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Language-related gamma EEG frontal reduction is associated with positive symptoms in schizophrenia patients

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ABSTRACT

Objectives: Frontal hypoactivation has been consistently found in schizophrenia. We hypothesized that patients' deficit is asymmetrical, i.e., centred over the left frontal locations, associated with loss of language-related asymmetry, and correlated with positive symptoms.
Method: The amplitude of EEG gamma band (36–48 Hz) was measured during the processing of three linguistic (Phonological vs. Semantic vs. Visuo-perceptual) tasks and used as index of activation/connectivity in 18 schizophrenia patients and 18 healthy participants.
Results: Healthy controls showed higher gamma in frontal sites, revealing a significantly greater left vs. right asymmetry in all linguistic tasks, whereas patients exhibited decreased and bilateral gamma amplitude (i.e., reduced activation/connectivity) in frontal regions. The patients' left hypofrontality during phonological processing was positively correlated with higher levels of Delusions (P1) and Hallucination (P3) PANSS subscales. A significantly greater left posterior gamma amplitude was found in patients compared with controls.
Conclusion: Results suggest, in schizophrenia patients, a functional deficit of left frontal regions including Broca's area, a key site playing a fundamental hierarchical role between and within hemispheres which integrates many basic processes in linguistic and conceptual organization. The significant correlation between lack of the left anterior asymmetry and increased positive symptoms is in line with Crow's hypothesis postulating the aetiological role of disrupted linguistic frontal asymmetry on the onset of the key symptoms of schizophrenia.

1. Introduction

Abnormal brain organization and functioning in schizophrenia patients have been consistently investigated, one of the most important and reliable finding being a significant dysfunction in the activation of the prefrontal cortex, which is typically associated with deficits in attention, action planning and working memory (Andreasen et al., 1992; Goldberg and Gold, 1995; Wienberger and Berman, 1996; Tan et al., 2007 for an extensive review). Schizophrenia patients' hypofrontality has been especially demonstrated with electrophysiological/neuromagnetic methods analysing slow and fast EEG/MEG rhythms, and dipole density (Tauscher et al., 1998; Fehr et al., 2001; Mientus et al., 2002). Most EEG studies carried out in schizophrenia patients found, compared with controls, both increased levels of delta activity (0.1–3.9 Hz), and reduced delta coherence in frontal sites, which was usually inversely correlated with the PANSS positive syndrome subscale, thus suggesting a direct link between the severity of positive symptoms and patients' hypofrontality (Tauscher et al., 1998). Whereas past literature on slow EEG rhythms provided converging evidence that increased delta EEG activity is a quantitative and reliable index of schizophrenia patients' frontal inhibition, most of past research measuring beta (20–35 Hz) and gamma (36–50 Hz) oscillations during auditory or visual working memory tasks revealed less consistent results (Kwon et al., 1999; Basar-Eroglu et al., 2007; Barr et al., 2010). In particular, increased or reduced gamma activity has been found depending on modality of stimulus presentation (auditory vs. visual), levels of task complexity (and the extent of working memory engagement) as well as prevalent symptom content (positive vs. negative; Herrmann and Demiralp, 2005). Research carried out by measuring high-frequency neural oscillations in schizophrenia patients and healthy controls includes various visual perceptual tasks (e.g., Tan et al., 2013), or working memory paradigms mainly based on the N-back task (Basar-Eroglu et al., 2007; Barr et al., 2010). In these studies, the main result was a significant greater frontal gamma activity in patients regardless of cognitive load (low vs. high) manipulations (Basar-Eroglu et al., 2007; Barr et al., 2010), the N-back performance being negatively correlated with negative symptoms (Barr et al., 2010).

In three previous studies we used a working memory paradigm, validated for language (Spironelli and Angrilli, 2010), in order to assess Crow's hypothesis (1997, 2000) on schizophrenia disorder. By analysing

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automatic recognition potential (Spironelli et al., 2008), Contingent Negative Variation (Angrilli et al., 2009) and delta hypofrontality (Spironelli et al., 2011), we found evidence, in schizophrenia patients, of a significant lack of left-hemisphere dominance for language as a consequence of their primary deficit in functional linguistic integration. This was in line with prior literature showing lack of left hemisphere dominance for linguistic stimuli (e.g., Bruder et al., 1999; Rockstroh et al., 2001; McCarley et al., 2002) Therefore, the inter- and intra-hemispheric hierarchical roles of Broca's area (Bookheimer, 2002; Hagoort, 2005) would explain the lack of linguistic integration and the metalinguistic disorganization observed in schizophrenia (Crow 1997, 2000; Kuperberg, 2010a,b). In turn, the deficit in linguistic dominance, leads to lack of hemispheric integration, confusion between inner and external voices (hallucinations), thought disorders and delusions (Crow 1997, 2000; Kuperberg, 2010a,b). From a more general point of view, in agreement with Andreasen et al. (1999), schizophrenia patients are characterized by abnormal integration of brain networks: for this reason, gamma EEG band should represent the most appropriate marker for studying patients' dysfunctional cortical integration. The present experiment analysed the amplitude of gamma EEG band as an index of cognitive functioning and integration mechanisms (Herrmann et al., 2004): compared with controls, schizophrenia patients were expected to exhibit lower gamma amplitude over anterior left cortical sites, i.e., in regions currently considered essential for the organization of the whole linguistic network. In addition, we expected to find a correlation between schizophrenia key psychiatric indices (i.e., delusions and hallucinations measured by the Positive and Negative Syndrome Scale, PANSS; Kay et al., 1987) and the frontal linguistic left asymmetry, in line with Crow's etiological hypothesis (1997, 2000) on the main mechanism postulated at the origin of the schizophrenic disorder, the disruption of the typical language-related asymmetry measured in healthy individuals.

2. Materials and methods

2.1. Participants

The psychiatric group consisted of 18 schizophrenia inpatients (4 women, 14 men; mean age ± SD: 39.11 ± 11.05 years, range 24–70 years; educational level: 10.11 ± 2.70 years, range 7–17 years) recruited from the *Ospedale Psichiatrico Giudiziario* of Castiglione delle Stiviere (Mantova, Italy) according to the following criteria: all patients were right-handed (Oldfield, 1971); they had been diagnosed as schizophrenic during the acute phase, on the basis of positive or negative symptoms exhibited for more than 6 months according to DSM-IV-R criteria; at the time of the study, all patients were in a chronic state (average time from onset: 14 ± 8.57 years). The diagnosis, ascertained by the psychiatrists of the ward at the time of the experiment by administering Structured Clinical Interview for DSM Disorders, classified two patients as disorganized (ICD-10 F20.1), two with paranoid/residual (F20.0/F20.5) and fourteen with paranoid schizophrenia (F20.0). In addition, prior to the experimental session, schizophrenia patients were screened to assess the severity of symptoms according to the Italian version of PANSS (Table 1).

Six patients were treated with typical antipsychotic drugs (i.e., chlorpromazine, clotiapine, clucopenthixol, haloperidol and methotrimeprazine), six patients with atypical antipsychotic drugs (i.e., aripiprazole, clozapine, olanzapine, quetiapine, risperidone), and six patients with both typical and atypical antipsychotic drugs.

The control group consisted of 18 right-handed healthy volunteers (7 women, 11 men; $\chi^2(1) = 1.18$, *ns*), matched for age (mean ± SD: 42.39 ± 19.80 years, range 21–69 years; $t(34) = 0.61$, *ns*), educational level (11.72 ± 3.00 years, range 8–17 years; $t(34) = 1.69$, *ns*) and handedness (98.47 ± 3.55%; $t(34) = 1.08$, *ns*) to the patient group.

Table 1
Demographic characteristics of healthy controls and schizophrenia patients, and average scores obtained from the Italian version of PANSS (Kay et al., 1987), administered to ascertain patients' symptoms' severity.

	Healthy controls		Schizophrenia patients		Test	*p*
	Mean	SD	Mean	SD		
Age (years)	42.39	±3.00	39.11	±11.05	$t(34) = 0.61$	*ns*
Gender	7 females 11 males		4 females 14 males		$\chi^2(1) = 1.18$	*ns*
Education (years)	11.72	±3.00	10.11	±2.70	$t(34) = 1.69$	*ns*
Handedness	98.47%	±3.55%	93.05%	±10.01%	$t(34) = 1.08$	*ns*
Years from onset	–	–	14.00	±8.57	–	–
Positive And Negative Syndrome Scale (PANSS)						
Positive symptoms						
P1 (delusions)			4.56	±1.58		
P2 (conceptual disorganisation)			3.56	±1.29		
P3 (hallucinatory behaviour)			2.94	±1.63		
P4 (excitement)			2.83	±1.38		
P5 (grandiosity)			3.06	±1.86		
P6 (suspiciousness/persecution)			4.11	±1.64		
P7 (hostility)			2.78	±1.40		
Total			3.40	±1.65		
Negative symptoms						
N1 (blunted affect)			4.28	±0.89		
N2 (emotional withdrawal)			4.44	±1.04		
N3 (poor rapport)			4.11	±0.83		
N4 (passive/apathetic social withdrawal)			4.22	±1.17		
N5 (difficulty in abstract thinking)			4.28	±1.27		
N6 (lack of spontaneity and flow of conversation)			3.78	±1.00		
N7 (stereotyped thinking)			4.28	±1.02		
Total			4.20	±1.04		

Both healthy adults and patients signed their informed consent to participate in this study, which was approved by the Ethics Committee of the Department of General Psychology and the local Ethics Committee of the *Ospedale Psichiatrico Giudiziario*, and performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Stimuli, tasks and procedure

Stimuli consisted of bi- or trisyllabic Italian content words selected from a frequency dictionary of 5000 written Italian words, and presented in pairs on a 17″ computer monitor one at a time with an Inter-Stimulus Interval (ISI) of 2 s: thus, the first word (W1) remained on the screen for 1 s and, after an interval of 2 s, the second word (W2, or target) appeared on the screen, until the subject responded by pressing a keyboard button, in no case longer than 5 s (11). Word pairs were administered in three separate blocks, which corresponded to three linguistic tasks: according with the Hillyard principle, the same words were presented as W1, but in different randomized order across tasks. Upon W2-target presentation, participants had to decide whether word pairs rhymed (Phonological task), whether target word W2 was of the same category as W1 (Semantic task), and whether word pairs were written in the same upper or lower case[1] (Visuo-perceptual, control task; Spironelli and Angrilli, 2010). For motor responses, subjects used their left index or middle finger to press the keyboard buttons corresponding to match–mismatch conditions. Each task included 80 word-pairs, 50% matches being randomly interspersed with 50% mismatch trials; task order was randomly varied across participants. Since this paradigm requires efficient verbal working memory skills, we administered the forward digit span test to verify that groups had similar levels of working memory.

[1] All the letters in the same word were upper or lower case.