Spatial Working Memory Under Differential and Nondifferential Outcomes I: Effects of Scopolamine

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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. Common, differential and nondifferential 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.

Scopolamine is a medication commonly prescribed to treat nausea and vomiting by acting as an antagonist to the excitatory neurotransmitter, acetylcholine. Ravel, Elaagouby, and Gervais (1998) found that rats who had received scopolamine injections into the olfactory bulbs had impaired short-term memory when completing delayed matching tasks involving odor recognition; however this was only after a 30 second interval delay. Ferreira, Gervais, Durkin, and Lévy, (1999) found that scopolamine inhibited odor retention in ewes (female sheep), which prevented them from recognizing their lamb, but only for ewes who had eight hours of contact or less with their lamb. Some researchers found that scopolamine reduced the accuracy in delayed matching to position tasks in rats, but only when the subjects were required to complete the tasks over longer intervals of retention (Pontecorvo, Clissold, White & Ferkany, 1991). (Other studies have indicated working memory inhibition during non-matching to position tasks in rats that received scopolamine (Spencer, Pontecorvo, & Heise, 1985)). However, Savage (2008) presents data suggesting that performance under NDO is more affected by scopolamine than performance under DO, supporting a stronger cholinergic component to retrospective memory than prospective memory. Following this, it is hypothesized that scopolamine will significantly decrease memory performance in the NDO group, but less so in the DO group.

The Delayed Matching to Position (MTP) Task

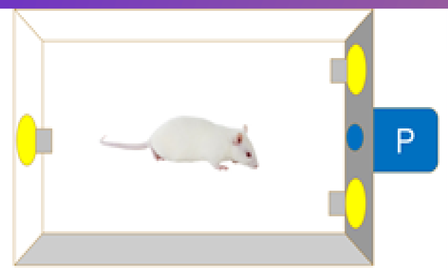
Matching-to-Position: Sessions ran for 80 trials. At the beginning of each trial, the stimulus above either the left or right lever is illuminated and that lever is extended into the chamber; this is the discriminative stimulus. Two responses on the illuminated lever have the effects of extinguishing this light, retracting the lever, and 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=8), the outcome was randomly determined. 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.

Order of drug/control administration was counterbalanced across subjects. Subjects were first administered an intraperitoneal injection of scopolamine dissolved in saline, at a dose of 0.6 mg/kg, 0.3 m/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; after another 48 hours, the 3rd. Order of treatments was varied according to a Latin-square design.

Figure 2. Depiction of the operant chamber setup (right = front, left = back). P = pellet feeder. Front levers are retractable, back lever is fixed in place.



Results and Discussion

Figures 3A and 3B shows accuracy on testing days as a function of group, delay, and drug condition, for DO and NDO groups respectively. A mixed-design ANOVA showed a significant effect of group, $F(1,14)=4.938$, $p=.043$, a significant effect of delay, $F(3,42)=47.264$, $p<.001$, a significant effect of drug dose, , $F(2,28)=21.223$, $p<.001$, a significant delay x group interaction, $F(3, 42)=6.051$, $p=.002$, a nonsignificant dose x group interaction, $F(2,28)=.62$, $p=.545$, a nonsignificant dose x delay interaction, $F(6,84)=1.327$, $p=.254$, and a significant group x delay x dose interaction, $F(6,84)= 2.348$, $p=.038$. * indicates individual dose that is significantly different from saline ($p \leq .05$). using Fisher's LSD.

The results of our study suggest that both prospective and retrospective memory are mediated by acetylcholine. Previous research by Savage (2008) suggested that performance under DO was less affected by scopolamine administration than NDO performance; our results stand in contrast to those findings, as scopolamine administration reduced accuracy in both groups and arguably reduced it more in the DO than NDO group (although this may be simply be because performance under DO was higher to begin with.)It is possible that some differences between their training procedure and our own are responsible for the difference (e.g. large vs. small food instead of food vs. sucrose for outcomes). Moreover, the two doses explored here were comparatively large; it is possible that smaller doses could yield a different effect for DO and NDO groups. However, it is clear that performance under both tasks is dependent on acetylcholine activity. Future studies from our labs will explore the effect of a wider range of scopolamine doses, as well as other kinds of amnestic drugs, on these two different forms of memory.

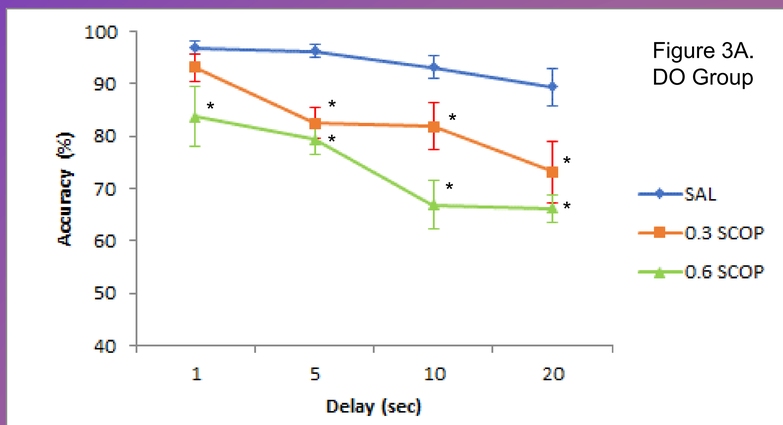


Figure 3A. DO Group

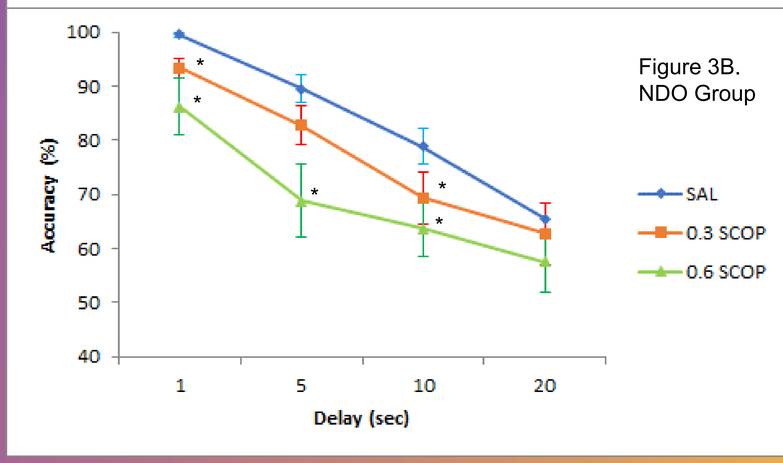


Figure 3B. NDO Group

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