Clinical Neurophysiology 128 (2017) 2037–2042

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Left hemispheric breakdown of LTP-like cortico-cortical plasticity in schizophrenic patients

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ARTICLE INFO

Article history:
Accepted 26 June 2017
Available online 14 July 2017

Keywords:
Schizophrenia
Connectivity
Paired associative stimulation
Transcranial magnetic
Stimulation
Parietal cortex
Plasticity

HIGHLIGHTS

- Schizophrenia is characterized by altered intra-hemispheric connectivity and cortical plasticity.
- We evaluated cortico-cortical associative plasticity of both hemispheres using cc-PAS protocol.
- Patients with schizophrenia showed weaker late LTP-like plasticity in left but not right hemisphere.

ABSTRACT

Objective: Altered cortical connectivity and plasticity seems to be asymmetrical between the hemispheres in patients with schizophrenia (SCZ). We evaluated long-term potentiation (LTP) in parietal-frontal circuits of both hemispheres using a cortico-cortical Paired Associative Stimulation (cc-PAS) protocol testing the rules of Hebbian-like spike timing dependent plasticity (SPTD).
Methods: 12 SCZ and 12 healthy subjects (HS) underwent a cc-PAS protocol to activate, by means of paired pulses of transcranial magnetic stimulation (TMS), the short-latency connection between posterior parietal cortex (PPC) and primary motor cortex (M1) of both hemispheres. Motor-evoked potentials (MEPs) were collected to assess the time course of the after effects of cc-PAS protocol measuring MEP amplitude as index of cortico-cortical associative plasticity.
Results: While HS showed a similar time course of LTP-like plasticity in the two hemispheres, SCZ revealed a weaker late-LTP-like plasticity in the left compared to the right hemisphere after cc-PAS protocol.
Conclusions: SCZ failed to show the typical long-lasting increase of M1 excitability observed after cc-PAS protocol in both hemispheres, with a greater reduction in the left one.
Significance: Our findings provide novel neurophysiological evidence for an asymmetric impairment of the left parietal-frontal network in SCZ patients.

1. Introduction

Schizophrenia is a devastating illness, with a prevalence of 1% (Stephan et al., 2009). It is characterized by positive symptoms (delusions, hallucinations and disorganized thoughts) and negative symptoms such as avolition, alogia, and apathy. An emerging hypothesis is that schizophrenia may be interpreted as a brain disconnection syndrome, with abnormal interactions between widespread brain areas (Ribolsi et al., 2009; Wheeler and Voineskos, 2014). Schizophrenia has been associated not only to a local dysfunction of specific brain areas but also with a disruption of communication trough a reduced inter-hemispheric connectivity (Stephan et al., 2009; Chang et al., 2015). In particular, it has been suggested that the functional connections within the left and right hemisphere show an asymmetric impairment, being more affected in the left hemisphere (Ribolsi et al., 2014). This asymmetric impairment of connectivity may be evident at both anatomical and functional level (Griffa et al., 2015; Fitzsimmons

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http://dx.doi.org/10.1016/j.clinph.2017.06.255
1388-2457/

et al., 2013) and has been interpreted in terms of altered strength of the connections as well as in terms of abnormality of plasticity (Friston, 2002). Abnormal neuronal plasticity contributes most to the pathophysiology and to several clinical aspects of schizophrenia (Hasan et al., 2011). Different lines of evidence support the hypothesis of altered plasticity in schizophrenia. First, studies conducted on animal models of schizophrenia have hypothesized a dysfunction of glutamatergic N-methyl-d-Aspartate receptors (NMDAR) with hyperglutamatergic transmission and consequently neurotoxicity and disturbed plasticity (Balu et al., 2013). For instance, glutamate antagonists like ketamine produces schizophrenia-like symptoms (Javitt, 2007). In particular, it has also been postulated that hypofunctional NMDA receptors placed on gabaergic inhibitory interneurons brings to an activation of pyramidal neurons, that has as a consequence an increase in glutamatergic transmission (Stone et al., 2007; Moghaddam and Krystal, 2012; Nakazawa et al., 2012) and in excitotoxic neuronal death (Coyle and Puttfarcken, 1993; Ghosh and Greenberg, 1995). A second line of evidence of altered plasticity in schizophrenia is highlighted by different neurophysiological studies that have reported in vivo abnormalities of long-term potentiation (LTP) and long-term depression (LTD). For example, several transcranial direct current stimulation (tDCS) studies failed to modulate cortical activity through induction of cortical plasticity in the primary motor cortex (Hasan et al., 2013). In particular, LTD-like plasticity was not induced by classical unilateral cathodal tDCS (Hasan et al., 2012), while anodal tDCS failed to evoke LTP-like plasticity (Hasan et al., 2011), supporting the hypothesis of a reduced responsiveness of the motor cortex and impairments of functional connections in schizophrenia (Hasan et al., 2012). Apart from TDCS, the paired associative stimulation (PAS) protocol (Stefan et al., 2000; Wolters et al., 2003; Jung and Ziemann, 2009; Muller-Dahlhaus et al., 2010) is considered another tool allowing to investigate LTP-like plasticity and LTD-like plasticity mechanisms in the primary motor cortex. The PAS-induced changes have been associated to mechanisms of LTP-like and LTD-like plasticity (Ziemann, 2004) because they share important features of LTP-like plasticity and LTD, such as NMDA receptor dependency, duration superior to 30 min, associativity and cooperativeness (Cooke and Bliss, 2006; Muller-Dahlhaus et al., 2010). Using the PAS paradigm, Frantseva et al. showed in schizophrenia patients a disruption of LTP-like plasticity, which may be associated with impaired motor skill learning (Frantseva et al., 2008). More recently, LTP-like plasticity has been induced in schizophrenia patients after anodal TDCS but not after a focal PAS protocol, suggesting an impairment of the functioning of NMDA receptors (Strube et al., 2016). Recently, we developed a novel cortico-cortical PAS (cc-PAS) protocol to investigate mechanisms of intra-hemispheric cortico-cortical plasticity (Koch et al., 2013; Veniero et al., 2013). Using this cc-PAS protocol we found evidence for Hebbian-like bidirectional spike timing dependent plasticity (STDP) occurring within the short-latency connection between the posterior parietal cortex (PPC) and the primary motor cortex (M1) (Koch et al., 2007). It's noteworthy to underline that parietal and frontal cortex are involved in both motor control/motor imagery and first rank psychotic symptoms such as passivity phenomena (Danckert et al., 2004; Maruff et al., 2005). Here we hypothesize that long lasting cortico-cortical associative plasticity in the PPC–M1 network is impaired and abnormally asymmetric in schizophrenia patients (SCZ) compared to healthy subjects (HS). For this purpose, we applied the same PAS protocol as in Koch et al. (Koch et al., 2013) in the two hemispheres to compare left and right PPC-M1 connectivity both in SCZ patients and in age-matched HS. Till now, although there is some evidence of an abnormal asymmetry of the functional connectivity in schizophrenia (Jalili et al., 2010; Ke et al., 2010), this is the first TMS study to investigate neural plasticity in both hemispheres in SCZ.

2. Methods

2.1. Subjects

Twelve patients with schizophrenia (SCZ) were enrolled in the study. All SCZ (9 males and 3 female; mean age: 38 ± 7.7) were inpatients and were recruited from the Psychiatric Clinic at Tor Vergata University in Rome. Diagnosis was established through consultation with physicians and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Furthermore, Positive and Negative Syndrome Scale and the Global Assessment of Functioning (GAF) scale was performed to evaluate the severity of the psychopathology (SCZ GAF mean score 46 ± 11.3). All the patients included in SCZ group were under antipsychotic treatment; drug doses were expressed in chlorpromazine equivalents (mean Chlorpromazine eq. 577.8 ± 331.89). The schizophrenia group exhibited primarily mixed (both negative and positive) symptomatology. In particular mean scores of PANSS positive subscale and PANSS negative subscale were 17.87 ± 4,94 and 17.5 ± 4,03 (mean ± SD) respectively. PANSS total mean score was 76.25 ± 10.53 (mean ± SD). As a control group, 12 age matched healthy subjects were evaluated (7 males, 5 females; mean age: 36.3 ± 5.4). Demographic and clinical features of all the subjects recruited are reported in Table 1. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). For both groups, exclusion criteria were: neurological disorders, the presence of a cardiac pacemaker and a history of brain trauma, seizures, or neurosurgery. All participants underwent two randomly neurophysiological assessments of both hemispheres within one week of each other. All participants provided written informed consent for participation in the study. Experimental procedures were authorized by the local ethics committee and conducted in conformity with the Declaration of Helsinki.*2.2 EMG recordings.*

Ag-AgCl surface cup electrodes with a 9-mm diameter were placed over the muscle belly and the reference electrode was placed over the metacarpophalangeal joint of the index finger to record Electromyographic traces (EMG). The electrical responses were amplified thanks to a Digitimer D360 amplifier; filters were set at 20 Hz and 2 kHz and the sampling frequency we used was a frequency of 5 kHz. Electromyographic traces were recorded through a software named SIGNAL software (Cambridge Electronic Devices) installed on a computer.

2.2. cc-PAS protocol

A paired-pulse TMS technique that made use of two high-power Magstim 200 machines connected to the coil that was responsible for the stimulation (Magstim Co., Whitland, Dyfed, United Kingdom) was applied to admninster the cc-PAS protocol between the PPC and M1 in both hemispheres (Koch et al., 2013). We first applied in each hemisphere a TMS pulse over the brain area responsible for the movement of the hand that was localized in the site of motor cortex where the stimulation aroused the greatest and more stable motor evoked potential (MEPs) response from the contralateral first dorsal interosseous (FDI) muscle (hot-spot). A small figure of eight coil (50 mm outer diameter) was connected to the stimulator for M1. To induce a posterior-anterior (PA) directed current, we placed the coil postero-laterally at an angle of 45° to the midline. During the cc-PAS protocol. The power of the TS was set at a level that could induce a MEP of about 1 mV