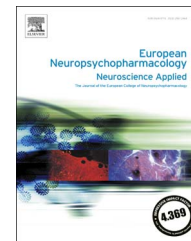




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Functional connectivity of the ventral tegmental area and avolition in subjects with schizophrenia: a resting state functional MRI study

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Abstract

Avolition, a deficit in goal-directed behavior, is a key aspect of negative symptoms. It is highly prevalent in schizophrenia and is associated to poor functional outcome and to measures of real life motivation, indicating that central to the concept is the lack of interest and motivation. In this study we tested the hypothesis that avolition is related to altered connectivity within dopaminergic cortico-striatal circuits involved in motivation processes. Since dopamine input to these circuits derives mostly from the ventro-ventral tegmental area (VTA), we investigated the relationships between the resting-state functional connectivity (RS-FC) of the VTA and avolition in twenty-six subjects with schizophrenia (SCZ), treated with second-generation antipsychotics only, compared to twenty-two healthy controls (HC). SCZ, in comparison to HC, showed significantly reduced RS-FC of the VTA with bilateral ventro-lateral prefrontal cortex (VLPFC), bilateral insular cortex (IC) and right (R) lateral occipital complex (LOC) and increased RS-FC of the VTA with bilateral dorso-lateral prefrontal cortex (DLPFC). Significant negative correlations were found between avolition and RS-FC of the VTA with the bilateral IC, R VLPFC and R LOC.

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According to our findings, avolition is linked to a disconnectivity of the VTA from several key cortical regions involved in the integration of value information with action selection. These findings are in line with translational animal models of “auto-activation apathy”.

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1. Introduction

Avolition, a deficit in goal-directed behavior, is a key aspect of negative symptoms. It is highly prevalent in schizophrenia and can be found already in the prodromal stage of the disorder (Galderisi et al., 2015; Galderisi et al., 2016a; Kaiser et al., 2016). It is correlated to poor functional outcome (Foussias et al., 2009; Galderisi et al., 2014; Galderisi et al., 2016b; Green et al., 2012) and to measures of real life motivation (Fervaha et al., 2015a; Fervaha et al., 2015c; Mucci et al., 2015), indicating that central to the concept of this domain is the lack of interest and motivation (Barch and Dowd, 2010; Fervaha et al., 2015a; Fervaha et al., 2015b; Foussias and Remington, 2010; Foussias et al., 2015; Strauss et al., 2016).

Motivation represents a multifaceted construct, including hedonic experience (the ability to enjoy in the moment pleasant experience), reward prediction (the ability to predict a pleasant experience), value encoding (the ability to determine current value in the context of a motivational state), action outcome contingency learning (the ability to know the causal consequences of an action) and the integration of value with action selection. All these functions are subserved by the circuit corresponding to the NIMH Research Domain Criteria (<https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>) “positive valence system” (Bissonette and Roesch, 2016; Bromberg-Martin et al., 2010; Miller et al., 2014; O'Doherty, 2016). Furthermore, motivation includes energetic aspects, such as vigor and persistence in goal-directed behavior, which can be induced by salient aversive or rewarding stimuli, corresponding to the “motivational salience system” (Bissonette and Roesch, 2016; Bromberg-Martin et al., 2010).

The two brain circuits implicated in motivation are dopamine (DA) pathways, with the highest number of DA neurons located in the ventral tegmental area (VTA). The positive valence circuit includes the VTA and ventro-medial substantia nigra pars compacta (VMSNpc) with projections to orbito-frontal cortex (OFC), ventro-medial prefrontal cortex (VMPFC), nucleus accumbens shell (sNA) and dorsal striatum (DS). The motivational salience system includes the VTA and dorso-lateral substantia nigra pars compacta (DLSNpc) with projections to dorso-lateral prefrontal cortex (DLPFC), ventro-lateral prefrontal cortex (VLPFC), nucleus accumbens core (cNA) and DS (Bromberg-Martin et al., 2010).

An important aspect of motivation to engage in goal-directed behavior is the dynamic adjustment of behavior with respect to changes in outcome valuation, depending on current motivational state (e.g., reduced motivation to look for food when satiated). As recently demonstrated in

rodents, insular connections within the motivational pathways, specifically those between insular cortex (IC), basolateral amygdala (BLA) and cNA, are involved in this function. BLA and IC form a circuit in which BLA encodes and updates changes in outcome value, while IC, through its connections with the cNA, plays a critical role for the retrieval of instrumental outcome values and for the subsequent choice between goal-directed actions based on those values (Parkes and Balleine, 2013; Parkes et al., 2015).

Several aspects of motivation were found impaired in subjects with schizophrenia, with the exception of the hedonic experience (Barch and Dowd, 2010; Foussias and Remington, 2010; Morris et al., 2015; Simpson et al., 2012; Strauss, 2013). In particular, patients seem to have difficulties in reward-related learning, as well as in the adaptive integration of value information with action selection (Barch et al., 2016; Deserno et al., 2016). These deficits might derive from altered connectivity between several areas along the dopamine pathways.

A number of functional Magnetic Resonance Imaging (fMRI) investigations concentrated on task-related activation of regions involved in reward anticipation and reported a deficit of ventral striatum (VS) activation in drug-naïve patients (Esslinger et al., 2012; Juckel et al., 2006a; Juckel et al., 2006b; Nielsen et al., 2012b; Schlagenhauf et al., 2009; Simon et al., 2010) or in patients treated with first-generation antipsychotics, but not in those treated with second generation antipsychotics (Juckel et al., 2006a; Mucci et al., 2015; Nielsen et al., 2012a; Schlagenhauf et al., 2008). The relevance of VS dysfunction to avolition has not been established yet. In fact, associations with overall negative symptom severity (as assessed by the negative subscale of the Positive and Negative Syndrome Scale, PANSS, which includes blunted affect and asociality - but not avolition), anhedonia, apathy or the factor avolition from the Brief Negative Symptom Scale (BNSS, which includes avolition, anhedonia and asociality) were reported, as well as correlations with positive symptoms and depression (Esslinger et al., 2012; Kirschner et al., 2016; Nielsen et al., 2012a; Nielsen et al., 2012b; Simon et al., 2010; Waltz et al., 2009).

A study (Waltz et al., 2009) investigated fMRI response during delayed or predictable juice delivery. Reduced left putamen and right insula activation was observed for delayed delivery in patients. Activity of the same regions during predictable delivery was inversely related to avolition scores.

Two studies reported a deficit of dorsal caudate (DC) but normal VS activation during reward anticipation (Mucci et al., 2015) and the performance of a task in which actions were guided by experienced values (Morris et al., 2015).

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