On the predictive validity of automatically activated approach/avoidance tendencies in abstaining alcohol-dependent patients

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\begin{abstract}
Background: Prominent addiction models posit that automatically activated approach/avoidance tendencies play a critical role in addiction. Nevertheless, only a limited number of studies have actually documented the relationship between relapse and automatically activated approach/avoidance tendencies. We compared automatically activated approach/avoidance tendencies towards alcohol in 40 abstaining alcohol-dependent patients and 40 controls. We also examined whether individual differences in automatically activated approach/avoidance tendencies towards alcohol are predictive of relapse in patients.

Methods: A Relevant Stimulus Response Compatibility task was used to measure relative approach/avoidance tendencies. In one block of trials, participants were asked to approach alcohol-related pictures and to avoid alcohol-unrelated pictures (i.e., compatible block). In a second block of trials, participants were asked to approach alcohol-unrelated pictures and to move away from alcohol-related pictures (i.e., incompatible block). Patients were tested between 18 and 21 days after they quit drinking. Relapse was assessed 3 months after patients were discharged from the hospital.

Results: Whereas abstaining alcohol-dependent patients were faster to respond to incompatible trials as compared to compatible trials, participants in the control group showed the exact opposite pattern. Within the patient group, the likelihood of relapse increased as participants were faster to respond to incompatible trials relative to compatible trials.

Conclusion: Unlike controls, abstaining alcohol-dependent patients revealed a relative avoidance bias rather than relative approach bias. Moreover, relapse rates were found to increase as the relative tendency to avoid alcohol increased. This finding suggests that an avoidance orientation towards alcohol can potentially be harmful in clinical samples.

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\end{abstract}

1. Introduction

During the past decade, a considerable body of evidence has accumulated to suggest that automatic cognitive processes play a critical role in addiction. It is now well-established, for example, that substance-related stimuli can grab the user's attention (for a review, see Field and Cox, 2008). It has also been demonstrated that substance-related stimuli can activate valence and arousal associations from memory in an automatic fashion (Houben et al., 2010; Wiers et al., 2002). Finally, there is also evidence showing that substance-related stimuli can trigger automatic approach/avoidance tendencies (Field et al., 2008; Palfai and Ostafin, 2003; Ostafin and Palfai, 2006; Wiers et al., 2009).

While there is little disagreement among addiction researchers that a systematic study of these phenomena will eventually lead to a better understanding of addictive behavior, the precise ways in which these automatic cognitive processes are related to addictive behavior remain an issue of intense debate. Consider, for instance, the observation that substance-related stimuli can grab the user's attention (for reviews, see Cox et al., 2006; Field et al., 2009). Whereas some authors have demonstrated that such an attentional bias is related to the risk of subsequent relapse (Cox et al., 2002), several others have failed to find a relationship between attentional bias and subsequent substance use (Carpenter et al., 2006; Waters et al., 2003). Moreover, whereas heavy drinkers typically show an attentional bias towards alcohol-related stimuli (Field...
et al., 2004; Townshend and Duka, 2001), it has also been found that abstaining alcohol-dependent patients show an attentional bias away from alcohol-related stimuli (Noel et al., 2006; Stormark et al., 1997; Vollstaedt-Klein et al., 2009). In sum, the relationship between behavioral indices of addiction and automatic cognitive processes may take on many forms and therefore requires a systematic examination across different populations (e.g., substance dependent patients, abstaining patients, heavy users, adolescents, etc.) and perhaps even across different types of addiction (e.g., alcohol addiction, nicotine addiction, etc.).

The aim of the present research was to examine the relationship between addictive behavior and automatically activated approach/avoidance tendencies towards alcohol-related stimuli in alcohol-dependent patients. Prior work in non-clinical samples strongly suggests that alcohol-related stimuli can activate approach/avoidance tendencies in an automatic fashion. Consider, for instance, the findings of Field et al. (2008). They examined automatic approach/avoidance tendencies in light and heavy drinkers using the Relevant Stimulus Response Compatibility (R-SRC) task developed by Mogg et al. (2003; see also Bradley et al., 2004). In this task, participants move a computer manikin towards alcohol-related pictures and away from alcohol-unrelated pictures in one block of trials (i.e., compatible block) whereas the reversed response assignment is used in a second block of trials (i.e., moving the manikin away from alcohol-related pictures and towards alcohol-unrelated pictures; incompatible block). Results showed that heavy drinkers were faster to respond to alcohol-related pictures in the compatible block as compared to the incompatible block. Light drinkers, on the other hand, did not show such an effect. Similar findings were reported by several other researchers (Palfai and Ostafin, 2003; Ostafin and Palfai, 2006; Wiers et al., 2009).

There is also evidence showing that automatically activated approach/avoidance tendencies are causally related to alcohol consumption. Consider, for example, the findings obtained by Wiers et al. (2010). They examined alcohol consumption in participants who were either trained to avoid or to approach alcohol during a computer task. Results showed that participants in the approach-alcohol condition drank more alcohol than participants in the avoid-alcohol condition during a bogus taste test, provided that a post-training assessment of their approach/avoidance behavior revealed training effects in the expected direction (i.e., analyses were restricted to participants in the approach-alcohol condition who became faster to approach alcohol stimuli relative to control stimuli and participants in the avoid-alcohol condition who became faster to avoid alcohol stimuli relative to control stimuli). Likewise, Wiers et al. (2011) found reduced relapse rates in a sample of abstaining alcohol-dependent patients who were trained to avoid alcohol-related stimuli.

In sum, a large number of studies corroborate the assumption that alcohol addiction is mediated or maintained by automatic approach tendencies (Deutsch and Strack, 2006; Robinson and Berridge, 1993; Stacy and Wiers, 2010; Tiffany, 1990; Wiers and Stacy, 2006). Several recent studies suggest, however, that a strong automatic tendency to approach alcohol-related stimuli is not always present in populations that are known to have consume(d) high levels of alcohol. Barkby et al. (2012), for example, found no differences in terms of automatically activated approach/avoidance tendencies between a group of abstaining alcohol-dependent patients and a group of controls. Using an adapted version of the R-SRC task, van Hemel-Ruiter et al. (2011) even found automatically activated avoidance tendencies rather than automatically activated approach tendencies in a group of early-adolescent heavy drinkers (aged 13–17 years). Likewise, Wiers et al. (2011) observed a relative avoidance bias in abstaining alcohol-dependent patients. More specifically, they found abstaining alcohol-dependent patients to exhibit a much stronger approach bias in response to pictures of non-alcoholic drinks as compared to pictures of alcoholic drinks.

We speculate that the occurrence of such a relative avoidance bias arises as the result of a conflict between immediate temptations to drink alcohol when confronted with alcohol-related cues and the goal not to drink alcohol. Such an interpretation would not only be in line with the idea that conflicts between immediate temptations and long-term goals can lead to an automatic behavioral predisposition to avoid temptation-related cues (Fishbach and Shah, 2006), it is also consistent with a number of attentional bias studies showing that alcohol-dependent patients can develop an attentional bias away from alcohol-related stimuli (Noel et al., 2006). It still remains to be seen, however, whether and to what extent an automatic tendency to avoid alcohol-related cues has beneficial long-term effects in terms of addictive behavior. As described above, Wiers et al. (2011) found reduced relapse rates in a group of participants who were trained to avoid alcohol-related stimuli. Despite this overall group effect, however, a direct relationship between treatment outcome and the extent to which automatic approach/avoidance tendencies actually changed as a result of the training manipulation was not observed. Further research on the role of automatically activated approach/avoidance tendencies in alcohol addiction is thus needed.

We therefore examined alcohol-related approach/avoidance tendencies in a group of 40 abstaining alcohol-dependent patients and a group of 40 controls. The measure of automatically activated approach/avoidance tendencies used in this study was the R-SRC task (Bradley et al., 2004; Mogg et al., 2003). Our first aim was to compare both groups with regard to the R-SRC effect. This allowed us to verify whether abstaining alcohol-dependent patients tend to develop an automatic tendency to avoid alcohol-related stimuli during the early stages of treatment. Our second aim was to examine whether individual differences in automatically activated approach/avoidance tendencies towards alcohol (as measured by the R-SRC task) are predictive of relapse in abstinent alcohol-dependent patients. To that end, relapse in the patient group was assessed after a period of 3 months. We also administered the Attentional Control Scale (ACS), a measure of individual differences in the ability to focus perceptual attention, switch attention between tasks, and flexibly control thought (Derryberry, 2002; Derryberry and Reed, 2002). Several studies have shown that heavy drinkers are characterized by an attentional orienting response towards alcohol-related stimuli (Fadardi and Cox, 2009; Field and Cox, 2008; Townshend and Duka, 2001). We reasoned that automatically activated response tendencies are more likely to affect addictive behavior in participants who have difficulty controlling the attention-grabbing power of alcohol-related stimuli. We therefore expected the predictive validity of automatically activated approach/avoidance tendencies to be more pronounced in abstaining alcohol-dependent patients who score low on the ACS than in alcohol-dependent patients who score high on the ACS.

2. Methods

2.1. Participants

Participants were 40 abstaining, alcohol-dependent patients and 40 controls. Summary statistics describing both groups are provided in Table 1. All participants from the patient group met DSM-IV criteria for alcohol dependence. They were recruited at the Psychiatric Institute of the Brugmann University Hospital, Brussels, Belgium. They all volunteered to receive treatment. The detoxification regimen consisted of vitamin B administration and a gradual decrease in the doses of sedatives. All patients followed standard cognitive-behavior counseling and were discharged immediately.
after successful detoxification. Participants from the control group were recruited by means of advertisement posters displayed at public places in the near surroundings of the Brugmann University Hospital. None of the participants in the control group reported a history of alcohol-related problems. Controls were paid €15 in exchange for their participation. All participants gave their informed consent before participating. The study was approved by the Ethics Committee of the Brugmann University Hospital.

2.2. Materials and measures

2.2.1. Alcohol use and problems. Based on self-reports of past drinking behavior, we derived an estimate of how many grams of alcohol each participant consumed on a daily basis (three participants of the control group did not specify their daily intake). Half a pint of ordinary strength beer, 25 ml of spirits (40% alcohol by volume), 50 ml of fortified wine such as sherry or port (20% alcohol by volume), and 100 ml of ordinary strength wine were assumed to contain one unit of alcohol (8 g). As can be seen in Table 1, daily alcohol consumption was much higher in the patient group than in control group. We also administered the Alcohol Expectancy Questionnaire (AEQ), a measure of the extent to which an individual believes that alcohol consumption will serve certain functions or result in desirable consequences (Brown et al., 1987; Vautier and Moncany, 2008) and the Obsessive Compulsive Drinking Scale (OCDS), a questionnaire that measures cognitive aspects of alcohol craving (Ansseau et al., 2000; Anton et al., 1995, 1996). In comparison to participants from the control group, abstaining alcohol-dependent patients experienced much more alcohol craving and expected more desirable consequences after alcohol consumption (see Table 1).

2.2.2. R-SRC task. The stimulus set used for the R-SRC task consisted of 16 alcohol-related pictures (e.g., a glass of beer) and 16 matched, alcohol-unrelated pictures (e.g., a glass of water). The height of all pictures was 246 pixels. The width of the pictures varied between 182 and 343 pixels. All pictures were presented in the center of the computer screen. The manikin was 51 pixels wide and 79 pixels high. The R-SRC task was programmed using Affect 4.0 (Spruyt et al., 2010).

In total, the R-SRC task consisted of two blocks of 64 trials. Within each block, all pictures were presented twice, once with the manikin presented above the picture and once with the manikin presented below the picture. In the compatible block, participants were asked to make the manikin approach alcohol-related pictures and to avoid alcohol-unrelated pictures. In the incompatible block, participants were asked to avoid alcohol-related pictures and to approach alcohol-unrelated pictures. The order of both blocks was counterbalanced across participants. Each block was preceded by 8 practice trials. Participants used the arrow keys of a standard computer keyboard to move the manikin up and down. They were allowed to move the manikin in any direction until the manikin reached either its highest or its lowest position possible (i.e., the upper/lower edge of the computer screen or picture, ten steps in each direction). Participants were free to keep the arrow keys down steadily or to move the manikin through frequent key strokes.

2.2.3. Attentional Control Scale (ACS). The ACS is a 20-item questionnaire that measures individual differences in the ability to focus perceptual attention, switch attention between tasks, and flexibly control thought (Derryberry, 2002; Derryberry and Reed, 2002). The instrument was translated into French for use with francophone participants. Participants were asked to use a 6-point rating scale to respond to each item. Higher scores reflect higher attentional control with scores ranging between 0 and 100. One participant in the patient group did not complete the ACS.

3. Results

3.1. R-SRC task

Data from trials on which the first response was incorrect were excluded (5.04%). To reduce the impact of outliers, we first eliminated all response latencies above 5000 ms (2.79%). Next, for each response condition separately (compatible vs. incompatible), response latencies that deviated more than 2.5 standard deviations from a participant’s mean latency (2.77%) were also discarded (Ratcliff, 1993). Finally, we calculated individual R-SRC scores. For each participant separately, the mean response latency in the compatible block was subtracted from the mean response latency in the incompatible block. R-SRC scores were then submitted to a one-way ANOVA (Group: patient vs. control).

As can be seen in Table 2, the mean R-SRC score was positive in the control group (i.e., 62 ms), suggesting a stronger bias to approach than to avoid alcohol. In contrast, the mean R-SRC score was negative in the patient group (i.e., –49 ms). Patients thus revealed a stronger bias to avoid than to approach alcohol. The difference between both groups was statistically reliable, F(1,}

Table 1
Group characteristics: summary statistics.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Control group</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>Proportion men</td>
<td>57.5</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>45.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Years of alcohol abuse</td>
<td>9.8</td>
<td>.6</td>
</tr>
<tr>
<td>Number of earlier withdrawal attempts</td>
<td>2.2</td>
<td>.3</td>
</tr>
<tr>
<td>Daily alcohol consumption (g/day)</td>
<td>174.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Obsessive Compulsive Drinking Scale</td>
<td>17.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Alcohol Expectancy Questionnaire</td>
<td>29.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* p > .10.
* p < .001.
Table 2
Mean response latencies in the R-SRC task as a function of group and block. Mean R-SRC effects as a function of group. Standard errors in parentheses.

<table>
<thead>
<tr>
<th>Group</th>
<th>Block Compatible</th>
<th>Block Incompatible</th>
<th>R-SRC effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>1563(84.62)</td>
<td>1515(83.82)</td>
<td>−49 (30.64)</td>
</tr>
<tr>
<td>Control group</td>
<td>1454(103.11)</td>
<td>1516(114.31)</td>
<td>62(44.90)</td>
</tr>
</tbody>
</table>

Note: R-SRC effect = mean response latency in the incompatible block minus the mean response latency in the compatible block.

71) = 4.35, p < .05. The error data revealed no effect, F < 1. The split-half reliability of the R-SRC was acceptable (r = .54, p < .001).

3.2. Relapse

In total, 25 patients (62.5%) relapsed within 3 months. A univariate logistic regression analysis revealed a clear relationship between relapse and individual R-SRC scores, χ²(1) = 7.82, p < .005, Nagelkerke R² = .25. In contrast to our expectations, however, the odds ratio (OR) for the R-SRC measure was smaller than 1, OR = .994 (95% CI = .990–.999), Wald = 5.86, p < .05. That is, the odds of relapse to dependence decreased by a factor .994 for each millisecond that participants responded faster in the approach–alcohol block relative to the avoid–alcohol block of the R-SRC task. Next, we performed a hierarchical logistic regression analysis to assess the predictive validity of the R-SRC over and above other predictors. In a first step, we entered age, gender, the quantity of daily alcohol intake, the number of earlier attempts to quit drinking, the amount of time that patients had been abusing alcohol, the AEO, and the OCDS. These variables did not predict relapse, χ²(7) = 4.68, p = .699, Nagelkerke R² = .15. In a second step, we entered the R-SRC measure. Entering this variable resulted in a significant better model fit, χ²(1) = 7.81, p < .01, Nagelkerke R² = .36. In the final model, the only significant predictor was the R-SRC measure with an odds ratio of .993 (95% CI = .987–.999), Wald = 5.19, p < .05. That is, the odds of relapse to dependence decreased by a factor .993 for each millisecond that participants responded faster in the approach–alcohol block relative to the avoid–alcohol block of the R-SRC task. Overall, 71.8% of all cases were classified correctly. Finally, we examined whether the predictive validity of the R-SRC measure was moderated by individual differences in attentional control. As expected, the relationship between the R-SRC measure and relapse was reliable in the group of participants that scored low on the ACS, χ²(1) = 11.19, p < .005, Nagelkerke R² = .64 (ACS score < 44), but not in the group of participants that scored high on the ACS, χ²(1) < 1 (ACS score > 43).

4. Discussion

We used the R-SRC task to compare automatic approach/avoidance tendencies towards alcohol cues in a group of 40 abstaining alcohol-dependent patients and a group of 40 control participants. In addition, we tested whether R-SRC effects in the patient group were predictive of relapse over a 3-month period. Our findings can be summarized as follows. First, patients showed a stronger relative tendency to avoid alcohol than controls. Second, whereas explicit measures of alcohol problems failed to predict relapse, logistic regression analyses revealed a clear relationship between relapse and R-SRC performance: relapse rates increased rather than decreased as alcohol patients were faster to avoid alcohol-related pictures compared to alcohol-unrelated pictures. Both observations are at odds with prior work showing that alcohol-related stimuli elicit approach tendencies rather than avoid tendencies (Field et al., 2008; Palfai and Ostafin, 2003; Ostafin and Palfai, 2006; Wiers et al., 2009, 2010). They are also at odds with the more general assumption that addiction is mediated or maintained by automatic approach tendencies towards alcohol (Deutsch and Strack, 2006; Robinson and Berridge, 1993; Stacy and Wiers, 2010; Tiffany, 1990; Wiers and Stacy, 2006).

To account for these findings, one might argue that the negative R-SRC effect found in the patient group was mainly driven by nonautomatic, strategic processes. For several reasons, we consider this possibility unlikely. First, if this hypothesis were true, one would expect the overall speed of responding to be faster in the control condition than in the patient condition. This was not the case (F < 1). Second, the correlation between R-SRC effects and mean response latencies within the patient condition was virtually zero (r = −.03). This observation is also inconsistent with the idea that slow–acting, corrective processes were driving the negative R-SRC effect in the patient condition. Third, bin analyses showed that the R-SRC effect in the patient group was negative in each of four 1/4-bins (Balota et al., 2008). So, even on trials on which patients responded relatively fast, the R-SRC effect was still negative. Finally, and most importantly, the nature of the relationship between performance in the R-SRC task and relapse did not depend on the speed of responding. To evaluate this possibility, we calculated R-SRC effects for each of the four bins and used these measures as predictors in four separate logistic regression analyses, one for each bin. Results showed that the relationship between the R-SRC effects and relapse was negative in each case. If anything, the weakest effect emerged in the slowest bin.

Having ruled out an interpretation in terms of slow–acting, nonautomatic processes, the question remains how one can account for the results that were obtained with the R-SRC task. Let us first consider the fact that the R-SRC effect was negative in the patient group. Although several studies did indeed reveal an approach bias in heavy drinkers (Field et al., 2008; Palfai and Ostafin, 2003; Ostafin and Palfai, 2006), there is also evidence showing that abstaining alcohol-dependent patients are sometimes inclined to avoid rather than to approach alcohol (Breiner et al., 1999; Smith-Hoerter et al., 2004). A similar pattern can be found in research on attentional bias towards alcohol-related cues. As already explained in the introduction, heavy drinkers typically show an attentional bias towards alcohol-related stimuli (Field et al., 2004) whereas abstaining alcohol-dependent patients often show a tendency to avoid alcohol-related stimuli, at least at longer stimulus presentations (Noel et al., 2006). As suggested by Townsend and Duka (2007), this pattern can be accounted for if one assumes that abstaining alcohol-dependent patients, in contrast to heavy drinkers, develop an active avoiding strategy during the early stages of treatment (Vollstaedt-Klein et al., 2009). Our R-SRC findings are consistent with this reasoning and suggest that maintaining an active avoidance strategy can have an effect on lower-level, automatic behavioral tendencies.

We also found that relapse rates increased rather than decreased as patients were inclined to avoid rather than to approach alcohol cues. This finding is important because it suggests that maintaining an active avoidance strategy is potentially harmful. One way to explain this data pattern is to assume that the extent to which abstaining alcohol-dependent patients show an avoidance bias in the R-SRC task depends on the perceived appeal of alcohol-related cues (Fishbach and Shah, 2006). Given that relapse rates must be higher in abstaining patients for whom alcohol related-cues result in a significant self-control dilemma, one can thus expect a positive relationship between relapse and the extent to which abstaining patients are inclined to avoid alcohol-related cues. Alternatively, it could be argued that successful relapse prevention requires in-depth emotional processing that is precluded by active avoidance. Similar to the widely accepted idea that successful treatment of pathological fear requires the activation of a pathological fear structure in memory and the incorporation of corrective information in
this structure (Foaa and Kozak, 1986; Lang, 1977, 1979), one could argue that substance-related memory structures are available for modification only if they become fully activated (Rachman, 1980). If this is true, one can understand why abstaining alcohol-dependent patients are more likely to relapse the more they are oriented toward avoiding than approaching alcohol-related stimuli. The less they engage in emotional processing and the less they acquire new coping skills and response strategies while actively facing alcohol cues, the more vulnerable they are to relapse, at least in the long run. Consistent with this interpretation, we found that the negative relationship between R-SRC performance and relapse was reliable in patients who scored low on the ACS but not in patients who scored high on the ACS. Most likely, this finding resulted from the fact that abstaining alcohol-dependent patients who score high on attentional control were more effective in maintaining their avoidance strategy when dealing with alcohol-related cues than patients who score low on attentional control. Once attentional control breaks down, however, what matters is the extent to which alcohol-related memory structures were modified during exposure. Therefore, patients who rely heavily on (cognitive) avoidance are more susceptible to relapse, especially when they lack a large amount of attentional control.

It is important to point out, however, that our study focused on just one potential outcome measure, i.e., relapse to dependence. It could thus be worthwhile to study the relationship between automatically activated approach/avoidance tendencies and other outcome measures such as the number of abstinent days, etc. In addition, it would be interesting to examine whether relapse rates depend on the extent to which automatically activated behavioral tendencies shift under treatment. A final avenue for future research would be the inclusion of an assessment of the extent to which alcohol-dependent patients are able to achieve positive, meaningful goals. According to the motivational model of alcohol use developed by Cox and Klinger (1988, 2011), alcohol use occurs whenever people expect more positive affective consequences from drinking than from not drinking. Any treatment technique that enables alcohol-dependent patients to stop drinking but does not provide them with alternatives sources of emotional satisfaction is therefore doomed to fail. It could thus be worthwhile to examine whether the relationship between automatically activated approach/avoidance tendencies and relapse is qualified by the extent to which abstinent alcohol-dependent patients are able to achieve meaningful goals.

Irrespective of the outcome of this research, however, our findings have important implications for future studies on the (causal) role of automatic action tendencies in alcohol addiction. As explained in the introduction, researchers have recently begun to manipulate automatically activated approach/avoidance tendencies, both in heavy drinkers (Wiers et al., 2010) and alcohol-dependent patients (Wiers et al., 2011). Although initial findings suggest that alcohol-avoidance training could help reduce relapse rates in abstaining-alcohol dependent patients (Wiers et al., 2011), it is still unclear whether changes in automatically approach/avoidance tendencies are directly responsible for the observed changes in treatment outcome. Our findings suggest that actually inducing an avoidance orientation towards alcohol might have harmful effects, at least in a clinical population. Therefore, new studies are needed to shed light on the precise relationship between automatically activated approach/avoidance tendencies and addictive behavior, both in clinical and subclinical populations.

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Contributors

Adriaan Spruyt, Jan De Houwer, Xavier Noël, Helen Tibboel, and Geert Crombez contributed to the design of the study. Adriaan Spruyt managed the literature searches, undertook the statistical analyses, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

All other authors declare that they have no conflicts of interest.

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