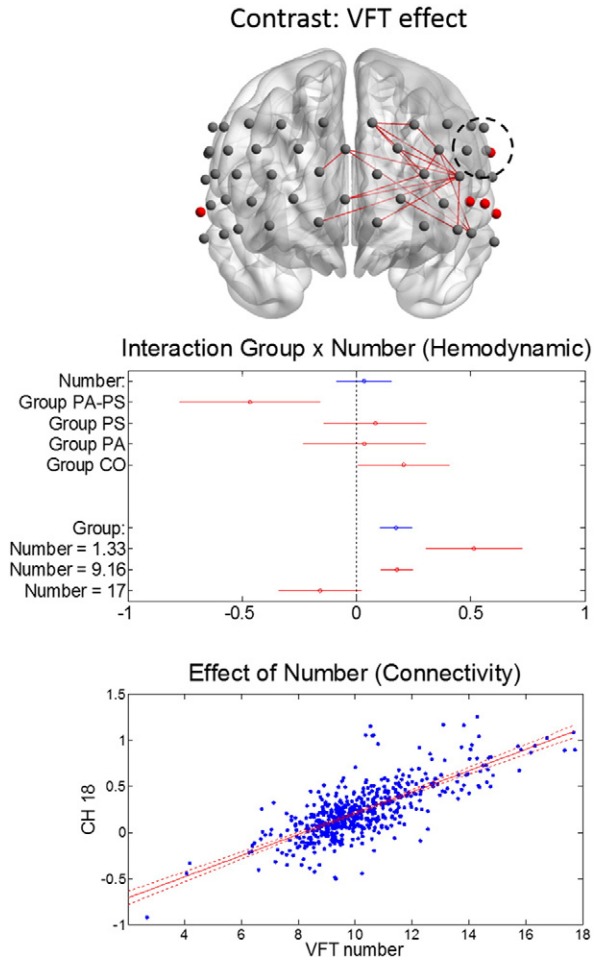

Fig. 5. VFT number. (Top) Illustration of significant effect of the factor 'VFT number' on hemodynamic and connectivity. (Bottom) Significant interaction of the factors 'group' and 'VFT number' ($F_3 = 4.406$, $p = 0.0045$) on $\Delta[O_2Hb]$ hemodynamic over temporal cortex (CH 41, dashed circle), and adjusted interaction model for factor 'VFT number' on $\Delta[O_2Hb]$ connectivity (CH 18) ($F_1 = 16.583$, $p < 0.0001$).

neurobiological markers of illness onset in psychosis and schizophrenia (Pantelis et al., 2009). 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; Fusar-Poli et al., 2011; Jung et al., 2012; Sabb et al., 2010), with a gradual decline in prefrontal activation from the subthreshold state to chronic psychosis (Fusar-Poli, 2012; Pantelis et al., 2009).

The present study focused on the assessment of subthreshold psychotic symptoms in the general population, which do not necessarily have clinical relevance, and do not represent individuals at clinical high risk for psychosis. It is therefore interesting that the results of the present study are in line with the previous literature. The present findings in a large community sample provide evidence that neural correlates of subthreshold psychotic symptoms can be identified in the general population. In particular, our findings suggest that both prefrontal and temporal cortical hemodynamic responses as well as connectivity patterns between these areas during verbal fluency are associated with reduced responses in high levels of subthreshold psychotic symptoms.

4.1. Hemodynamics and connectivity patterns

Two main observations showed differences in subjects with subthreshold psychotic symptoms compared to the control group. First, the present analysis showed main effects of the verbal fluency performance (Fig. 2) on average hemodynamic responses. In particular, the results demonstrated larger responses to the phonemic and semantic conditions as compared to the control condition. Although all groups exhibited a similar response pattern to these three conditions, subjects with subthreshold psychotic symptoms elicited significantly reduced hemodynamic magnitudes compared to the control group (Fig. 3).

Second, the present analysis showed significant connections between prefrontal and temporal areas. People with subthreshold psychotic symptoms have been shown to exhibit reduced connectivity between frontal brain regions involved in inhibitory control, suggesting that disruption in integration between these distributed neural networks may be a neurobiological feature of subthreshold psychosis (Jacobson McEwen et al., 2014). In line with the previous literature, our data showed reduced connectivity within and between prefrontal and temporal cortical areas, a finding that was primarily observed in the left hemisphere (Fig. 4). However, in contrast to the hemodynamic responses, the connectivity analysis did not reveal task-specific differences, i.e., no effects of the verbal fluency conditions. This indicates that the subjects with subthreshold psychotic symptoms included in

this study differed in overall cortical connectivity patterns, i.e., by means of a reduction in connectivity, but not in a VFT task-related manner.

Taken together, while fNIRS hemodynamics reflected both group- and task-specific contrasts, fNIRS connectivity was only associated group-specific contrasts. It should, however, be noted that none of the results presented here showed differences between the groups with subthreshold psychotic symptoms (PA, PS, PA–PS), but only contrasted these groups from the control group. The contrasts between groups PA, PS, and PA–PS, were presumably very subtle and therefore not detectable using the current experimental and methodological design.

4.2. Effects of VFT performance on hemodynamics and connectivity

VFT performance exhibited a direct relationship to the fNIRS hemodynamics and/or connectivity. Linear regression revealed that both the hemodynamics and connectivity patterns correlated with VFT performance. In particular, we observed a positive relationship between the number of correct words and the hemodynamic and connectivity patterns (Fig. 5). This observation was made over the left prefrontal and temporal cortices, indicating more activation within and more connectivity between these areas along with an increasing number of correct words (in this case both phonemic and semantic performance). Further, this observation was made for all subjects, indicating group-independent performance processing.

As summarized (Baldo et al., 2006), several early functional neuroimaging studies have assessed letter and category fluency, implicating a prefrontal–temporal response model. These studies found greater left temporal activation during category fluency performance and greater left prefrontal activity during letter fluency performance (Baldo et al., 2006; Gourovitch et al., 2000; Mummery et al., 1996). Although, results were not strictly consistent in that additional activations were found (such as with letter fluency activating right temporal regions, and category fluency activating medial prefrontal cortex), this dissociation accorded with concepts suggesting roles of the frontal cortex for basic word construction and strategic word retrieval, and temporal cortex for associating concepts with lexical labels.

The present data, however, did not reveal differences between phonemic and semantic fluency performance (as represented by the factor 'VFT number' over both conditions), and the hemodynamics and connectivity. Besides methodological aspects, it might therefore be assumed that the positive relationship found to VFT performance might have been (additionally) associated with other cognitive functional aspects. For example, temporal and prefrontal cortices have been implicated in functions related to memory (temporal), attention or problem solving (prefrontal), respectively (Siddiqui et al., 2008). It might therefore be suggested that (in addition to VFT-specific performance), general cognitive functional aspects such as short-term memory and attention required for proper VFT performance are reflected in the hemodynamic and connectivity patterns. In other words, subjects in the present study might have recruited larger activity of the temporal and prefrontal cortices the more their memory and attentional functions were demanded.

4.3. Conclusion

In conclusion, the present findings show neurophysiological differences during VFT based on subthreshold psychotic symptoms using fNIRS in a unique community sample. Taken all results together, the present findings suggest that the combined assessment of verbal fluency performance, hemodynamic and connectivity patterns in neural networks, particularly between prefrontal and temporal regions, may be a neurobiological feature of subthreshold psychotic symptoms.

Role of the funding source

Elsevier listed no existing agreements and policies with the funding sources of this study.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Authors WR, WK, HH, VA, and AF, designed the study and wrote the protocol. Authors FH, AA, and MM, collected the data. Author LH undertook the statistical analysis. Author LH wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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