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Letter to the Editor

Hemispheric specialization of mood processing is abnormal in patients with schizophrenia

To the Editor,

Abnormalities of brain lateralization are among the most consistent neurobiological signatures of the schizophrenia syndrome (Schweitzer et al., 1978; Hirnstein and Hugdahl, 2014). Most studies have focused on alterations in the lateralization of language, sensory processing, macroscopic brain morphology, and motor dexterity, which have been long known to exhibit hemispheric specialization in *H. sapiens* (Newcombe and Ratcliff, 1973). In fact, it has been proposed that language and psychosis might share a common origin related to the development of brain lateralization in *H. sapiens*, presumably when our species diverged from other hominins some 160,000 years ago (Crow, 2008). Implicit language functions and social cognition have also been proposed to stem from lateralization deficits (Guinjoan et al., 2015), which might bear significant clinical value in schizophrenia as the syndrome presents remarkable disturbances in mood processing and social behavior. Healthy individuals display hemispheric specialization in emotion processing (e.g., Craig, 2009; Costanzo et al., 2015). We hypothesized that development of abnormal brain lateralization in schizophrenia involves emotion processing in addition to language and motor dexterity, and specifically predicted that patients with schizophrenia would display deficits in left hemisphere activation during language tasks and impairments in right hemisphere activation during the induction of sadness, as evidence of an overall deficit in hemispheric specialization in this group. We studied 15 right-handed medicated patients with chronic stable schizophrenia (31 ± 9 years, 47% women) and 20 right-handed healthy individuals (26 ± 5 years, 55% women) with a functional magnetic resonance imaging paradigm of phonological fluency and sadness induction described in detail elsewhere (Costanzo et al., 2015). Briefly, a block design was employed in a GE Hx 3T for both word generation and sadness induction with the help of faces showing strong emotion (Costanzo et al., 2015). Handedness was assessed with the Edinburgh questionnaire (Oldfield, 1971). All participants gave written informed consent as approved by the local bioethics committee. Groups were similar regarding age, sex, and estimated premorbid intelligence, but controls had more years of education. We examined whole hemisphere lateralization effects of each task and then studied four regions of interest during activation induced by sadness: amygdala, thalamus, hippocampus, and insula.

Healthy individuals showed a significant leftward hemispheric lateralization of brain activation during a phonological fluency task ($t = -2.384$, $p < 0.05$), which was not present in patients. Right hemisphere activation was greater during sadness induction in healthy participants ($t = 2.253$, $p = 0.036$), whereas no significant right-left differences were present in patients. Degree of hemispheric activation during a phonological fluency task correlated with degree of lateralization of insular cortex activation during sadness induction in healthy individuals only (Fig. 1). Patients displayed an inverse correlation of the lateralization of activation induced by sadness between amygdalae and thalami ($r = -0.65$, $p = 0.01$), which was not present in healthy participants.

In conclusion, the present results offer evidence on abnormal lateralization of brain activity associated to mood processing in schizophrenia. To our knowledge, lateralized mood processing has not been previously studied in this disorder. The present observation adds to burgeoning evidence on a widespread deficit of brain lateralization in psychosis, probably underlying language-related abnormalities such as delusions and auditory hallucinations (Crow, 2008), social cognitive deficits (Guinjoan et al., 2015), and motor dexterity (Hirnstein and Hugdahl, 2014). The relative contribution of genes and environment to such lateralization deficits, as well as the nature of the gene/s involved in the abnormal development of brain lateralization in schizophrenia remain to be determined. A recent report on an essentially symmetric gene expression in the human neocortex throughout the life cycle (Pletikos et al., 2014) suggests the observed differences could be driven by alocortical abnormalities, the environment (including experience-

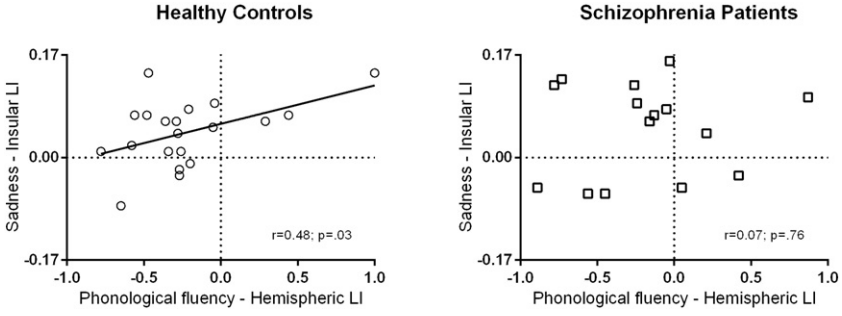

Fig. 1. LI: lateralization index.

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dependent and infectious/immune mechanisms), epigenetic changes, or hormonal factors.

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