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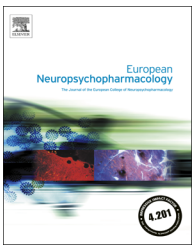

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Anhedonia, avolition, and anticipatory deficits: Assessments in animals with relevance to the negative symptoms of schizophrenia

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Abstract
Schizophrenia represents a complex, heterogeneous disorder characterized by several symptomatic domains that include positive and negative symptoms and cognitive deficits. Negative symptoms reflect a cluster of symptoms that remains therapeutically unresponsive to currently available medications. Therefore, the development of animal models that may contribute to the discovery of novel and efficacious treatment strategies is essential. An animal model consists of both an inducing condition or manipulation (i.e., independent variable) and an observable measure(s) (i.e., dependent variables) that are used to assess the construct(s) under investigation. The objective of this review is to describe currently available experimental procedures that can be used to characterize constructs relevant to the negative symptoms of schizophrenia in experimental animals. While negative symptoms can encompass aspects of social withdrawal and emotional blunting, this review focuses on the assessment of reward deficits that result in anhedonia, avolition, and abnormal reward anticipation. The development and utilization of animal procedures that accurately assess reward-based constructs related to negative symptomatology in schizophrenia will provide an improved understanding of the neural substrates involved in these processes.

1. Introduction

In recent years, research has advanced our understanding of the neural substrates that contribute to the neuropathology of schizophrenia. However, there is a distinct lack in our ability to effectively manage the domain of negative symptoms evident in many schizophrenia patients. The negative

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symptoms domain includes deficit symptoms that reflect a reduction of emotions or behaviors usually present in the healthy population, such as anhedonia, avolition, flat affect or emotional blunting, reductions of verbal fluency or poverty of speech, and defects in social behavior. This cluster of symptoms is largely unresponsive to current antipsychotic medications. The severity of negative symptoms has been suggested to impact and predict the functional and occupational outcome of schizophrenia patients (Ho et al., 1998; Kirkpatrick et al., 2006). Because of the detrimental effects of negative symptoms, coupled with the unmet therapeutic need in addressing this symptomatic domain, much research in recent years has focused on improving the understanding and treatment of negative symptoms associated with schizophrenia (Kirkpatrick et al., 2006).

The purpose of the present review is to describe experimental animal procedures that allow investigators to evaluate constructs thought to be central to the negative symptomatology of schizophrenia. Various experimental manipulations used to induce deficits in reward processes will be discussed briefly, but the focus will be primarily on describing the specific behavioral tasks used to characterize these deficits. Anhedonia, avolition, emotional blunting, alogia, and social withdrawal all fall under the umbrella that encompasses negative symptoms. Some of these features may not be mutually exclusive (e.g., avolition may promote social withdrawal), and some are difficult to assess in animals (e.g., emotional blunting and alogia). Procedures that model social withdrawal in experimental animals are reviewed elsewhere in this Special Issue (Koenig et al., in this issue).

2. Reward deficits and anhedonia in schizophrenia patients

Anhedonia refers to the inability or diminished capacity to experience pleasure and is thought to reflect deficits in brain reward system function. Anhedonia has long been suggested to be a core symptom of schizophrenia, falling within the cluster of features that encapsulates the negative symptomatology associated with schizophrenia. Anhedonia was originally described by Kraeplin in his first descriptions of dementia praecox (later come to be known as schizophrenia) as a central component of the disorder (Kraepelin, 1921; Bleuer, 1924; Strauss and Gold, 2012), and it is included as a symptom in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-V*) (American Psychiatric Association, 2013). The definition of anhedonia is sometimes extended incorrectly to encompass additional deficits in reward-related processes, such as the pursuit of pleasure. This extension of the definition of anhedonia should be avoided because the ability to experience pleasure and the desire to engage in pleasurable activities are subserved by distinct neural pathways (Berridge and Robinson, 2003; Der-Avakian and Markou, 2012) and should be treated as separate constructs. Interview-based measures or self-report style questionnaires are often used to assess anhedonia in schizophrenia patients. However, it has been suggested recently that schizophrenia is not associated with diminished capacity to experience pleasure per se (Horan et al., 2006), but rather may reflect deficits in other components of the reward system. Deficits in brain reward function are multifaceted and can include other features in addition to hedonic capacity, such as altered reward prediction, anticipation or valuation. Deficits in any one of these processes may lead to a reduction in the engagement of pleasurable activities, even when the individual still has the capacity to experience pleasure. Given the dissociation between anhedonia and other deficits of brain reward systems, anhedonia may not be as central to schizophrenia as it was once thought to be. Schizophrenia patients have been reported to indeed have the ability to experience affective consummatory pleasure (Gard et al., 2007; Heerey and Gold, 2007), indicating that schizophrenia patients are not necessarily anhedonic. Rather, these patients may have a dissociation of hedonic capacity from motivated behavior (Heerey and Gold, 2007), deficits in reward anticipation (Dowd and Barch, 2012; Gard et al., 2007), and/or a reduced ability to draw upon memories of previous pleasurable activities (Simpson et al., 2012). Deficits in accurately recalling previously pleasurable activities or predicting pleasure from future events likely gives the impression of a global reduction of the capacity to experience pleasure. As a result, these deficits may elicit the false impression of anhedonia, reflected in interview-based questionnaires, while not necessarily being attributable to deficits in the pleasure systems of the brain that mediate hedonic reactions.

3. Motivational deficits and avolition in schizophrenia patients

Like anhedonia, a deficit in motivational capabilities, or avolition, is also a symptom included in the original descriptions of schizophrenia (Kraepelin, 1921; Foussias and Remington, 2010). Deficits in a patient's ability to become motivated and engage in a given task has been suggested to considerably affect their quality of life, leading to a reduced drive to initiate or persist in goal-directed behavior (Barch and Dowd, 2010). Moreover, the severity of these deficits is believed to be closely correlated with the functional outcome of schizophrenia patients (Simpson et al., 2012). In fact, reductions of volition or impairments in the patient's motivational capabilities have been suggested to be not only one of the most disabling facets of schizophrenia but is also likely to underpin some of the accompanying negative symptoms, such as social withdrawal, and cognitive impairments associated with schizophrenia (Brebion et al., 2009).

To address this fundamental aspect of negative symptomatology and understand the process of avolition, one must explore the factors that drive an organism to become motivated. Reward processing has many facets, including aspects of learning, reward valuation, emotional or affective factors, and purely motivational components (Berridge and Robinson, 2003; Gold et al., 2008). Two of these elements may be particularly important to motivated behavior. First is the affective component. If an organism derives pleasure from something, then it is more likely to expend energy to obtain it (Salamone, 2009). Thus, consummatory pleasure is conducive to motivation because it provides the hedonic component that drives motivated behavior. However, as described above, evidence suggests that the hedonic reactions to evoked stimuli are unimpaired in schizophrenia, and