The effect of midazolam on visual search: Implications for understanding amnesia

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he distinction between explicit (declarative) memory and implicit (nondeclarative) memory involves whether or not a memory is accompanied by conscious recollection, that is, an ability to report the memory. Studies of neuropsychological patients have shown that individuals who suffer from amnesia have impairment on explicit memory tasks but no performance deficit on measures of implicit memory (1, 2). Because of this selective impairment, it has been claimed that different memory systems are subserved by different brain regions (e.g., refs. 3 and 4). Accessibility to consciousness has been considered as the criterion for different memory systems (3, 5), although others have suggested using as the distinction whether the formation of new memories depends on the medial temporal lobe (4, 6).

Recently, the notion of multiple memory systems based on consciousness has been questioned. Studies of neuropsychological patients have begun to explore whether these patients have problems learning the association between pieces of information or have difficulty only in acquiring new explicit memories (7, 8). For example, amnesic patients showed a deficit on a visual search task such that performance was not facilitated when displays were repeated (7). When the contextual cues were repeated (i.e., when the configuration of the distractors in relation to the target remained constant), normal participants showed facilitation in locating the target without any awareness of display repetition. In other words, this enhancement, i.e., the contextual-cuing effect, was acquired implicitly. Therefore, amnesic patients, who were thought to manifest only explicit memory deficits, have now been shown to be impaired on an implicit memory task. Interestingly, general performance on the search task did improve with practice for both controls and patients. Thus, the deficit in neuropsychological patients seems to lie in whether a task requires associative or relational processing, as in contextual cuing, rather than in whether it relies on explicit memory.

However, another patient study recently showed that amnesiacs were still able to demonstrate an effect of contextual cuing (9), supporting the validity of a dichotomous memory distinction, i.e., an explicit (declarative) vs. implicit (nondeclarative) memory system. This result calls into question the previous result (7), which found that amnesic patients were impaired on the same implicit task. Thus, controversy still surrounds the question of whether memory dichotomies should be based on conscious accessibility and, conversely, whether conscious accessibility is the critical feature underlying the dichotomous neural bases of distinct memory systems.

Although patient studies have provided invaluable information to further the understanding of human memory, there are inherent problems involving neuropsychological patients that raise some doubt about conclusions based on the data in these

degree of impairment has been much larger for tests of explicit memory, and the interpretation of the finding is open to debate.[§]

In this study we examine both implicit and explicit memory performance in healthy participants with a double-blind drug administration using a within-subject design to control participant variability. Of particular interest is whether there are types of implicit memory performance that are impaired under midazolam analogous to the recent findings with amnesic patients (7). Each participant performed two versions of a visual search task (adapted from refs. 21 and 22) one under the influence of midazolam and one under the influence of saline. The task required participants to locate a target in a display of distractors and then make a binary decision based on the identity of the target. The time and accuracy of making these judgments were examined as a function of practice at the task and whether the particular display had been seen previously.

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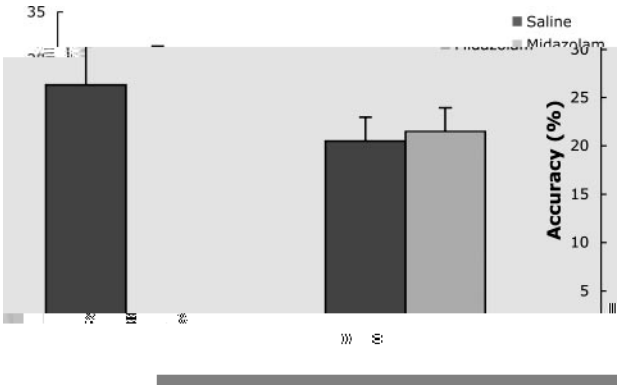
P . The 30 participants were healthy, paid volunteers (age range 19–29). Three participants were excluded from all analyses because they fell asleep due to excessive sedation effects. Informed consent was obtained from all participants before participation, and the study was performed under a protocol approvcausees(and)n.[6tandIns(iduicip-547.1(abeen)c6iduicip-w(abeeBoards(abee(of)-eeCari-)]TJT*[negien)-337.8Mfeloen)-337.8U



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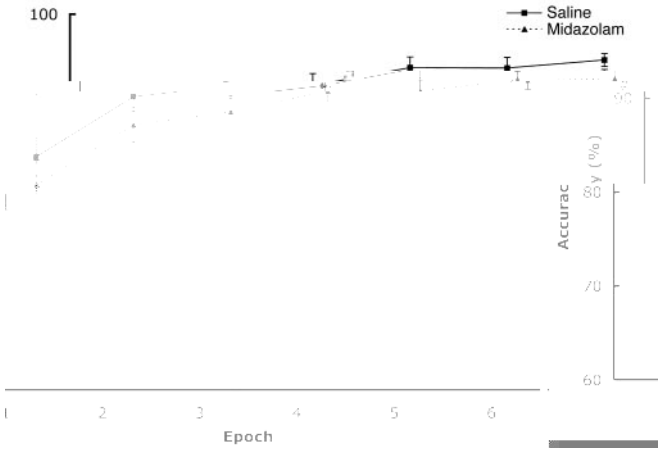
participants in both conditions demonstrated no explicit awareness of any repeated patterns, we examined whether the administration of midazolam also diminished performance on an implicit task. Specifically, we looked to see whether the facilitation of repeated patterns in the visual search task was reduced. For each drug condition, performance (latency and accuracy of response) was compared by block, between Old and New configurations. For the RT analysis, only correct responses were included, and all RTs that exceeded three standard deviations of that participant's mean RT were discarded. Less than 1% of the data was removed because of outliers. To reduce statistical noise, blocks of trials were grouped into sets of four, yielding six epochs for analysis.

Collapsing over the Old versus New configuration factor, the percentage of correct trials is displayed in Fig. 2 as a function of drug condition and epoch. Fig. 3 displays the mean correct RTs as a function of these same factors. Both figures show general improvement in the task over time, such that accuracy increased over epochs, $F(5,130) = 33.66$, $P < 0.001$, and search time decreased over epochs, $F(5,130) = 96.55$, $P < 0.001$, regardless of drug condition. This result means that participants performed better with more experience in terms of both speed and accuracy, consistent with the literature on skill learning (e.g., ref. 24). There was no main effect of drug condition on accuracy or RT, both $F < 1.7$, but the pattern suggests that midazolam produces slightly degraded performance, as would be expected because of the drug's sedative effects.

In an analysis that included Old versus New configurations as a factor, accuracy did not differ between Old and New configurations or between drug conditions. The treatment order (midazolam–saline vs. saline–midazolam) did not yield any differences. Fig. 4 displays the correct RTs for Old and New configurations as a function of epoch and drug condition. No differences were expected for New configurations as a function of drug condition, and no interaction was found between drug condition and epoch, $F(5,130) = 0.37$, $P > 0.8$. However, the epoch effect was robust, $F(5,130) = 65.88$, $P < 0.001$. The important contrasts involved comparisons between drug conditions for the Old configurations. There was no significant main effect of drug condition but there was an effect of epoch for the Old configurations, $F(5,130) = 88.59$, $P < 0.001$. Unlike for the New configurations, there was a significant interaction between drug and epoch for the Old configurations, $F(5,130) = 2.51$, $P < 0.05$, such that the improvement due to specific practice with Old configurations was limited to the saline condition.

To determine whether the advantage of an Old configuration increased with additional repetitions, we compared priming scores for Old and New configurations for each epoch. Table 1 shows an RT-priming measure, comparing the speed in subsequent epochs with performance in the original epoch. That is, the RTs in epochs 2, 3, 4, 5, and 6 for each condition are subtracted from the corresponding RT in epoch 1. There was a reliable difference between Old and New configurations in the saline condition that came from the last two epochs, but there



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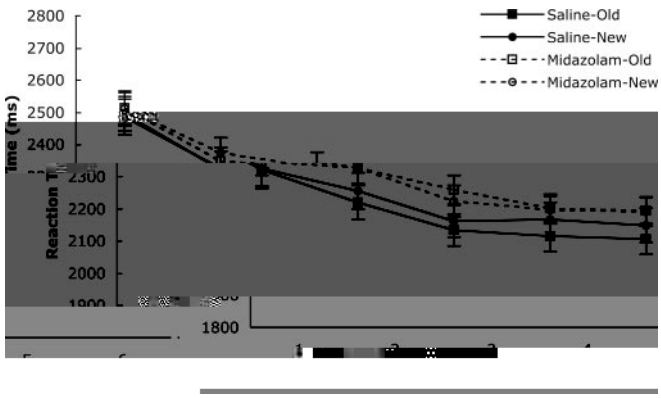

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was no reliable difference between Old and New configurations for any epoch in the midazolam condition.

We also compared the benefit of contextual cuing, defined as the difference in RT for Old configurations compared to New configurations, for each epoch. Fig. 5 displays the contextual-cuing effects in the saline and midazolam conditions. Unlike the general improvement in skill learning shown in Fig. 3, the contextual-cuing effect was limited to the saline condition. There was a significant linear trend over epochs for the saline condition, $F(1,26) = 6.22$, $P < 0.05$; however, no such trend was found for the midazolam condition, $P > 0.2$. When epochs were grouped into the first half and the second half of the experiment, a significant interaction between drug and epoch was found, $F(1,26) = 10.39$, $P < 0.005$, such that the contextual-cuing scores did not differ between the two drug conditions for the first half of the experiment, $(26) = 0.07$, but the scores were greater in the saline condition for the second half of the experiment, $(26) = 2.60$, $P < 0.05$.

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In this study, healthy participants were tested on two versions of

midazolam. $GABA_A$ receptors are distributed throughout the brain, not only in the hippocampal system. Although it would be appealing to assert that the locus of effect of midazolam is in the hippocampal regions, there is no evidence that any neuropharmacological drug is that specific, and, furthermore, there is the