Spatial Working Memory Under Differential and Nondifferential Outcomes: Effects of Dextromethorphan

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Introduction:

Trapold (1970) found that, in a biconditional discrimination task, subjects who were trained with unique and distinct outcomes following each discriminative stimulus-response (S-R) sequence acquired the task in significantly fewer trials than those subjects for whom only one outcome was employed. This training procedure, referred to as differential outcomes (DO), is shown in Figure 1, along with the more traditional common outcomes (CO) procedure where only one outcome is employed, or a nondifferential outcomes (NDO) procedure where two outcomes are employed but the outcome presented after each S-R sequence is random.

Common Outcomes	Differential Outcomes	Nondifferential Outcomes
S1 --> R1 --> O1 S2--> R2 --> O1	S1 --> R1 --> O1 S2--> R2 --> O2	S1 --> R1 --> O1 or O2 S2--> R2 --> O1 or O2

Figure 1: training procedure for common, nondifferential, and differential outcomes

This improvement in performance, called the differential outcomes effect (DOE) is also seen across delays as an improvement in working memory; that is, subjects trained under DO perform with greater accuracy across delays, even at delay intervals where subjects trained under CO or NDO are performing at near chance levels. This DOE is strong enough to allow subjects to overcome the effects of amnestic drugs and lesions designed to mimic the effects of Korsakoff's syndrome (Savage, 2008).
The difference in performance may be due to the separate procedures engaging different forms of memory. To solve a choice task under CO or NDO, subjects must remember the discriminative stimulus presented at the beginning of the trial using retrospective memory. However, we theorize that subjects under DO develop outcome-specific expectancies of the specific outcomes associated with each sample and it is these prospective memories of what is to come (rather than memory of what has already happened) that guides behavior on any given trial (Holden and Overmier, 2015). These retrospective and prospective codes may well be mediated by different memory systems in the brain, dependent on different classes of neurotransmitters and different areas of the brain (e.g. frontal lobes and limbic system). Our laboratory has conducted a series of pilot studies examining how a number of drugs linked to memory influence behavior under DO and NDO in the hopes of establishing neurochemical similarities and differences between the two systems.

Dextromethorphan (DXM), as stated by Scholar (2007), is an effective antitussive agent for treating uncomplicated, non-productive coughs. DXM is an N-methyl-D-asparatate receptor (NMDA) antagonist, which when put into effect inhibits the glutamate-induced excitation and excitotoxicity in the CNS and spinal regions (Scholar, 2007; Chez, Kile, Lepage, Parise, Benabides, and Hankins, 2018). In the treatment of coughs, the drug is able to suppress the cough reflex by elevating the cough threshold in the medulla (Scholar, 2007). It is available over the counter and has been cited as a safer alternative to the cough suppressant codeine due to its production of less gastrointestinal disturbances and drug dependence and abuse (Scholar, 2007). However, because of its accessibility, drug abusers often mix DXM with drugs like heroin and morphine to increase pharmacological effects and decrease their drug dependency. In a recent study, evidence of DXM creating a psychological dependency was found in 46.5% of drug abusers studied (Ziaee, Hamed, Hoshmand, Amini, Kebriaeizadeh, and Saman, 2005).

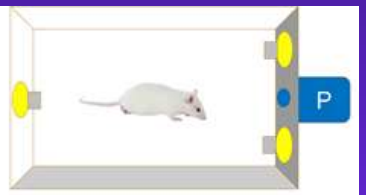
Adverse side-effects of DXM include drowsiness, fatigue, dizziness, psychotic reactions, slurred speech, and light-headedness. The elderly population are most at risk for experiencing these symptoms due to the heavy push of sales of drugs like Neudextra, a dextromethorphan and quinidine prescription originally created for the treatment of pseudobulbar affect, being expanded to treat symptoms in patients who have dementia and Alzheimer's disease (Ellis & Hicken, 2017). These previous studies and side effect evidence make us believe that dextromethorphan would interfere heavily with the working memory system when taken. Thus, we hypothesize that dextromethorphan would have adverse effect on the memory system, causing a significant decrease in task accuracy and differential outcome effects when compared to placebo trials.

Savage (2001) had previously presented evidence suggesting greater involvement of glutaminergic NMDA receptors in memory under DO than under NDO using the NMDA receptor antagonist MK-801 (dizocilpine). Should this be the case, we should expect to see other NMDA receptor antagonists (i.e. dextromethorphan) have stronger effects on working memory under DO than under NDO. As such, we hypothesized that DXM would significantly impair working memory under DO but not under NDO.

Subjects and Methods:

Subjects were 15 male Sprague-Dawley rats, approximately 4 months old at the beginning of the study. Subjects were housed under a reversed 12:12 light:dark cycle with lights off at 1000, with water available freely. Subjects were reduced to 85% of their free-feeding weight shortly before training began. Subjects were magazine-trained and autoshaped to press the three retractable levers before beginning the matching-to-position task.

Figure 2. Depiction of the operant chamber setup (right = front, left = back). P = pellet feeder.



Matching-to-Position:

Sessions ran for 80 trials in operant chambers, as described in figure 2. At the beginning of each trial, the stimulus above either the left or right lever is illuminated and that lever is extended into the chamber; this is the discriminative stimulus. Two responses on the illuminated lever have the effects of extinguishing this light, retracting the lever, and extending, and illuminating the light, over the back wall lever. For the trial to progress, the subject must then turn to the back wall lever and press. (This is done to ensure subjects do not bridge a delay period by merely remaining in front of the correct lever.) The first response after a 1-second delay period leads to the extinguishing of the back light and the illumination of both left and right lever lights.

The subject's task is now to press the same lever that was illuminated in the first part of the trial. Correct responses are rewarded with either a) three sucrose pellets accompanied by illumination of the feeder light and a 1 sec train of 8 clicks/second from the clicker (the "large" outcome) or b) three 0.5 sec flashes of the feeder light, followed by a single pellet (the "small" outcome). For subjects in the DO group (n=8), each stimulus-response sequence was consistently followed by a specific outcome (e.g. left-left-small & right-right-large or left-left-large & right-right-small). For subjects in the NDO group (n=7), outcomes were random. Incorrect responses lead to a repeating of the trial; three incorrect responses in a row leads to a repeating of the trial, but with only the correct lever illuminated at the end of the trial (a forced choice procedure). Only the initial choice on each trial is included in overall calculations of accuracy.

Once subjects learned this task to criterion (3 consecutive days at 85% accuracy or above), they were switched to a delayed version of the task, where the delay period between the illuminating of the back wall light and the time when the trial could be advanced was set to 1, 5,10, or 20 seconds on any given trial. After meeting criterion on this task (3 straight days of 85% or above at 1-second delay and 70% or above at 5-sec delay), subjects began drug testing. Previous to this set of tests, subjects had been exposed to intraperitoneal injections of 0.3 mg/kg and 0.6 scopolamine, 10 mg/kg caffeine, 0.3 mg/kg of nicotine, and three saline injections, in the course of other projects.

Drug Testing:

Order of drug/control administration was counterbalanced across subjects. Subjects were first administered an intraperitoneal injection of dextromethorphan dissolved in saline, at a dose of 40 mg/kg, or saline alone, 30 minutes before testing in the delayed-version of the task. After an approximately 48-hour interval, the second treatment was administered (e.g. if saline was administered on the first testing day, then dextromethorphan was administered 48 hours later, or vice versa).

Results:

Figures 3A and 3B shows accuracy on testing days as a function of group, delay, and drug condition, for DO and NDO groups respectively. For subjects under DO, there was a significant effect of drug, $F(1,7)=6.667$, $p=.036$, a significant effect of delay, $F(3, 21)=6.525$, $p=.003$, and no significant drug x delay interaction, $F(3,21)=.763$, $p=.527$. For subjects under NDO, there was no significant effect of drug, $F(1,6)=0$, $p=1$, a significant effect of delay, $F(3,18)=11.724$, $p<.001$, and no significant drug x delay effect, $F(3,18)=.238$, $p=.869$.
Pairwise Comparisons (Within-Subjects): For the DO group, performance was significantly lower under dextromethorphan at the 5 and 10 second delays, $t(7)=-2.966, -2.393$, $p=.011, .024$, respectively.

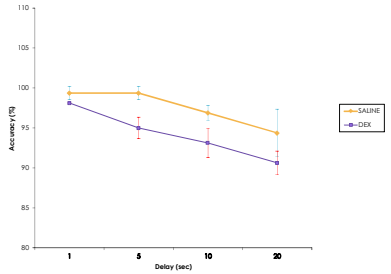


Figure 3A: accuracy on testing days as a function of group, delay, and drug condition, for the DO group.

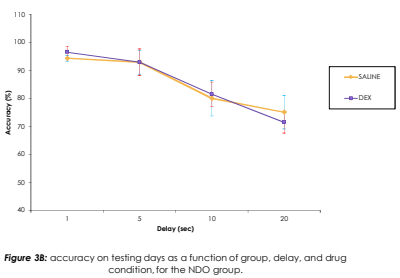


Figure 3B: accuracy on testing days as a function of group, delay, and drug condition, for the NDO group.

Discussion:

Our hypothesis was partially confirmed in that performance was significantly affected under DO but not under NDO under 2 of the 4 . This supports the contention of Savage (2008) that NDO and DO procedures tap different memory systems, with the prospective, expectancy based system driving behavior under DO being more influenced by NMDA activity. DXM may interfere with performance by disrupting the formation of, use of, or proper recall of outcome expectancies. Currently we are running a second study with the intent of replicating these results.

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