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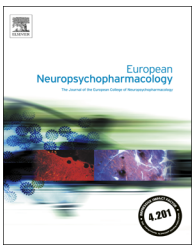

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Re-evaluating the PCP challenge as a pre-clinical model of impaired cognitive flexibility in schizophrenia

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Abstract
NMDA-R antagonists are a popular translational pharmacological challenge to induce cognitive deficits associated with schizophrenia. Amongst their many cognitive and non-cognitive effects is an ability to impair cognitive flexibility in general, and reversal learning in particular. Here, we test the hypothesis that the NMDA-R antagonist phencyclidine when given acutely selectively effects reversal learning by simultaneously measuring reversal learning and baseline responding, or acquisition and baseline responding, under identical conditions. Animals were trained to simultaneously perform two different visual discriminations in a touch-screen equipped operant box. Accordingly the reward contingencies associated with one pair could be altered, while the second pair acted as an experimental control. As such, the effect of a manipulation on reversal learning, stimuli acquisition, or baseline responding can be more accurately evaluated through the use of a double visual discrimination. A similar approach was also used to investigate the influence of sub-chronic phencyclidine administration on cognitive flexibility. Phencyclidine (1 mg/kg) given before testing caused a slowing in acquisition and reversal learning, while having a minimal effect on secondary measures. Sub-chronic phencyclidine administration had no significant effect on any of the measures used within this study. While acute phencyclidine impairs reversal learning, it is clear from these results that other aspects of cognition (learning/relearning) are also impaired, potentially questioning the specificity of acute phencyclidine in conjunction with reversal learning paradigms as a model of impaired cognitive flexibility.

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1. Introduction

A well-established body of literature has demonstrated that NMDA-R antagonists, such as phencyclidine (PCP), ketamine, and MK-801 can be used to induce cognitive impairments and model specific aspects of schizophrenia (Gilmour et al., 2012). NMDA-R antagonists, when combined with reversal learning paradigms have proven particularly popular as a means to model deficits in cognitive flexibility in schizophrenia (as examples see Neill et al., 2010; Jentsch and Taylor, 2001; Gastambide et al., 2013a,b). It is well established that the NMDA receptor plays a key role in the process of long term potentiation, and that LTP can be inhibited by acute blockade of the NMDA receptor (Collingridge et al., 1988a,b; Bliss and Collingridge, 2013), giving rise to various transient cognitive deficits (Morris et al., 1986, Gilmour et al., 2012). Importantly, acute ketamine is also used in clinical studies to induce schizophrenia like symptoms. NMDA-R antagonists in general, and ketamine in particular, may serve as a model of cognitive impairment that may translate across species (Gilmour et al., 2012). However interpretation of the effects triggered by acute administration of NMDA-R antagonists can be difficult owing to the variety of processes that may be disrupted, the variety of assays used to test these potentially disrupted processes, as well as the variety of dosing regimens used to induce these impairments. Moreover the use of acute NMDA-R antagonists is potentially further complicated by the fact that these compounds can also induce non-specific changes like ataxia or hyper-locomotion at concentrations near, or actually overlapping, with those used to induces cognitive changes (Gilmour et al. 2009, Dix et al., 2010; Smith et al., 2011). As such it is difficult to distinguish what is a cognitive impairment, from a non-selective effect, on behavior.

An alternative to acute NMDA-R challenges is the use of a sub-chronic NMDA-R antagonist challenge. In this approach an NMDA-R antagonist is administered for several consecutive days resulting in changes in the brain and behavior days, and even weeks, after administration of compound has stopped (for review see Jodo, 2013). Like an acute NMDA challenge, this manipulation is thought to cause changes to a brains function that may mirror some aspects of schizophrenia. Unlike the use of acute NMDA-R antagonists, the animals are not tested under the influence of a challenge drug removing the possibility of acute drug/drug interactions. While perhaps less well described than the effects of acute NMDA-R challenges, sub-chronic administration of PCP (generally 5–10 days, once or twice a day, depending upon the regime), has on numerous occasions been shown to disrupt reversal learning in an operant environment (Idris et al., 2010, McLean et al., 2009,2010, 2011, and others), while in general it is not thought to influence task acquisition. However the variety of dosing regimens used, and the potentially transient nature of the manipulations make it extremely difficult to determine the selectivity of this manipulation across behavioral paradigms and cognitive domains.

The ability to dissociate cognitive processes is particularly germane to reversal learning. When measured in the rodent using operant paradigms reversal learning is often a slow process that can take hundreds of trials and days to complete. While reversal learning may be used to measure cognitive flexibility, successful reversal learning is likely dependent upon multiple facets of cognition such as procedural memory, attention, sensitivity to reward, as well as learning in general. As such a change in reversal learning performance cannot be conclusively linked to a change in cognitive flexibility unless this effect is happening in isolation of changes to other measures. While controlling for these various measures may sound straightforward, it is in fact very difficult to achieve within a standard operant box owing to a paucity of stimulus variety. However the touch-screen approach circumvents this problem by allowing multiple stimuli to be used within a single testing session. By using two pairs of stimuli within the same modality and requiring the animals to perform two visual discriminations, as demonstrated here, it is possible to measure an animal's discriminative abilities on a learned pair, while simultaneously measuring the learning of the contingencies associated with a second pair of stimuli, without potential confounding effects due to different sensory sensitivities. As such the influence of non-specific processes can be better evaluated. For example an animal can be trained to a steady state of behavior on two sets of stimuli and then tested under a condition where one set of contingencies is reversed while the other stays the same. With such an approach the unaltered pair serves as an excellent control for any non-specific effects that may be influencing reversal learning. A similar approach can also be used for acquisition of a stimulus pair, where an animal could first be trained on "pair 1" until steady state behavior was achieved, and then tested while performing the original discrimination and simultaneously learning the second discrimination. In this way it may be easier to separate true "cognitive" effects from non-selective effects that may impair performance and thus present themselves as deficits in cognition. This is particularly germane when using pharmacological models of cognitive impairment, as higher doses consistently cause non-specific effects (for a review of NMDA antagonists, and the muscarinic antagonist scopolamine see Gilmour et al., 2012; and Klinkenberg and Blokland, 2010).

Little is known about the influence of NMDA receptor antagonists on acquisition or reversal of a visual discrimination. Talpos et al. (2012) have shown that acute administration of MK-801 or PCP is capable of inducing a small but selective impairment in performance of a visual discrimination, an effect not seen with other NMDA receptor antagonists. Similarly Winters et al. (2010) showed that administration of the NMDA receptor antagonist APV into the perirhinal cortex could impair task acquisition, albeit, with stimuli that may be more "perceptually challenging" then those typically used in a touch-screen setting. Accordingly we predict that when given acutely via a systemic injection, acute PCP (aPCP) will impair acquisition and reversal, although it is unclear if this effect will occur in the absence of non-specific effects, like increased latency to respond to the screen, or impairments in baseline responding. While little is known about the effects of acute NMDA-R antagonists in a touch-screen setting, even less is known about the influence of sub-chronic models of NMDA-R induced cognitive impairment. Till date one study, in the mouse, has been published looking at the influence of sub-chronic NMDA-R antagonists in a touch-screen based visual