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Review

A novel visuospatial priming task for rats with relevance to Tourette syndrome and modulation of dopamine levels

Nurith Amitai[1], Martin Weber[1,2], Neal R. Swerdlow, Richard F. Sharp, Michelle R. Breier, Adam L. Halberstadt, Jared W. Young*

Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804, USA

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ABSTRACT

Individuals with Tourette syndrome (TS) exhibit deficits in inhibitory information processing which may reflect impaired neural mechanisms underlying symptoms and which can be detected using a negative priming (NP) task. NP is the normal reduction of performance when identifying target stimuli that appear where non-target stimuli appeared previously. TS subjects exhibit diminished NP and their NP levels predict their response to behavioral therapy. Here we review relevant literature on this issue and also report a novel rat NP task. In the latter, rats respond to target stimuli (continuous light) while ignoring non-target stimuli (blinking light). Each trial was preceded by a prime in which target and non-target stimuli were briefly presented. Performance was challenged by shortening prime duration and by administering amphetamine. During the short prime challenge, rats exhibited lower accuracy in NP vs. baseline trials, indicative of inhibitory information processing. Modulation by amphetamine administration indicates that this drug had rate-dependent effects. Evidence is provided of individual differences in NP and response to the drug, with priming being reduced in high NP rats, while it was increased in low NP subjects. The rat NP task represents a novel and suitable tool for investigating the neural bases of inhibitory information processing and its dysfunction in TS.

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1. Introduction

The capacity to automatically inhibit or modify motor responses to sensory stimuli is crucial for proper goal-directed behavior. Conversely, impairments in inhibitory information processing, defined as the ability to suppress reactions to irrelevant or inappropriate information, may contribute to symptoms of conditions

* Corresponding author. Tel.: +1 619 543 3582; fax: +1 619 735 9205.
E-mail address: jaredyoung@ucsd.edu (J.W. Young).
[1] These two authors contributed equally to this work.
[2] Present address: Neurodegeneration Labs, Department of Neuroscience, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA.

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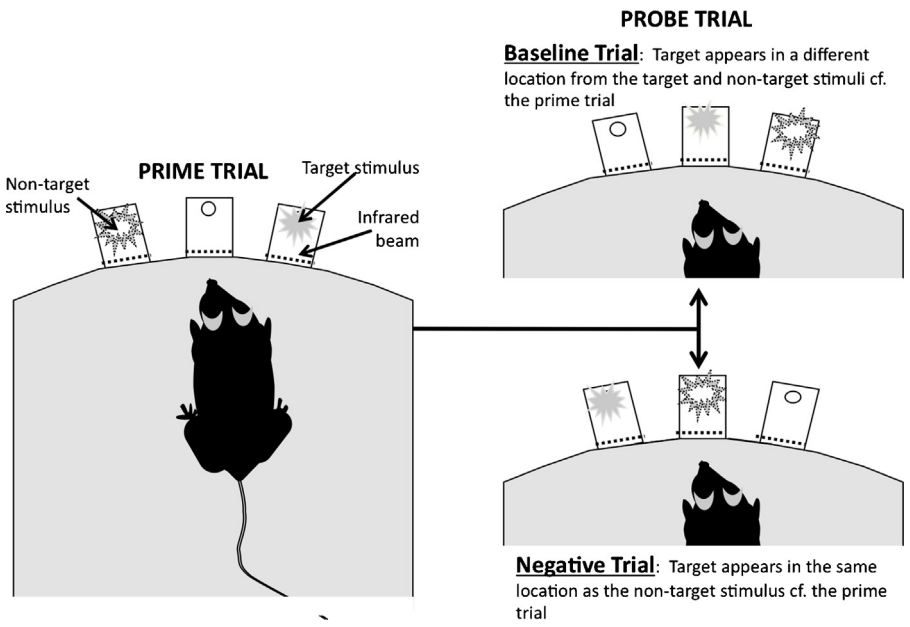

Fig. 1. Task schematic for the negative priming task exemplifying the different trial types. Training and testing are conducted in 9-hole operant testing chambers enclosed in ventilated sound-attenuating chambers (Med Associates Inc., St. Albans, VT and Lafayette Instrument Company, Lafayette, IN). Each testing chamber contains a curved rear wall with nine contiguous apertures. Metal inserts cover six of the apertures, leaving open apertures 3, 5, and 7, so that the rodent faces a curved wall with three equidistant apertures. Each aperture contains an infrared beam at the entrance to detect nosepoke responses and a LED stimulus light at the rear to present stimuli. Liquid reinforcement in the form of strawberry milkshake (Nesquik® plus non-fat milk, 40 μl) can be delivered into a magazine located in the opposite wall via peristaltic pump; an infrared beam detects head entries into the magazine. A house light is located in the middle of the chamber ceiling. The control of stimuli and recording of responses is managed by a SmartCtrl Package 8-In/16-Out with additional interfacing by MED-PC for Windows (Med Associates Inc., St. Albans, VT) using custom programming. During the prime trial, the target stimulus (continuous light) and the non-target stimulus (5 Hz flashing light) are briefly presented simultaneously in pseudorandom locations. After a short period of time (interstimulus interval), a probe trial follows. In the case of a *baseline trial*, the location of the target stimulus in the probe trial is unrelated to the location of either stimulus in the prime trial. In the case of a *negative priming trial*, the target stimulus in the probe trial is located in the same aperture that contained the non-target stimulus during the preceding prime trial.

characterized by repetitive or otherwise disordered stimulus-driven behaviors. For example, such inhibitory deficits may underlie both the premonitory urges and the motor and vocal tics in Tourette syndrome (TS). Deficient inhibitory information processing is also apparent in other neuropsychiatric disorders, such as schizophrenia and obsessive-compulsive disorder, and may contribute to cognitive and behavioral abnormalities in these conditions.

Unlike motor and vocal tics, information processing can be operationally assessed in specific laboratory measures. For example, a visuospatial priming task measures the ability of a subject to respond to a target stimulus while ignoring a non-target distractor stimulus. Performance during a given "probe" trial is evaluated in the context of the location of cue stimuli in the preceding "prime" trial. When the target stimulus in a probe is presented in the same location as the non-target stimulus in the preceding prime ("negative priming trial"), healthy subjects exhibit slower reaction times and lower accuracy compared to probes in which target location is unrelated to non-target location during the prime ("baseline trial") (Tipper, 1985, 2001). Possible explanations of this negative priming (NP) phenomenon include the activation of inhibitory processes that suppress attention to the location of the non-target stimulus; in an NP trial, the individual must then activate a previously inhibited strategy in order to attend to, and respond in, the location that previously held the non-target stimulus. An alternative theory postulates the formation of a "memory trace" of the location holding the non-target stimulus marking this location as inappropriate for responding; in an NP trial, presentation of the target stimulus in this location during the probe triggers retrieval of this "do not respond" memory trace, which impairs response in this location (Tipper, 1985, 2001).

Negative visuospatial priming is significantly reduced in TS subjects (Deckersbach et al., 2006; Swerdlow et al., 1996), and the severity of NP deficits in TS patients correlates significantly with the therapeutic impact of habit reversal therapy (Deckersbach et al., 2006), an effective behavioral treatment for TS (Azrin and Peterson, 1988; Piacentini et al., 2010). This finding suggests that NP deficits may reflect neural mechanisms that are intrinsically linked to TS symptoms (Wright et al., 2006, 2005), and that NP may be useful for predicting the therapeutic potential of interventions, including pharmacological treatments, for TS. Conceivably, treatments that normalize NP might also target other disorders characterized by impaired inhibitory processing and reduced NP, such as schizophrenia (Elkins and Cromwell, 1994).

No rodent paradigm measuring negative visuospatial priming has been reported. Such a paradigm would facilitate the systematic, controlled investigation of the neural mechanisms underlying inhibitory information processing and enable the generation of animal models of inhibitory deficits relevant to TS. A predictive animal model of NP might also allow for the development of novel TS medications; conceivably, NP-enhancing medications might directly reduce TS symptoms, or – based on the relationship reported by Deckersbach et al. (2006) – enhance the therapeutic impact of behavioral therapies. In this study, we aimed to describe the characteristics and heuristic values of a novel rat negative visuospatial priming paradigm (Fig. 1), based on a well-established human visuospatial priming task (Swerdlow et al., 1996; Tipper, 1985). Because dysfunction of dopaminergic signaling has been implicated in both the pathophysiology of TS (Albin et al., 2003; Leckman et al., 2010) and the mediation of visuospatial priming (Swerdlow et al., 1997; Wylie and Stout, 2002; Yamaguchi and Kobayashi, 1998), we also report on the impact on NP of modulation of dopaminergic