



Review

Neural substrates underlying effort computation in schizophrenia

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ABSTRACT

The lack of initiative, drive or effort in patients with schizophrenia is linked to marked functional impairments. However, our assessment of effort and motivation is crude, relying on clinical rating scales based largely on patient recall. In order to better understand the neurobiology of effort in schizophrenia, we need more rigorous measurements of this construct. In the behavioural neuroscience literature, decades of work has been carried out developing various paradigms to examine the neural underpinnings of an animal's willingness to expend effort for a reward. Here, we shall review this literature on the nature of paradigms used in rodents to assess effort, as well as those used in humans. Next, the neurobiology of these effort-based decisions will be discussed. We shall then review what is known about effort in schizophrenia, and what might be inferred from experiments done in other human populations. Lastly, we shall discuss future directions of research that may assist in shedding light on the neurobiology of effort cost computations in schizophrenia.

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1. Introduction

Schizophrenia is a chronic and debilitating disorder characterized by a constellation of signs and symptoms including positive (e.g. hallucinations and delusions), negative (e.g. lack of pleasure and drive) and cognitive (e.g. planning) symptoms (Freedman, 2003; Mueser and McGurk, 2004). Most individuals afflicted manifest poor functional outcomes, with the majority of patients not engaging in vocational or role functioning (Henry et al., 2010; Robinson et al., 2004; Rosenheck et al., 2006). These psychosocial impairments have been closely linked to the negative symptoms of schizophrenia (Ho et al., 1998; Milev et al., 2005; Pogue-Geile and Harrow, 1985; Rabinowitz et al., 2012; Rosenheck et al., 2006), particularly amotivation (Fervaha et al., 2013; Foussias et al., 2011; Kiang et al., 2003; Konstantakopoulos et al., 2011); although neurocognition has also been implicated (Green, 1996; Green et al., 2000). While amotivation appears inextricably linked to the poor functional outcomes that characterize schizophrenia, our assessment strategies, and therefore our fundamental understanding of amotivation, relies on rudimentary clinical assessments. In the present paper, we argue for more rigorous neuroscience-driven assessments of effort, or deficits therein, in guiding our search for novel therapeutics. Specifically, we focus on amotivation as a cardinal symptom of schizophrenia, and how we may better understand this symptom, especially the neural substrates, if we adopt a translational viewpoint and conceptualize this symptom as reflecting, at least in part, an abnormality in effort cost computations.

2. Assessment of amotivation in schizophrenia

2.1. Clinical assessment of negative symptoms

Negative symptoms have figured prominently in historical descriptions of the phenomenology of schizophrenia (Bleuler, 1950; Kraepelin, 1919; Meehl, 1962; Rado, 1953). The construct of negative symptoms includes symptoms of blunted affect, avolition, asociality, anhedonia and avolition/apathy (Kirkpatrick et al., 2006). Notably, these symptoms are distinct from other domains of psychopathology such as psychosis, depression and cognition (Andreasen et al., 1995; Bell and Mishara, 2006; Harvey et al., 2006; Kopelowicz et al., 2008; Lewine, 1990; Marder et al., 1997; McGlashan and Fenton, 1992; Sergi et al., 2007). Furthermore, negative symptoms have been found to aggregate into two broader factors of diminished expression which includes symptoms of blunted affect and avolition, and amotivation which includes symptoms of asociality, anhedonia and avolition (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Messinger et al., 2011). This distinction between amotivation and diminished expression as separable negative symptom constructs is based, in part, on

evidence from numerous factor analytic studies (Emsley et al., 2001; Horan et al., 2011; Keefe et al., 1992; Kelley et al., 1999; Kimhy et al., 2006; Kirkpatrick et al., 2011; Kring et al., 2013; Liemburg et al., 2013; Malla et al., 2002; Minas et al., 1994; Mueser et al., 1994; Nakaya and Ohmori, 2008; Peralta and Cuesta, 1999; Sayers et al., 1996; Strauss et al., 2012; Toomey et al., 1997).

Historically, clinical rating scales have represented the primary source of outcome measures in psychiatry and the assessment of illnesses such as schizophrenia. In the case of schizophrenia, the Brief Psychiatric Rating Scale (BPRS) (Overall and Donald, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) are amongst the most common in assessing negative symptoms, although other scales have also been used less frequently (Earnst and Kring, 1997). Of note, none of these instruments were primarily developed to assess amotivation in schizophrenia; rather they include specific items that tap into the construct. For example, the SANS has two items within the avolition/apathy subdomain: (1) impersistence at work or school; and (2) physical anergia. These items are rated on a six-point ordinal scale based largely on frequency of reported activity. The SANS also includes an anhedonia/asociality subdomain that includes four items that are rated based partially on patients' recall of their experience of pleasure during recreational and interpersonal activities. Amotivation scores can be inferred from these two subdomains, as suggested by factor analytic studies noted above. Recently, the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition (MATRICS) initiative issued a consensus statement on negative symptoms, calling for newer instruments to assess those symptoms which build on advances in behavioural and clinical science and are better positioned to stimulate translational research (Kirkpatrick et al., 2006; Marder et al., 2011). In response to these concerns, newer scales are in the process of development (Kirkpatrick et al., 2011; Kring et al., 2013), although the incremental success of these novel instruments over the SANS in furthering our understanding regarding underlying neurobiology remains to be seen.

2.2. Clinical assessment of amotivation/apathy

While most of the aforementioned scales, with the exception of the BPRS, have been developed specifically for schizophrenia, other instruments not specifically designed for schizophrenia have been employed to measure amotivation. Most notably, Marin's Apathy Evaluation Scale (AES) (Marin et al., 1991), which was originally developed for patients with neurological insults, has shown adequate psychometric properties in individuals with schizophrenia (Faerden et al., 2008). This dimensional scale specifically assesses amotivation by reviewing patients' behaviours (example item: "S/He gets things done during the day") as well as internal motives

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