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Exaggerated acquisition and resistance to extinction of avoidance behavior in treated heroin-dependent males

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Abstract

Objective—Addiction is often conceptualized as a behavioral strategy for avoiding negative experiences. In rodents, opioid intake has been associated with abnormal acquisition and extinction of avoidance behavior. Here, we tested the hypothesis that these findings would generalize to human opioid-dependent subjects.

Method—Adults meeting *DSM-IV* criteria for heroin-dependence and treated with opioid medication (n=27), and healthy controls (n=26), were recruited between March–October 2013 and given a computer-based task to assess avoidance behavior. On this task, subjects controlled a spaceship and could either gain points by shooting an enemy spaceship, or hide in safe areas to avoid on-screen aversive events.

Results—While groups did not differ on escape responding (hiding) during the aversive event, heroin-dependent males (but not females) made more avoidance responses during a warning signal

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that predicted the aversive event (ANOVA, sex × group interaction, p=0.007). This group was also slower to extinguish the avoidance response when the aversive event no longer followed the warning signal (p=0.011). This behavioral pattern resulted in reduced opportunity to obtain reward without reducing risk of punishment. Results suggest that differences in avoidance behavior cannot be easily explained by impaired task performance or by exaggerated motor activity in male patients.

Conclusion—This study provides evidence for abnormal acquisition and extinction of avoidance behavior in opioid-dependent patients. Interestingly, data suggest abnormal avoidance is demonstrated only by male patients. Findings shed light on cognitive and behavioral manifestations of opioid addiction, and may facilitate development of therapeutic approaches to help affected individuals.

Keywords

Addiction; avoidance; extinction; opioid dependence; heroin dependence; sex differences

Introduction

Addiction is often conceptualized as an avoidance behavior: alcohol addicts often drink to avoid dysphoric emotions or negative mood,[1] gamblers often gamble to block out their problems,[2] and substance users report using addictive substances in an attempt to cope with stress, escape reality, as well as to avoid the aversive drug-withdrawal symptoms.[3–8] Indeed, escape and avoidance of negative affect was argued to be the principal motive for addictive drug use, where addicts attempt to reduce aversive internal states.[9, 10] Surprisingly, while both avoidance behavior and substance misuse are strategies for coping with negative and painful effects, evidence for the link between these two constructs in humans is scant and is based on self-report measures.[11–13] The animal literature, however, has provided important empirical parallels between avoidance behavior and drug intake, and suggests addictive behavior to be a form of avoidance learning.[14] One type of addiction that has been extensively studied in animals, including in the context of avoidance behavior, is opioid addiction.[5–7, 15–24] While reports often showed increased avoidance behavior in rodents that were given opioids,[15–19] this was not always the case.[20–22, 24]

Extinction of conditioned avoidance behavior, i.e., refraining from avoidance responding when the aversive event no longer occurs, may also be affected by opioid intake. In rodents, opioid receptors in the midbrain have been shown to regulate extinction of aversive conditioning,[25] opioid agonists decreased avoidance during extinction of free-operant avoidance,[24] and opiate seeking behavior is extinguished slowly, with a high risk of relapse.[26] Indeed, evidence suggests that rodents with history of opioid use tend to respond to drug cues even when drugs are absent.[27, 28]

Importantly, avoidance paradigms often include an appetitive component, which might compete with the avoidance response. Thus, any observed impairment on avoidance behavior might be the result of reduced motivation to obtain reward, rather than an increased motivation to avoid punishment. One might argue that such motivational imbalance represents anhedonia, impaired capacity to experience pleasure. Anhedonia is a symptom in

various psychiatric conditions including substance use disorders.[29] Since anhedonic patterns might affect avoidance behavior, it is of importance to dissociate the appetitive versus aversive components of the observed behavior.

In this study, we assess the balance between reward-seeking and avoidance behavior in treated heroin-dependent patients, as compared with healthy controls. By using a simple computer-based task that captures several key features of common animal avoidance paradigms,[30–32] we attempt to bridge the gap between human and non-human opioid addiction research. We hypothesize that, as in the animal literature, patients will show abnormal acquisition and/or extinction of avoidance behavior.

Methods

Subjects

The patient group consisted of 27 individuals with history of heroin addiction (mean age=41.3 years, SD=10.6; 44.4% female), recruited from the Opioid Treatment Program Clinic at the Drug Health Services at the Royal Prince Alfred Hospital in Sydney, Australia. Opioid dependence was confirmed using *DSM-IV* criteria and urine drug screening; dependence for substances other than heroin was an exclusion criteria. All patients were being treated with opioid medication; 22 were on methadone (mean dose=66.7 mg, SD=42) and five were on buprenorphine (mean dose=19.6 mg, SD=6.4). One patient was transferred to another site after testing and his medical record was not available. For the remaining 26 patients: mean admission time to the clinic was 3.8 years (SD=4.2) before the experiment, and testing was conducted 1–6 hours after daily dose. These patients reported mean heroin addiction duration of 15.8 years (SD=10.5), with a daily dose of 353.8 mg (SD=248.6) before treatment. Twelve patients were diagnosed with no other *DSM-IV* psychiatric disorders (Axis I or Axis II), while others were diagnosed with schizophrenia (7), depression (4), panic disorder (1), bipolar disorder (1) and cluster B personality disorder (1). Clinical diagnosis was based on interview with a psychiatrist and retrieved from patients' medical records. There were no differences in sex or age between patients who were or were not diagnosed with other disorders.

The control group consisted of 26 healthy adults recruited from the community via referrals and word of mouth (mean age=38.3 years, SD=11.1; 65.4% female). Subjects who reported current substance dependence or other *DSM-IV* psychiatric disorders were excluded. No differences were observed between patients and controls on age and sex. Ethics approval was obtained from the Royal Prince Alfred Hospital Ethics Committee and from the Ethics Committee at the University of Western Sydney. All subjects provided written informed consent and the experiment was conducted in accordance with guidelines established by the Declaration of Helsinki for the protection of human subjects.

Escape-avoidance task

To test avoidance behavior, subjects were administered a simple computer-based task recently developed by our group,[31, 32] and based on earlier work by Molet et al.[30] On this task (Figure 1), subjects controlled a spaceship and were instructed to gain points by

shooting and destroying an enemy spaceship that randomly appeared on the screen. Every 20 s, rectangles appeared for 5 s at the top of the screen (warning period). On each of the 12 acquisition trials, a warning period was always followed by appearance of a bomb for another 5 s (bomb period). During the bomb period there was an explosion of the subjects' spaceship and a reduction of points. The bomb period was followed by a 10-s intertrial period during which subjects could gain points without any risk of aversive events. Twelve extinction trials followed, during which no bombs appeared. At the bottom corners of the screen, there were two "safe areas" where subjects could protect themselves from the aversive events, but were unable to gain points.

Variations of this task have been previously used to test different aspects of human avoidance behavior.[30, 33–35] Importantly, recent work using a similar task revealed that subjects with increased anxiety vulnerability demonstrated greater avoidance.[31, 32]

Data analysis

For each trial, the program computed the percentage of time the subject spent hiding during the 5-s warning period, the 5 s that followed the warning period, and the remaining 10-s intertrial period. On acquisition trials, the bomb period follows the warning period, whereas on extinction trials there is no bomb period, and the intertrial period is extended to 15 s for consistency with the acquisition trials. Hiding during the bomb period represents an escape response, and terminates point loss, while hiding during the warning period represents an avoidance response that might completely prevent any point loss. To assess overall performance on the task, total points gained during the entire session, number of shooting attempts (presses on the FIRE key) and subjects' motor activity (presses on the LEFT/RIGHT keys), were recorded.

To test behavioral differences between groups, we used mixed analysis of variance (ANOVA) with within-subject factor of trial (12 trials per phase) and between-subject factors of group (patients versus controls) and sex. Dependent variables were percentage of time spent hiding during acquisition and extinction phase on each period (warning, bomb and intertrial). Sphericity was checked by Mauchly's test and Greenhouse-Geisser correction was used when sphericity was violated. Univariate ANOVA was used to analyze total points, shooting and motor activity, with group and sex as the independent variables.

Results

We first analyzed hiding during the 5-s warning period (Figure 2). On the acquisition phase, mixed ANOVA revealed main effects of Trial [$F(6.2,301.4)=2.348$, $p=0.030$], Sex [$F(1,49)=5.022$, $p=0.030$] and Group [$F(1,49)=12.567$, $p=0.001$], and a Sex × Group interaction [$F(1,49)=7.974$, $p=0.007$]. On the extinction phase, analyses revealed main effects of Trial [$F(7.9,385.8)=2.441$, $p=0.014$] and Group [$F(1,49)=10.824$, $p=0.002$], and a Sex × Group interaction [$F(1,49)=6.945$, $p=0.011$]. Tukey's HSD tests revealed that male patients hid more than all the other groups on both the acquisition and extinction phases (all $p<0.010$).

We next analyzed hiding during the 5 s that followed the warning signal (Figure 3). On the acquisition phase, when this period is the bomb period, mixed ANOVA revealed a main effect of trial [$F(4.9,242)=22.869$, $p<0.001$]. While a Trial × Group interaction was also found [$F(4.9,242)=2.663$, $p=0.024$], post-hoc investigation found no differences between groups on any of the trials (independent t-tests, all $p>0.100$). On the extinction phase, when this period is the first 5-s of the intertrial period, analyses revealed a main effect of Group [$F(1,49)=8.274$, $p=0.006$] and a Sex × Group interaction [$F(1,49)=4.749$, $p=0.034$]. Tukey's HSD test revealed that, during extinction, male patients hid more than male and female controls (both $p<0.010$) and tended to hide more that female patients ($p=0.052$).

We then analyzed hiding during the intertrial period (Figure 4). On the acquisition phase, mixed ANOVA revealed a main effect of Group, with patients hiding more than controls [$F(1,49)=6.250$, $p=0.016$], while the effect of Sex approached significance [$F(1,49)=3.911$, $p=0.080$]. On the extinction phase, only the main effect of Group appeared again [$F(1,49)=6.012$, $p=0.018$].

We also tested overall task performance. Univariate ANOVA on total points gained during the entire session revealed a main effect of Group [$F(1,49)=16.911$, $p<0.001$] and Sex × Group interaction [$F(1,49)=6.180$, $p=0.016$]. Tukey's HSD tests showed that male controls gained more points than all the other groups (all $p<0.050$; Figure 5A). Similarly, when shooting was analyzed, while a main effect of Sex approached significance [$F(1,49)=3.458$, $p=0.069$], a significant Sex × Group interaction was shown [$F(1,49)=6.175$, $p=0.016$]. Tukey's HSD tests revealed that male controls shot more than female controls ($p=0.022$) and tended to shoot more than male patients ($p=0.057$; Figure 5B). However, when we analyzed motor activity, no significant main effects or interactions were found (all $p>0.100$; Figure 5C).

When analyses were repeated on only the methadone treatment group, behavioral differences remained the same (data not shown). It is also important to note that patients' medication maintenance dose did not correlate with any of the described behavioral variables (all $p>0.100$).

Lastly, we tested whether comorbidity with other *DSM-IV* psychiatric disorders affected behavior. During the warning signal on acquisition phase, patients with comorbidities made approximately twice more hiding responses than patients without comorbidities (mixed ANOVA, $p=0.013$). Thus, we repeated analysis of hiding during this period (Figure 2; acquisition phase), with the inclusion of comorbid status as a covariate. As in the original analysis, mixed ANCOVA revealed a Sex × Group interaction [$F(1,47)=6.303$, $p=0.016$], with male patients hiding more than other groups. Hiding during other task periods, as well as overall task performance, did not differ between the two comorbidity groups (all $p>0.090$).

Discussion

The purpose of the current study was to examine acquisition and extinction of avoidance behavior in opioid-dependent patients. Consistent with prior results in the animal literature,

these findings show abnormal learning of avoidance behavior in humans treated for heroin dependence. Specifically, male patients demonstrated more overall hiding during the warning period for the acquisition and extinction trials and more hiding during the 5-s that follow the warning period for the extinction trials. Exaggerated hiding during these periods represents non-optimal behavior in the current paradigm, as it prevents the ability to obtain reward (points), without minimizing punishment (explosions and point loss). This behavioral pattern is reminiscent of the compulsive nature of substance addiction, where drug use continues despite negative consequences.[10,36]

Male patients' high levels of hiding during the warning periods on the acquisition trials represent exaggerated learning of avoidance behavior. Such responding, before the initiation of the aversive event, might relate to impaired impulse control that could contribute to addicts' difficulty in inhibiting drug-taking action.[37] Increased learning of the association between the warning signal and the following aversive event is also consistent with the idea of exaggerated associative learning in addicts, where increased tendency to associate discrete stimuli with specific drugs might underlie addictive behavior.[38, 39] Moreover, male patients extinguished more slowly, and exhibited more hiding during the extinction phase. Continued responding during extinction is believed to represent increased impulsivity, impaired disinhibition,[28, 37] might result in responding to drug-related cues when the drugs themselves are no longer available, and closely resembles the diagnostic criterion for substance dependence that addresses the subject's difficulty in restricting drug use.[40]

Many prior studies examining opioid-dependence in humans have been based solely on male addicts.[41–43] However, females compose a significant portion of the general addict population,[44] and often show distinct personal characteristics and patterns of abuse.[45, 46] In the current study, while all patients demonstrated increased overall hiding responding compared to controls, exaggerated avoidance was demonstrated only by male patients. It is possible that female patients are more sensitive to the reward in the current task, leading them to hide less.[47, 48] However, neither female patients nor female controls gained more points or shot more times than their male counterparts, arguing against the idea of higher reward sensitivity in females. While interpretation of the observed sex effect remains speculative and awaits further investigation, the current results suggest that including both sexes should be of a high priority in any addiction research.

Differences in reinforcement sensitivities might also be involved in the unique avoidance pattern in male patients. The current task is characterized by a motivational conflict between the need to hide to avoid possible punishment and the option to stay at the center, to shoot the enemy spaceship and obtain point reward. Thus, the exaggerated avoidance in male patients might actually be the result of decreased reward-seeking, rather than increased tendency to avoid punishment. This idea of decreased motivation for reward is partially supported by fewer total points and fewer shooting attempts in male patients compared to male controls, and is consistent with a large literature that shows reduced reward sensitivity (i.e., anhedonia)[29, 49, 50] and undervaluation of nondrug-related reward[51, 52] in substance users. However, decreased reward-seeking behavior is insufficient to explain avoidance differences on the current task, since female controls obtained less reward (fewer points) than male controls but showed no differences on avoidance responding. It is possible that

male patients had abnormal learning of both the appetitive and aversive components of the current task[53] or had lower learning rates, which impaired the ability of reinforcement to alter their behavior.[54]

One can also argue that the exaggerated hiding by male patients in the current study might be the result of elevated baseline responding, rather than a specific learning pattern.[22] To address such a possibility, we analyzed motor activity, as indicated by subjects' tendency to move their spaceship, and found no group differences. Furthermore, male patients showed generally more hiding during the warning period than during the intertrial period, and demonstrated a clear understanding of the protective nature of the hiding response, as demonstrated by their rapid learning during the bomb period. All these suggest that exaggerated avoidance behavior in male patients is a learned response that can not be simply explained by increased motor activity.

This study has important implications for therapy. First, while previous reports of avoidance behavior in addicts have relied on self-report,[11–13] the current study presents a more objective tool to assess specific behavior patterns that might be abnormal in this population. Second, better understanding of sex-related differences in heroin patients might help explain why males and females often differ on treatment outcomes,[45, 55] and why sex-specific treatments should be considered.[56] Specifically, since treatment strategies often focus on facilitating extinction of drug-related memories,[26, 57–59] the current results suggest that male patients might have more trouble extinguishing and thus, might better benefit from such therapies. Future work could also test whether the addition of specific "safety signals" during therapy could attenuate the exaggerated avoidance behavior, as suggested by a recent study examining the effect of adding such "safety signals" to this task.[32]

This study comes with the following limitations. First, 53.8% of patients in the current study reported comorbidity with other *DSM-IV* psychiatric disorders. While some previous studies reported comparable rates (e.g. 47–55%[60, 61]), other studies reported higher rates (e.g. 70–75%[62, 63]). Indeed, a review of 14 studies found that among treatment-seeking opioid-users, comorbidity rates are typically between 40–80%.[64] Such heterogeneity in reported comorbidities might be associated with variations in methods and populations,[60, 65] as well as with increasing availability of opioid substitution clinics, which could result in the admission of individuals with milder symptoms.[60] Low prevalence of psychiatric comorbidity in the current study might also be due to the treatment itself, as previously suggested by a study that reported a comorbidity rate of 57.6% in patients receiving treatment for drug use.[66] Importantly, since avoidance behavior is a predominant symptom in anxiety disorders, such comorbidity could potentially affect avoidance behavior in the current study. To address this possibility, we repeated analyses only for those subjects without comorbidity and showed that the group differences were maintained, suggesting a basic association between opioid addiction and avoidance behavior. The low comorbidity rate in the current study further supports this association, irrespective of other confounding variables. To promote generalizability of the results to clinical populations, future studies could examine larger and more heterogenic patient groups, or alternatively, specifically target and compare groups of opioid addicts with different diagnosed comorbidities. A

special attention to comorbidity with schizophrenia would also be important, as participants in the current study had a comorbidity rate two-fold higher than previously reported.[67]

Second, as subjects were tested a relatively short time after daily medication dose (1–6 hours), the acute and the chronic effects of the medication cannot be dissociated.[68] To this end, future work could better control dosing and testing times and test patients immediately after and just before the daily medication dose,[69] as well as analyzing withdrawal symptoms that might be differentially experienced during the inter-dosing interval.[70] It would also be important to dissociate the overall effects of opioid medication in treated addicts from the behavior that characterizes treatment-naïve addicts. Furthermore, although both methadone and buprenorphine are opioid medications that have been recommended and shown to provide positive effects in opioid-dependent patients,[71–75] differences do exist.[72–74] While the current study included both medications in the patient group, when analyses were repeated only for the methadone group, the behavioral differences remained the same. Future studies could specifically compare different medication groups, or alternatively, focus on one specific medication.

Another issue is whether sex differences in avoidance are related to treatment outcomes. Assuming that drug-taking involves a desire to avoid an aversive state, successful maintenance therapy should normalize or at least decrease avoidance behavior. It is interesting to note that female addicts might have better treatment outcomes than male addicts,[76] so what emerged as a sex effect in the current study could actually reflect a treatment effect. Future studies could specifically examine whether reduced avoidance on the computer task is correlated with treatment success, perhaps via a longitudinal study that compared baseline versus post-treatment performance as a function of treatment success. However, it is also entirely possible that the current results reflect a true sex difference, particularly given known gender differences in drug pharmacokinetics and pharmacodynamics.[45] Other physiological, psychological and cultural factors could also contribute to different treatment effects in males and females.[45, 55] However, these ideas remain speculative and require further work that would specifically study the effects of medication in opioid addicts.

It is also important to address the validity of the described computer-based task. The use of such “spaceship” tasks to study human avoidance behavior has been gaining popularity in recent years.[30–35] These prior reports suggest that subjects are generally motivated to gain points and successfully learn to avoid on-screen aversive events on these tasks. They further suggest that the tasks can be used to study specific aspects of avoidance behavior (e.g., passive avoidance,[33] active avoidance,[30–32] differential effects of reinforcement contingencies and contextual variables,[34] and discriminative learning and context-dependent latent inhibition[35]). Our recent work has demonstrated that this task is also adequate for studying individual differences, specifically showing that anxiety vulnerable individuals demonstrate more hiding on both the acquisition and extinction phases of the task.[31, 32] However, all these prior studies tested undergraduate students in European or American institutions, while the current study examined opioid-dependent patients and healthy controls in Australia. Additional large-scale multi-site studies with healthy and psychiatric populations, including more racial and ethnic diversity, would be useful to establish

normative values for the various dependent variables on this task. Thus, rather than proposing a diagnostic tool where numerical values are the focus (i.e., defining cutoffs for diagnosis criteria), we here targeted relative group differences that could teach us about basic mechanisms responsible for pathological outcomes in addicts.

It should be noted that the current study has primarily targeted the differences between patients and healthy controls. The reported interaction with sex is interesting, but should be treated with caution and awaits further confirmation from studies with larger group sizes of males and females in each experimental condition. Further, while overall task performance in male versus female controls (Figure 5) is generally consistent with recent findings,[32] prior studies in healthy young adults reported longer avoidance duration in females than males,[31, 32] a pattern which was not observed in the current study. Such discrepancy could be the result of different demographic characteristics, as well as the overall lower hiding rates by control subjects in the current study; specific investigations of sex-related differences in various healthy populations should be performed. Lastly, future studies would also benefit from inclusion of self-report questionnaires regarding subjects' experience with computer games and incentive for good performance,[77] as well as the change in their experience of negative affect (between baseline and directly after task completion)[78, 79] - factors that could bias performance on the computer task.

In sum, while limitations do exist and should be addressed in future work, this is a novel study that assessed escape-avoidance behavior in opioid-dependent patients. As hypothesized, patients showed abnormal learning of this behavior, compared to healthy controls. Overall, the current findings may help bridge the gap between human and non-human research on opioid addiction, promote our understanding of the cognitive and behavioral manifestations of this condition and advance therapeutic approaches to help affected individuals.

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Clinical Points

- While addiction in general, and opioid-addiction in particular, are often conceptualized as avoidance strategies, the literature on avoidance behavior in opioid-dependent patients is little and is primarily based on self-report measures.
- Consistent with reports from animal literature, opioid-dependent patients in the current study exhibited greater acquisition and impaired extinction of the avoidance behavior. Interestingly, these differences were found only within male subjects. Results support the idea that avoidance might be a mechanism that underlies addiction and contributes to its growth and persistence.
- This study demonstrates an objective tool to assess avoidance behavior in opioid addicts. Furthermore, the results suggest abnormal behavior patterns and sex-related differences that might facilitate personalized therapeutic approaches (e.g., exposure-based therapies) in this patient group.

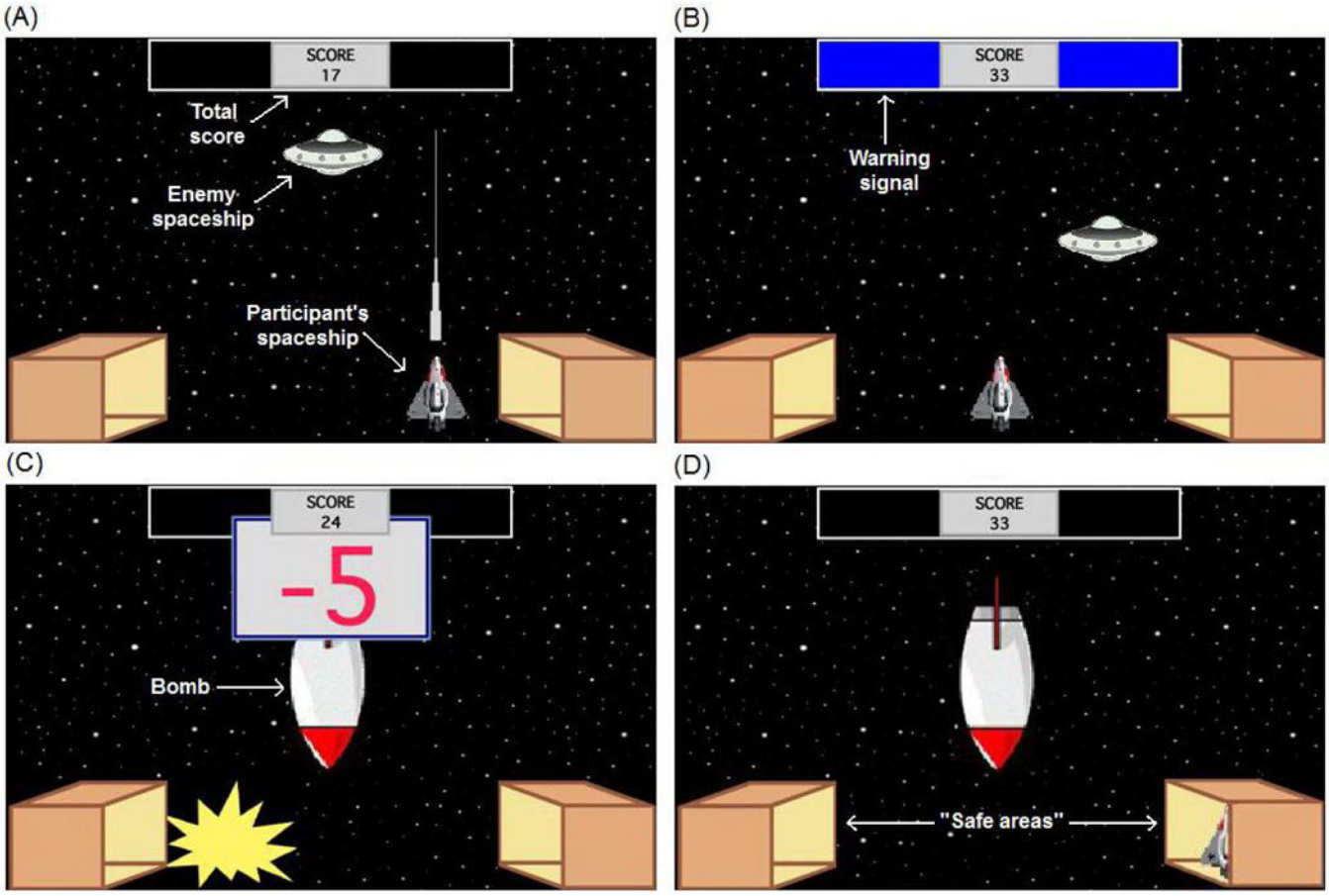

Figure 1.

Computer-based escape-avoidance task. (A) An enemy spaceship appears in one of six locations on the screen, approximately every 1 s. The participant's goal is to gain points by shooting and destroying this spaceship (1 point for each hit). (B) The warning signal is two colored rectangles at the top of the screen, which appear every 20 s and remain visible for 5 s (warning period). (C) The warning signal is always followed by appearance of a bomb, which remains onscreen for 5 s (bomb period). The bomb period is divided into five segments of equal duration; during each segment there is an explosion and loss of 5 points to a maximum of 25 points. (D) At the bottom corners of the screen, there are two box-shaped areas representing "safe areas." Moving the subject's spaceship to one of those boxes is defined as "hiding." While hiding, the subject's spaceship cannot be destroyed and no points can be lost, but neither can the subject shoot the enemy spaceship and gain points. Subjects were not given any explicit instructions about the safe areas or the hiding response. Labels shown in white text are for illustration only and do not appear on the screen during the task.

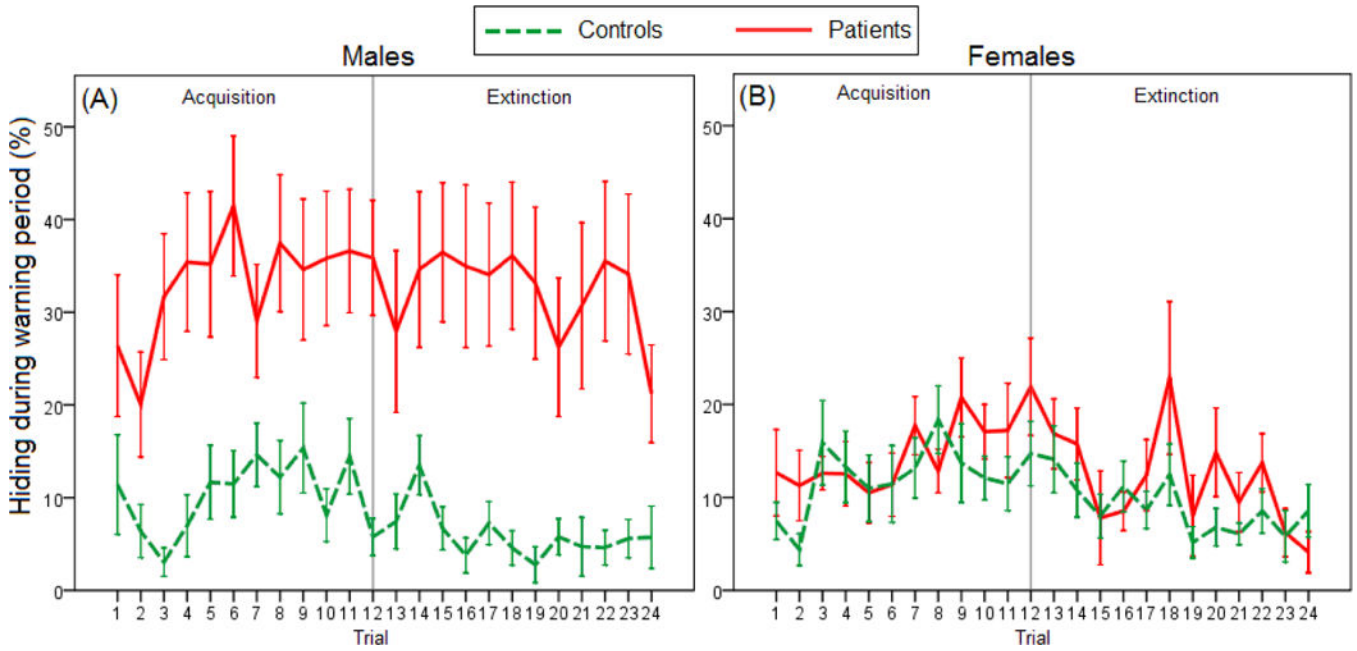

Figure 2.

Acquisition and extinction of hiding behavior during the warning period in (A) male patients versus male controls (n=15 and 9, respectively), and in (B) female patients versus female controls (n=12 and 17, respectively). On the acquisition phase, there were main effects of Trial, Sex and Group, as well as a Sex x Group interaction (mixed ANOVA, all p<0.050). On the extinction phase, analyses revealed main effects of Trial and Group and a Sex x Group interaction (all p<0.050). Tukey's HSD tests revealed that male patients hid more than all the other groups on both the acquisition and extinction phases. Error bars indicate SEM.

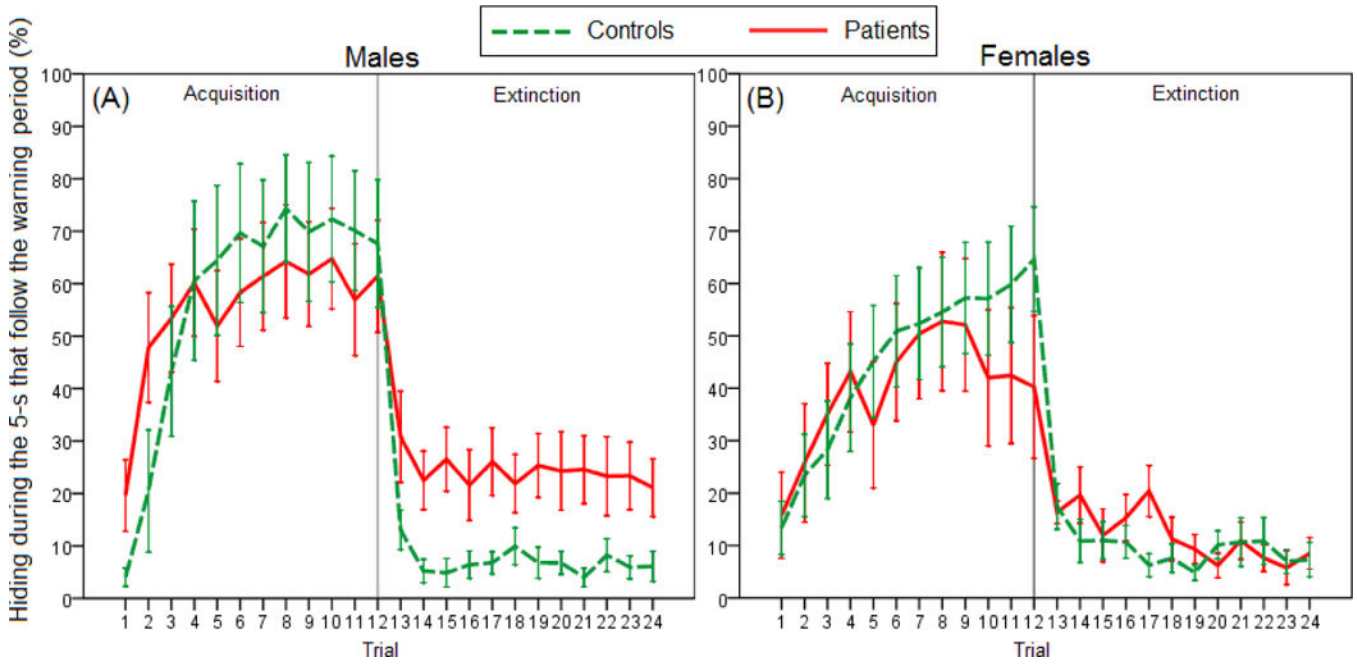

Figure 3.

Acquisition and extinction of hiding behavior during the 5 s that follow the warning period in (A) male patients versus male controls (n=15 and 9, respectively), and in (B) female patients versus female controls (n=12 and 17, respectively). On the acquisition phase, when this period was a bomb period, there was a main effect of Trial and Trial x Group interaction (mixed ANOVA, both p<0.050), although post-hoc investigation of the interaction did not show significant effects. On the extinction phase, when this period was the first 5 s of the intertrial period, there were main effects of Group and Sex × Group interaction (both p<0.050), with male patients hiding more than male and female controls and a tending to hide more than female patients. Error bars indicate SEM.

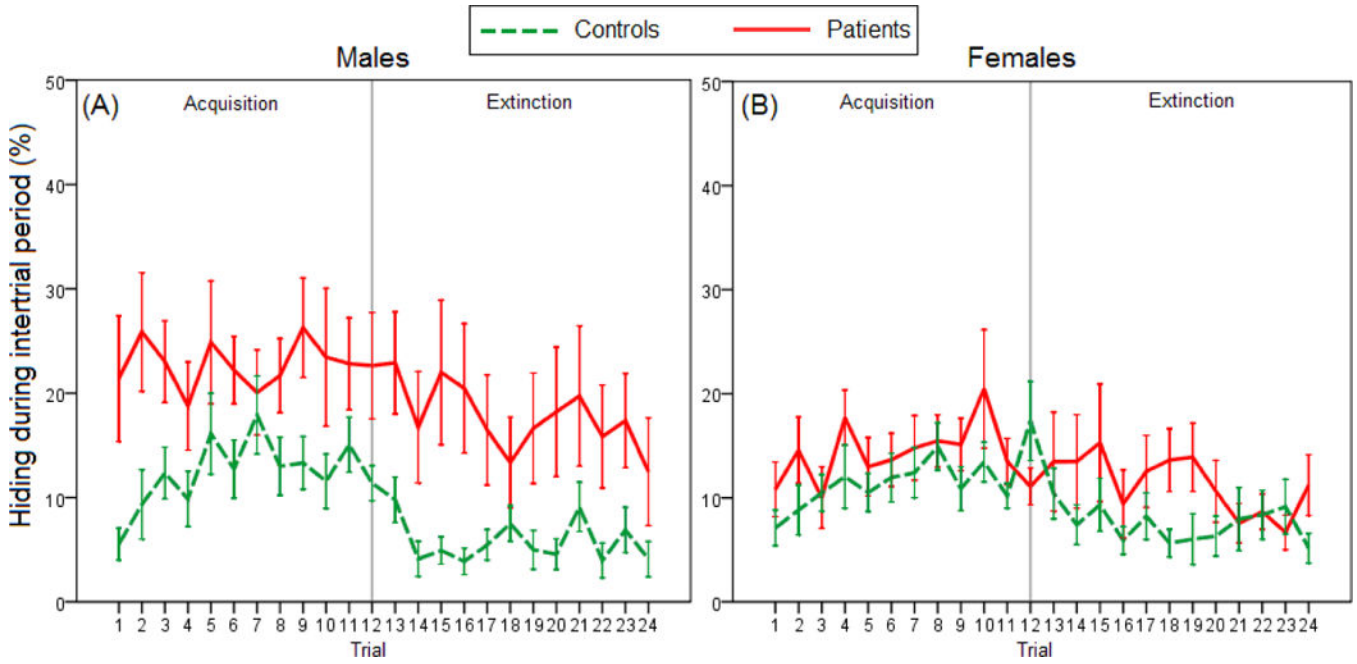

Figure 4.

Hiding behavior during the 10-s intertrial period in (A) male patients versus male controls (n=15 and 9, respectively), and in (B) female patients versus female controls (n=12 and 17, respectively). On both acquisition and extinction phases, there was a main effect of Group, with patients hiding more than controls overall (mixed ANOVA, both p<0.050). Error bars indicate SEM.

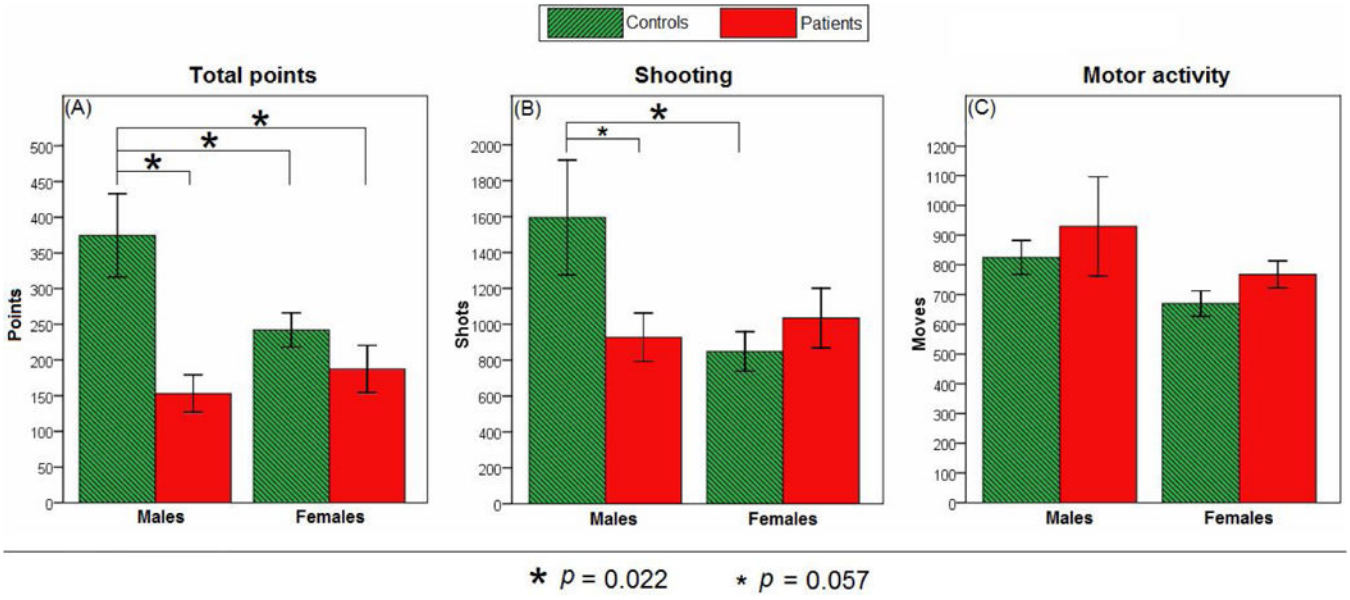

Figure 5.

Overall performance on the computer-based task in male and female patients (n=15 and 12, respectively) versus male and female controls (n=9 and 17, respectively). (A) Total points gained during the entire session. Main effect of Group and Sex × Group interaction were shown (both p<0.050); male controls gained more points than all the other groups (all p<0.050). (B) Number of shooting attempts (FIRE keypresses). A Sex × Group interaction was shown (p<0.050); male controls shot more than female controls (p=0.022) and tended to shoot more than male patients (p=0.057). (C) Motor activity (LEFT and RIGHT keypresses). No differences were found (all p>0.100).