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Using concurrent EEG and fMRI to probe the state of the brain in schizophrenia

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ABSTRACT

Perceptional abnormalities in schizophrenia are associated with hallucinations and delusions, but also with negative symptoms and poor functional outcome. Perception can be studied using EEG-derived event related potentials (ERPs). Because of their excellent temporal resolution, ERPs have been used to ask *when* perception is affected by schizophrenia. Because of its excellent spatial resolution, functional magnetic resonance imaging (fMRI) has been used to ask *where* in the brain these effects are seen. We acquired EEG and fMRI data simultaneously to explore *when* and *where* auditory perception is affected by schizophrenia.

Thirty schizophrenia (SZ) patients and 23 healthy comparison subjects (HC) listened to 1000 Hz tones occurring about every second. We used joint independent components analysis (jICA) to combine EEG-based event-related potential (ERP) and fMRI responses to tones.

Five ERP-fMRI joint independent components (JIC) were extracted. The "N100" JIC had temporal weights during N100 (peaking at 100 ms post-tone onset) and fMRI spatial weights in superior and middle temporal gyri (STG/MTG); however, it did not differ between groups. The "P200" JIC had temporal weights during P200 and positive fMRI spatial weights in STG/MTG and frontal areas, and negative spatial weights in the nodes of the default mode network (DMN) and visual cortex. Groups differed on the "P200" JIC: SZ had smaller "P200" JIC, especially those with more severe avolition/apathy. This is consistent with negative symptoms being related to perceptual deficits, and suggests patients with avolition/apathy may allocate too few resources to processing external auditory events and too many to processing internal events.

1. Introduction

1.1. Perception and schizophrenia

Perception involves the identification and interpretation of sensory information in the service of understanding and navigating the environment (Schacter et al., 2015). It is influenced by expectations and attention (Schroger et al., 2015) and results from a convergence of bottom-up and top-down processes (Joos et al., 2014), as the brain predicts the content and arrival of information (Friston, 2010). Its disruption in schizophrenia has been associated with a range of symptoms, the most obvious being hallucinations (Woodruff et al., 1995) and the inability to distinguish between what is real and what is not (e.g., Brebion et al., 1996). Recently, disruptions in perception have been associated with defeatist beliefs, negative symptoms, and poor functional outcome (Green et al., 2012).

Assessing perception has traditionally been done with a variety of behavioral methods, but is also studied using EEG-derived event related potentials (ERPs) (Joos et al., 2014; Woodman, 2010). Because of their excellent millisecond temporal resolution, ERPs have been used to inform us about *when* auditory processing is affected by a variety of psychological variables, such as attention and distraction (Hillyard et al., 1973; Hillyard et al., 1971; Näätänen and Picton, 1987). The different components of the ERP can also provide information about the transition from sensation to perception (Joos et al., 2014).

1.2. Brief history of ERPs to study perception

Over 50 years ago, ERPs were used in audiometry to assess hearing in people whose behavioral reports could not be obtained or trusted. A negative going potential, peaking 100 milliseconds (ms) after stimulus onset, was called N1 or N100. Because its amplitude increased with increasing loudness, N100 was considered a reasonable index of hearing. N100 is followed by P2 or P200, a positive going potential, peaking at about 200 ms. The N100-P200 complex was largest at the

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vertex of the head and called the "vertex potential." For years, it was measured as the peak-to-peak difference between N100 and P200 (i.e. "N100-P200" or "N1-P2").

Although P200 invariably follows N100, they can be distinguished both experimentally (Ford et al., 1976; Ford et al., 1999; Oades et al., 1997; Wang et al., 2014) and topographically on the scalp (Vaughan et al., 1980; Verkindt et al., 1994; Wang et al., 2014). Yet, N100 and P200 often co-vary (Paiva et al., 2016). Thus, although structures that generate them may overlap to some extent, N100 and P200 waves are unlikely to reflect a single underlying neural process, and therefore, are best measured and studied independently of each other.

1.3. N100

In the 1970s, its sensitivity to attention (Hillyard et al., 1973) and arousal (Naatanen and Michie, 1979) shifted N100 out the realm of audiometry and into cognitive neuroscience. There is general consensus that N100 to a tone is augmented by selective attention, when that tone is in an attended channel (Hillyard et al., 1973). Data from a variety of sources suggest that N100 emanates generally from primary and secondary auditory cortical areas, namely superior temporal gyrus (STG) and middle temporal gyrus (MTG) (Chen et al., 2011; Flinker et al., 2010; Hari et al., 1987; Krumbholz et al., 2003; Ozaki et al., 2003; Pantev et al., 1996; Reite et al., 1994; Sams et al., 1985; Verkindt et al., 1995; Verkindt et al., 1994; Zouridakis et al., 1998), indirectly suggesting that attention to auditory events is associated with increased activity in these regions of the temporal lobe.

1.4. P200

The functional significance of P200 is poorly understood (Crowley and Colrain, 2004; Woodman, 2010). P200 may reflect an attention-modulated process required for the performance of an auditory discrimination task (Novak et al., 1992), or when elicited by a non-target stimulus in an oddball paradigm, it may reflect an attentional shift towards the stimulus and some aspects of the classification process (Garcia-Larrea et al., 1992). The brain areas responsible for P200 generation are also less well studied, but likely include both STG and MTG (Crowley and Colrain, 2004). Thus, although both are obligatory responses to tones, N100 and P200 might be considered reflections of different perceptual stages in the auditory processing stream.

1.5. N100, P200, and schizophrenia

N100 amplitude is typically, but not always, reduced in schizophrenia patients (see review by (Rosburg et al., 2008)). Indeed, its reduction has been proposed as a trait marker of functional brain changes related to genetic predisposition to schizophrenia (Ahveninen et al., 2006). N100 to probe tones may also be a state marker of the illness, as it is reduced during auditory hallucinations (Hubl et al., 2007), perhaps reflecting distraction by the voices. It may also reflect a readiness to attend to voices rather than probe tones in patients who tend to have auditory hallucinations (Ford et al., 2009). In spite of its prominence in the schizophrenia literature and its importance for understanding the pathophysiology of schizophrenia, the precise neural generators of N100 have not been adequately explored.

P200 amplitude reductions are sometimes (Ethridge et al., 2015; Roth et al., 1991; Roth et al., 1980; Salisbury et al., 2010), but not always (Potts et al., 1998) reported in schizophrenia. A meta-analysis indicated that P200s elicited by infrequent target tones are larger in schizophrenia, while P200s elicited by standard frequent tones are smaller (Ferreira-Santos et al., 2012), contributing to ongoing confusion about the relevance of this ERP component to understanding the pathophysiology of schizophrenia.

1.6. Goals of this experiment

To understand the different neural basis of N100 and P200, and how they are differentially affected by schizophrenia, we recorded EEG and fMRI data concurrently from patients and age-matched healthy controls. The EEG data provided the millisecond temporal precision needed to distinguish between rapidly resolving reflections of early (N100) and later (P200) stages of information processing, and the fMRI data provided the spatial/neuroanatomical precision needed to distinguish between areas of the brain involved in all stages of processing tones. Joint group Independent Components Analysis (jICA) allowed us to determine the patterns of spatial (with fMRI) and temporal (with ERP) covariance associated with processing tones. We focused on components in the temporal domain that load on traditional ERP waves (e.g. N100, P200) and their association with brain regions activated or even inhibited by tones in the spatial/neuroanatomical domain. Using jICA to integrate ERP and fMRI data allowed us to identify temporal-spatial relationships and their potential disruption in schizophrenia. We used a simple passive listening task to avoid confounding diagnostic effects with differences in cognition and motivation.

JICA is a blind source separation, unsupervised learning technique used to explain the underlying structure of multi-modal data. Thus, it is exploratory and data-driven in nature. Nevertheless based on the literature, we predicted that an "N100" joint component would reflect covariation of N100 amplitude and activity in STG, that a "P200" joint component would reflect covariation of P200 amplitude and activity in higher order cortical association areas. We also predicted that patients with schizophrenia would have smaller "N100" and "P200" joint independent components.

2. Materials and methods

2.1. Participants

Data are reported here from 30 patients with DSM-IV schizophrenia (N = 24) and schizoaffective disorder (N = 6) (hereinafter referred to as schizophrenia (SZ) patients), and 23 age- and gender-matched healthy comparison (HC) subjects (see below for description of why 8 SZ and 5 HC were dropped from the initial sample of 66 subjects.) Diagnoses were based on the Structured Clinical Interview for DSM-IV (First et al., 1995). Community outpatient clinicians referred SZ to us; both groups were recruited by advertisements and word of mouth.

Exclusion criteria for HC included any past or current major DSM-IV Axis I disorder based on a Structured Clinical Interview for DSM-IV Disorders, or having a first-degree relative with a psychotic disorder. For both groups, exclusion criteria were a history of a significant medical or neurological illness, head injury resulting in loss of consciousness, or substance abuse in the past 3 months. Additionally, HC did not have history of substance dependence (except nicotine), whereas SZ did not meet criteria for substance dependence within the past year. A psychiatrist or clinical psychologist conducted all interviews. Institutional Review Boards at the University of California at San Francisco and the San Francisco Veterans Affairs Medical Center approved the study, and all participants provided written informed consent. Clinical and demographic data are presented in Table 1 for those subjects included in the final analysis.

2.2. Clinical ratings

A trained research assistant, along with a psychiatrist or clinical psychologist, rated schizophrenia symptoms using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983).