Increased dopamine release in the human amygdala during performance of cognitive tasks

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Accumulating data support a critical involvement of dopamine in the modulation of neuronal activity related to cognitive processing. The amygdala is a major target of midbrain dopaminergic neurons and is implicated in learning and memory processes, particularly those involving associations between novel stimuli and reward. We used intracerebral microdialysis to directly sample extracellular dopamine in the human amygdala during the performance of cognitive tasks. The initial transition from rest to either a working memory or a reading task was accompanied by significant increases in extracellular dopamine concentration of similar magnitude. During a sustained word paired-associates learning protocol, increase in dopamine release in the amygdala related to learning performance. These data provide evidence for sustained activation of the human mesolimbic dopaminergic system during performance of cognitive tasks.

Studies in rodents and non-human primates implicate dopamine as a modulator of cognitive processing[1]. In the prefrontal cortex, dopamine potentiates the firing of delay-active neurons thought to be critical for working memory[2]. In the amygdala, dopamine projections from the midbrain are thought to modulate associative learning processes, especially those involving behavioral responses to rewarding or aversive stimuli[3–5]. For instance, dopamine potentiates sensory input to the amygdala[6], and inhibition of the mesoamygdala dopamine pathway impairs the retrieval of conditioned fear associations[7]. Furthermore, midbrain dopamine neurons projecting to the forebrain show increased firing rates in non-human primates during certain reward-contingent learning and memory protocols[8–10]. Dopamine modulates long-term depression, believed to be one of the cellular mechanisms of learning, in the mesolimbic system of rodents[11]. Moreover, the amygdala and prefrontal cortex are interconnected, and activity in one region may influence the other during cognition, as illustrated by amygdalar modulation of prefrontal cortex activity during fear conditioning[12].

Despite evidence from animal studies for involvement of dopamine in learning and memory, there is no direct evidence of an associated increase in dopamine release in the human brain. We sought to provide such evidence by sampling extracellular dopamine in the human amygdala with microdialysis during associative learning and working memory tasks.

Results

Subjects of the study were patients undergoing evaluation for epilepsy surgery using chronically implanted intracranial electroencephalographic depth electrodes to identify the location of the seizure focus[13]. Using magnetic resonance imaging (MRI) and angiographic guidance, electrodes were implanted stereotaxically into temporal and frontal lobe targets. Neurochemical sampling was conducted by means of a microdialysis probe inserted through the lumen of the depth electrode[13]. The data are from 16 such probes implanted in the amygdala in 10 patients. The probes were placed such that sampling occurred predominantly from the central and basolateral nuclei of the amygdala (Fig. 1).

Cognitive testing was conducted three to six days following probe implantation. Two tests were used in this study: a working memory task accompanied by a control reading task, and a word paired-associates learning task. The working memory and reading tasks used in the first protocol involved identical sensory input and motor output, but different cognitive processing. In the reading task, subjects were presented with a sequence of words, each for one second, with a four-second delay between consecutive words; subjects were asked to read each word aloud as it was presented. In the memory task, subjects were similarly presented with a sequence of words, but this time they were asked, with the presentation of each word, to say aloud the word just previously presented. Thus, in this working memory task, the subjects had to 'keep in mind' a record of each word until the next was presented. Dialysate was continuously collected and assayed for dopamine in five-minute blocks during the task period, as well as during intervening rest periods. To control for order effect in task sequence, two different sequences were used: mem-

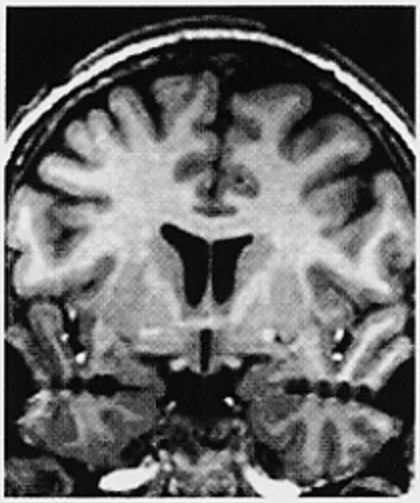


Fig. 1. Coronal MRI section depicting electrodes placed horizontally in the left and right amygdala (left side of the brain is on the right and vice versa). Each electrode had platinum contacts for electroencephalographic recording along the electrode, a microdialysis probe and four microwires at the tip (seen particularly well in the image of the electrode in the right amygdala). MR-related artifact exaggerates the size of the guide screws placed in the skull and the diameter of the electrodes and contacts.

ory–reading–memory (four subjects, six probes), and reading–memory–reading (four other subjects, six probes).

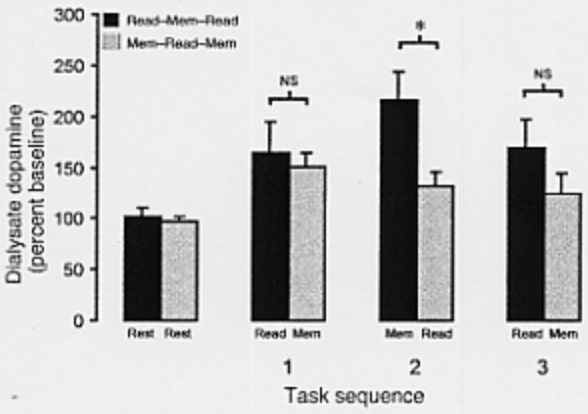
Overall, a significant change in extracellular dopamine level occurred throughout the presentation of the various tasks ($F_{3,30}$ = 9.39, $p < 0.0002$; Fig. 2). Moreover, the pattern of change was dependent on the order of the tasks ($F_{3,30} = 2.95$, $p < 0.05$). The dopamine level reached during the first task in the sequence was similar whether the first task was a working memory or a reading task (mean, 51% versus 66% above baseline, respectively). However, the dopamine level during the second task in the sequence (following an intervening period of rest) was dependent on the nature of the task; dopamine reached higher levels during the memory task (mean, 120% above the initial rest period) than during the reading task (mean, 30% increase, $p < 0.05$, Duncan new multiple range *post-hoc* test). The dopamine level reached during the third task in the sequence did not significantly differ depending on task type. Thus, on average in each of the two task sequences, peak dopamine levels were reached during the first presentation of the memory task (Fig. 2).

The dopamine increase from the initial rest period to the first task was apparent in all six probes where working memory was the first task in the sequence (Fig. 3), and in four of the six probes where the reading task was presented first (Fig. 4). Dopamine levels often remained elevated during the early phase of the ensuing period of rest, such that dopamine was significantly elevated for 15 minutes or longer and frequently did not return to baseline before administration of the second task. The increase in dopamine during the second and third tasks in the sequence was more variable between probes, but nevertheless, a pattern of increase during the tasks and decrease during the intervening rest periods was apparent.

The second protocol, the paired-associates task, differed from the previous one in that the temporal profile of extracellular dopamine levels in the amygdala was examined throughout a learning task sustained over 50–60 minutes. At the beginning of the paired associates task, following a 20-minute pre-test rest period, 20 word pairs were presented, each pair for one second, with a four-second delay between pairs. The subject was asked to learn the list (encoding phase). Subsequently, the subject was presented with the first word in each pair and, upon presentation of a recall cue four seconds later, was required to repond verbally with the paired associate (retrieval phase). This sequence of encoding and retrieval was repeated seven times, with the same word pairs being presented, but in random order. Following completion of the protocol, the subject rested for 20 minutes (post-learning rest). As before, microdialysate samples were collected at five-minute intervals throughout the periods of rest and during the task. A learning curve was computed for each subject by recording the number of correct items learned at each retrieval cycle.

Seven subjects (with 13 probes) underwent this protocol. Averaging data across all 13 probes revealed a statistically significant pattern of increased dialysate dopamine concentration during performance of the paired associates task ($F_{18,216} = 3.00$, $p < 0.005$; Fig. 5a). However, the distribution of performance learning scores across subjects during the paired associates task was bimodal. Four patients learned 95% or more of the word pairs and had at least 75% correct by the third trial. The remaining three patients never learned more than 60% of the pairs and learned 40% or less of the items by the third trial. When the dopamine data were divided according to these two groups, two distinct profiles became apparent. In the first group, the rise in dopamine was transient, and was coincident with the early phase of the task when most of the learning occured (Fig. 5b), whereas in the second group, the rise in dopamine was protracted (Fig. 5c). The difference in dopamine response between the two subsets of subjects was statistically significant ($F_{1,11} = 6.05$, $p < 0.05$) and showed a significant time dependence ($F_{18,198} = 2.37$, $p < 0.02$). In general, the five subjects who did both the paired-associates learning proto-

Fig. 2. Changes in extracellular dopamine in the amygdala during the two sequences: reading–memory–reading and memory–reading–memory. Dopamine increased throughout the sequence of the tasks ($F_{3,30}$ = 9.39, $p < 0.0002$), and the pattern of change was dependent on the order of the task sequence ($F_{3,30} = 2.95$, $p < 0.05$). Each bar represents the mean ± s.e.m. of dopamine concentration in the last five-minute sample collected during each test period, expressed as a percentage of the mean of three initial five-minute rest samples. Data were from six probes in four patients for each task sequence. NS, not significant. *$p < 0.05$, Duncan's new multiple range *post-hoc* test.



col and the working memory/reading task showed an initial increase in dopamine release in one or both probes. However, dopamine response magnitude between the two protocols showed no significant correlation. Although dopamine response magnitude varied between the left and right amygdala in some patients, no consistent pattern occurred across the data set.

Discussion

Extracellular dopamine in the human amygdala was elevated during the transition from rest to performance of a cognitive task. This initial increase in dopamine release occurred not only during working memory and associative learning tasks, but also during simple reading of a series of words. The amplitude of the increase observed was substantial; in some subjects, the increase was more than 100% above baseline.

In non-human primates, electrophysiological recording of midbrain dopamine neurons, the source of the dopamine innervation of the amygdala[14], shows them to be particularly responsive to novel, reward-predicting stimuli[10]. The response of these cells is attenuated upon training such that once task performance is established, only a few neurons respond to the conditioned stimulus[8,15]. In this situation, the dopamine neurons respond only when the stimulus is presented in an unpredictable manner[8]. These observations have led to the concept of dopamine neurons being particularly important during learning, when the animal adapts its behavior to new situations and directs its attention to salient stimuli in the environment[10]. The mesoamygdaloid dopamine pathway, in particular, is implicated in learning and retrieval of associations[7]. Furthermore, the dopamine input to the extended amygdala has been emphasized in 'associative learning' or 'incentive salience' theories of drug addiction[16–18]. Indeed, the amplitude of the dopamine response during the various tasks used in this study is comparable to that observed in rodents given moderate doses of cocaine[16].

Our paired associate data are consistent with an involvement of dopamine in the human amygdala in learning: elevation in dopamine during this task coincided with the learning phase of the task. In subjects whose maximal learning occurred early in the task, dopamine levels peaked during this initial phase and rapidly returned to pre-test levels, before the task ended. Subjects whose learning curves were more protracted presented a dopamine profile that was similarly prolonged. Whereas novelty may have been an important component of the initial dopamine response, the sustained nature of the dopamine elevation during extended periods of learning suggests there was a component related to the level of cognitive processing.

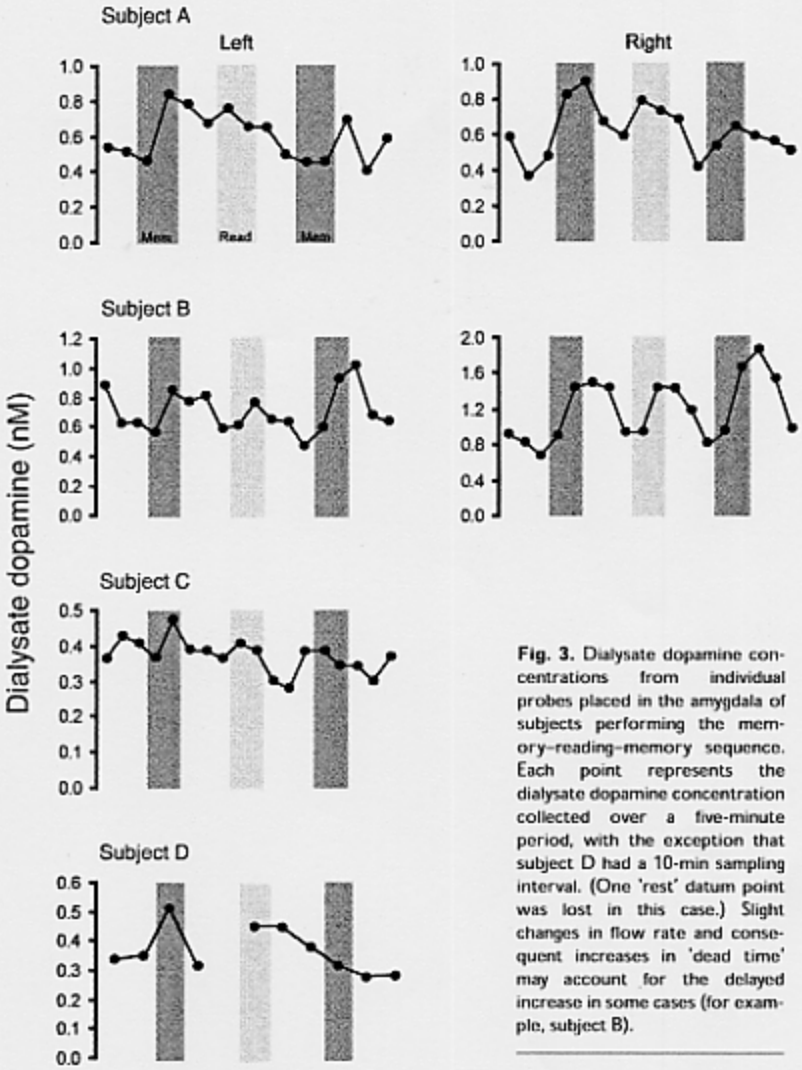


Fig. 3. Dialysate dopamine concentrations from individual probes placed in the amygdala of subjects performing the memory–reading–memory sequence. Each point represents the dialysate dopamine concentration collected over a five-minute period, with the exception that subject D had a 10-min sampling interval. (One 'rest' datum point was lost in this case.) Slight changes in flow rate and consequent increases in 'dead time' may account for the delayed increase in some cases (for example, subject B).

Non-human primate electrophysiological data show population responses of midbrain dopamine neurons to cognitive challenge to be highly transient, of the order of fractions of a second[9,10]. Thus, it is noteworthy that dopamine release was sustained during the paired associates learning and, to a lesser extent, the reading and working memory tasks. This discrepancy may reflect the task differences between animal studies and the current study, in which it was possible that repeated bursts of dopamine neuronal firing resulted in sustained dopamine release. Alternatively, the sustained increase in extracellular dopamine may have resulted from modifications at the dopamine terminal fields in the amygdala, such as changes in the presynaptic regulation of dopamine release[19] or dopamine reuptake[20], which would not be apparent when recording the firing rate of dopamine cells in the midbrain. Similarly, extended elevations in extracellular dopamine during learning and memory tasks are reported in non-human primate[21] and rodent[22] prefrontal cortex. Furthermore, prolonged elevation in extracellular dopamine occurs in

the human striatum during goal-directed motor tasks, as shown by positron emission tomography[23]. Irrespective of the mechanism, our findings suggest that sustained elevations in 'ambient' extrasynaptic concentrations of dopamine may influence synaptic function in the human amygdala throughout prolonged periods of cognitive activity, rather than briefly during the transition between low and high levels of cognition.

There is increasing evidence from studies in non-human primates that dopamine has a major role in working memory[1,24]. Midbrain dopamine neurons are activated[8] and dopamine release is increased in the monkey prefrontal cortex[21] during performance of working memory tasks. Computational models conceptualize dopamine as providing a mechanism for stabilizing active neural representations by providing protection from interfering stimuli[25]. We found that performance of a simple reading task was associated with increased extracellular dopamine in the human amygdala of the same magnitude as dopamine increase during a working memory task, when either task was presented first in the sequence. Therefore, it would seem that, in the amygdala at least, activation of dopamine release is not related to working memory specifically. However, when presented as the second task in a sequence of tasks (after an intervening period of rest), the dopamine level reached during working memory was significantly higher, on average, than during the corresponding reading task. These results are consistent with a relationship between amygdala dopamine release and novelty. Both reading and working memory were novel tasks when presented first. However, reading following the working memory task did not represent novelty (as the subject also read during the working memory task), whereas the working memory task still entailed novelty even when it followed the reading task. Alternatively, the higher level of dopamine observed during the working memory task compared to reading when presented second, but not first, in a sequence may reflect an underlying relationship between the dopamine released and the level of cognitive processing, revealed only when the effect of novelty was reduced upon repeated exposure.

Factors other than learning and novelty may account for the increases in dopamine observed, specifically, attentional and motivational factors[26,27]. These are difficult to separate from learning and memory, given the limited temporal resolution of the microdialysis technique. The reading/working memory data can certainly be interpreted as having been affected by these factors. The greater dopamine response during the more engaging working memory task when presented following the reading task may reflect increased attention or motivation. The two temporal patterns of dopamine release observed in the paired associate data may also be explained in these terms if one considers that motivation and/or attention might have been heightened when learning occurred.

Perhaps not surprisingly, given individual differences inherent to human subjects, considerable individual variability occurred in the data. This could be accounted for not only by subject variability and by differences in performance, but also by variability in the exact region within the amygdala from which the probes sampled. For instance, extracellular dopamine levels in the rodent amygdala vary among the several amygdaloid nuclei and along the rostral–caudal axis within these structures[28].

On the basis of studies in rodents and non-human primates, the three major mesencephalic rostral dopaminergic projections—to prefrontal cortex, striatum and limbic areas—are believed to modulate a large behavioral repertoire. The current data demonstrated sustained elevation in extracellular dopamine

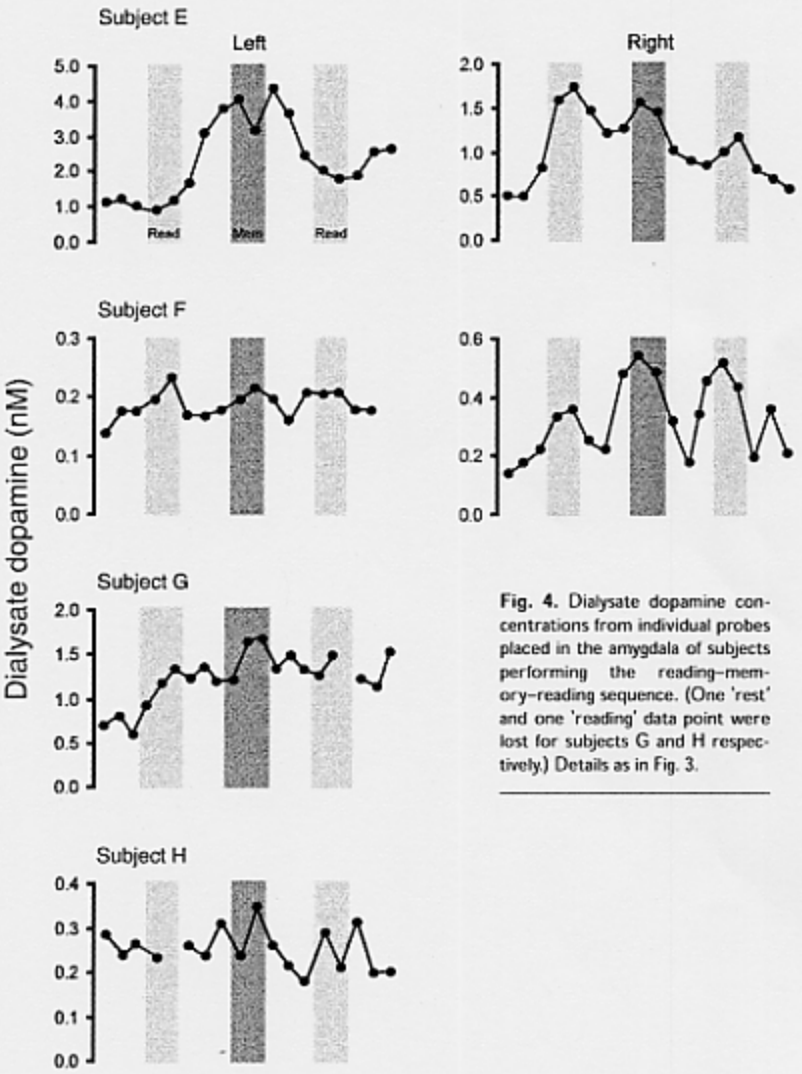


Fig. 4. Dialysate dopamine concentrations from individual probes placed in the amygdala of subjects performing the reading–memory–reading sequence. (One 'rest' and one 'reading' data point were lost for subjects G and H respectively.) Details as in Fig. 3.

concentration during cognition in an important part of the human limbic system, the amygdala. Although factors such as novelty, attention and motivation, in addition to learning *per se*, may have contributed to the dopamine changes observed, the temporal correlation of the dopamine response with that of the learning curve supports the concept, arising from the animal literature, of dopamine as a facilitator of sustained information processing in the human brain.

Methods

Subjects. Subjects were 10 patients (five females; mean age, 34 years; age range, 19–45) with pharmacologically resistant epilepsy requiring implantation of intracranial electrodes to identify an epileptogenic focus for potential surgical resection. The sites of implantation of the electrodes were based exclusively on clinical criteria. Subsequent to sterotaxtic placement of the electrodes, the patients were monitored for one to two weeks, and spontaneous seizures were recorded. Sixteen probes were implanted in the amygdala (left side, 10; right side, 6). Neurochemical sampling was conducted by means of a microdialysis probe inserted through the lumen of the depth electrode (1.25 mm diameter), such that a 10-mm length of active membrane was in contact with the brain parenchyma. The electrode and the microdialysis probe, as well as the technique of implantation and microdialysis sampling, have been described in detail previously[13]. The locations of the probes were verified by MRI obtained before removal of the electrodes. The data described here are derived from probes implanted in the amygdala. Patients doing the tasks described here were occasionally implanted with microdialysis probes in other sites, including extratemporal regions, but the numbers were too small for meaningful analysis. Previous consent for these studies was obtained from the patients according to the protocol approved by the institutional Internal Review Board. A potential limitation of this study was the subject population, that is, patients with chronic seizures who were on antiepileptic medications. Tasks were not administered for at least three hours following a seizure, and if a seizure occurred during the protocol, the data were discarded. However, in none of the patients participating in this study was seizure onset found to be in the amygdala. Furthermore, we found no relationship between the side of the brain containing the seizure onset zone and the pattern of dopamine release on that side during the protocols.

Experimental protocol. The tasks were conducted as the subject sat in bed in a quiet room. The nature of the task to be performed was first explained to the subject, followed by a 15–20 min period of rest. During the tasks, stimuli were presented on a laptop computer. For the reading/working memory protocol, dialysate was continuously collected in 5-min aliquots during the task periods as well as during the initial and intervening rest periods (with the exception of one subject, implanted unilaterally, for whom the sampling interval was 10 min). In the majority of cases, tasks were administered in 10-min blocks separated by rest periods of 15 min. (In one case, the tasks were presented for 15 min, and in 2 other cases, the rest periods were 10 and 20 min.) Eight subjects participated in this protocol: four subjects (A, B, C and D; six probes) did the memory–reading–memory sequence and the other four subjects (E, F, G and H; six probes) did the reading–memory–reading sequence. During the paired-associates learning protocol, dialysate was similarly continuously collected in 5-min periods during the entire task as well as during 20 minutes of pre- and post-task rest. Seven subjects (A, B, E, F, H, I and J; with a total of 13 probes) underwent this protocol. Six of these had bilateral probes, and the other subject (J) had only a left probe placed. Five of these subjects (A, B, E, F and H) also participated in the working memory/reading protocol.

Microdialysis. A detailed description of the microdialysis probe construction and perfusion procedure, together with the analytical method for quantitation of dopamine in dialysates has been provided elsewhere[13]. Briefly, microdialysis probes were constructed using a Cuprophan membrane (Akzo Nobel, Wuppertal, Germany; 215 μm o.d., 10 mm active length) and continuously perfused with an artificial cerebrospinal fluid at

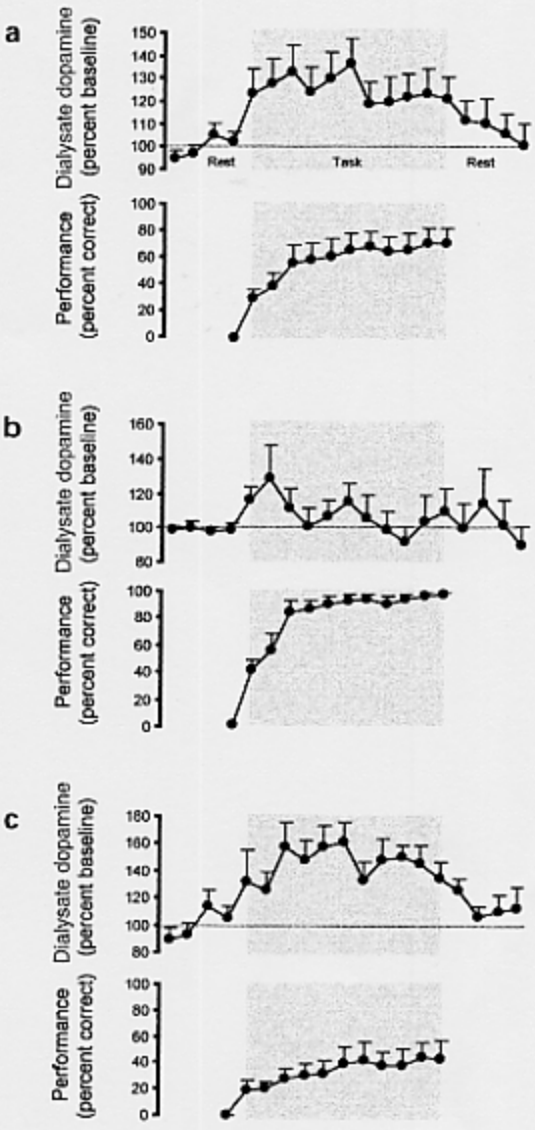


Fig. 5. Increase in amygdala dialysate dopamine concentration during execution of a paired associates task. (**a**) Top, dialysate dopamine levels expressed as mean percentage ± s.e.m. of baseline for 13 probes from seven subjects; the average of the four rest-period samples preceding the task were assigned as 100%. The mean ± s.e.m. absolute basal dialysate dopamine concentration was 0.56 ± 0.21 nM. Dopamine levels changed significantly over the course of the experiment ($F_{18,216} = 3.00$, $p < 0.005$). Bottom, average learning curve for all seven subjects and percentage of learned pairs as a function of time. Because the retrieval periods were not in phase with the five-minute dialysis sampling interval throughout the task, the performance scores represent interpolated values encompassing each five-minute dialysate sampling period. Dividing the data into two groups on the basis of performance in the task revealed two significantly different patterns of dopamine increase during the task ($F_{1,11} = 6.05$, $p < 0.05$). (**b**) Four subjects (B, H, I and J; seven probes) who attained near-maximum performance scores early in the task showed a transient increase in dopamine at the beginning of the task. (**c**) Three subjects (A, E and F; six probes) who presented slower learning curves exhibited a protracted elevation in dialysate dopamine levels.

a rate of 1.2 µl/min. Two fused silica tubes, 120 cm long, were used for inflow and outflow, providing an outflow 'dead time' of approximately 20 min. Dialysate samples were immediately frozen on dry ice and subsequently stored at –80°C. High performance liquid chromatography with electrochemical detection (HPLC-ECD) was used to determine the concentration of dopamine in each sample, and provided a limit of detection of approximately 0.05 nM for a 5-µl sample. Dialysate dopamine concentrations were normalized for each probe using the average of three (reading/working memory protocol) or four (paired-associates learning protocol) pre-task baseline samples as 100%. The data were then analyzed by one- or two-way analysis of variance, as appropriate, using the SuperAnova statistical software package (Abacus, Canoga Park, California). Duncan's new multiple range *post-hoc* test was used to determine the significance of differences between individual group means. A value of $p < 0.05$ was considered statistically significant.

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