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Patterns of brain acetylcholine release predict individual differences in preferred learning strategies in rats

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Abstract

Acetylcholine release was measured simultaneously in the hippocampus and dorsal striatum of rats before and during training on a maze that could be learned using either a hippocampus-dependent spatial strategy or a dorsal striatum-dependent turning strategy. A probe trial administered after rats reached a criterion of 9/10 correct responses revealed that about half of the rats used a spatial strategy and half a turning strategy to solve the task. Acetylcholine release in the hippocampus, as well as the ratio of acetylcholine release in the hippocampus vs. the dorsal striatum, measured either before or during training, predicted these individual differences in strategy selection during learning. These findings suggest that differences in release of acetylcholine across brain areas may provide a neurobiological marker of individual differences in selection of the strategies rats use to solve a learning task.

Keywords: Acetylcholine; Learning strategies; Memory modulation; Hippocampus; Striatum; Place learning; Spatial learning; Response learning

1. Introduction

Multiple, dissociable neuroanatomical systems appear to support distinct forms of learning and memory. Selective loss of some forms of memory, with sparing of other forms of memory, has often been reported after brain damage in humans and other animals (Cohen & Squire, 1980; Gabrieli, 1998; Gold, McIntyre, McNay, Stefani, & Korol, 2001; Kesner, 1998; Kim & Baxter, 2001; Packard, 2001; White & McDonald, 2002; Willingham, 1998).

Dissociations of memory systems can be clearly identified in laboratory animals given localized lesions. For example, lesions of the hippocampal area result in impaired place (spatial) memory in rats, while other forms of learning, such as motor response learning, remain intact (O'Keefe & Nadel, 1978). Lesions of the dorsal striatum can affect motor response learning, leaving place memory unaffected (Kesner, Bolland, & Dakis, 1993). Results obtained with converging techniques such as imaging (Poldrack et al., 2001) and pharmacology (Gold et al., 2001; Packard, 2001; Packard & Teather, 1997) generally support these findings.

Although different brain areas may have special importance for mediating different classes of memory, most experiences have a mix of features and attributes likely to involve the combined functions of multiple memory systems. The nature of those interactions is evident in some lesion experiments in which damage to one neural system not only impairs functions associated with that system but also enhances functions associated with another system (e.g., Ferbinteanu & McDonald, 2001; Matthews & Best, 1995; Matthews, Ilgen, White, & Best, 1999; McDonald & White, 1995). The evidence for competition between memory systems suggests that, when the brain is intact, the expression of learning is not based on a single neural system.

Using in vivo microdialysis to measure release of ACh in the brains of rats during learning, we recently obtained evidence suggesting that an increase in ACh release may be a useful marker of the relative participation of different neural systems in learning and memory (Gold et al., 2001). With this technique, it is

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possible to observe the dynamic interaction that occurs between multiple neural systems in an intact brain during learning. For example, release of ACh in the hippocampus and amygdala is related to performance on tasks associated with those structures on the basis of lesion experiments (McIntyre, Pal, Marriott, & Gold, 2002a; McIntyre, Marriott, & Gold, 2002b; Ragozzino, Unick, & Gold, 1996; Ragozzino, Pal, Unick, Stefani, & Gold, 1998). In addition to finding ACh release associated with the functions within a brain area, ACh release patterns in one brain area can exhibit important relationships with memory classes associated with a different brain area. For example, ACh release in the hippocampus is negatively related to learned performance on an amygdala-dependent conditioned cue preference task (McIntyre et al., 2002a), suggesting that increased hippocampal activation results in increased competition for control over learning in an amygdala-dependent task. Consistent with results from pharmacological and lesion studies (Packard, Cahill, & McGaugh, 1994; Packard & Teather, 1998; White & McDonald, 1993), the reciprocal relationship between the hippocampus and amygdala appears to be quite different when examined using ACh release as a marker for participation in memory formation. ACh release in the amygdala is positively related to learned performance on a hippocampus-dependent spontaneous alternation task (McIntyre et al., 2002b), suggesting that increased amygdala activation cooperates with the hippocampus during learning of a hippocampus-dependent task. Thus, the balance of activation between memory systems may impart information about which strategies are likely to be used to learn or to solve memory tasks in different individuals.

The issue of selection of learning strategy has been debated for many years (Restle, 1957; Tolman, Ritchie, & Kalish, 1946). One way in which this matter has been tested is through the use of a T-maze (Fig. 1) that can be solved using either a response or a place strategy. In this maze, the start arm (stem of T) and the reward arm are stationary. After rats are trained to criterion, the maze is rotated 180° so that the rat enters from the direction opposite that used during training. Rats that return to the same location relative to the room are judged to exhibit place learning while those that turn in the same direction as during training are judged to exhibit response learning. In this task, rats with lesions of the hippocampus generally use a response strategy (Means & Douglas, 1970). Also, strategy selection can be modulated by immediate post-training or pre-testing injections of glutamate or lidocaine, respectively, into either the striatum or hippocampus (Packard, 1999; Packard & McGaugh, 1996) and strategy has been shown to differ on the basis of estrogen status in female rats (Korol & Kolo, 2002).

Using ACh release as a marker of activation of the brain regions, the present experiment investigated the participation of the hippocampus and dorsal striatum concurrently both before and during training in the T-maze. The issue was whether ACh release in either or both brain regions would predict or reflect the strategy preferred while rats were trained to criterion and able to solve the task freely with either place or response solutions.

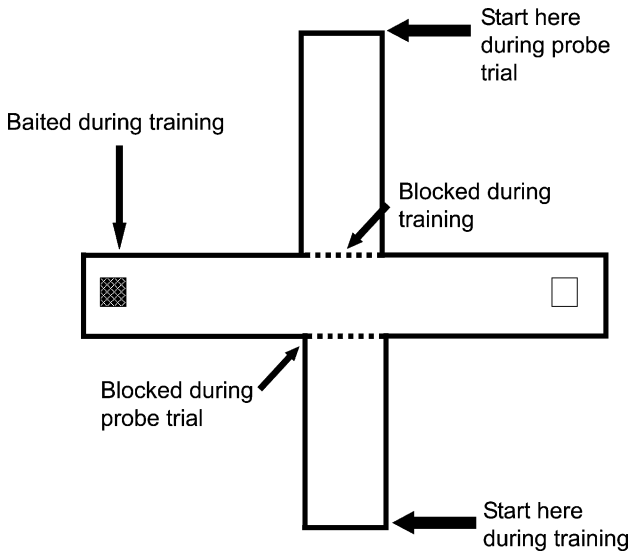

Fig. 1. T-maze training apparatus. Rats were trained to make the same turn and to return to the same location in the room across trials. A single probe trial was given after a rat reached criterion (9/10 correct choices). The start arm was blocked and rats were placed in the opposing arm to begin the probe trial. Rats that returned to the same location were assigned to the group of rats that used a "place" strategy while rats that made the same turn (i.e., left vs. right) were assigned to the group of rats that used a "response" strategy.

2. Materials and methods

Subjects. Thirteen male Sprague–Dawley rats (Hilltop) weighing 300–350 g were housed individually on a 12-h light/dark cycle (lights on at 0700) before and during the microdialysis experiment. Twenty-eight rats were used as unoperated controls.

Surgery. Two plastic microdialysis guide cannulae (CMA/12 type; Carnegie Medicin, Stockholm) were implanted under stereotaxic control in rats under sodium pentobarbital anesthesia (50 mg/kg i.p.). The cannulae were aimed at the hippocampus and dorsal striatum. With the nosebar set at +5 mm, stereotaxic coordinates (in millimeter) were: hippocampus (unilateral) AP − 3.8, ML − 5.0, DV − 4.3; dorsal striatum (contralateral) AP + 2.0, ML + 3.0, DV − 3.8 according to the atlas of Pellegrino, Pellegrino, and Cushman (1979).

Behavioral procedures. One week after surgery, food was restricted and rats were handled daily (5 min/day). After 5 days of handling, T-maze training was completed in a single session in a well-lighted, novel room

with many visual cues. The black Plexiglas maze was plus-shaped with one arm closed on each trial to make a T configuration. The maze was placed on a table elevated 80 cm from the floor. The length of each arm was 55 cm and walls were 12 cm high. To eliminate the possible contribution to learning of odor or other intramaze cues, the maze was rotated 90° between each trial (30-s intertrial interval), with the start arm remaining in the same position relative to the room cues. Rats were trained to go to one arm of the T-maze (for each rat, always right or left arm), which was baited with one Frosted Cheerio. When rats reached criterion (9/10 correct choices), they were given a single probe trial in which the original start arm was blocked and rats entered the maze from the opposite direction, i.e., the arm located across from the original start arm. Those rats that entered the arm in the same location relative to room cues (turning in the direction opposite that used during training) were assigned to the "place" group and those rats that made the same turning response (going to a room position opposite that used during training) were assigned to the "response" group.

Microdialysis procedures. Probes (3 mm) were inserted into and removed from both cannulae 24 h before sample collection. One hour prior to collection of the first sample, probes were inserted again and perfused at a rate of 2.1 μl/min with aCSF (127.7 mM NaCl, 4.0 mM KCl, 0.9 mM NaH_2PO_4, 2.0 mM Na_2HPO_4, 3.39 mM glucose, 0.93 mM $MgCl_2$, and 1.29 mM $CaCl_2$). Neostigmine (1 μM) was added to the aCSF to inhibit the actions of the breakdown enzyme, acetylcholinesterase. Previous findings indicate that the training-related percent increase from baseline in release of ACh in the hippocampus of rats is consistent with neostigmine doses ranging from 0.1 to 6 μM (Ragozzino et al., 1996; Stefani & Gold, 2001). These results were recently confirmed by direct comparisons within an experiment (Chang and Gold, unpublished results). Prior to training, microdialysis samples were collected simultaneously from the hippocampus and dorsal striatum of each rat for four 12-min baseline measurements while the rat was in its home cage. Sample collection continued while rats were trained on the T-maze until criterion was reached. Dialysis was ceased during the probe trial in order to eliminate contamination of the samples obtained during training with changes in neurotransmitter release during testing. Following the probe trial, rats were returned to their home cages and four more samples were collected. ACh concentrations were analyzed using high performance liquid chromatography with electrochemical detection as previously reported (Ragozzino et al., 1996) and were compared across groups of rats assigned on the basis of performance on the probe trial to place or response groups.

Statistical analysis. Mean ACh levels in the samples at baseline and during training were compared across groups (place vs. response for hippocampal ACh and striatal ACh) using unpaired, two-tailed *t* tests. In addition, each rat was given a ratio score, which reflected the ratio of ACh concentrations (pmoles/20 μl) in the microdialysis samples from hippocampus vs. caudate collected during baseline and behavioral training. Ratios were compared across groups using unpaired, two-tailed *t* tests.

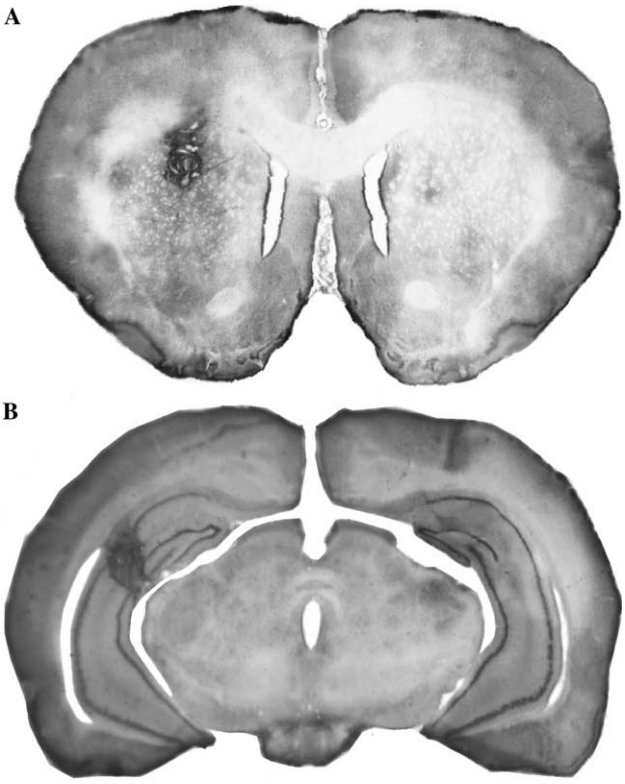

Fig. 2. Histology examples showing acceptable probe placement in the dorsal striatum (A) and hippocampus (B).

Histology. Following training and microdialysis, rats received a lethal dose of sodium pentobarbital and were perfused with 0.9% saline and a 10% formalin solution. Brains were removed and placed in a 30% sucrose/formalin solution. At least 24 h after submersion in sucrose/formalin solution, brains were frozen and cut in coronal sections (40–80 μm) on a cryostat. Sections were mounted onto slides, stained with cresyl violet, and examined under a light microscope to determine probe location and extent of damage. Rats with misplaced probe insertions or obvious damage that extended beyond the probe placement were excluded from analysis (Fig. 2).

3. Results

On probe trials administered after rats reached the criterion of 9/10 correct, 14 of 28 unoperated rats used a turning and 14 used a place response. Unimplanted rats

had comparable trials to criterion regardless of strategy used (20.9 ± 1.6 vs. 18.9 ± 2.0 for place vs. response, respectively). Consistent with these results, of the 13 implanted rats used for ACh measurements, seven used a turning response and six used a place response on the probe trial. In the rats used for microdialysis, place learners took more trials to reach criterion than did response learners (28.5 ± 4.3 vs. 17.3 ± 2.2, respectively).

Consistent with previous findings (Ragozzino et al., 1996, 1998; Stefani & Gold, 2001), extracellular concentrations of ACh increased in both the hippocampus and the dorsal striatum of all rats (all Ps $< .01$) during training. This increase was seen in all rats, regardless of the strategy the rats exhibited on the probe trial (Fig. 3). However, ACh levels in samples collected from the hippocampus during training were significantly higher in those rats that used a place strategy than in rats that used a response strategy ($P < .0001$). Conversely, extracellular concentrations of ACh in the striatum during training were higher in rats that used a response strategy than in those that used a place strategy, but this difference was not statistically significant ($P < .31$).

An unexpected and important finding was that extracellular ACh concentrations in the hippocampus during baseline measurements—i.e., *before* the rats had experienced any maze training—were higher in those rats that would soon learn the T-maze problem using a place strategy ($P < .0001$). As in training samples, extracellular ACh concentrations in the striatum at baseline were greater in rats that used a response strategy; however, this difference was not statistically significant ($P < .14$). When the ratios of extracellular concentrations of ACh in the hippocampus vs. the dorsal striatum were compared on the basis of individual differences in learning, the hippocampus/striatum ratio was significantly greater in rats that used a place strategy than in those that used a response strategy ($P < .001$; Fig. 4). Consistent with the results presented for hippocampal ACh, the ratio of extracellular concentrations of ACh in the hippocampus vs. the dorsal striatum was significantly greater in the rats that exhibited a place strategy even before they were exposed to the maze ($P < .02$).

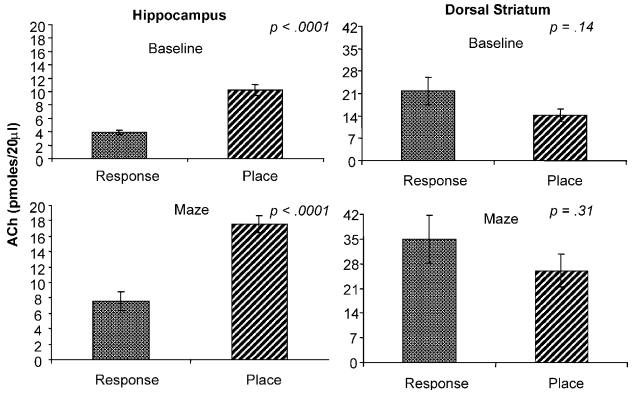

Fig. 3. ACh content in microdialysis samples collected concurrently from the hippocampus and dorsal striatum. Note the difference in y-axes for the two brain areas. Extracellular concentrations of ACh were greater in the striatum than in the hippocampus. Within the hippocampus, ACh release was significantly greater in rats that used a spatial strategy than in rats that used a response strategy. This was evident both prior to and during training. Although the scores were not significantly different at baseline or during training, the relationship between ACh release in the striatum of rats in the two groups was in the direction opposite that seen in the hippocampus.

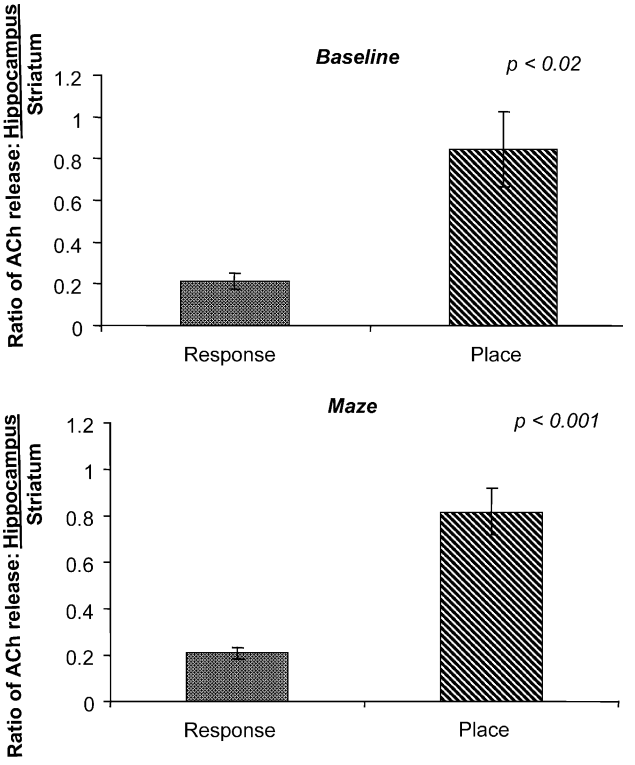

Fig. 4. Ratios of extracellular concentrations of ACh in the hippocampus vs. dorsal striatum for microdialysis samples collected during baseline and training. Ratios of ACh release in hippocampus/striatum for rats that used a place strategy on the probe trial administered after rats reached a criterion of 9/10 correct were significantly higher than those for rats that used a response strategy. This difference was apparent before rats were exposed to the training apparatus as well as during training.

4. Discussion

These findings suggest that individual differences in selection of learning strategies can be predicted by the magnitude of ACh release in different neuroanatomical regions, even when measured before initial exposure to the training apparatus. The results obtained with baseline measures of ACh release imply that pre-training differences in neural systems for memory may play a role in the process of strategy selection during learning. The relationship between the strategy and neurochemistry

was somewhat clearer for the hippocampus than the striatum, perhaps because of differential heterogenity of function in the striatum compared to the hippocampus relative to the area sampled by the microdialysis probe.

On the basis of the behaviors the rats show when multiple probe trials are used in this and similar tasks, it appears that most rats initially use a place strategy to perform the task but later, after extensive training, switch to the use of response strategy (Chang & Gold, 2002; Packard & McGaugh, 1996). In the present experiment, at the time rats reached a criterion of 9/10 correct, half of the rats used each strategy. Therefore, because the rats make a transition from place to response learning with extensive training, it must be the case that it is the time during training when a rat makes the switch from place to response performance that is predicted by ACh release in the hippocampus and striatum. This transition may reflect a change from declarative to procedural or habit memory (Packard, 1999). Chang and Gold (2002) examined ACh release in both hippocampus and striatum throughout 100 training trials, i.e., from early training through criterion performance to overtraining. Probe trials were administered after each 20 training trials. The findings indicated that ACh release in the hippocampus increased substantially on initial trials and remained at that elevated level throughout training, while ACh release in the striatum did not increase until well into training. This later increase in ACh release in the striatum corresponded to the probe trials on which rats began to use response solutions. Thus, the ratio of release of ACh in the hippocampus and striatum changed during the course of extensive training. Viewed with the present findings, the results indicate that baseline levels of ACh release in the hippocampus and striatum may bias the rat to prefer place or response strategies but most rats switch to response strategies later in training at a time coincident with an increase in ACh release in the striatum.

In considering the cognitive bases of these findings, it is possible that certain stimuli are more salient to some rats than to others during training on the T-maze task, resulting in a different pattern of behavior when asked to recall the learning environment. An early paper addressing this subject suggested that there is nothing in the nature of a rat that makes it a "Place" vs. "Response" learner, concluding that inconsistent findings obtained with the T-maze reflected differences in the training environment such as extramaze cues, lighting, and size of maze walls (Restle, 1957). While such variables are certainly important, the results here suggest that there is indeed something in the nature of rats that determines what each rat learns, including individual differences in the brain present even before the rat's first exposure to the training apparatus. However, the present findings do not determine whether the differences in ACh release patterns might best be characterized as differences associated with learning, attention, or retrieval. For example, differential release of ACh in different neural systems might lead some rats to attend to certain features more than do other rats, with a resultant expression of a different learning strategy. This view integrates closely ideas of the functions of ACh in mechanisms of attention with those of ACh in mechanisms of learning and memory (e.g., Stoehr et al., 1997; Thiel, Huston, & Schwarting, 1998).

Whether the individual differences in neurochemistry have their bases in genetic or experiential differences is unclear. Supporting contributions from experience to the differences seen here, after rats were trained on a food-reinforced spatial maze, levels of release of ACh in the hippocampus were greater in trained rats than in control rats when exposed to the training environment (Fadda, Melis, & Stancampiano, 1996). Whether there are adequate opportunities for use of different learning strategies by rats housed in standard cages, as in the present experiment, is uncertain. Of related interest is the issue of whether the individual differences seen here reflect permanent or transient differences in brain function. Stated simply, might the same rats have a different neurochemical and behavioral predisposition at a different time? For example, the dominant strategy, neural system, and ACh release profiles might fluctuate throughout the day or across hormonal cycles. Supporting this view, female rats choose different strategies to solve a T-maze, as used here, depending on estrogen status (Korol & Kolo, 2002). The phase of the estrous cycle and changes in estrogen levels are associated with morphological and functional changes in the hippocampus that might serve as a basis for a shift in dominant memory system (Daniel & Dohanich, 2001; Korol & Manning, 2001; Woolley, 1998).

The findings that differences in baseline levels of ACh release in the hippocampus, and perhaps elsewhere, predict preferred learning strategy have implications not only for normal memory, but also for studies of age- and disease-related memory impairments. While a great amount of research has shown that aging is associated with a loss of memory abilities in humans and other animals (e.g., Craik & Salthouse, 1992; Gold, 2001; Grady & Craik, 2000; Korol & Gold, 1998; Powell, 1999), it is possible that aging also brings a change in dominant memory system, with consequent memory differences that are qualitative rather than quantitative in nature. For example, Barnes, Nadel, and Honig (1980) reported that senescent rats preferentially used a turning response to solve a T-maze while middle-aged rats preferentially use a place strategy. Therefore, some age-related differences in memory might reflect changes in preferred solution to a problem on the basis of activation of different neural systems, rather than on the basis of differences in learning or memory capacity.

Furthermore, changes in ACh levels within the hippocampus and striatum have been associated with selective memory impairments that accompany neurodegenerative disorders such as Alzheimer's and Huntington's disease (Bartus, Dean, Beer, & Lippa, 1982; Suzuki, Desmond, Albin, & Frey, 2001). In studying the cognitive changes in these diseases, it may be important to consider the relative contributions of loss of learning abilities vs. shift in learning strategies. A revised understanding of contributions of altered learning strategy to these dysfunctions might lead to new behavioral approaches to exploit the types of learning available to people with these pathologies and to new clinical approaches to target specific memory systems.

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