Impaired stimulus-outcome but preserved stimulus-response shifting in young substance-dependent individuals

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Substance dependency has been related to an impairment in executive functions and to a dysfunction of the frontal cortex. In this study we developed two experimental tasks, which are physically identical, to analyze whether substance-dependent individuals are impaired in shifting response patterns (stimulus response links) or preferences (stimulus outcome links). To increase the specificity of the dependent variable, we also used two control tasks to analyze for unspecific performance deficits. We included 35 young subjects with polysubstance abuse (International Classification of Diseases, F19.2 ICD 10 diagnosis, mean age of 22 years, maximum age < 27 years) and 18 normal controls, but for a first step focused on only 22 patients and 15 age-matched controls, because we excluded all patients with an IQ below 100. The results show that the substance-dependent individuals are selectively impaired in shifting object preference (stimulus–outcome links) and not in shifting response patterns. They moreover show a higher general impulsivity as reflected in their faster responses than controls on all tasks except the stimulus–outcome task. In a second step we replicated these results by analyzing the original groups of 35 patients and 18 controls. We argue that substance-dependent subjects show an impairment only on specific executive tasks, and these tasks concern stimulus–outcome link shifting, which has been associated with the functioning of the orbitofrontal cortex, not of the lateral prefrontal cortex.

Keywords: Polysubstance dependence; Executive functions; Reversal learning; Stimulus–outcome learning; Impulsivity.

INTRODUCTION

Addiction is a social, psychological, and biological phenomenon, which can be studied on many different levels. On the psychological level it has been associated with cognitive dysfunctions, especially with deficits in executive functions. As summarized by Bechara (2003), three different hypotheses have been proposed for addiction: (a) disinhibition of prepotent motor impulses, which leads to a lack of control in situations in which strongly preferred stimuli are present; (b) inflexibility in shifting between stimulus–response rules (response inflexibility), which leads to problems in learning new behavior, replacing (over) learned responses; (c) inflexibility in shifting between emotional expectations, in particular from short-term to long-term reward (reward inflexibility). The first two hypotheses can explain why so many substance-dependent people relapse into addictive behavior when...
confronted with drugs. The main difference is that the disinhibition hypothesis presupposes a general tendency for responding inadequately, whereas the response inflexibility hypothesis associates the risk of a relapse to the learning history of the addicted individual. The reward inflexibility hypothesis differs from the other two by suggesting a specific impairment in emotional shifting and relates addiction to a dysfunction of the orbitofrontal cortex and the basal ganglia.

The difference between the response and reward inflexibility hypotheses resembles a distinction between two learning mechanisms described in animal studies—namely, the shifting between stimulus–response links and the shifting between stimulus–outcome links (Cools, 2006; Dayan & Balleine, 2002; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Shifting between stimulus–response links implies the learning of new responses to the same stimuli, depending on the context of the situation. A typical task that investigates stimulus–response links is extradimensional shift learning, in which a subject has to shift his response to a class of stimuli or features, which has not been presented on foregoing trials, while stimuli are present that have been targets during the recent trials. Reversal learning, on the other hand, is an example of shifting between stimulus–outcome links (Clark, Cools, & Robbins, 2004; Fellows & Farah, 2003; Marschner et al., 2005): A subject has to learn that a stimulus, which had been a target before, now has become irrelevant and that another stimulus, which was present but was irrelevant, has now become a target. In other words, stimulus–response learning implies holding on to a specific goal and a change of strategy if necessary. Stimulus–outcome learning, on the other hand, implies that one sticks to the strategy (for example, to eat something), but changes the preferred object (not this cake but that piece of chocolate). Stimulus–response links therefore concern the choice of the best way (“action routines”) to get a preferred object; stimulus–outcome links concern the relative preference for different objects.

In a series of studies we (Brokate et al., 2003; Hildebrandt, Brokate, Eling, & Lanz, 2004; Hildebrandt, Brokate, Hoffmann, Kröger, & Eling, 2006) analyzed cognitive deficits in alcohol-dependent people using an instructed variant of the object alternation task (which we called in our first publication response shifting task). We found that alcohol-dependent subjects of similar premorbid intelligence, similar nonverbal intelligence, and attentional capacities as controls, and without any memory deficit, were impaired on the object alternation task either by producing more erroneous responses or by responding significantly slower than controls. The impairment appeared to be primarily restricted to object alternation, not involving, for instance, working memory or perseverative tendency in the Wisconsin Card Sorting Test (WCST) or word fluency tasks. We speculated that object alternation may belong to a class of tasks involving conditional responding and that alcohol-dependent individuals may be impaired more generally in this type of task (Hildebrandt et al., 2006). This speculation was also based on the fact that alcohol-dependent people showed more erroneous responses in a spatial stimulus–response incompatibility task, in which a subject had to base his response on the place on the screen where an arrow was presented and not on the direction the arrow was pointing to (Hildebrandt et al., 2006).

We can now relate our conditional-learning hypothesis for addiction to the response inflexibility and reward inflexibility hypotheses by assuming that they refer to deficits in two different kinds of conditional learning: stimulus–response learning and stimulus–outcome learning. This offers an opportunity to specify the nature of the executive function deficits of the substance-dependent individuals (Bechara, 2003) or of their conditional-learning problems (Hildebrandt et al., 2004). The response inflexibility hypothesis would predict a deficit in stimulus–response learning, but not in stimulus–outcome learning. The reward inflexibility hypothesis would predict the reverse—namely, that addicts should be impaired in stimulus–outcome learning but not in stimulus–response learning.

These different predictions for response and reward inflexibility are not only of interest for a functional explanation. They also may help to differentiate different neuronal structures involved in substance dependency. Recent investigations examining these two different types of inflexibility have shown that they can be dissociated in Parkinson’s disease, where—at least in the early stages—stimulus–response but not stimulus–outcome learning is impaired (Cools, 2006). Moreover, L-dopa enhances performance in stimulus–response learning, but not in stimulus–outcome learning (Cools, Barker, Sahakian, & Robbins, 2003). This dissociation has been interpreted as a consequence of the prototypical progression in Parkinson’s disease. The degeneration of dopaminergic fibers from the substantia nigra to the striatum starts at the dorsal and lateral parts of the striatum and progresses into the more ventral parts only in a late stage of the disease. Therefore L-dopa normalizes the performance of patients with Parkinson’s disease on tasks, tapping the dorsal and lateral striatum.
(learning stimulus–response links). But, at the same time, this medication influences the intact functioning of the ventral parts thus leading to a decrease in stimulus–outcome learning. Therefore the response inflexibility hypothesis predicts impairment in a different fronto-striatal loop (Alexander, DeLong, & Stuck, 1986) from that predicted by the reward inflexibility hypothesis (O’Doherty et al., 2004), and thus contrasting these hypotheses may help to get additional insight in the neuronal structures involved in substance dependency.

Against this background and based on our earlier research, we developed two experimental and two control tasks, all identical with respect to the stimulus presentation: The digits 0, 1, and 2 were presented sequentially in random order. All tasks were go/no-go tasks (to prevent spatial mapping of responses), but they differed with respect to the response rules. In the stimulus–response (SR) task the rule was defined in relation to the digits: The subject had to switch between responses (from go to no-go, or vice versa) if the current stimulus differed from the former, otherwise he had to continue his response strategy. In order to prevent a simple association of a single stimulus to a specific response (e.g., 1 indicates go) we used three stimuli. In the stimulus–outcome (SO) task a subject had to alternate on every trial between two stimulus classes, between zero and “not zero,” and he had to press a button if the currently valid stimulus was presented, otherwise he did not have to respond. This latter task resembles object alternation as far as the subject has to alternate the relevant stimulus–outcome from trial to trial.

Obviously both tasks involve specific components—respectively, the stimulus–response shift and the stimulus–outcome shift—but also other features may determine a subject’s performance. To control for such unspecific factors we used two control tasks. In the stimulus change (SC) task a subject had to press the button if the digit differed from the one presented on the former trial. This task served as a control task for the stimulus–response shift task, because in this task subjects have to notice a simple stimulus change. In the response change (RC) task a subject had to switch between responses (go/no-go), irrespective of the specific stimulus presented. This task served as control test for the stimulus–outcome shift task, because it tested the ability of subjects to switch between instances (sequential trials) independent of the stimulus presented. If our hypothesis that addicts suffer from a general deficit in conditional learning is correct, then addicts should be impaired on both tasks. If the response inflexibility hypothesis of Bechara (2003) is correct, they should be impaired selectively on the stimulus–response task; if the reward inflexibility hypothesis of Bechara (2003) is correct, they should be impaired on the stimulus–outcome task.

METHOD

Patients

Thirty-five young patients with substance dependence were recruited from a rehabilitation hospital, where they lived for about 3 months for therapeutic interventions to prevent a relapse and to start with their reintegration in housing and jobs. They were not in an acute phase of drug intoxication or in a withdrawal state, but residents of a rehabilitation center with irregular blood probe controls for abuse, and the last consumption took place, on average, 4.2 months before testing. All patients fulfilled the criteria of an International Classification of Diseases (ICD) F19.2 ICD 10 diagnosis and were older than 18 years. A total of 15 substance-dependent individuals (SDIs) used morphine types of drug (heroin, cocaine, etc.), and 20 SDIs used only non-morphine types of drug (alcohol, amphetamine, cannabis, etc.), but all used different kinds of drugs at the same time. A total of 22 of the patients had some legal problems; 13 had not been accused.

Addiction for different drugs in young years may be associated with lower social status, fewer educational years, and lower intelligence (Fergusson, Horwood, & Beautrais, 2003; Mortensen, Sørensen, Jensen, Reinisch, & Mednick, 2005; Windle & Blane, 1989), and this may affect results in executive functioning. We therefore decided only to include patients with an intelligence quotient of at least 100, in order to focus on cognitive well-functioning subjects.

A total of 18 age-matched controls were investigated with the same experimental tasks and neuropsychological tests. Controls were members of the hospital staff (physiotherapists, nurses, etc.) and students.

All patients and controls gave their informed consent. The study was approved by the ethical board of the University of Oldenburg.

Neuropsychological investigation

The Culture Fair Intelligence Test was used to assess the intelligence quotient and to exclude participants below an intelligence quotient of 100. We used the Mehrfachwahl–Wortschatz–Intelligenztest (Lehrl, Merz, Burkard, & Fischer, 1991) as a measure
for premorbid intelligence. The Benton Visual Retention Test served as a task to assess memory impairments. The Trail Making Test A (Reitan, 1956) was used as a measure for psychomotor speed, and Trail Making B was taken as a measure of behavioral flexibility.

Experimental tasks

Stimulus presentation was identical in all conditions. A number (0, 1, 2) was presented in the center of the screen (approx 1.5 cm wide, 1 cm high) for 500 ms. Participants had to press, as quickly as possible, a button (“go” trials) or not (“no-go” trials), depending on the task instructions. After a 2-s response interval the next trial started. After 15 successive correct responses the task was finished. Otherwise the task was continued for a maximum of 75 trials. Before each task, participants received a written instruction, and they were told that they could read the instruction as long as necessary, but that no additional explanation of the task would be given. Then a series of 15 practice trials was presented, and participants were allowed to read the instruction again. The number of trials to reach the criterion (TTC) and response times (RTs) to go trials served as dependent variables. The tasks were presented in a fixed order: RC, SC, SO, SR.

The four tasks differed only in the instruction given to the participants (see Table 1). In the first task, response change (RC), participants had to alternate between pressing and not pressing. The number on the screen only served as starting signal. This task served as control task for the SO task, because participants had to switch spontaneously between response patterns.

In the second task, stimulus change (SC), participants had to press the button only if the number on the screen differed from the previous number and not to press the button if the numbers were the same. This task served as control task for the SR task, because participants had to note stimulus shift without changing their response pattern.

In the third task, stimulus outcome (SO), participants had to alternate in their minds between 0 and a nonzero number (1 or 2). If the number presented on the screen corresponded (that is, either 0 or not-0) they had to press the button, otherwise they had to wait for the next number presentation.

In the fourth task, stimulus response (SR), the participants had to change their response pattern if the stimulus changed between trials. If the stimulus did not change they had to stick to either the go pattern or the no-go pattern.

<table>
<thead>
<tr>
<th>Stimulus sequence</th>
<th>Experimental conditional-learning tasks</th>
<th>Control tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>go</td>
<td>go</td>
</tr>
<tr>
<td>1</td>
<td>go</td>
<td>go</td>
</tr>
<tr>
<td>2</td>
<td>no-go</td>
<td>no-go</td>
</tr>
<tr>
<td>0</td>
<td>go</td>
<td>go</td>
</tr>
<tr>
<td>0</td>
<td>go</td>
<td>no-go</td>
</tr>
<tr>
<td>1</td>
<td>no-go</td>
<td>go</td>
</tr>
<tr>
<td>1</td>
<td>no-go</td>
<td>go</td>
</tr>
<tr>
<td>2</td>
<td>go</td>
<td>no-go</td>
</tr>
</tbody>
</table>

Note. SR = stimulus-response task. SO = stimulus-outcome task. SC = stimulus change task. RC = response change task. The instructions for the tasks were as follows: SR: Switch from pressing to not-pressing, or vice versa, if the current number differs from the former. SO: Switch in your mind continuously between 0 and not-0, and if the number on the screen matches (a 0 or not a 0, respectively), press the button. SC: Press the button if the current digit is different from the former. RC: Press the button on one trial, not on the next trial, press on the next, and so on, independent of the numbers. Immediate feedback was given for incorrect trials in SR and SO, and participants were informed how to go on during the next trial.

Immediate feedback was given for SO and SR: In the case that participants produced an incorrect response the presentation stopped, and an instruction concerning the correct response on the next trial was given.

Statistical analysis

We used nonparametric testing throughout the whole study to avoid influences of skewed distributions (Kolmogorov–Smirnov Test showed deviation from normal distribution in three of four TTCs as expected because of a fixed termination criterion for the tasks). We therefore used the Mann–Whitney U Test to analyze group differences on RT and TTC for each task and then the Wilcoxon Test to look for performance differences between tasks. We correlated scores between tasks and between response times and trials with Spearman’s rho.

RESULTS

Patient groups

A total of 22 of the 35 SDIs had an intelligence quotient of at least 100 and remained in the further analysis (mean age 22 years). Their age...
range led to an inclusion of 3 controls, resulting in a control group of 15 participants (mean age 24 years; for further information about the patients’ characteristics see Table 2). Of the SDI, 7 did not finish school education, 17 departed from school after 9 years, 9 reached a 10-years degree (high-school degree), and 2 a diploma to enter university (13 years of education). Only 5 of the SDIs finished a professional education. All of the control participants had at least a 10-years school degree.

SDIs started their drug abuse at a mean age of 14 years, which explains to some degree their restricted educational level. Duration of drug abuse was on average 8 years.

**Neuropsychological investigation**

Patients and controls did not differ in age, Culture Fair Intelligence Test (intelligence quotient), Benton Visual Retention Test (memory), and Trail Making A (visual attention, psychomotor speed), but did differ in Mehrfachwahl–Wortschatz–Intelligenztest [Multiple Choice Vocabulary Intelligence Test] (premorbid intelligence) and in Trail Making B (see Table 2).

**Experimental tasks**

The patient and the control groups differed on mean RT for all tasks except for the SO task. In

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Group characteristics and results</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>N</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>General characteristics</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.4 ± 2</td>
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<tr>
<td>Gender (female/male)</td>
<td>3/19</td>
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<tr>
<td>School education average (years)</td>
<td></td>
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<tr>
<td>not finished</td>
<td>4</td>
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<tr>
<td>9 years</td>
<td>10</td>
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<tr>
<td>10 years</td>
<td>6</td>
</tr>
<tr>
<td>13 years</td>
<td>2</td>
</tr>
<tr>
<td>Duration of drug abuse (years)</td>
<td>min. 3/max. 13</td>
</tr>
<tr>
<td>Time since last abuse (months)</td>
<td>min. 0.5/max. 28</td>
</tr>
<tr>
<td>Age drug abuse was started (years)</td>
<td>min. 12/max. 19</td>
</tr>
<tr>
<td>Type of drug abuse</td>
<td></td>
</tr>
<tr>
<td>With morphine-type substance</td>
<td>9</td>
</tr>
<tr>
<td>Without morphine-type substance</td>
<td>13</td>
</tr>
<tr>
<td>Neuropsychological assessment</td>
<td></td>
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<tr>
<td>Culture Fair Intelligence Test</td>
<td>113.1 ± 8.6</td>
</tr>
<tr>
<td>MWT</td>
<td>91.2 ± 5.1</td>
</tr>
<tr>
<td>Benton Visual Retention Test (scaled score)</td>
<td>8.3 ± 1.2</td>
</tr>
<tr>
<td>TMT A (in s)</td>
<td>30.2 ± 7.4</td>
</tr>
<tr>
<td>TMT B (in s)</td>
<td>73.3 ± 22.1</td>
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<tr>
<td>Experimental results</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td></td>
</tr>
<tr>
<td>RC</td>
<td>348 ± 77.1</td>
</tr>
<tr>
<td>SC</td>
<td>530.5 ± 91.0</td>
</tr>
<tr>
<td>SR</td>
<td>597.9 ± 145.3</td>
</tr>
<tr>
<td>SO</td>
<td>648.3 ± 164.1</td>
</tr>
<tr>
<td>SR – SC</td>
<td>249.1 ± 150.0</td>
</tr>
<tr>
<td>SO – RC</td>
<td>117.8 ± 157.1</td>
</tr>
<tr>
<td>TTC</td>
<td></td>
</tr>
<tr>
<td>RC</td>
<td>18.5 ± 5.1</td>
</tr>
<tr>
<td>SC</td>
<td>28.6 ± 16.3</td>
</tr>
<tr>
<td>SR</td>
<td>32.2 ± 19.2</td>
</tr>
<tr>
<td>SO</td>
<td>37.8 ± 19.5</td>
</tr>
<tr>
<td>SR – SC</td>
<td>19.3 ± 20.8</td>
</tr>
<tr>
<td>SO – RC</td>
<td>3.6 ± 25.6</td>
</tr>
</tbody>
</table>

general, patients were faster than controls in their responses (compare Table 2).

Looking at the TTC (see Figure 1), the patients needed significantly more trials than controls in the SO task but in none of the other tasks.

Subtracting the TTC of the RC from that of the SO task, the TTC of the SC from that of the SR task, the RTs of the RC from those of the SO task, and the RTs of the SC from those of the SR task revealed no significant group differences.

We then compared the results of the four different tasks for the two different groups (Table 3). There were two differences in group results: The group of SDI showed an increase in RTs from SC to SR and from SC to SO, whereas the controls did not show such an increase. Moreover the SDI demonstrated a significant increase of TTC for the subtraction scores comparing SO and SR, whereas the controls did not show such an increase.

To analyze the impact of education and cognitive functions on the experimental tasks, we performed a nonparametric correlational analysis between these results on the one hand and premorbid intelligence scores on the Trail Making Test A and B and memory performance on the other hand. For the control group we found no significant correlations at all. In the patient group Trail Making Test A correlated with trials in the SR experiments.

TTCs on the experimental tasks did not correlate with age, duration of drug dependence, days after detoxification, and age at which drug consumption was started. There were moreover no differences in performance between abusers with and without heroin or with and without alcohol.

We also analyzed the correlation between RTs and trials to look for a response bias of speed on TTC. In the patient group Spearman rho was about zero for SC, SR, and SO, and \(-.306 (p > .05)\) for RC. There was also no significant correlation between speed and TTC in the control group.

Replication of statistical analyses in the larger group

As a last step we replicated all statistical analyses with the original group of 35 SDI patients and 18 controls (ignoring the exclusion criterion of an IQ of 100 or above). This led to additional significant difference in the Benton Visual Retention Test and the Culture Fair Intelligence Test and also in TTC of the stimulus change task between the groups, but not in SR. All the other results remained the same.

## DISCUSSION

In this study we investigated whether young substance-dependent individuals (SDIs) have deficits on different aspects of conditional learning. In particular, we distinguished between two types of conditional learning. Stimulus–response learning depends on a context-sensitive association of a motor response to the presence of a specific stimulus. A long and rich history of research (summarized in Passingham, 1993) shows that the premotor and dorsolateral areas of the frontal cortex are involved in this type of learning, depending on the task structure and task load. Specific subcortical structures play a role too, in particular the dorsolateral striatum and the thalamus. Stimulus–outcome learning is a different kind of conditional learning.
learning and depends on a context-sensitive association between a stimulus and an expected reward. In stimulus–outcome learning the same response is guided by different expectations about the relevance of an object on the current trial. The major aspect is a shift in the relevance of objects (expectations of outcome), not in the correct action pattern, and it has mainly been studied under the heading of reversal learning. The orbitofrontal cortex and the nucleus accumbens play a major role in stimulus–outcome learning (O’Doherty et al., 2004; Robbins, 2000). Imaging studies (Dao-Castellana et al., 1998; Gansler et al., 2000; Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001; Moselhy, Georgiou, & Kahn, 2001; Vogel-Sprott, Easton, Fillmore, Finn, & Justus, 2001) have revealed structural changes in these neuronal structures for substance-dependent patients. We therefore examined whether addicts were impaired in one or both of these two aspects of conditional learning—either in their ability to shift between stimulus–response links or in their ability to shift between stimulus–outcome links.

The main results of our study are:

1. SDIs did not have a deficit in stimulus–response shifting (SR task, rejecting the response inflexibility hypothesis described in the Introduction).
2. However, they did show a deficit in stimulus–outcome shifting (SO task, in accordance with the reward inflexibility hypothesis). Related to the control tasks the SO led to more TTCs in the SDI group than did the SR task, but this was not the case in the control group.
3. They also showed an increase in impulsiveness, reflected in the faster responses in three of the experimental tasks (which would be in line with the disinhibition hypothesis).

The finding of a specific deficit on the SO task is in line with our earlier finding of a specific impairment in object alternation or response shifting (Brokate et al., 2003; Hildebrandt et al., 2004; Hildebrandt et al., 2006). The stimulus–outcome task resembles the object alternation task, because participants have to shift their preference from trial to trial. The main difference is that participants have to respond only in trials on which the preferred object is present. On the other hand, SDIs were not impaired on the SR task, and therefore they did not show a generalized deficit in conditional responding. This is of considerable interest, because in earlier studies (Brokate et al., 2003; Hildebrandt et al., 2004) we found that alcoholics without Korsakoff’s syndrome have no problems on a 2-back working-memory task compared to age- and education-matched controls. Taken together, these results suggest that the executive impairment in SDIs concerns only performance in a specific set of tasks, which we termed the reward inflexibility hypothesis of addiction in the Introduction, and this deficit may be closely linked to medial prefrontal or orbitofrontal structures, because normal performance in the SR task and 2-back task argues for unimpaired lateral frontal functioning.

A similar selective pattern of findings has been reported for the IOWA Gambling Task (GT; Bechera, Dolan, Denburg, Hindes, & Anderson, 2001). Most of these studies show that SDIs have problems with anticipating long-term losses and therefore choose systematically the response with the highest short-term gain (Bechera & Damasio, 2002; Bechera, Dolan, & Hindes, 2002; Bechera & Martin, 2004; Ernst et al., 2003; Fein, Klein, & Finn, 2004; Monterosso, Ehrman, Napier, O’Brien, & Childress, 2001; but see Hildebrandt et al., 2006). Moreover, these studies also showed that SDIs are not consistently impaired in other executive tasks like the Wisconsin Card Sorting Test or working-memory tasks. These findings support the notion that addiction is associated only with a specific set of executive tasks.

What do tasks like the Gambling Task and the SO learning task have in common, which might explain this similarity? At a neuronal level, both tasks depend on the integrity of the orbitofrontal and the ventromedial prefrontal cortex (Adinoff et al., 2003; Bolla et al., 2003; Clark et al., 2004; O’Doherty et al., 2004; Tucker et al., 2004). At a functional level, during the first trials of the Gambling Task the participant learns which decks result in high gains while no great losses occur. Only during the later trials should the choices be shifted to decks with low gains, because of the losses that occur in the decks with high gains. Therefore, the Gambling Task requires a shifting of expected outcomes for decks. In stimulus–outcome shifting tasks a participant also has to shift his expectations for expected stimulus outcomes (Clark et al., 2004; Marschner et al., 2005). Changing expectation for outcomes therefore might be the common structure of the Gambling Task and our SO task. Assuming that this interpretation is correct, our data add to the Gambling Task findings that the problem of SDIs not only involves a cognitive deficit in balancing short-term gains and long-term losses, but is also apparent in a task involving the direct alternation between two stimulus–outcome links (preferences).
It should also be noted that in this study we tried to keep all irrelevant aspects as constant as possible. Whereas previous investigations with the Gambling Task (Bechara & Damasio, 2002; Bechara et al., 2002; Bechara & Martin, 2004; Ernst et al., 2003; Fein et al., 2004; Hildebrandt et al., 2006; Monterosso et al., 2001) and with object alternation (Brokate et al., 2003; Hildebrandt et al., 2004, 2006) used physically dissimilar presentation patterns to analyze different executive functions (like decision making and working memory), in this investigation stimulus–response learning and stimulus–outcome learning did not differ in presentation and response patterns, but only in the instruction given to the participants. This underscores that the difference between SDIs and controls really concerned the studied cognitive functions and not any other side-aspect of the investigation.

In our view the dissociation between impaired stimulus–outcome shifting and preserved stimulus–response shifting has also some face validity and may help to understand the core problem of addiction. To get their drugs these individuals sometimes develop ingenious strategies, which fit in their daily life activities. This indicates that they can develop flexible stimulus–response links to achieve their goal. On the other hand, they are not able to shift stimulus–outcome links: Drug consumption remains in the center of their interest, and they are unable to switch to different goals, in particular other ways of getting satisfaction, although they are aware of the negative long-term outcome. This dissociation in cognitive structures of SDIs is exactly what we found in this investigation.

A second finding of this study is that SDIs responded significantly faster than controls in different tasks, while they performed at the same or nearly the same level. Increased speed did not appear to result from a different response bias, because in neither group did RTs correlate with TTCs. Interestingly, the patients also differed on the Trail Making Test B, but not on the Trail Making A. The Trail Making Test has been used several times for investigating executive dysfunctions in alcohol-dependent patients (Chao, Meyerhoff, Cardenas, Rothlind, & Weiner, 2003; Ihara, Berrios, & London, 2000; Kleinknecht & Goldstein, 1972; Lodberg, 1980; Noel et al., 2001), and recovery after withdrawal has been proposed as an explanation for contradictory results (Kleinknecht & Goldstein, 1972; Mann, Günther, Stetter, & Ackermann, 1999; Templer, Ruff, & Simpson, 1975). Within the framework of Bechara (2003), the TMT B belongs to the group of go/no-go tests, because participants tend to continue with either the set of numbers or that of letters and forget to shift between sets.

A deficiency in such tasks may be interpreted as resulting from an increase in impulsiveness (not to shift) and is reflected in the time difference between Trail Making Test A and Trail Making Test B. That alcohol affects the control aspect of behavior has also been demonstrated with go/stop and cued go/no-go paradigms (Fillmore, 2003; Mulvihill, Skilling, & Vogel-Sprott, 1996). Our study underlines the problem of disinhibition, not only because of the increase of time needed for the Trail Making Test B, but also because of the significantly faster RTs in three of the four tasks. A similar pattern was present in our previous study (Hildebrandt et al., 2006) where we used a spatial stimulus response incompatibility task and found that alcohol-dependent people produced more incorrect responses especially in the incompatible trials.

Therefore, we interpret the results of this study, but also of our previous study (Hildebrandt et al., 2006), that SDIs not only suffer from impairment in stimulus–outcome shifting, but also have a problem in response inhibition.

On the other hand, SDIs did not differ in the RTs in the SO learning task, but only in the three other experimental tasks. We would like to argue that this endorses our interpretation of a specific impairment in SO learning leading to a relatively slowing of SDIs in this condition compared to the other tasks. The lack of correlation between the RTs and TTCs in any of the four experimental condition also argues against an interpretation in form of an accuracy–speed of effect.

There are two critical arguments, which may be raised against these interpretations of our results. First, our tasks differ in several respects from traditional stimulus–response and stimulus–outcome learning tasks. For instance, we did not use trial-and-error probabilistic learning, but informed the participants about the rules. The high number of TTCs in the SO and SR task shows that this is only half of the truth. Clearly, our participants (SDIs and controls) had to learn how to perform the rules. In our view, telling the participants the rules in advance has the advantage to better focus on the capacity to shift between responses and outcome expectation, rather than on learning such a response rule. Moreover, the task structures of our SR and the SO tasks resemble in significant aspects the traditional stimulus–response and stimulus–outcome learning paradigms. In our SR task a participant has to change the response to a particular stimulus (in the stimulus sequence the participant has to respond to the same stimulus with two different responses), and in the SO task the meaning of a stimulus changes during the sequence, while the response itself remains the same. We therefore
believe that the results of the experimental tasks can be interpreted within the theoretical framework developed for stimulus–response and stimulus–outcome learning.

Another objection that could be made is that the patient group and the control group differed in premorbid intelligence and education. We have already argued in the Method section that it is almost impossible to match properly young SDIs to controls in education (and therefore also in premorbid intelligence), because the former often do not finish the schools they are visiting. Therefore we decided to focus on SDIs with at least average intelligence (see our exclusion criterion) and checked the influence of this exclusion criterion by recalculating all results in the larger group of 35 patients. Yet, the results remained more or less the same, and for the topic of this study differences concerned irrelevant aspects such as visual memory. There are two additional reasons to argue that the education difference did not influence our results: (a) The patient group was significantly faster in three of the four RT tasks and differed in only one of the four tasks with respect to TTC. This suggests that the two groups performed at least at a similar level in three of the four experiments; (b) there was no difference in TTC of SR between the patient group and the controls, but there was in the SO task. Given that both only differ in instruction how to perform, this argues for a specific deficit in SO shifting in SDIs.

Of course, the psychological mechanisms involved in addiction and interfering with the impact of therapeutically interventions are still not fully understood, but during recent years it has become evident that impairment in executive functions may play a prominent role. This investigation shows that the range of executive functions that are impaired in SDIs may involve mainly two components—stimulus–outcome learning and impulsivity—whereas other aspects of executive functions, such as working memory (Brokate et al., 2003; Hildebrandt et al., 2004), stimulus–response learning (this study), and set shifting (Bechara et al., 2001; Hildebrandt et al., 2004) do not differ consistently between SDIs and controls. Hopefully, future research will show that measures of stimulus–outcome learning and impulsivity also can help to identify individuals with a high risk for a relapse and to develop interventions with enhanced therapeutic efficacy.

REFERENCES


