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

Angela Gifford, Rowan McGlasson, Whitney McShane, Erin Seabright, Nick Wobig, Nora Freetry and John M. Holden (Faculty Sponsor)
Winona State University - Department of Psychology

**Introduction:**
Support (1975) found that, in a biconditional discrimination task, subjects who were trained with unique and distinct outcomes following each discriminative stimulus-response (S-R) sequence were more accurate in their performance than 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.

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 trial 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, 2013). 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 (DMX), as studied by Scholar (2007), is an effective antitussive agent for treating uncomplicated, non-productive coughs. DMX is an N-methyl-D-aspartate receptor (NMDA) antagonist, which when put into effect inhibits the glutamate-induced excitation and excitotoxicity in the CNS and spinal regions (Scholar, 2007; Chaz, Kils, Lepe, Paris, Benabides, and Hankins, 2018). In the treatment of coughs, the drug is able to suppress coughing in the CNS and spinal regions. Cough threshold in the medulla (Scholar, 2007). It is available over the counter and has been cited as a safer alternative to codeine. 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 (Bills & 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 effects on working memory under DO but not under NDO.

Savage (2001) had previously presented evidence suggesting greater involvement of glutamergic NMDA receptors in memory under DO than under NDO using the NMDA receptor antagonist MK-801 (dizocilpine). Should this be the case, we would 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 DMX would significantly impair working memory under DO but not under NDO.

**Subjects and Methods:**
Subjects were 15 adult Sprague-Dawley rats, approximately 4 months old at the beginning of the study. Subjects were housed on 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.

<table>
<thead>
<tr>
<th>Common Outcomes</th>
<th>Differential Outcomes</th>
<th>Nondifferential Outcomes</th>
</tr>
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<tbody>
<tr>
<td>S1 → R1 → O1</td>
<td>S1 → R1 → O2</td>
<td>S1 → R1 → O1 → O2</td>
</tr>
<tr>
<td>S2 → R2 → O2</td>
<td>S2 → R2 → O3</td>
<td>S2 → R2 → O2 → O3</td>
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**Matching-It-Position:**
Depicted in Figure 3, 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 to the chamber. This is the discriminative stimulus. Two responses on the illuminated lever have the effects of extinguishing the light, retracting the lever, and extending, and illuminating the light over the back wall. 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 merely remaining in front of the correct lever.) The first response after 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 next move is 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 lever light and a 1 sec. train of 6 flashes/second from the controller (the “large” outcome), or b) three 0.5 sec flashes of the lever light, followed by a single pellet (the “small” outcome). For subjects in the DO group (Mb), each stimulus-response sequence was consistently followed by a specific outcome (e.g. left-left-small & right-right-large & right-right-small). For subjects in the NDO group (Mn), outcomes were random. Incorrect responses led to a repeating of the trial but with only one 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.

**Results:**
As can be seen in Figure 3B and 3C, the accuracy on testing days as a function of drug, delay, and drug condition for the DO group. Figure 3A 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(3, 18) = 3.457, p = .039, and no significant drug × delay interaction, F(D, 3) = 7.53, p > .027. For subjects under NDO, there was no significant effect of drug, F(3, 18) = 1.724, p > .201, and a significant drug × delay effect, F(D, 18) = 3.86, p < .05. **Panel B:** Accuracy on testing days as a function of group, delay, and drug condition for the DO 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. DMX may interfere with performance by disrupting the formation, use of, or proper recall of outcome expectancies. Currently we are running a second study with the intent of replicating these results.

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

**Figure 4:** Accuracy on testing days as a function of group, delay, and drug condition for the NDO group.

**Figure 5:** Accuracy on testing days as a function of group, delay, and drug condition for the NDO group.