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Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits

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Abstract

Aims—Agitation and aggression are common behavioral sequelae of traumatic brain injury (TBI). The management of these symptoms is critical for effective patient care and therefore antipsychotics are routinely administered even though the benefits vs. risks of this approach on functional outcome after TBI are unclear. A recent study from our group revealed that both haloperidol and risperidone impaired recovery when administered *prior* to testing. However, the results may have been confounded by drug-induced sedation. Hence, the current study reevaluated the behavioral effects of haloperidol and risperidone when provided *after* daily testing, thus circumventing the potential sedative effect.

Main methods—Fifty-four isoflurane-anesthetized male rats received a cortical impact or sham injury and then were randomly assigned to three TBI and three sham groups that received haloperidol (0.5 mg/kg), risperidone (0.45 mg/kg), or vehicle (1.0 mL/kg). Treatments began 24 hrs after surgery and were administered (i.p.) every day thereafter for 19 days. Motor and cognitive function was assessed on post-operative days 1–5 and 14–19, respectively.

Key findings—Hippocampal CA₁/CA₃ neurons and cortical lesion volume were quantified at 3 weeks. Only risperidone delayed motor recovery, but both antipsychotics impaired spatial learning relative to vehicle ($p < 0.05$). Neither swim speed nor histological outcomes were affected. No differences were observed between the haloperidol and risperidone groups in any task.

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Significance—These data support our previous finding that chronic haloperidol and risperidone hinder the recovery of TBI-induced deficits, and augment those data by demonstrating that the effects are not mediated by drug-induced sedation.

Keywords

antipsychotics; brain injury; functional recovery; water maze

Introduction

Antipsychotic drugs have been used for over half a century to treat the behavioral symptoms of schizophrenia (Karl et al., 2006; Li et al., 2007). Typical antipsychotic drugs, such as haloperidol, attenuate positive symptoms, but also induce extrapyramidal symptoms, which are comprised of tremor, rigidity, akinesia, and bradykinesia (Karl et al., 2006). Newer atypical antipsychotic drugs, such as risperidone, exert superior therapeutic efficacy in the treatment of both positive and negative symptoms, but their differential receptor affinity results in a much lower risk of extrapyramidal symptoms (Karl et al., 2006; Elovic et al., 2008).

Antipsychotic drugs are also administered to traumatic brain injured (TBI) patients, albeit this practice is controversial (Mysiwi and Sandel, 1997; Elovic et al., 2003, 2008). Indications may include agitation with or without concurrent psychotic features, extreme aggression or rage, TBI-induced mania, and thought disorders (Elovic et al., 2003; Lombard and Zafonte, 2005). Post-traumatic agitation has a frequency of 11% to 50% and its role in motor, cognitive, and psychological recovery is pivotal, because agitation may delay rehabilitation. Sandel and Mysiw (1996) defined post-traumatic agitation as a subtype of delirium unique to TBI patients who are still in posttraumatic amnesia with excessive behaviors that include aggression, akathisia, disinhibition, and emotional lability. Despite the indications, the contraindications of antipsychotic drug treatment on the recovering brain after TBI are unclear.

The few studies to date investigating the effects of antipsychotic drugs after experimental TBI show that they generally impair the recovery process and in some instances exacerbate the TBI-induced behavioral deficits. Feeney and colleagues demonstrated that even a single administration of haloperidol provided after TBI in adult rodents delayed motor recovery (Feeney et al., 1982). Moreover, administration of haloperidol after the animals were deemed recovered, as indicated by normal traversal of a narrow beam, led to a reinstatement of the deficits (Feeney et al., 1982). Similar findings were reported by Goldstein and Bullman (2002). Other studies have shown that antipsychotic drugs after brain trauma not only impair motor recovery, but also cognitive function. Wilson et al (2003) showed that haloperidol led to slower acquisition of spatial learning in a water maze task. Recent studies from our laboratory have demonstrated that both haloperidol and risperidone impair motor and cognitive performance after cortical impact injury, but only when administered chronically (Kline et al., 2007 and manuscript in review). Importantly, the administration of antipsychotic drugs induces CNS depression and catalepsy in a dose-dependent manner, which may have contributed to the deleterious effects, particularly because the tasks utilized are dependent on normal motor function.

The current study sought to reevaluate the effect of chronic administration of the typical and atypical antipsychotic drugs, haloperidol and risperidone, respectively, on functional outcome after controlled cortical impact injury. A modified version of our standard treatment protocol was implemented in an attempt to circumvent the sedative effects observed during testing in our previous study (in review, 2008). Briefly, the antipsychotic drugs were administered *after* the daily neurobehavioral assessments were completed. The data revealed that haloperidol

and risperidone hindered the recovery of TBI-induced deficits despite administering the drugs after behavioral testing when sedation was not a factor.

Material and Methods

Fifty-four adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 300–325 g on the day of surgery were initially housed in standard steel-wire mesh cages and maintained in a temperature ($21 \pm 1^\circ\text{C}$) and light controlled (on 7:00 a.m. to 7:00 p.m.) environment with food and water available *ad libitum*. After one week of acclimatization the rats underwent beam-walk training and then were prepared for surgery. Surgical procedures have been reported in detail elsewhere (Dixon et al., 1991; Kline et al., 2001, 2002, 2004, 2007). Briefly, isoflurane (4% in 2:1 $\text{N}_2\text{O}/\text{O}_2$) anesthetized rats were intubated, mechanically ventilated, and then subjected to either a right hemisphere controlled cortical impact (2.8 mm tissue deformation at 4 m/sec) or sham injury. Core temperature was maintained at $37 \pm 0.5^\circ\text{C}$ during surgery. Following surgery, the rats were randomly assigned to 3 TBI [haloperidol (0.5 mg/kg; n=12), risperidone (0.45 mg/kg; n=12), vehicle (1.0 mL/kg; n=12)] or 3 Sham [haloperidol (0.5 mg/kg; n=6), risperidone (0.45 mg/kg; n=6), vehicle (1.0 mL/kg; n=6)] groups. All experimental procedures were approved by the Animal Care and Use Committee at the University of Pittsburgh and were conducted in accordance with the recommendations provided in the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, 1996). Every attempt was made to limit the number of subjects used and to minimize animal suffering.

Acute neurological evaluation

Hind limb reflexive ability was assessed by gently squeezing the rats paw every 5 sec following the cessation of anesthesia and recording the time to elicit a withdrawal response. Return of the righting reflex was determined by the time required for a rat to turn from the supine to prone position.

Drug administration

Haloperidol (Sigma, St. Louis, MO) and risperidone (Research Diagnostics, Flanders, NJ) were prepared daily by dissolving in 1:1 dimethyl sulfoxide (DMSO)/saline v/v, which also served as the vehicle. Rats were injected intraperitoneally after cortical impact or sham surgery once daily, after behavioral testing, for three weeks. The doses of haloperidol (0.5 mg/kg) and risperidone (0.45 mg/kg) were chosen because these concentrations have been reported to be comparable to those used clinically to control psychosis (Rosengarten and Quartermain, 2002). Furthermore, these were the same doses used in our previous study (in review) where the treatments were provided *before* behavioral assessments and thus it is critical to evaluate the same doses to determine a timing effect, which is one of the goals of this study.

Motor performance

Beam-balance and beam-walk tasks were utilized to assess gross and fine motor function, respectively. The beam-balance task consists of placing the animal on an elevated (90 cm) narrow wooden beam (1.5 cm wide) and recording the duration it remains on for a maximum of 60 sec. The beam-walk task, originally devised by Feeney and colleagues (1982), allows for the assessment of refined locomotor activity. Briefly, the task consists of training/assessing animals using a negative-reinforcement paradigm to escape ambient light and high decibel white noise by traversing an elevated (90 cm) narrow wooden beam (2.5×100 cm) and entering a darkened goal box at the opposite end. Performance was assessed by the latency to traverse the beam. Subjects were pre-trained on beam-balance and beam-walking ability one day prior to surgery and assessed on the day of surgery to determine baseline performance. Post-operative testing occurred on days 1 to 5 and consisted of providing three trials (60 sec allotted time) per day on each task. The average daily scores for each subject were used in the statistical analyses.

Cognitive function (acquisition of spatial learning and memory)

A water maze task that is sensitive to cognitive function/dysfunction following TBI (Hamm et al., 1992; Kline et al., 2000, 2002, 2004; Cheng et al., 2007; Hoffman et al., 2008) was used to compare acquisition rates among groups. The maze consisted of a plastic pool (180 cm diameter; 60 cm high) filled with water ($26 \pm 1^\circ\text{C}$) to a depth of 28 cm and was situated in a room with salient visual cues that remained constant throughout the study. The platform was a clear Plexiglas stand (10 cm diameter, 26 cm high) and was positioned 26 cm from the maze wall in the SW quadrant and held constant throughout the study for each animal. Acquisition of spatial learning began on post-operative day 14 and consisted of providing a block of four daily trials for five consecutive days (days 14–18) to locate the platform when it was submerged 2 cm below the water surface (i.e., invisible to the rat), followed by an additional day (day 19) to locate the platform when it stood 2 cm above the water surface outlined with white tape (visible to the rat). For each daily block of trials the rats were placed in the pool facing the wall at each of the four possible start locations (North, East, South, and West) in a randomized manner. Each trial lasted until the rat climbed onto the platform or until 120 sec had elapsed, whichever occurred first. Rats that failed to locate the goal within the designated time were manually guided to it. All animals remained on the platform for 30 sec before being placed in a heated incubator between trials (4-min inter-trial interval). The data were obtained using a spontaneous motor activity recording & tracking (SMART) system (San Diego Instruments, San Diego, CA), which in addition to providing time, also calculates pathlength and swim speed.

Histology

Quantification of hippocampal cells—An observer blinded to experimental conditions analyzed one coronal section underlying the area of contusion (~ 3.5 mm posterior to bregma) from all rats in each group for determination of treatment efficacy on selectively vulnerable hippocampal CA₁ and CA₃ neurons. To reduce counting errors associated with false positive identification of dying neurons, the total number of CA₁ and CA₃ morphologically intact neurons (i.e., those with a clearly defined cell body and nucleus) were counted using a Nikon Eclipse E600 microscope (Nikon Corporation, Tokyo, Japan) with a 40x objective. The data are reported as the percent of total neurons in the ipsilateral (injured) CA₁ and CA₃ regions relative to the contralateral hippocampus.

Cortical lesion volume

The area of the lesion (mm^2) was calculated in a subset of TBI animals from each drug group ($n=5$) by outlining the cortical lesion for each section taken at 1 mm intervals through the extent of the lesion (MCID, Imaging Research, Ontario, Canada). The volume (mm^3) of the lesion was determined by summing the areas of the lesion obtained from each section.

Data analyses

All statistical analyses were performed on data collected by observers blinded to treatment conditions using Statview 5.0.1 software (Abacus Concepts, Inc., Berkeley, CA). The behavioral data were analyzed by repeated-measures analysis of variance (ANOVA). When the ANOVA showed a significant effect, the Bonferroni *post hoc* test was utilized to determine specific group differences. The histological data, swim speed, and path length were analyzed by a one-factor ANOVA. The results are expressed as the mean $\pm$ standard error (SE) and were considered significant when p values were < 0.05 or as determined by Bonferroni corrections for multiple comparisons.

Results

One rat from the TBI + haloperidol group was excluded from the study because of an inadvertent dura mater tear during the craniectomy that caused herniation and prohibited the precise placement of the impact tip. Hence, statistical analyses are based on fifty-three rats. No significant differences were observed among the sham groups, regardless of treatment in any of the behavioral assessments and thus the data were pooled and analyzed as one group (denoted as “SHAM”).

Acute neurological evaluation

No significant differences were observed among the injured groups in time to recover the hind limb withdrawal reflex (range, 186.00 ± 11.31 to 208.58 ± 11.44 sec; $p > 0.05$). This has been reported to be a reliable index of injury severity (Hamm et al., 1992; Dixon et al., 1999; Kline et al., 2007). Additionally, no significant difference was observed for return of the righting reflex (range, 391.66 ± 9.86 to 425.41 ± 16.09 sec; $p > 0.05$). These acute neurological evaluations suggest that all injured groups experienced equivalent injury severities and level of anesthesia.

Motor performance

Beam-balance—All groups were able to balance on the beam for the designated 60 sec on each of three trials prior to surgery (Fig. 1). A repeated measures ANOVA revealed a significant group ($F_{3,49} = 8.13$, $p = 0.0002$), day ($F_{5,245} = 37.68$, $p < 0.0001$), and group by day interaction effect ($F_{15,245} = 6.31$, $p < 0.0001$). Bonferroni *post hoc* analyses revealed that the TBI + risperidone group performed significantly worse than the TBI + vehicle group ($p = 0.0002$). Additionally, both the TBI + risperidone and TBI + haloperidol groups were significantly worse than the SHAM group ($p < 0.0001$). No overall difference was observed between the SHAM and TBI + vehicle group ($p = 0.0577$) or between the TBI + risperidone and TBI + haloperidol groups ($p = 0.0875$).

Beam-walk—There were no significant differences in time to traverse the beam among groups prior to surgery ($p > 0.05$). A repeated measures ANOVA revealed significant group ($F_{3,49} = 32.83$, $p < 0.0001$) and day ($F_{5,245} = 120.62$, $p < 0.0001$) effects, as well as a significant group by day interaction ($F_{15,245} = 16.38$, $p < 0.0001$). As depicted in Fig. 2, no overall significant differences were observed among the TBI groups as determined by Bonferroni *post hoc* analyses ($p > 0.05$). However, individual day analyses showed greater traversal times (i.e., more impairment) for the TBI + haloperidol group vs. the TBI + vehicle group on days 1 and 2 ($p = 0.007$ and $p = 0.002$, respectively). SHAM controls performed significantly better than all TBI groups ($p < 0.0001$).

Cognitive performance

Acquisition of spatial learning—Analysis of spatial learning acquisition revealed significant TBI-induced water maze performance deficits. A repeated measures ANOVA revealed significant group ($F_{3,49} = 33.99$, $p < 0.0001$) and day ($F_{4,196} = 26.78$, $p < 0.0001$) differences, as well as a significant group $\times$ day interaction ($F_{12,196} = 2.38$, $p = 0.0067$). As shown in Fig. 3, all TBI groups were significantly impaired vs. SHAM controls ($p < 0.0001$). Moreover, both the TBI + haloperidol and TBI + risperidone groups were significantly impaired vs. the TBI + vehicle group ($p = 0.0035$ and $p = 0.0007$, respectively). Lastly, no significant difference was observed between the TBI + risperidone and TBI + haloperidol groups ($p = 0.6813$; Bonferroni). Analysis of pathlength, as a function of spatial learning, revealed significant TBI-induced performance deficits. A repeated measures ANOVA revealed significant group ($F_{3,49} = 34.82$, $p < 0.0001$), and day ($F_{4,196} = 16.82$, $p < 0.0001$) differences, as well as a significant group $\times$ day interaction ($F_{12,196} = 4.22$, $p < 0.0001$). All TBI groups

swam farther, which suggests significant impairments in spatial learning vs. SHAM controls ($p < 0.0001$). However, the post-hoc test revealed that both the TBI + haloperidol and TBI + risperidone groups had longer pathlengths (i.e., traveled longer distances) to find the escape platform vs. the TBI + vehicle group ($p = 0.0017$ and $p = 0.0024$, respectively), but did not differ from one another ($p > 0.05$; Fig. 4). A one-factor ANOVA on postoperative day 19 revealed significant differences in the time required to find the visible platform among groups. Specifically, while there were no differences between the TBI + haloperidol and TBI + risperidone groups ($p = 0.38$), they both required longer search times vs. SHAM controls ($p < 0.0001$). The TBI + risperidone group also spent more time searching relative to the TBI + vehicle group ($p = 0.0056$), which did not differ from SHAMs. There were no significant differences among any of the TBI groups for probe trial assessment as evidenced by the percentage of time spent searching in the target quadrant (25.9 ± 2.5 , 27.2 ± 4.1 , and 24.6 ± 4.0 % for the TBI + vehicle, TBI + haloperidol, and TBI + risperidone groups respectively, $p > 0.05$). However, all TBI groups differed from the SHAM group that spent 39.3 ± 3.2 % of the time searching in the appropriate zone, which is well above chance performance ($p < 0.05$). Swim speed did not differ among any of the groups ($p > 0.05$; Fig. 5).

Histology

Quantification of hippocampal cells—CCI injury produced marked decreases in morphologically intact CA₁ and CA₃ cells in the ipsilateral hemisphere vs. SHAM controls. However, no significant differences were observed among the TBI groups, regardless of treatment. CA₁ cell survival ranged from 35.8 ± 5.7 % to 38.6 ± 3.2 % and CA₃ survival ranged from 36.5 ± 2.3 % to 40.8 ± 5.2 %.

Cortical lesion volume

No significant differences were revealed for cortical lesion volume ($F_{2,17} = 0.347$, $p = 0.7120$). The mean lesion volumes were 34.2 ± 2.9 mm³, 35.9 ± 1.7 mm³, and 33.1 ± 2.3 mm³ for the TBI + haloperidol, TBI + risperidone, and TBI + vehicle groups, respectively.

Discussion

The present study reevaluated the effect of chronic administration of haloperidol and risperidone on motor recovery, acquisition of spatial learning, and memory retention after experimental brain trauma produced by a controlled cortical impact device that mimics many of the characteristics of human TBI (Kline and Dixon, 2001). The impetus for the reevaluation was based on the findings of a recent study from our group showing that both haloperidol and risperidone impaired recovery when administered *prior* to behavioral testing. However, the results may have been confounded by drug-induced sedation as indicated by significantly slower swim speeds in haloperidol and risperidone treated TBI and sham groups. The fundamental difference between the previous study and the current is that here the antipsychotics were administered *after* daily behavioral testing as a means to circumvent potential sedative effects on functional outcome. With reported half-lives in rats of 1.5 hrs and 1 hr for haloperidol and risperidone, respectively (Naiker et al., 2006), the alternative drug administration paradigm served its purpose as neither of the antipsychotic-treated groups displayed overt signs of sedation, as evidenced by beam-walking times and swim speeds that were comparable to the vehicle-treated TBI and sham groups. However, in accord with the previous study, both haloperidol and risperidone hindered the recovery of TBI-induced deficits vs. vehicle-treated controls. These findings suggest that the detrimental effects of chronic haloperidol and risperidone on cognitive performance after TBI in our model are not due to sedative effects.

Potential explanations for the effects of haloperidol and risperidone on cognitive performance are varied, but the vast literature has focused on alterations in neurotransmitter systems. Both haloperidol and risperidone demonstrate high affinity for dopamine D₂ receptors, where they act as antagonists. Furthermore, it is well established that TBI produces significant changes in catecholaminergic neurotransmission (McIntosh et al., 1994; Dunn-Meynell et al., 1998; Yan et al., 2001, 2002; Massucci et al., 2004; Wagner et al., 2005), which is thought to mediate, at least in part, the deficits in cognitive and motor performance. Both basic science studies and clinical investigations have shown that D₂ receptor agonists improve functional outcome after brain trauma (Plenger et al., 1996; Whyte et al., 1997; McDowell et al., 1998; Dixon et al., 1999; Kline et al., 2000, 2002). In contrast, haloperidol hinders motor recovery when given singly (Feeney et al., 1982, 1993; Goldstein and Bullman, 2002) or chronically (Feeney and Westerberg, 1990) after TBI. Haloperidol has also been reported to impair cognitive performance when administered chronically after fluid percussion brain injury (Wilson et al., 2003). In contrast, neither a single low dose of clozapine nor multiple doses of olanzapine, antipsychotics that have a low affinity for dopamine D₂ receptors, have been reported to negatively affect motor and cognitive performance, respectively (Goldstein and Bullman, 2002; Wilson et al., 2003).

Haloperidol and risperidone also have moderate affinity for the α_1 and α_2 adrenergic and sigma-1 receptors (Schotte et al., 1993, 1996). Feeney and colleagues (1982) have shown that drugs that exert antagonistic effects on the noradrenergic system, such as haloperidol and clonidine, impede recovery after brain injury and can reinstate deficits (for excellent reviews see Feeney and Westerberg, 1990 and Feeney et al., 1993). The sigma-1 receptor, which has been reported to be important for normal or enhanced cognitive processing is antagonized by haloperidol, and to a lesser extent by risperidone. Sigma-1 receptor agonists facilitate cortical dopaminergic transmission (Kobayashi et al., 1997) and restore memory (Espallargues et al., 2007) suggesting that activation of this receptor is beneficial for functional recovery and that antagonizing it with haloperidol and risperidone could be deleterious. Sigma-1 receptor agonists also enhance acetylcholine in both the cortex and hippocampus (Kobayashi et al., 1996), which are crucial regions of cognitive function. In support of this assertion, Terry and colleagues (2002, 2003, 2006) have shown that long-term administration of haloperidol or risperidone, but not olanzapine, impaired learning and decreased choline acetyltransferase and nerve growth factor, which are important substrates of memory. Taken together, these studies indicate that cognitive function can be manipulated by various neurotransmitter systems. However, given the complexity of the interactions and the different receptor affinities for haloperidol and risperidone, it is difficult to ascribe the deleterious effects of these antipsychotics to a single neurotransmitter system.

In the current study, we saw significant impairment in the acquisition of learning and memory as well as beam-balance ability, with a lesser extent on beam-walking performance after 19 days of haloperidol and risperidone treatment. However, previous work from our laboratory has shown that significant impairments in cognitive and motor performance after TBI are seen when both are administered for only 5 days (Kline et al., 2007). Moreover, the magnitude of the deficit with a 5-day treatment regimen is similar to that seen with 19 days. Even a dose of risperidone 10-fold lower than that provided in the current study was sufficient to impair outcome in our injury model (Kline et al., 2007). We have also shown that haloperidol and risperidone reinstated motor and cognitive deficits in rats that appeared to be fully recovered, and that the cognitive impairments were still present even after a 3-day drug washout period (Kline et al., 2007). A limitation of the current study is that we did not reassess function after a drug abstinence period. However, based on the previous study we would expect to see persistent deficits. The evaluation of other antipsychotics is needed so that a clearer perspective emerges regarding the effects of antipsychotics in the recovering brain.

Despite numerous studies reporting detrimental effects with antipsychotic treatments (Skarsfeldt 1996; Gemperle et al., 2003; Didriksen et al., 2006; Karl et al., 2006; Kline et al., 2007), Yulug and colleagues (2006a, 2006b) recently showed that both risperidone and olanzapine attenuated brain damage after permanent focal cerebral ischemia in mice, as evidenced by smaller infarcts compared to vehicle-treated controls. In contrast, Zhao et al (2005) did not see significant differences in cortical infarct volumes between the ischemic controls and the ischemic risperidone-treated rats. In the current study, no differences were observed in either cortical lesion volume or hippocampal cell survival, indicating a lack of neuroprotection. This finding suggests that neither cortical lesion nor TBI-induced hippocampal cell loss were determining factors in the poorer acquisition of spatial learning in the antipsychotic-treated groups.

Conclusion

Antipsychotics are routinely administered after TBI to control behavioral disturbances. The current data suggest that chronic administration of either haloperidol or risperidone hinder recovery in an experimental model of TBI and hence caution should be exercised when administering these agents to human TBI patients as similar detrimental effects may be presented.

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Fig. 1. Mean ($\pm$ SE) time (sec) to maintain balance on an elevated narrow beam before and after TBI or SHAM injury. While all groups demonstrated significant deficits after TBI, only the TBI + risperidone group was significantly delayed in regaining beam-balance ability. * $p = 0.0002$ vs. TBI + vehicle. ** $p < 0.0001$ vs. TBI + haloperidol and TBI + risperidone.

Fig. 2.

Mean ($\pm$ SE) time (sec) to traverse an elevated narrow beam prior to, and after, TBI or SHAM injury. All TBI groups exhibited significant impairment vs. SHAM. $**p < 0.0001$ vs. all TBI groups. No overall statistical difference was observed among the TBI groups ($p > 0.05$), but individual day analyses showed longer traversal times for the TBI + haloperidol group vs. the TBI + vehicle group on days 1 and 2 ($*p = 0.007$ and $*p = 0.002$, respectively).

Fig. 3.

Mean ($\pm$ SE) time (sec) to locate a hidden (submerged) platform in a water maze. While all TBI groups performed at the same level initially, only the TBI + vehicle group exhibited a significant decrease in time to locate the platform over time. No such reduction was observed in the TBI + haloperidol and TBI + risperidone groups. * $p < 0.05$ vs. TBI + vehicle. ** $p < 0.0001$ vs. all TBI groups.

Fig. 4.

Mean ($\pm$ SE) pathlength (cm) during acquisition of spatial learning in the water maze. While all TBI groups swam similar distances initially, only the TBI + vehicle group reduced the distance to the platform over time. No such reduction was observed in the TBI + haloperidol and TBI + risperidone groups. * $p < 0.05$ vs. TBI + vehicle. ** $p < 0.0001$ vs. all TBI groups.

Fig. 5. Mean ($\pm$ SE) swim speed (cm/sec). No differences were observed among groups, regardless of injury assignment or drug treatment, suggesting that impairment of spatial learning was not influenced by drug-induced sedation.