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Male rats treated with subchronic PCP show intact olfaction and enhanced interest for a social odour in the olfactory habituation/dishabituation test

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ABSTRACT

The olfactory system participates in many sensory processes, and olfactory endophenotypes appear in a variety of neurological disorders such as Alzheimer's and Parkinson's disease, depression and schizophrenia. Social withdrawal is a core negative symptom of schizophrenia and animal models have proven to be invaluable for studying the neurobiological mechanisms and cognitive processes behind the formation of social relationships. The subchronic phencyclidine (PCP) rat model is a validated model for negative symptoms of schizophrenia, such as impaired sociability. However, the complete range of social behaviour and deficits in the model are still not fully understood. Intact rodent olfaction is essential for a wide range of social behaviour and disrupted olfactory function could have severe effects on social communication and recognition. In order to examine the olfactory ability of male rats treated with subchronic PCP, we conducted an olfactory habituation/dishabituation test including both non-social and social odours. The subchronic PCP-treated rats successfully recognized and discriminated among the odours, indicative of intact olfaction. Interestingly, the subchronic PCP-treated rats showed greater interest for a novel social odour compared to the saline-treated rats and the rationale remains to be elucidated. Our data indicate that subchronic PCP treatment does not disrupt olfactory function in male rats. By ruling out impaired olfaction as cause for the poor social interaction performance in subchronic PCP-treated rats, our data supports the use of NMDA receptor antagonists to model the negative symptoms of schizophrenia.

1. Introduction

The neuronal circuitry involved in social behaviour is immensely complex and normal social interactions require a high degree of flexibility, making social behaviour especially vulnerable to disruption [1]. Animal models have proven to be invaluable tools for studying the neurobiological mechanisms and cognitive processes behind the formation of social relationships [2]. Social interaction deficits and social withdrawal are crucial early indicators for autism [3], core behavioural symptoms of schizophrenia and important readouts in animal models of negative symptoms of schizophrenia [4,5].

Rodents utilize olfactory cues for a wide range of social behaviours, including recognition of individuals and for the expression of appropriate sexual behaviours [6,7,2]. Blockade of olfactory social cues by anosmia or hyposmia would hence have major impact on rodent social behaviour by making it impossible for the animal to differentiate and recognize individual conspecifics. Therefore, to prevent data misinterpretation it is vital to verify normal olfactory function in animals used for tests with an odour component, such as social interaction, recognition and novelty preference tests [3,7,8].

The olfactory habituation/dishabituation test represents a simple yet sophisticated method for assessment of olfactory function in rodents [9]. The olfactory habituation test relies on the animals' tendency to investigate novel odours. It evaluates the animals' ability to detect, recognize, and differentiate between odours, including both non-social and social odours. It also assesses olfactory responsiveness and the capacity to habituate to the odours, as defined as a progressive decrease in olfactory investigative behaviour over sequential trials. Dishabituation on the other hand, implies that the animal can recognize a novel olfactory stimulus and show reinstated interest and investigation of the new odour [10,7].

The olfactory system participates in sensory functions, emotionality and in memory formation [11]. Hence, not surprisingly, olfactory endophenotypes appears in several neurological disorders like Alzheimer's disease (AD), Parkinson's disease (PD), depression and schizophrenia [12–14]. In many neurodegenerative disorders, particularly AD and PD, dysfunction of the olfactory system represents one of the earliest symptoms of the disorder [15,16]. In schizophrenia, patients often demonstrate reduced odour detection threshold and odour identification ability [17]. Accumulating evidence furthermore suggests that

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social dysfunction and the well-described smell identification deficits (SID) share a common pathophysiology. Especially patients with deficit syndrome schizophrenia (characterized by severe and enduring negative symptoms, including disturbed social functioning; particularly reduced social drive) has been associated with more SID [18–21].

The subchronic phencyclidine (PCP) rat model represents a validated pharmacological model with relevance for the negative symptomatic in schizophrenia, especially social withdrawal [22–26]. Subchronic PCP treatment reliable induces social interaction deficits in rats, when they are tested in the low-anxiety-test version of the social interaction test following a drug-withdrawal phase [27,28, for review on the social interaction test, see 29].

Surprisingly, the effect of subchronic PCP on sociality is nonetheless explained in regards of which social behaviour deficit that causes the reduced interaction [30]. It has been suggested that social withdrawal [28] or lack of social approach resulting from a lack of social motivation [30] in the subchronic PCP rat, causes the reduced interaction in the dyadic social interaction test. However, these parameters are principally indistinguishable from each other in the social interaction test setup and other processes such as impaired social cognition cannot be assessed [26]. Some studies have therefore aimed to disseminate the social deficits in the subchronic PCP rat model using the sociability and preference for social novelty paradigm. However, this test can measure either social motivation or lack of social cognition, hence producing ambiguous results [31,26].

To further extend our understanding of the complex neurobiology of the negative symptoms and social impairments seen in schizophrenia, we need to first understand the animal models we use [32,33]. Explicitly ruling out the presence of basic sensory abnormalities, such as anosmia, in the subchronic PCP model is therefore of utter importance. There is however a striking lack of publications on olfactory function in PCP-treated animals. The effect of acute PCP on odour detection was investigated in 1981 by Kesner [34], who found profound disruptions after injections of 12, 16 and 24 mg/kg PCP in male rats. For subchronic PCP-treated rats however, the literature is scarce of tests explicit for olfactory function. Nonetheless, Seillier and Giuffrida [26] who used a modified version of the sociability and preference for social novelty test [3,35], did include a two-phase social odour discrimination task to control for olfactory sensory function and the ability of PCP-treated rats to discriminate between neutral and social odours. During the task each rat could investigate petri dishes containing either clean bedding, dirty bedding from the familiar home cage, dirty bedding from a cage with unfamiliar rats or no bedding at all. The result showed that both PCP and vehicle treated rats preferred the quadrants where the social odours were contained, and the authors interpreted this as a sign of intact olfactory function. However, both the PCP and vehicle rats failed to show preference for the novel smell of dirty bedding from the unfamiliar cage and the lack of novelty preference was interpreted as a sign of deficient recognition memory, similarly to the deficit seen in PCP-treated rats during the novel object recognition task [26]. Nonetheless, the novelty preference deficit was equally evident in both the PCP- and vehicle treated groups, and this could indicate a methodological problem, such as the bedding not being soiled enough to enable the rats to detect the novel odour or due to a high degree of overlapping elements present in the stimuli, such as food or the bedding material itself.

Furthermore, other studies implicitly investigated olfactory function after subchronic PCP treatment as they used odours in the attentional set shifting task and found no impairments in intradimensional shifts between odours, indicating intact olfactory function [36–39]. Sahin et al. [32] used two newly developed preclinical tests for the often-neglected domain “blunted effect”, to assess anticipatory motivation and affective state. In the optimistic- and affective-bias tests, female rats treated with subchronic PCP, were trained to associate cues and odours with high-valued and less-valued rewards. The results showed that subchronic PCP-treated rats performed fewer optimistic choices during the optimistic-bias test and that PCP-treatment diminished the ability of the rats to form a preference for any of the reward-containing bowls during the affective-bias test, implicating a lack of a positive affective state [32].

In both the above-mentioned tasks, an association between an odour and a food reward was formed; meanwhile Audet et al. [40] used a cat odour to investigate the emotional response and anxiety when rats treated with subchronic PCP were exposed to the smell of a predatory threat. The result showed that the PCP-treated rats sniffed the cat collar significantly less than the vehicle treated rats, what the authors concluded an effect of heightened anxiety in the PCP-treated rats as these also spent more time inside the dark compartment during the emergence test for anxiety [40].

To our knowledge, there is no previous study investigating the effect of subchronic PCP on the performance of rats in the olfactory habituation/dishabituation test. We recently showed that subchronic PCP treatment significantly reduced the time spent in social interaction with an unfamiliar conspecific rat. The previously performed social interaction test was part of a recent drug-treatment study in our lab [41] in which the rats tested for olfactory function here, served as the positive (subchronic PCP-treated) and negative (subchronic saline-treated) controls.

With the aim to further disseminate the subchronic PCP rat model and validate the absence of anosmia or hyposmia, we performed the olfactory habituation/dishabituation experiment presented here, three days after completion of the social interaction test.

The results from the olfactory habituation/dishabituation test have important implications for several previously performed, and future studies on the social behaviour in the subchronic PCP rat model. Finally, these data are important to verify that the social interaction deficit in subchronic PCP-treated rats is not merely a consequence from deficient olfactory function, but truly mimic the complex negative symptoms of schizophrenia.

2. Experimental procedures

2.1. Animals

The olfactory habituation/dishabituation experiment was carried out with 16 male Sprague-Dawley rats (Élevage Janvier, Le Genest Isle, France) with mean weight 450 g at 10 weeks of age. Groups of three to four rats were housed together in standard type open-top IV polycarbonate cages (Ehret, Emmendingen, Germany) under standard laboratory conditions (room temperature 22 ± 2 °C; relative humidity 55 ± 10%). The cages were enriched with metal tubes and paper tissues. Water and food (standard laboratory chow; Ssniff, Soest, Germany) were available ad libitum. The lightning followed a 12 h light-dark schedule (light on at 6 a.m.) and all experiments were conducted during the first half of the light phase (between 9 a.m. and 2 p.m.). The animals were permitted one week of habituation to the premises before being gently handled by the person performing the experiments during the second week (5 min/day). The Berlin State Authority (“Landesamt für Gesundheit und Soziales”) approved all experimental procedures and they were performed in compliance with the German Animal Protection Law and the EU Directive 2010/63/EU for animal experiments.

2.2. Drugs and treatment regime

We recently established the subchronic PCP model in our laboratory in order to study the effect of a novel antipsychotic drug on PCP-induced social interaction and object recognition deficits [previously published data see, 41]. Therefore, we conducted pilot experiments and studied the effect of different doses subchronic PCP (2.0 or 5.0 mg/kg) with different washout period lengths (1, 2 or 6 weeks) on behavioural test performance. In our laboratory setting and for both above-mentioned test paradigms, the most robust deficits were detected after the