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Treatments for neuropathic pain differentially affect delayed matching accuracy by macaques: Effects of amitriptyline and gabapentin

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ABSTRACT

Current clinical treatments for neuropathic pain include amitriptyline, a tricyclic antidepressant with mixed pharmacology that is also clinically reported to impair cognitive performance; and gabapentin, a compound that selectively interacts with α2δ-1 calcium channel subunits. Since few assessments of cognitive performance have been made in non-human primates with these marketed treatments, the purpose of this study was to determine their relative abilities to alter working memory as measured in mature macaques in their performance of a delayed matching-to-sample task. Four delay intervals of increasing duration provided increasing impairment in task accuracies during vehicle sessions. Administration of clinically relevant doses of amitriptyline significantly decreased task accuracy at the highest dose tested (3 mg/kg). Administration of gabapentin increased mean task accuracy, though the effect was not statistically significant until intra-subject variability was reduced by selecting the individual best dose for each animal (which averaged 12.8 mg/kg). Most of the effect was obtained during the presentation of long delay trials (18.2% above vehicle). Task improvement was sustained during sessions run 24 h after gabapentin administration. In a series that used a task-relevant distractor to determine gabapentin's effect on attention, drug treatment reversed distractor-impaired accuracy during long delay trials (25.4% above vehicle). The selective improvement in long delay accuracy in both paradigms suggests improvement in encoding or retention components of working memory. It is currently unclear whether the ability of acute administration of gabapentin to modestly improve working memory occurs by a mechanism that could be related to its anti-allodynic mechanism of action.

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1. Introduction

The identification of potential drug targets for improving memory and attention has dramatically increased over the past decade. Through the use of established and novel agonists and antagonists in a variety of animal models, almost every major neurotransmitter and many of their target receptors have been implicated [12,13,15]. Also, from a drug development standpoint, the specific pathology of human diseases and disorders of cognition have suggested potential therapeutic approaches. The most common example of this scenario might be the use of inhibitors of acetylcholinesterase in the treatment of Alzheimer's disease. This pharmacological approach was suggested by the loss of basal forebrain cholinergic neurons associated with the disease (see [4]). Somewhat less recognized is a decrease in cognitive function associated with chronic and neuropathic pain [38,44]. Unfortunately, many existing therapies to treat chronic pain do not restore cognitive performance. For example, topirimate which is used to prophylactically treat migraine can cause selective loss of attentional processing and decreases in verbal recall [28]. Tricyclic antidepressants such as amitriptyline are among the most effective means to treat chronic pain [5,39,60]. However, in view of the amnestic, anti-muscarinic cholinergic side-effect profile associated with amitriptyline [46,48,58,59], impaired cognitive performance limits its utility in the treatment of chronic pain, especially in the elderly [49]. Somewhat surprisingly, and even though the acute effects of morphine, a central nervous system depressant, can produce sedation and drowsiness, therapeutic doses are associated with little impairment of cognition function [24]. In fact, under certain conditions, this opiate can improve cognitive task performance [3,30].

The anticonvulsive agent gabapentin has gained substantial use in the treatment of postherpetic neuralgia and other painful neuropathies without having the abuse or severe side-effect liabilities

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normally associated with opioids [6,7,34,62]. Its mechanism of action is decidedly non-opioid in nature [56] and the drug is particularly active in models of allodynia [7,41]. The present study makes use of adult, healthy, non-human primates with normal cognitive capacity. The computer-assisted delayed matching-to-sample (DMTS) task in use at our facility has provided data pertaining to the effects of drugs impacting working memory in macaque subjects for over 20 years. More importantly, the procedure has offered excellent translational efficacy from preclinical studies to clinical evaluations for numerous compounds of differing pharmacological and chemical classes [13]. It has been our experience that the evaluation of compounds designed to improve working memory in non-human primates allows for a greater level of predictability in terms of clinical potency and efficacy as compared with lower species. The DMTS task allows for the measurement of abilities which are relevant to human aging such as attention, strategy formation, reaction time in complex situations and memory for recent events (e.g. [12,32,43]). The present study was designed to determine whether acute gabapentin administration would display a reduced potential to impair the aspects of working memory than amitriptyline, which is known to have amnestic pharmacology [21,48]. The compound also was studied in a model of task-relevant distractibility [13] to determine whether gabapentin exerts specific effects on attentional components of working memory.

2. Methods

The subjects were 3 male and 3 female pigtail macaques (*Macaca nemestrina*). Subject information is summarized in Table 1. Each animal was well trained (>100 individual sessions) in the delayed matching-to-sample (DMTS) task. The animals were maintained on tap water (unlimited) and standard laboratory monkey chow (Harlan Teklad Laboratory monkey diet, Madison, WI) supplemented with fruits and vegetables. Food was removed from cages at about 0630 h, and was replaced after the completion of testing of all subjects for the day (at about 1630 h). Additional nourishment was derived from 300 mg reinforcement food pellets (commercial composition of standard monkey chow and banana flakes, Noyes Precision food pellets, P.J. Noyes Co., Lancaster, NH) obtained during the experimental sessions. On weekends animals were fed without time restrictions. Room temperature and humidity were maintained at 22 ± 0.6 °C and 52 ± 2%, respectively. Test panels attached to each animal's home cage presented the task by using a computer-automated system. The test system included a touch-sensitive screen (15 in. AccuTouch LCD Panelmount TouchMonitor) and pellet dispenser units (Med Associates) mounted in light-weight aluminum chasses [14]. The stimuli included red, blue, and yellow rectangles presented against a black background. A trial was initiated by presentation of a sample stimulus composed of one of the three colors. The sample stimulus (located above and centered between the two choice stimuli) remained in view until the monkey touched the screen within the borders of the sample rectangle to initiate a pre-programmed delay interval. Touching a stimulus provided the illusion that the figure was actually depressed. Following the delay interval, the two choice stimuli were presented. One of the two choice colors was presented so that the color of one stimulus matched the color of the sample stimulus. A correct (matching) choice was reinforced. Non-matching choices were neither reinforced nor punished. The inter-trial interval was 5 s and each session consisted of 96 trials. The presentation of stimulus color, choice colors, and choice position were fully counterbalanced so as to relegate non-matching (mediating) strategies to chance the levels of accuracy. Three to five different presentation sequences were rotated through each daily session to prevent the subjects from memorizing the first several trials. Delay (memory retention) intervals were established during several non-drug or vehicle sessions prior to initiating the study. The duration for each delay interval was adjusted for each subject until three levels of group performance accuracy were approximated: zero delay (85–100% of trials answered correctly); short delay interval (75–84% correct); medium delay interval (65–74% correct); and long delay interval (55–64% correct). The assignment of delay intervals was necessary to avoid ceiling effects in the most proficient animals during drug studies, and to insure that each animal began testing at relatively the same level of task difficulty. Failure to respond during a trial initiated the next trial in the sequence. Task accuracy (% trials correct) was determined only from the total number of trials actually completed.

Table 1
Subject information.

ID No.	Sex	Years old	Weight (kg)	Species	Delay intervals (s)		
					Short	Medium	Long
770	F	19	7.8	Pigtail	5	7	15
c8r	M	8	9.6	Pigtail	5	15	30
p18	F	11	7.6	Pigtail	10	25	50
PPa1	M	14	14.8	Pigtail	5	10	15
tp8	F	16	7.4	Pigtail	5	10	20
v6t	M	8	18	Pigtail	15	20	40
Mean		12.67	10.87		7.50	14.50	28.33
S.E.M.		1.82	1.83		1.71	2.81	5.87

These data were obtained at the start of the first experimental series. Short, medium, and long refer to the duration of assigned delay intervals for each subject (time interval between extinguishing the sample stimulus and the appearance of the choice stimuli). The delay interval durations were not changed over the course of the study.

In a separate experimental series, distractor stimuli (interference trials) were presented on 24 of the 96 trials completed during distractor DMTS sessions. The stimuli were presented simultaneously on the sample and choice keys for 3 s and they consisted of a random pattern of the three colored rectangles flashing in an alternating manner. The distractor rectangles comprised the same three colors used for sample and choice stimuli presentation. The total duration of presentation for a given colored light was 0.33 s. Distractor stimuli were presented an equal number of times on trials with short, medium, and long delay intervals. The distractor sequence was initiated 1 s into the delay interval. Three response latencies were also measured: the "sample latency", which is the time between the presentation of the sample color and the animal pressing in sample rectangle; and the "choice latency" which is the time between the presentation of the choice colors and the animal pressing one of the choice rectangles. Choice latencies were divided into those associated with correct and incorrect responses.

All procedures were reviewed and approved by the Medical College of Georgia Institutional Animal Care and Use Committee and are consistent with AAALAC guidelines. Each subject had previously participated in one or more short-term studies assessing the effects of reversible drugs on DMTS performance. Prior drug experience produced no observable untoward effects in the animals, and each subject received at least a 4-week washout period (with continued weekday DMTS testing) prior to the start of this study.

2.1. Drug administration

The following doses of gabapentin were administered: 1, 3, 10, and 30 mg/kg. Vehicle (sterile normal saline) was administered twice during the study. Injections were given in the thigh muscle 30 min prior to testing. Gabapentin was dissolved in saline within a total injection volume of 0.04 ml/kg. For the 30 mg/kg dose, the compound was dissolved in ~30 μl DMSO and then brought up to volume with saline. A separate set of DMSO vehicle sessions

were included, although this alternate vehicle was previously shown not to affect baseline accuracies relative to the saline vehicle. The following doses of amitriptyline were administered: 0.3, 1.0, and 3.0 mg/kg. Vehicle (sterile normal saline) was administered twice during the study. Injections were given in the thigh muscle 30 min prior to testing. The dose ranges selected for gabapentin and amitriptyline were based on those used, respectively, for the clinical treatment of neuropathic pain [39].

2.2. Statistical analyses

Data for percent correct were subdivided according to delay interval for each 24-trial delay component of the session. All statistical analyses were performed on raw data (% trials correct). Data were analyzed by use of a multi-factorial analysis of variance (ANOVA) with repeated measures (SAS, JMP statistical software package). An orthogonal multi-comparison t-test was used to compare individual means. For each table/figure (below) error values denoted by ± indicate the standard error of the mean. Differences between means from the experimental groups were considered significant at the $P < 0.05$ level (2-sided test). Trends toward significance were considered at the $P < 0.10$.

3. Results

3.1. Gabapentin series

As a group the performance accuracies in the standard DMTS task for vehicle sessions approximated the criteria set forth above: zero delay: 99.24%, short delay: 83.9%, medium delay: 71.1% and long delay: 59.2% trials correct. Administration of gabapentin 30 min before testing did not produce a statistically significant change in task accuracies measured during zero, short, and medium delay intervals ($P > 0.30$). Long delay trial accuracies were increased relative to vehicle ($F_{1,143} = 7.12$, $P = 0.009$). The data associated with each delay interval were analyzed separately because they can be regarded as separate components of working memory [13]. These data are summarized in Fig. 1. Examination of the memory retention curves presented in the figure confirms gabapentin's selectivity for improving long delay trial accuracy. The data are more easily visualized in the inset of Fig. 1. Individual *t*-tests were performed on the long delay trial accuracy values for each dose. The alpha values are presented in the parentheses nearby the respective data points shown in the inset of Fig. 1. The individual variability across doses during long delay trials can be visualized in Fig. 3A where the changes from baseline in task accuracy are plotted as a function of dose for each subject. All subjects except #770 responded with an increase over baseline (horizontal 0 line) after receiving at least two of the four doses. Subject 770 responded only to the lowest dose (1 mg/kg) suggesting that this animal could be more sensitive to gabapentin than the other animals. A separate analysis was performed to determine whether there were any differences between the sexes related to drug treatment. There were no significant treatment × sex ($P > 0.13$) or delay interval × treatment × sex ($P > 0.90$) components of the ANOVA.

This pattern of mean long delay trial enhancement relative to vehicle also was apparent during sessions run 24 h after gabapen-

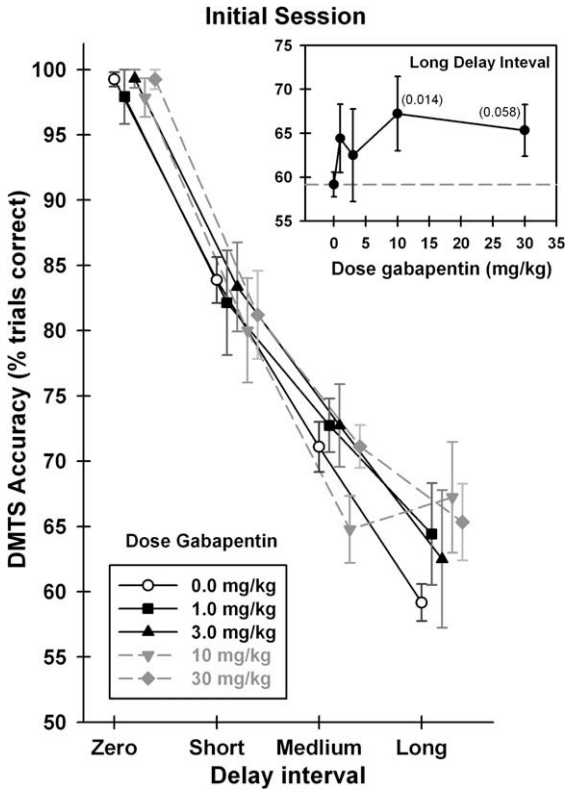

Fig. 1. The effect of vehicle or gabapentin administration on DMTS task accuracies by mature Pigtail monkeys. For each drug dose, DMTS testing was initiated 30 min after i.m. injection of vehicle or gabapentin. Each value represents mean ± S.E.M. Data curves were slightly offset to better visualize the error bars. Inset: task accuracy during long delay trials plotted as a function of gabapentin dose. The values in parentheses indicate the alpha values based on a multiple *t* analysis; however, there was no significant ANOVA component for the entire data set.

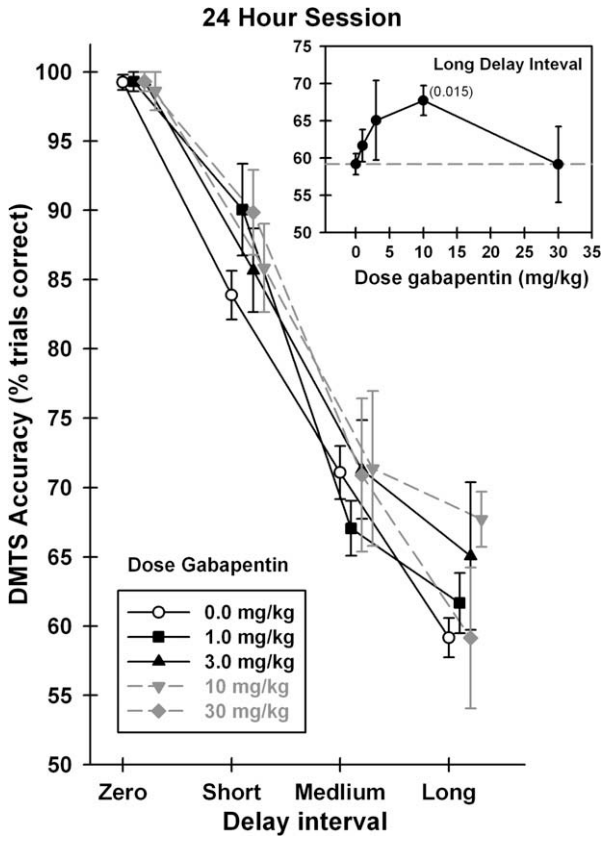

Fig. 2. The effect of vehicle or gabapentin administration on DMTS task accuracies by mature Pigtail monkeys. For each drug dose, DMTS testing was initiated 24 h after i.m. injection of vehicle or gabapentin with no additional pre-test administration. Each value represents the mean ± S.E.M. Data curves were slightly offset to better visualize the error bars. Inset: task accuracy during long delay trials plotted as a function of gabapentin dose. The value in parentheses indicates the alpha value based on a multiple *t* analysis; however, there was no significant ANOVA component for the entire data set.

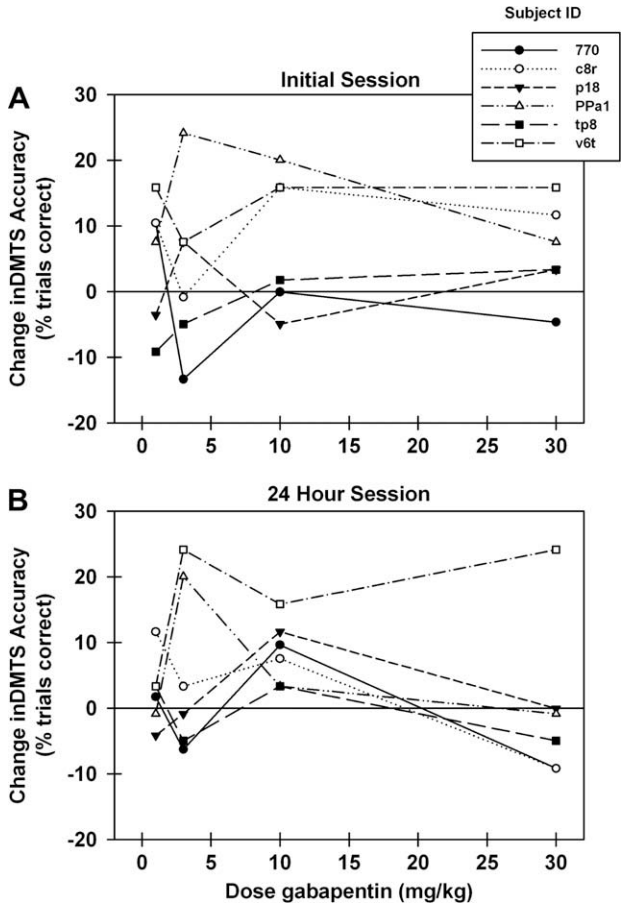

Fig. 3. The changes in DMTS accuracy from baseline (averaged vehicle sessions) produced by gabapentin administration during long delay trials as a function of dose. (A) Data derived from individual subjects during DMTS sessions run 30 min after gabapentin administration. (B) Data derived from individual subjects during sessions run 24 h after gabapentin administration with no intervening treatment.

tin administration (with no intervening treatment). These data are summarized in Fig. 2. Again, gabapentin treatment was associated with no significant change in task accuracies measured during zero, short, and medium delay intervals ($P > 0.50$). Long delay trial accuracies were nearly significantly increased relative to vehicle ($F_{1,143} = 3.41$, $P = 0.067$). Mean accuracy values during long delay trials are plotted vs. the dose of gabapentin in the inset of Fig. 2. As with the 30-min session, the effect peaked at the 10 mg/kg dose, but unlike the 30-min session, the effect was not maintained at the 30 mg/kg dose. The individual variability across doses during long delay trials can be visualized in Fig. 3B. All subjects except #p18 responded with an increase over baseline after receiving at least two of the four doses. Subject p18 responded only to the 10 mg/kg dose, which was also the group maximum.

Next the task accuracies associated with each of the four delay intervals after each dose of gabapentin administration were averaged. An individual best dose of gabapentin was selected for each subject that was based on the maximal increase in accuracy across all four delay intervals. One subject's best dose was 1 mg/kg, two subjects' best dose was 3 mg/kg, one subject's best dose was 10 mg/kg, and two subjects' best dose was 30 mg/kg; providing an average best dose of 12.8 mg/kg. The accuracy data associated with the best dose are summarized in Fig. 4. There was a statistically significant improvement in task accuracies relative to vehicle during best dose sessions ($F_{2,5} = 4.81$, $P = 0.010$). The significant improvements in task accuracy were restricted to long delay trials during sessions run 30 min ($t = 3.59$, $P = 0.001$) and 24 h ($t = 2.69$, $P = 0.008$) after compound administration. During the 30-min trials mean long delay accuracy increased by 18.2% above vehicle accuracy (the difference between treatment and vehicle accuracies/vehicle accuracy × 100).

As a group, median task latencies associated with vehicle administration were as follows: sample latency 3.04 ± 0.29 s; choice latency associated with correct choices 2.30 ± 0.15 s; and choice latency associated with incorrect choices 2.98 ± 0.36 s. Gabapentin treatment did not significantly alter the three task latencies at any of the doses tested ($P > 0.50$, data not shown).

3.2. Gabapentin distractor series

The same subjects that participated in the previous series (after a 2-week washout period) were administered a series of distractor sessions spaced at least 4 days apart (intervening sessions were always standard DMTS sessions with pre-test vehicle administration). Two highest doses of gabapentin (10 and 30 mg/kg) from the previous series were evaluated in the distractor paradigm. The data summarized in Fig. 5 also present a comparison between vehicle standard DMTS accuracies and distractor DMTS accuracies. Four vehicle standard DMTS sessions were equally interspaced during the distractor series. There was a significant effect of the presence of the distractor relative to the standard DMTS task ($F_{3,5} = 15.1$, $P < 0.0001$). Post hoc analysis revealed significant decrements in task accuracies associated with the presence of the distractor associated with vehicle administration and with

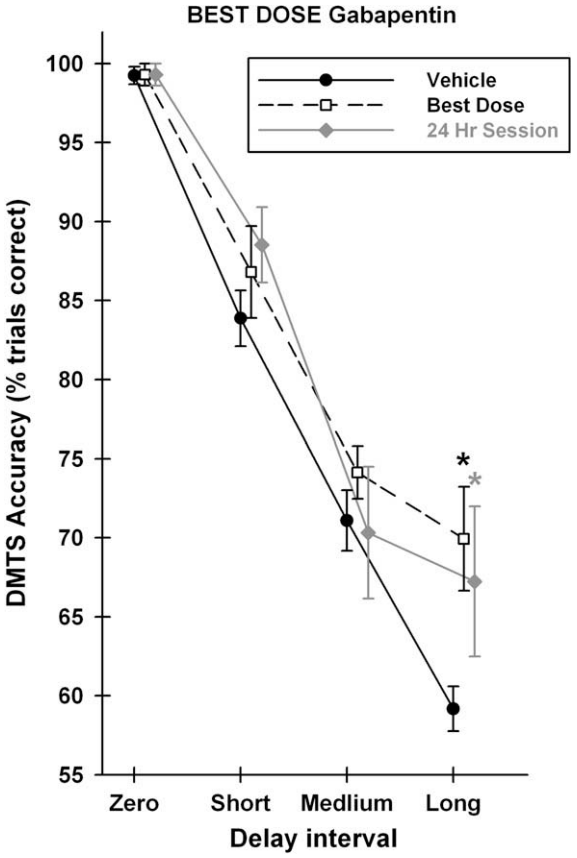

Fig. 4. The effect of vehicle or an individual best dose of gabapentin on DMTS task accuracies by mature Pigtail monkeys. The best dose for each animal was selected from their individual responses (as presented in Fig. 1) across all four delay trials. Data are present for both the initial (30 min) session (best dose) and their respective sessions run 24 h later (24-h session). Each value represents mean ± S.E.M. Data curves were slightly offset to better visualize the error bars. *Significantly different ($P < 0.01$) from the respective vehicle mean values.

both doses during short and medium delay intervals (Fig. 5). The only exception was for long delay, in which case both doses of gabapentin were associated with mean accuracies that were not significantly different from respective standard DTMS means. In fact, long delay trial distractor accuracy after the administration of the 10 mg/kg dose was significantly increased relative to distractor vehicle accuracy ($t = 2.32$, $P = 0.022$). Gabapentin treatment increased distractor accuracy during long delay trials by 24.5% above the distractor vehicle mean.

3.3. Amitriptyline series

As a group the performance accuracies in the standard DMTS task approximated the criteria set forth above: zero delay: 99.4%, short delay: 83.3%, medium delay: 68.4% and long delay: 62.3% trials correct. Administration of amitriptyline produced a statistically significant change in task accuracies measured during sessions run 30 min after drug administration ($F_{3,5} = 12.60$, $P < 0.0001$). These data are summarized in Fig. 6. Post hoc analysis indicated that the effect of drug treatment was to decrease task accuracy. The effect was restricted to the 3 mg/kg dose, though trials associated with all four delay intervals were affected by this dose of amitriptyline: zero delay ($t = 2.17$, $P = 0.032$); short delay ($t = 2.29$, $P = 0.024$); medium delay ($t = 4.51$, $P \leqslant 0.0001$); and long delay ($t = 2.78$, $P = 0.006$). There was no significant effect of compound treatment during sessions run 24 h after administration (inset of Fig. 1).

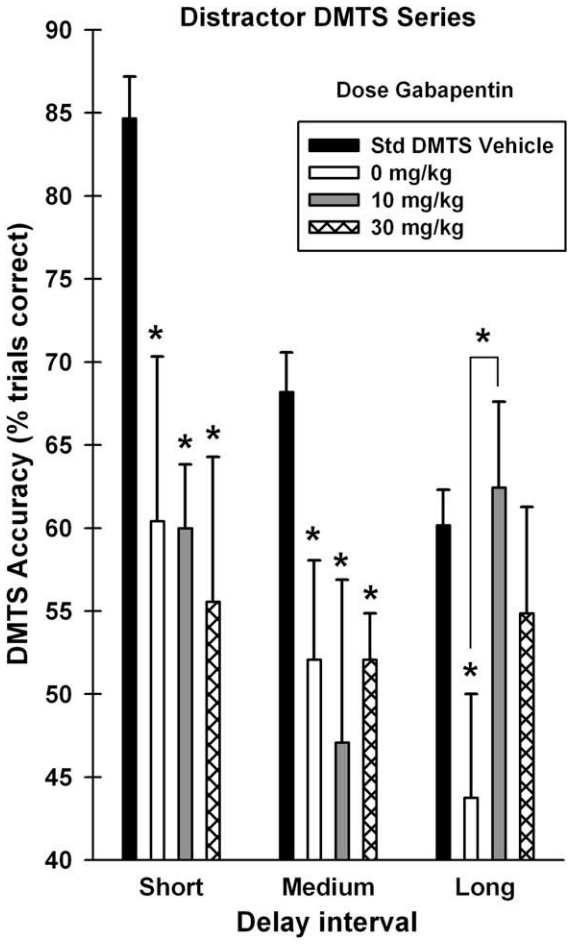

Fig. 5. The effect of vehicle or gabapentin on distractor DMTS task accuracies by mature Pigtail monkeys. For each drug dose, DMTS testing was initiated 30 min after i.m. injection of vehicle or gabapentin. Each value represents the mean ± S.E.M. "Std DMTS Vehicle" indicates data derived from a separate series of standard DMTS sessions (no distractor present) in which the same cohort was treated with vehicle. "0 mg/kg" indicates the vehicle pretreatment sessions during distractor DMTS sessions. *Significantly different ($P < 0.02$) from the respective "Std DMTS" Vehicle mean. *Over the parentheses indicates significantly different from the respective "0 mg/kg" mean $P = 0.022$).

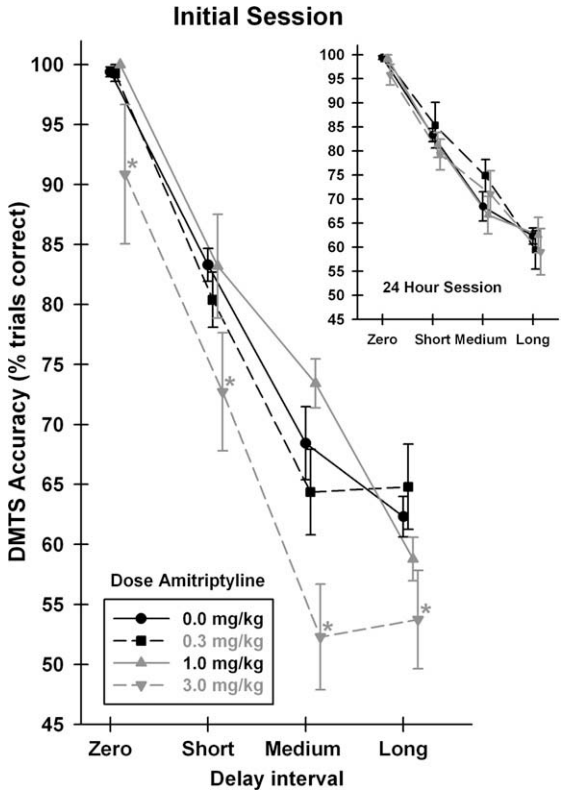

Fig. 6. The effect of vehicle or amitriptyline on DMTS task accuracies by mature Pigtail monkeys. For each drug dose, DMTS testing was initiated 30 min after i.m. injection of vehicle or amitriptyline. Each value represents mean ± S.E.M. Data curves were slightly offset to better visualize the error bars. *Significantly different from the respective vehicle (0.0 mg/kg) mean, $P < 0.05$. Inset: task accuracies during sessions initiated 24 h after i.m. injection of vehicle or amitriptyline with no additional pre-test administration.

As a group, median task latencies associated with vehicle administration were as follows: sample latency 3.11 ± 0.36 s; choice latency associated with correct choices 2.35 ± 0.14 s; and choice latency associated with incorrect choices 2.90 ± 0.23 s. Amitriptyline treatment did not significantly alter the three task latencies at any of the doses tested ($P > 0.30$, data not shown).

Well-trained mature subjects as were used in this study generally complete all or nearly all trials in each session unless they experience some untoward effect of drug treatment. Fig. 7 compares the number of trials completed per session for gabapentin treatment with that for amitriptyline treatment. Gabapentin produced no significant effect on this parameter ($P > 0.20$). This was not the case for amitriptyline ($F_{3,5} = 5.28$, $P < 0.006$) which significantly decreased the number of trials completed after the administration of the 3.0 mg/kg dose ($t = 3.83$, $P = 0.001$).

4. Discussion

As less than two-thirds of patients with chronic pain obtain sufficient pain relief with available drugs [22], the cost-benefit considerations for the clinical management of pain have become increasingly important. Indeed, the functional limitations of ineffectively treated pain can be translated to functional physical limitations normally represented in a population several decades more senior [19]. The results of this study suggest that cognitive

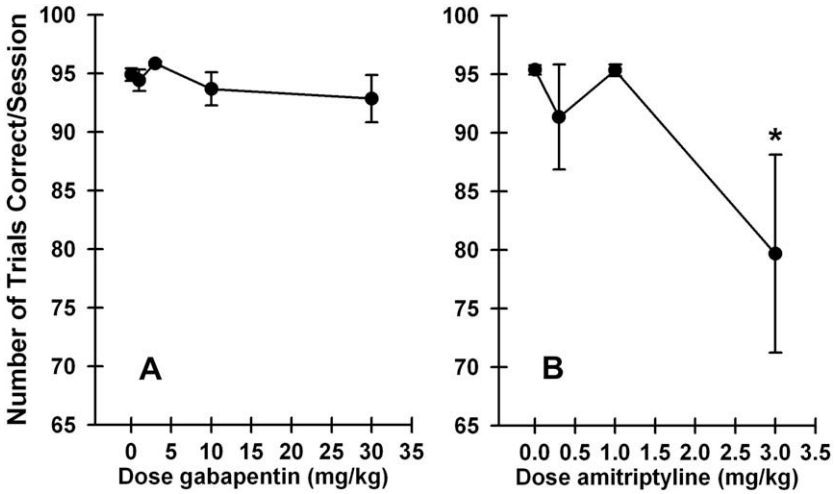

Fig. 7. The effect of gabapentin (A) or amitriptyline (B) administration on the number of trials completed during the standard DMTS task plotted as a function of dose. These data were obtained from the experimental series identified in Figs. 1 and 6, respectively. *Significantly different from respective vehicle (0.0 mg/kg) mean, $P < 0.05$.

performance could be an important consideration in the choice of neuropathic pain treatment. The association between chronic painful conditions and cognitive impairment has received increased recognition as clinically relevant symptoms to manage [1,44]. It has been suggested that pain intensity and duration is associated with the extent of cortical reorganization; i.e., pain memories that can influence the processing of both painful and non-painful input to the somatosensory cortex [23]. The degree of cognitive impairment though mild (Mini Mental State Examinations scores between 18 and 24 points) has the potential to worsen with pain chronicity, and cognitive impairment is highly prevalent – up to 43% in certain categories of patients [44]. The impact of analgesic agents and other interventions that reduce the intensity of chronic neuropathic pain on pain-associated cognitive impairment is less well understood. Part of the challenge is that many of the potential pharmacological interventions that relieve pain can have a negative impact on cognition. The results of this study suggest that gabapentin could represent one neuropathic pain treatment that is less prone to negatively impact domains of attention or working memory over a clinically relevant dose range.

Recent treatment guidelines for the use of gabapentin and amitriptyline in the clinical management of chronic pain take into account an array of efficacy, side effects and cost considerations [42]. Tricyclic antidepressants such as amitriptyline are first-line medications that have advantages including low cost, once-daily dosing, and beneficial effects on depression. The tricyclic antidepressants block monoamine transporters, cholinergic receptors, *N*-methyl-D-aspartate receptors and sodium channels [54]. The biggest disadvantages include anticholinergic side effects (e.g., dry mouth, constipation, urinary retention and memory impairment) and orthostatic hypotension. Gabapentin, also a first-line medication, has complicated nonlinear pharmacokinetics with accompanying dizziness and sedation that requires gradual titration. However, gabapentin has a beneficial mood elevating effect that is independent of analgesia [25]. Gabapentin presumably exerts its pain relieving action by binding to auxiliary subunits of calcium ion channels to reduce neurotransmitter release [20]. Recently, the differential actions of gabapentin and nortriptyline (the metabolite of amitriptyline) have been shown to be more efficacious than either drug [25], and to result in clinically significant improvement of sleep interference, a major complication of neuropathic pain.

Although significant memory or cognitive impairment is not usually associated with gabapentin in its standard use as an anticonvulsive agent or in pain modification, the preclinical and clinical literature reveal a considerable lack of consistency in studies designed to measure cognitive function after treatment with the drug [8,9,11,36,40,50–53]. The reason for this variability is not clear, though the usual suspects include species differences, alternate assessment paradigms, different doses and dose regimens, concomitant illness, and the presence of pain during assessments. In some instances the experimental design is more attuned to an expected hypothesis of cognitive impairment rather than cognitive enhancement. In this study we were also surprised to find that gabapentin produced a significant degree of improvement in DMTS task accuracy in our subjects. The effect was repeatable in a separate series designed to focus on attentional aspects of memory. In each case gabapentin increased long delay trial accuracies by more than 18%. This effect is in the range of cognitive improvement produced by several cognitive enhancing agents tested in our subjects and in human clinical studies [12,13].

As noted in the introduction, gabapentin lacks agonist and antagonist properties at both $GABA_A$ and $GABA_B$ receptor sites and it does not appear to block GABA uptake (see [18]). The drug has been observed to increase the apparent rate of the synthesis of GABA in several brain regions [37] to increase GABA-release [29] and to inhibit GABA-transaminase which metabolizes GABA to succinic semialdehyde and glutamate [27]. This could be important in the context of our findings since GABA is involved in the control of short-term memory formation and its action (i.e., at enhancing or inhibiting memory formation) depends on the level of GABA released at the time of learning [26]. But gabapentin's clinical actions have largely been attributed to its ability to potently and selectively bind to the $\alpha 2\delta$ subunit of voltage-dependent calcium channels, reducing calcium influx and modulating the release of downstream excitatory neurotransmitters, including glutamate [10]. Therefore it is perplexing why a compound that reduces excitatory neural activity in the CNS (hence its anticonvulsive action) can enhance cognitive function. One explanation could reside in the abilities of gabapentin and the related drug pregabalin to enhance descending bulbo-spinal noradrenergic antinociceptive systems, an effect mediated through the upregulation of the $\alpha 2\delta$-1 subunit of voltage-dependent calcium channels located on locus coeruleus neurons [31,55]. The spinal response is mediated through the activation of α2-noradrenergic receptors. The possibility that gabapentin also enhances prefrontal cortical noradrenergic activity (and hence α2-adrenergic receptors) has not been explored, although in autoradiographic studies [57], relatively high levels of [3H] gabapentin binding sites were identified in frontal

cortex and hippocampus, regions known to support working memory and attentional processes. This potential mechanism is relevant because noradrenergic pathways innervating prefrontal cortex contribute to the cognitive improvements produced by α2 receptor agonists acting on post-synaptic α2 receptors in this region [2].

In one respect the pharmacodynamic (task improvement up to 24 h after single dose administration) actions of gabapentin as revealed in this study mimic those produced by clonidine and nicotine, which directly and indirectly (through norepinephrine release) activate central α2-adrenergic receptors. Like gabapentin, clonidine and nicotine produce protracted improvements in task accuracy after a single administration. In each case the protracted mnemonic action outlives the presence of active compound in the body [16,17]. One additional similarity among gabapentin, clonidine, and nicotine is their partial selectivity for improving long delay trial accuracy in the DMTS task, suggesting that encoding and/or retention components of working memory experience the most benefit. Unlike nicotine [45], however, gabapentin did not improve short delay distractor trial accuracy, suggesting that the drug is not as effective as nicotine in improving attentional aspects of memory. The significant outcome of the distractor series did, however, serve to support the results of the best dose analysis of gabapentin in the standard DMTS task with respect to the selective effect of the drug to improve long delay trial accuracy.

Lastly, we studied three clinically equivalent doses of amitriptyline in the standard DMTS task. Unlike gabapentin, the drug did not improve task accuracies, and instead, the highest dose shifted the memory retention curve downwards in a manner consistent with classical amnestic agents like scopolamine [14,47]. This dose also was associated with a decrease in trials completed – an effect likely attributed to some untoward effect of the drug decreasing task motivation.

Both amitriptyline and gabapentin share some overlapping pathways to alleviate allodynia. Amitriptyline clearly enhances noradrenergic mechanisms [33] that would augment descending inhibitory α2-noradrenergic transmission at the level of the dorsal horn [61]. Amitriptyline, in addition, has some pharmacological action via endogenous opioids, whereas the anti-allodynic action of gabapentin is naloxone insensitive [5]. Although amitriptyline can also facilitate ascending α2-adrenergic transmission to forebrain structures involved in cognitive processing [35], the strong anti-muscarinic (i.e., amnestic) pharmacology of amitriptyline dominates its effect on cognitive functions [58]. Based on the action of gabapentin to affect locus coeruleus mediated descending noradrenergic transmission [31], it is possible that the modest beneficial effects of gabapentin on attention and working memory are related to the activation of some ascending noradrenergic pathways to the prefrontal cortex, and to the local inhibition of neurotransmitter release by gabapentin in other areas [10]. As more is learned about the mechanism(s) of action of gabapentin, both as an anti-allodynic drug and as a drug that can enhance some domains of working memory and attention, it may be possible to design improved treatments for chronic pain disorders with the corresponding pain relief and full restoration of cognitive function.

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