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Computational approaches to schizophrenia: A perspective on negative symptoms

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ABSTRACT

Schizophrenia is a heterogeneous spectrum disorder often associated with detrimental negative symptoms. In recent years, computational approaches to psychiatry have attracted growing attention. Negative symptoms have shown some overlap with general cognitive impairments and were also linked to impaired motivational processing in brain circuits implementing reward prediction. In this review, we outline how computational approaches may help to provide a better understanding of negative symptoms in terms of the potentially underlying behavioural and biological mechanisms. First, we describe the idea that negative symptoms could arise from a failure to represent reward expectations to enable flexible behavioural adaptation. It has been proposed that these impairments arise from a failure to use prediction errors to update expectations. Important previous studies focused on processing of so-called model-free prediction errors where learning is determined by past rewards only. However, learning and decision-making arise from multiple cognitive mechanisms functioning simultaneously, and dissecting them via well-designed tasks in conjunction with computational modelling is a promising avenue. Second, we move on to a proof-of-concept example on how generative models of functional imaging data from a cognitive task enable the identification of subgroups of patients mapping on different levels of negative symptoms. Combining the latter approach with behavioural studies regarding learning and decision-making may allow the identification of key behavioural and biological parameters distinctive for different dimensions of negative symptoms versus a general cognitive impairment. We conclude with an outlook on how this computational framework could, at some point, enrich future clinical studies.

1. General introduction

Schizophrenia patients often report inability to experience pleasure, withdrawal from social interactions, reduced ability to pursue meaningful goals, and they are characterized by a reduction in emotional and verbal expression. These negative symptoms have a high prevalence in schizophrenia patients with more than half of the patients displaying at least two of the PANSS items: blunted affect, emotional withdrawal, poor rapport, social withdrawal, or reduced verbal fluency (Bobes et al., 2010). Clinical records show that more than a third of patients are described as having poor motivation and blunted affect (Patel et al., 2015). Negative symptoms are important for functional outcome (Fervaha et al., 2013a, 2014; Galderisi et al., 2013, 2014) and considerably influence a patient's quality of life (Eack and Newhill, 2007). While the assessment of the domain of negative symptoms has improved considerably, our understanding of the underlying pathophysiological mechanisms still remains limited.

On a phenomenological level, negative symptoms such as anhedonia suggest a link with neurobiological systems underlying motivational and reward processes (Wise, 2008). Thus, the dopaminergic system, also referred to as the brain's reward system, is a likely candidate system on a biological level. Reward anticipation in the ventral striatum, a core dopaminoceptive region, during reward anticipation has been found to be associated with the degree of negative symptoms (Juckel et al., 2006b). However, there have also been reports of null findings (Esslinger et al., 2012), of an association between ventral striatal activation and positive symptoms (Nielsen et al., 2012b) or of correlations between negative symptoms and activation in dorsal rather than ventral subregions of the striatum (Mucci et al., 2015). Furthermore, evidence shows that antipsychotic treatment affects these ventral striatal signals (Juckel et al., 2006a; Nielsen et al., 2012a; Schlagenhauf et al., 2008). Interestingly, a recent meta-analysis of the available fMRI studies in schizophrenia patients confirmed a reduction of ventral striatal activation and supports an association with negative symptom severity (Radua et al., 2015). On the other hand, while elevated striatal

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dopaminergic function is still a cornerstone in our pathophysiological understanding of schizophrenia, it has primarily been associated with positive symptoms (Heinz and Schlagenhauf, 2010; Howes and Murray, 2014). The aberrant salience hypothesis links dopaminergic hyperactivity with the development of positive symptoms via an inappropriate attribution of salience to otherwise neutral stimuli or internal representations (Heinz, 2002; Kapur, 2003). Besides the striking evidence for an involvement of hyperdopaminergic state with psychosis and especially positive symptoms (Howes and Murray, 2014), findings also suggest a link between dopaminergic dysfunction and negative symptoms. For example, negative symptoms were demonstrated to be negatively associated with D2 receptor availability (Heinz et al., 1998). Further, change in D2 receptor availability due to dopamine depletion, mirroring lower dopamine concentration, was inversely correlated with negative symptoms (Kegeles et al., 2010). Moreover, the inability to differentiate relevant compared to irrelevant stimuli, as a measure of aberrant salience, was not only associated with delusion severity but also significantly correlated with negative symptoms in patients with schizophrenia (Roiser et al., 2009). An involvement of the dopaminergic reward system in the development of both negative and positive symptoms seems to require a dysregulation in opposite directions (with an overactivation related to positive symptoms and an underactivation contributing to negative symptoms) or a contribution of distinct subsystems to either symptom dimension (Ziauddeen and Murray, 2010).

Taken together, while evidence exists for dysfunctions in reward processing in schizophrenia, our understanding of how these relate to different aspects of psychopathology, in particular the different facets of negative symptoms, is still limited. It is noteworthy that there is shared variance of negative symptoms with well-known cognitive deficits of schizophrenia patients (Hartmann-Riemer et al., 2015; Strauss and Gold, 2012). A meta-analysis showed that dimensions of negative symptom dimensions are significantly but only modestly associated with cognitive deficits (effect sizes: −0.29 to −0.12, Dominguez et al., 2009). For example, a longitudinal study in first-episode schizophrenic patients revealed working memory performance to be a predictor of the degree of negative symptoms after a 5-year follow-up (Gonzalez-Ortega et al., 2013). As well as negative symptoms, cognitive deficits predict functional outcome (Bowie et al., 2008; Nuechterlein et al., 2011) and also the transition to schizophrenia (Fusar-Poli et al., 2012). Unfortunately still unrevised, conventional treatment strategies have largely failed to reduce working memory deficits and negative symptoms (Fusar-Poli et al., 2015; Hyman and Fenton, 2003; Lieberman et al., 2005). Accordingly, studies investigating associations between neurobiological measures and negative symptoms have not yet revealed a consistent pattern (Galderisi et al., 2015). Heterogeneity with regard to study design, sample characteristics and assessment of psychopathology may have contributed to this picture. For example, neuroimaging studies investigating reward anticipation and processing in schizophrenia often lack a detailed differentiation of negative symptom subdomains with some notable exceptions (Mucci et al., 2015). Psychometric research has defined different aspects of negative symptoms such as avolition, anhedonia, social withdrawal, reduced emotional and verbal expression (Kirkpatrick et al., 2006), which can be grouped into the factors avolition (including amotivation, anhedonia and asociality) and deficit of expression (including affective flattening and alogia) hypothetically arising from distinct pathophysiological mechanism. Nevertheless, a correlation between a certain symptom and a neurobiological measure in a particular sample does not allow any causal conclusions. For example, the presence (or absence) of an association might be due to other mediating factors or change over the course of the illness. This is further complicated by the fact that neuroimaging techniques like fMRI only provide limited mechanistic insights into the neurophysiological processes because they rely on proxy measures of neuronal activation, a problem we describe in more detail in Section 3 of this article.

In this review, we strive to demonstrate that computational approaches may help to characterize behavioural and neurobiological processes contributing to negative symptoms more precisely. In the emerging field of computational psychiatry (Huys et al., 2016; Montague et al., 2012; Stephan and Mathys, 2014; Wang and Krystal, 2014) the term 'computational' is used broadly. In this article, we follow a nomenclature as in Stephan et al. (2015) by using the "umbrella term" computational models. Further, Stephan et al. (2015) summarized three categories of computational models: 1) biophysical network models; 2) so-called model-based neuroimaging analysis building upon computational models of behaviour; 3) generative models of neuroimaging data. In this article, we include the latter two of these three categories since these models can be inverted (see comment in Section 3). In Section 2, we first review evidence for altered reinforcement learning and decision-making in schizophrenia and their putative contribution to understand the origin of negative symptoms focusing on the behavioural level. We then discuss in Section 3 an example of how mechanistic models of functional imaging data measured during a cognitive task revealed distinct biological subgroups with regard to severity of negative symptoms. In the final Section 4, we outline how model parameters carrying mechanistic information (as discussed in Sections 2 and 3) could enable a biological characterization and stratification of cognitive and motivational mechanisms contributing to negative symptoms.

2. Understanding flexible goal-directed decision-making: a potential origin of the formation of negative symptoms

It has been hypothesized that negative symptoms could arise from deficits in representing and using values for decision-making (Barch and Dowd, 2010; Gold et al., 2008). This notion has also received empirical evidence with particular noteworthy contribution from Gold, Waltz and colleagues (for reviews see: Gold et al., 2008; Strauss et al., 2014; Waltz and Gold, 2015). Schizophrenia patients are surprisingly unimpaired in hedonic ("in-the-moment") experiences (Barch and Dowd, 2010). For example, it was demonstrated that stable-medicated, chronic patients do not differ in ratings of affective pictures with respect to either motor responses to repeat or to endure viewing affective material (Heerey and Gold, 2007). Similar results were reported in other studies using similar affective picture material (Dowd and Barch, 2010; Pankow et al., 2013; Ursu et al., 2011) and have been confirmed by meta-analysis (Cohen and Minor, 2010).

Interestingly, and in contrast to these apparently intact in-the-moment experiences, schizophrenia patients are impaired in value-based decision-making. Using a probabilistic selection task in medicated chronic patients, Waltz et al. (2007) found an overall impairment in learning acquisition. Interestingly, however, in a novel post-acquisition test-phase, the preference for previously rewarded stimuli was weakened in patients compared to controls, but patients were able to avoid stimuli associated with negative outcome (Waltz et al., 2007). Following up this finding in medicated, chronic schizophrenia patients showed an overall Go-bias together with a deficit in Go-learning during a Go–NoGo learning task. Although patients were impaired in rapid trial-by-trial adaptation to negative feedback, they gradually learned from negative feedback. These findings were predicted by a neurocomputational model of learning in fronto-striatal circuits (Frank et al., 2004) when increasing presynaptic (tonic) dopamine input: high levels of presynaptic dopamine may specifically impair learning in Go-pathways via D1 receptors due to drowning of phasic dopamine bursts facilitating reward-approach behaviour. However, spared punishment avoidance may result either from D2 hypersensitivity or antipsychotic medication. This deficit in Go-learning together with relatively intact NoGo-learning was confirmed in a subsequent study and was most pronounced in patients with high levels of negative symptoms (Strauss et al., 2011). Interestingly, the same study also showed that schizophrenia patients had reduced uncertainty-driven explorative behaviour (by applying computational modelling of behaviour) and that this was specifically correlated with inter-individual differences in anhedonia. This points towards the possibility of separating specific dimensions of negative symptoms via