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Differential effects of paclitaxel treatment on cognitive functioning and mechanical sensitivity

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ABSTRACT

Treatment for cancer has been indicated to negatively impact the quality of life for patients. Specifically, chemotherapy has been associated with fatigue, nausea, and peripheral neuropathy. More recently, chemotherapy has been found to be related to cognitive impairment in various domains including working memory, information processing speed, and visual attention. At this time, the mechanisms underlying cognitive impairment are not understood, and there is currently no treatment for this condition. The purpose of this study was to examine the development of chemotherapy-induced cognitive impairments and symptoms of peripheral neuropathy. While receiving the chemotherapeutic agent Taxol, animals were tested daily in the Five Choice Serial Reaction Time Task (5CSRTT), a task which requires animals to respond to a visually presented stimulus in order to obtain reinforcement. In addition, animals were tested for the development of peripheral neuropathy, measured by changes in sensitivity to mechanical stimulation. The results indicate Taxol treated animals developed mechanical sensitivity within 24 h after the first injection of chemotherapy. However, relative to control animals, Taxol treated animals did not exhibit alterations in cognitive function in the 5CSRTT. These differential findings may provide interesting insight into the mechanisms underlying chemotherapy-related cognitive impairment.

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Chemotherapy is the most commonly used treatment for cancer due to its expansive use and efficacy in managing cancer; however, this treatment results in injurious side effects such as fatigue and nausea. Further, while sensory side effects such as peripheral neuropathy have long been acknowledged, cognitive impairment has only recently been considered as a major side effect of chemotherapy. This impairment, often referred to as chemofog or chemobrain, is described as a subtle decline in general cognitive ability, leading to feelings of absentmindedness [26] and difficulty maintaining concentration. Chemotherapy-related cognitive impairments have been seen in the domains of working memory, executive function, processing speed, verbal fluency and verbal memory, and visuospatial memory [5,7,11,13,18,24,29]. Additionally, the prevalence of this impairment ranges from 17% to 75% of chemotherapy treated patients [23] and is seen up to 10 years after chemotherapy has ended [1].

Currently, little research has addressed a means to treat cancer-related cognitive impairment, primarily due to a lack of understanding of causal factors. Researchers have attempted to reproduce cognitive impairments in animal models with little success or conflicting results using chemotherapeutic agents. For instance, vincristine treatment leads to symptoms of peripheral neuropathy, but it does not produce alterations in sensorimotor gating [3]. Chemotherapy treatment has been shown to result in decreased retention in certain conditioning tasks in some studies [15,20,31], but not in others [9,22]. Use of the Morris Water Maze has also produced inconsistent results, with some researchers findings no decrements in this test of spatial ability as a result of chemotherapy treatment [19,20,30], and others finding *improved* performance in this task following chemotherapy [8]. Currently, the reason for these discrepancies is unclear.

One potential means to study cognitive impairment following chemotherapy treatment in an animal model is the Five Choice Serial Reaction Time Task (5CSRTT), which is an operant procedure that requires the animal to attend to randomly presented visual stimuli within a short period of time in order to receive reinforcement. The 5CSRTT is an established test of general cognitive function that is commonly used in rodents and primates. The test is sensitive to changes in sustained and divided attention, and has been used to study the interaction of attention and motivational drives, pharmaceutical effects, and brain lesions; further, by presenting a brief burst of white noise at the time of stimulus onset, the researcher can examine selective attention [16]. Changes in the cognitive domains of attention, executive function, and information processing speed can be detected by failures to respond (omissions), incorrect responses, and increased latencies to respond [4].

The purpose of this study was to examine the cognitive impairment that accompanies chemotherapy and measure these

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impairments using the 5CSRTT. The chemotherapeutic agent Paclitaxel (Taxol) was used for this study. This agent reliably produces peripheral neuropathy [2,10,12], which may be due in part to a down regulation of glutamate transporters [28], leading to impaired glutamate reuptake and an increase in spontaneous activity in dorsal horn neurons. It was hypothesized that animals receiving Taxol would show decrements in performance on the 5CSRTT relative to control animals and that these decrements would be accompanied by signs of peripheral neuropathy as measured by changes in sensitivity to mechanical stimulation.

Twenty adult male Long Evans rats were used for this study. Ten animals were treated with Taxol and ten animals received vehicle. All animals were housed singly due to the excretion of Taxol in urine and feces and to ensure caloric intake during food deprivation in a temperature controlled room on a 12:12 (7am–7pm) light/dark cycle with free access to water. Due to the use of operant procedures, animals were food deprived to 80%–85% ad libitum weight. All procedures were approved by the Institutional Animal Care and Use Committee for the University of Texas at Arlington.

All operant conditioning occurred in a $20 \times 28 \times 30$ cm Plexiglas enclosure (Med Associates, Vermont, USA) placed within a fan-ventilated, sound-attenuated chamber. Centered on one end of the chamber is a food hopper from where animals retrieve earned 45 mg pellets. On the wall opposite from the food hopper is a panel that contains 5 nose poke holes, each of which has a small light located within.

On Day 1 of training, animals were magazine trained for 15 min. On the following day, animals were exposed to the 5CSRTT. Briefly, a light in one of the 5 nose poke holes is randomly presented for a set amount of time (stimulus duration, or SD). If the animal correctly places its nose within the lit nose poke hole, a pellet is dispensed. If the animal responds incorrectly or fails to make a response (omission), the house light is turned off for a 5 s time-out period. The time from making a response, or failing to make a response, to reward collection is considered one trial. Each animal was tested daily for one session, which is the shorter of 100 trials or 30 min. Throughout training, animals were gradually moved from a 60 s SD to a 0.5 s SD as performance improved. To be included in the study animals had to maintain a criterion of 70% correct and fewer than 20% omissions for three consecutive sessions. Once an animal achieved criterion, the training phase was complete, and the chemotherapeutic agent was administered. The following session began the testing phase of the experiment, which continued for the remainder of the protocol.

On the eighth day following inclusion into the study, a noise paradigm was included in the regular 5CSRTT program. This day was chosen based on preliminary data indicating maximal mechanical sensitivity on this day. For this test day only, a brief 80 dB burst of white noise was randomly presented at the time of stimulus onset for approximately 20% of all trials.

At the end of each session data were transferred to Excel and the percentage of correct responses, the percent of omissions, the percentage of intertrial interval (ITI) responses (a measure of impulsivity), the average latency to make a correct response, and the average latency to collect an earned reward were calculated according to the following formulas [14]:

$$\text{Percent correct} = \frac{(\text{correct responses})}{(\text{correct responses+incorrect responses})}$$

$$\text{Percent omission} = \frac{(\text{number of trials in which the animal failed to make a response})}{(\text{sum of all trials for that session})}$$

$$\text{Percent ITI} = \frac{(\text{number of trials in which the animal made a response during the intertrial interval when no stimulus is being presented})}{(\text{correct responses} + \text{incorrect responses} + \text{number of trials in which the animal failed to make a response} + \text{number of ITI responses})}$$

Latency measures

$$= \frac{(\text{total latency for any given measure for the entire session})}{(\text{total number of trials for that session})}.$$

For a more detailed discussion of these measurements and their interpretations, please refer to Robbins [16].

To test for the development of peripheral neuropathy, animals were tested for changes in mechanical paw withdrawal threshold (MPWT) values every other day for the duration of the 20 day protocol (baseline and days 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19). For this test, the methods of Borzan et al. [3] were exactly followed. Briefly, animals were placed within a Plexiglas chamber ($20 \times 10.5 \times 40.5$ cm) positioned on top of a mesh screen so that mechanical stimuli could be administered to the plantar surface of both hindpaws using eight von Frey monofilaments (3.91, 5.91, 9.97, 19.81, 38.82, 78.14, 141.99, and 239.04 mN). Each trial began with a von Frey force of 9.97 mN delivered to the right hindpaw for approximately 1 s, and then the left hindpaw. If there was no withdrawal response, the next higher force was delivered. If a response was made, the next lower force was delivered. This procedure continued until no response was made at the highest force or until four stimuli were administered following the initial response. If an animal did not respond to the highest von Frey hair, the mechanical paw withdrawal response for that paw was calculated to be 424.30 mN. The MPWT testing was performed across three trials per session and the withdrawal values were averaged over the three trials to determine the mean mechanical paw withdrawal threshold for each animal.

Taxol (Sigma–Aldrich, St. Louis, MO) was dissolved into a 1:1 mixture of Cremaphore EL and ethanol to make a 10 mg/ml stock solution. On injection days, the stock solution was diluted to a 1 mg/ml solution with normal saline and given i.p. at 1 mg/kg. Animals in the control group received equivalent volumes of the vehicle solution.

Once animals reached the criteria of 70% correct and less that 20% omission for three consecutive days on the 5CSRTT (approximately 55 sessions following magazine training), a baseline measure (Day 0) of MPWT was taken. Immediately following this measure animals were injected with Taxol. MPWT measurements were taken on days 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 immediately following completion of the 5CSRTT. On days 2, 4, 6, 8, 10, and 12 animals were injected with Taxol 1 h following completion of the 5CSRTT. This dosing regimen has been shown by our lab (unpublished data) and others [28] to produce neuropathy without inducing the sickness behaviors observed with higher doses of Taxol. This same data also showed that conducting behavioral testing approximately 24 h following Taxol administration is optimal. The result is that animals were tested daily in the 5CSRTT and Taxol injections and MPWT measurements occurred on alternating days.

A repeated-measures mixed ANOVA was used for statistical analyses on the operant and MPWT data. All analyses were done using Statistica (StatSoft Inc., Tulsa, OK). Drug and Time served as the independent variables. A .05 significance level was used. Post-hoc analyses were performed using the Tukey test. Due to minimal

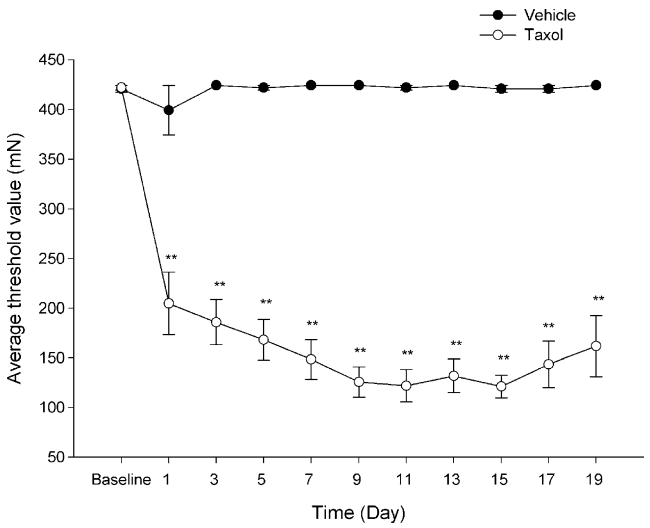

Fig. 1. Average mechanical paw withdrawal threshold values for Taxol and vehicle treated animals. Taxol treated animals exhibited significantly lower threshold values by day 1 ($p < .01$), with maximal differences seen by day 9 ($p < .01$).

baseline differences between the groups on some parameters, the data were normalized according to the following formula:

$$\frac{(\text{Day of interest} - \text{baseline})}{(\text{Baseline})} \times 100.$$

Beginning 24 h after the first injection, Taxol treated animals displayed significant increases in mechanical sensitivity (F (10, 180) = 429.65; $p < .01$). This sensitivity continued to increase until Day 9, when maximal group differences were seen (Fig. 1).

To assess changes in the percentage of responses made by Taxol treated animals, the parameters of percent correct, percent omission, and the percentage of intertrial interval responses were analyzed. Taxol treated animals did not show changes in the percentage of correct responses (F (18, 324) = .81; $p > .05$) (Fig. 2a), the percentage of omissions (F (18, 324) = .40; $p > .05$) (Fig. 2b), or the percentage of intertrial interval responses (F(18, 324) = 1.17; $p > .05$) (Fig. 2c) relative to vehicle treated animals, indicating that Taxol treated animals did not show decrements in 5CSRTT performance.

To assess the reaction times of Taxol treated animals, latencies to respond in the 5CSRTT were analyzed. Taxol treated animals did not have longer latencies to make a correct response (F(1, 18) = 2.71; $p > .05$) (Fig. 3a) or obtain earned food pellets from the food hopper (F (1, 18) = 1.67; $p > .05$) (Fig. 3b).

To isolate the effects of adding the noise paradigm on Day 8, a repeated-measures mixed ANOVA was conducted for each of the operant variables with day 8 excluded from the analysis. A 2 way ANOVA was then conducted on days 7 and 8, with day 7 serving as a posttest measure and day 8 serving as a test day. As can be seen in the figures and summarized in Table 1, the addition of noise did not significantly alter performance on any parameter in the 5CSRTT.

The purpose of this study was to use an animal model to investigate chemotherapy-induced cognitive impairments that are commonly observed in humans. It was hypothesized that animals treated with the chemotherapeutic agent Taxol would exhibit deficits in the 5CSRTT. Further, Taxol treated animals were expected to develop signs of peripheral neuropathy.

The results indicate that 1 mg/kg of Taxol administered every other day did lead to mechanical sensitivity, a finding that supports the reports of previous researchers [2,10,12,28]. The data from the 5CSRTT indicate that animals did not develop decrements in the ability to attend to a cognitively demanding task despite the fact that these animals displayed an increased sensitivity to mechanical stimulation.

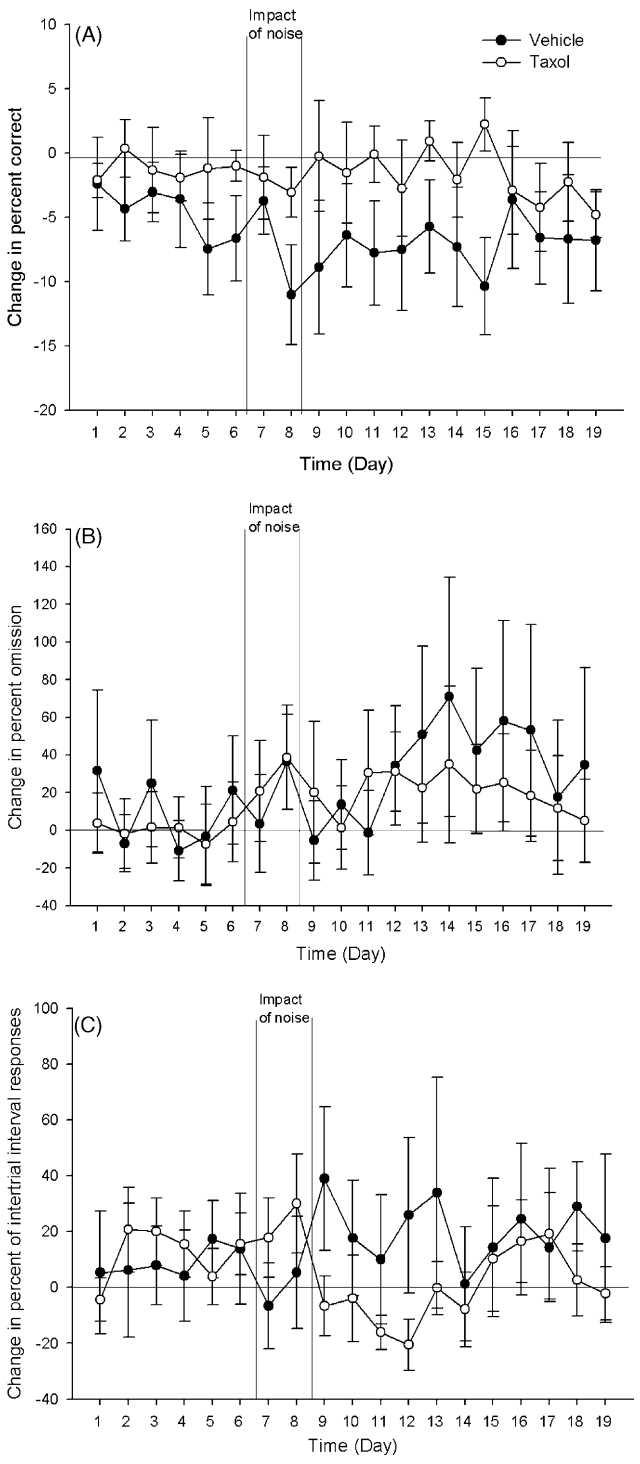

Fig. 2. (a) Average percentage of correct responses for Taxol and vehicle treated animals in the 5CSRTT. Overall, there were no decrements in percent correct for Taxol treated animals relative to vehicle treated animals. (b) Average percentage of omissions for Taxol and vehicle treated animals in the 5CSRTT. The analysis for percent omission indicate Taxol treated animals were not making fewer responses than vehicle treated animals. (c) Average percentage of intertrial interval responses for Taxol and vehicle treated animals in the 5CSRTT. The analysis for percentage of intertrial interval responses show that Taxol treated animals were not more impulsive than vehicle treated animals.

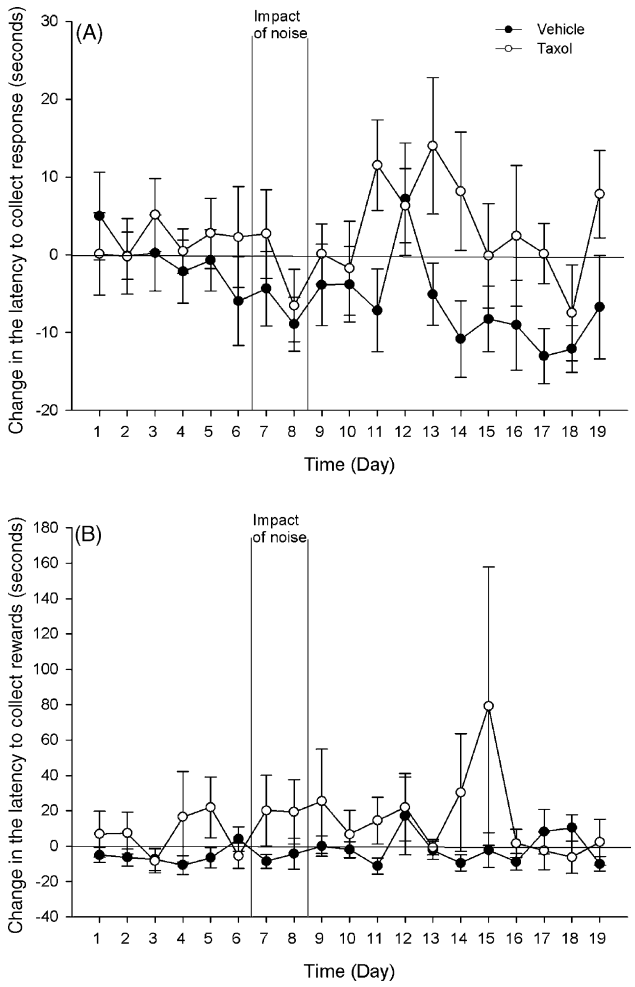

Fig. 3. Average latency data in the 5CSRTT for Taxol and vehicle treated animals. (a) Taxol treated rats did not take significantly longer to make a correct response than vehicle treated animals. (b) Further, Taxol treated rats did not take longer to obtain earned food pellets than vehicle treated animals. These data indicate that animals did not display altered reaction times as a result of Taxol treatment.

These differential findings are in accordance with clinical literature in multiple aspects. While many patients experience peripheral neuropathy during chemotherapy treatment, the incidence of chemotherapy-related cognitive impairment is highly variable. In humans, neuropathy is characterized by painful tingling and numbing sensations in the upper and lower extremities. Unlike some side effects of chemotherapy, the incidence of neuropathy is strongly associated with the specific chemotherapeutic agent used. Importantly, the plant alkaloids (i.e. paclitaxel and vincristine) frequently result in peripheral neuropathy [17,25], while other agents, such as the alkylating agents (i.e. cyclophosphamide) and antimetabolites (i.e. methotrexate and 5-fluorouracil), are rarely attributable to this condition [21]. It is possible that the greater effect of plant alkaloids is associated with their capacity to affect tubulins. Dina et al. [6] showed that the microtubule stabilization that results from Taxol administration activates systems that lead to hypersensitivity of the nociceptive system. Indeed, Taxol-induced neuropathy symptoms are associated with increased activity in certain spinal cord neurons [28].

The cognitive-related side effects of chemotherapy may also be associated with the type of chemotherapy used. To increase efficacy and decrease chemotherapy toxicity, most current regimens use a combination of chemotherapy agents, and most studies of chemotherapy-related cognitive impairments have been conducted on patients receiving multiple chemotherapeutic agents. This makes it difficult to determine the influence of any one agent on cognitive functioning in a patient. However, cognitive impairments have been found with individual chemotherapy agents using animal research. For example, Macleod et al. [9] found impairments in acquired fear conditioning in rodents receiving cyclophosphamide. Others have found impaired performance in spatial navigation using methotrexate [19,30]. Unfortunately, results from this line of research are inconsistent, with some studies reporting impairment and others finding little change in cognitive functioning. It is necessary to better understand the causes and full impact of chemotherapy on cognitive function, and perhaps this line of research could be augmented by further focusing on such differential findings as those obtained in this study.

There are alternative explanations for the obtained results. One possible explanation for these results is that chemotherapy may interfere with learning, or acquisition of a new task. Reiriz et al. [15] found impairment in a test of avoidance conditioning using the chemotherapeutic agent cyclophosphamide only if the chemotherapy was administered within 24 h prior to task training. Perhaps Taxol treated animals would have shown retardation of task acquisition had the chemotherapy been given prior to an animal reaching criterion. Future research should examine the effects of Taxol during task acquisition. Patients experiencing chemobrain are often advised to engage in mentally stimulating activities to combat cognitive decrements. If this is effective at decreasing the symptoms of chemobrain, it is also possible that Taxol-treated animals were effectively overcoming the symptoms by engaging in the 5CSRTT.

Another potential explanation of these findings is that it is the cancer or a combination of the cancer and the chemotherapy, and not the chemotherapy itself that most significantly contributes to cognitive impairment. Wefel et al. [26,27] showed that the incidence of pretreatment cognitive impairment in women with breast cancer was between 33% and 35%. However, both articles did report that cognitive abilities continued to decline following chemotherapy treatment. Animals in the present study did not have cancer so it was not possible to singly determine the effects of chemotherapy in the presence of cancer.

Alternative possibilities should not diminish the importance of the results presented here. This is the first study to investigate chemotherapy-related cognitive impairment using a broad

Table 1
The impact of noise on performance in the 5CSRTT. Values shown are mean (± SEM) normalized responses or latencies. Analyses performed to assess the impact of noise on performance for the percentage of correct responses ($F(1, 18) = 1.74$, $p > .05$), the percentage of omissions ($F(1, 18) = .09$, $p > .05$), and the percentage of intertrial interval responses ($F(1, 18) = 1.51$, $p > .05$) indicate no significant changes in responding as a result of noise introduction. Further, noise did not alter the latency to make a correct response ($F(1, 18) = 1.08$, $p > .05$) or the latency to obtain earned food pellets ($F(1, 18) = 2.08$, $p > .05$).

	Day 7		Day 8	
5CSRTT correct	Vehicle	Taxol	Vehicle	Taxol
Percent correct	−3.7078 (±2.63)	−1.8986 (±3.27)	−11.033 (±3.88)	−3.055 (±1.95)
Percent omission	3.3518 (±25.93)	20.7962 (±26.83)	36.2908 (±25.21)	38.552 (±27.68)
Percent of intertrial interval responses	−6.6061 (±15.44)	17.8315 (14.26)	5.3288 (20.09)	30.016 (±17.73)
Latency to make a correct response	−4.3573 (±4.79)	2.6714 (±5.70)	−8.9234 (±3.46)	−6.5441 (±4.63)
Latency to collect rewards	−8.6232 (±3.86)	20.1644 (±20.09)	−4.3152 (±−8.84)	19.3757 (±18.10)

measure of cognitive function. The results show that the chemotherapeutic agent Taxol did produce symptoms of peripheral neuropathy, but did not lead to detectable disturbances in general cognitive functioning.

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