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Review article

Compulsivity-related neurocognitive performance deficits in gambling disorder: A systematic review and meta-analysis

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ABSTRACT

Compulsivity is a core feature of addictive disorders, including gambling disorder. However, it is unclear to what extent this compulsive behavior in gambling disorder is associated with abnormal compulsivity-related neurocognitive functioning. Here, we summarize and synthesize the evidence for compulsive behavior, as assessed by compulsivity-related neurocognitive tasks, in individuals with gambling disorder compared to healthy controls (HCs). A total of 29 studies, comprising 41 task-results, were included in the systematic review; 32 datasets (n = 1072 individuals with gambling disorder; n = 1312 HCs) were also included in the meta-analyses, conducted for each cognitive task separately. Our meta-analyses indicate significant deficits in individuals with gambling disorder in cognitive flexibility, attentional set-shifting, and attentional bias. Overall, these findings support the idea that compulsivity-related performance deficits characterize gambling disorder. This association may provide a possible link between impairments in executive functions related to compulsive action. We discuss the practical relevance of these results, their implications for our understanding of gambling disorder and how they relate to neurobiological factors and other 'disorders of compulsivity'.

1. Introduction

1.1. Rationale

Pathological gambling has recently been reclassified as a behavioral addiction and renamed as Gambling Disorder (DSM-5; American Psychiatric Association, 2013). This decision was largely based on clinical and neurobiological similarities with substance-use disorders (Fauth-Bühler et al., 2017; Romanczuk-Seiferth et al., 2014). Similar to drug addiction, symptoms of gambling disorder include repeated unsuccessful efforts to stop gambling, feeling restless or irritable when attempting to stop and diminished ability to stop gambling despite the negative consequences of gambling. Gambling disorder was previously classified as an impulse control disorder and has long been associated with higher impulsivity (Verdejo-García et al., 2008). Now that gambling is reclassified as a behavioral addiction, there is an increased need to focus on the compulsive aspects of the behavior, which may be central to understanding the pathology of gambling disorder (e.g. El-Guebaly et al., 2012; Leeman and Potenza, 2012), and addiction in general.

Addiction can be viewed as the endpoint in a series of transitions: from initial goal-directed through habitual to eventually compulsive addictive behavior (Everitt and Robbins, 2005). Phenomenological models of addiction also highlight the motivational shift from impulsivity to compulsivity (El-Guebaly et al., 2012). Self-report questionnaires assessing addiction-specific compulsive tendencies indeed indicate the presence of compulsive behavior in addictive populations (Anton et al., 1995; Blaszczynski, 1999; Bottesi et al., 2014; Vollstädt-Klein et al., 2015). Moreover, in addition to compulsive drug use behavior, impairments in general compulsivity-related executive functions, such as perseverative behaviors or cognitive inflexibility, might also be related to addiction (Fineberg et al., 2014). Because gambling disorder may provide a model of drug-free addiction, it offers the opportunity to investigate compulsivity as an endophenotype for addiction. Other behaviors, such as food, sex, and Internet addiction, can potentially be compulsive too (Morris and Voon, 2016). However, these behaviors were outside the scope of the current review, as they are not included under the 'Substance-related and Addictive Disorders' category in the DSM-5 due to insufficient research.

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Studies investigating compulsivity, i.e. the performance of repetitive acts despite the negative consequences, in individuals with gambling disorder are scarce. This may be due to the complex, multi-faceted nature of the construct. Indeed, compulsivity can be conceptualized in various ways, which seem to differ between disorders and descriptions (Yücel and Fontenelle, 2012). Importantly, and as opposed to impulsivity, the number of research instruments to assess compulsivity is limited. Therefore it has been suggested that, although useful as a concept for clinicians, compulsivity "is too ambiguous and confusing for research studies of the topic" (Yücel and Fontenelle, 2012). On the other hand, new definitions of compulsivity have been proposed which account for its multi-dimensionality and offer opportunities to systematically study the mechanisms that contribute to compulsive behavior (e.g. Fineberg et al., 2010; Dalley et al., 2011).

Compulsive behavior is likely to result from disruptions in various cognitive processes, including attention, perception, and the regulation of motor or cognitive responses. A recent theoretical review of compulsivity by experts in this field has proposed a framework in which compulsivity is subdivided into four separate, neurocognitive domains: contingency-related cognitive flexibility, task/attentional set-shifting, attentional bias/disengagement, and habit learning (Fineberg et al., 2014). Each of these domains entails a separate component of compulsivity with a separate neural circuitry (Fineberg et al., 2014) and can be operationalized with specific neurocognitive tasks (see Table 1). One critical component of compulsive behavior, mainly associated with repetitive behavior, is the inability to adapt to a situation flexibly. Neurocognitive tasks assessing cognitive (in)flexibility either (i) manipulate contingencies, which is mainly dependent on learning/unlearning behavior (contingency-related cognitive flexibility), (ii) manipulate attentional response modes (task/attentional set-shifting) or (iii) test the ability to inhibit a prepotent, automatic response (attentional bias/disengagement) (Fineberg et al., 2014). Another component that may give rise to compulsivity is (iv) over-reliance on habit learning: the tendency of actions that are often repeated to become automatic and insensitive to goals. For heuristic purposes, we chose to use these four domains as a framework to organize and investigate the evidence for compulsivity in gambling disorder.

1.2. Objectives

The central aim of this systematic review and meta-analysis is to summarize and integrate, for the first time, the empirical evidence for impairments in compulsivity-related neuropsychological functions in gambling disorder. Accordingly, we set out to answer the following question (following PICO-criteria): in individuals suffering from gambling disorder, is there evidence for compulsive behavior, compared to HCs, as assessed by neurocognitive measures? To this end, we systematically reviewed the literature on gambling disorder to include all experimental studies measuring one of the four components of compulsivity (Table 1). In addition, meta-analyses were performed for all separate tasks within each domain (with a minimum of 3 studies per task) to summarize the available knowledge. We hypothesized that compulsivity-related neuropsychological functions are impaired in individuals with gambling disorder compared to HCs.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines (Moher et al., 2015) and has been registered in PROSPERO International Prospective Register of Systematic Reviews (crd.york.ac.uk/prospero, registration number: CRD42016050530). The PRISMA for Protocols (PRISMA-P) checklist for the review is also included in Supplementary File 1.

2.1. Information sources and search strategy

We started by searching the WHO International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov for potentially eligible ongoing trials. Original articles were searched using Ovid MEDLINE, Embase and PsycINFO. The searches were conducted in August 2016 and updated in February 2017.

A scoping search identified the following key concept [] combinations: [gambling disorder] AND ([compulsion] OR [neuropsychological tests] OR [measured relevant test parameters]). Subsequently, these key concepts were adapted for each bibliographic database applying appropriate (controlled) terms, database specific search fields and syntaxes. See Appendix A (Supplementary data) for a fully detailed search strategy.

It should be noted that tasks assessing disorder-specific attentional bias were not considered, because behavioral differences between individuals with gambling disorder and HCs are not (necessarily) related to cognitive flexibility per se, but rather to the addiction itself and, therefore, not relevant for the cross-diagnostic endophenotype of compulsivity. Moreover, disorder-specific attentional bias might reflect multiple underlying processes (Field and Cox, 2008). For these reasons,

Table 1
Four domains of compulsivity.

Neurocognitive domain[a]	Definition	Task	Outcome (# studies reporting this outcome)	# studies in GD
Contingency-related cognitive flexibility	Impaired adaptation of behavior after negative feedback	Probabilistic Reversal Learning Task	Number of reversals (1); money won (1); perseverative errors (1); reversal cost (1)	4
		Card Playing Task	Number of cards played (1); perseveration level (categories) (2)	3
		Deterministic Reversal Learning Task	Mean error rate (1)	1
		Contingency Learning Task	Commission/Perseveration errors (1)	1
Task/attentional set-shifting	Impaired switching of attention between stimuli	Wisconsin Card Sorting Task	Perseverative errors (8); total trials (1)	9
		Intra-Extra Dimensional Set Shift	Total errors (4)	4
		Switch task	Accuracy (1)	1
Attentional bias/disengagement	Impaired shifting of mental sets away from stimuli	Stroop task	Interference index (8); RT/% incorrect (4)	12
		Trail Making Task (B)	Time to complete (4)	4
Habit learning	Lack of sensitivity to goals or outcomes of actions	Two-step decision task	Model-based and model-free choices	0
		Fabulous Fruit Game	Slips-of-action errors	0
		Devaluation task	Valued versus devalued choice ratio	0

GD = Gambling Disorder; RT = Reaction Time.
[a] Domains from Fineberg et al. (2014).

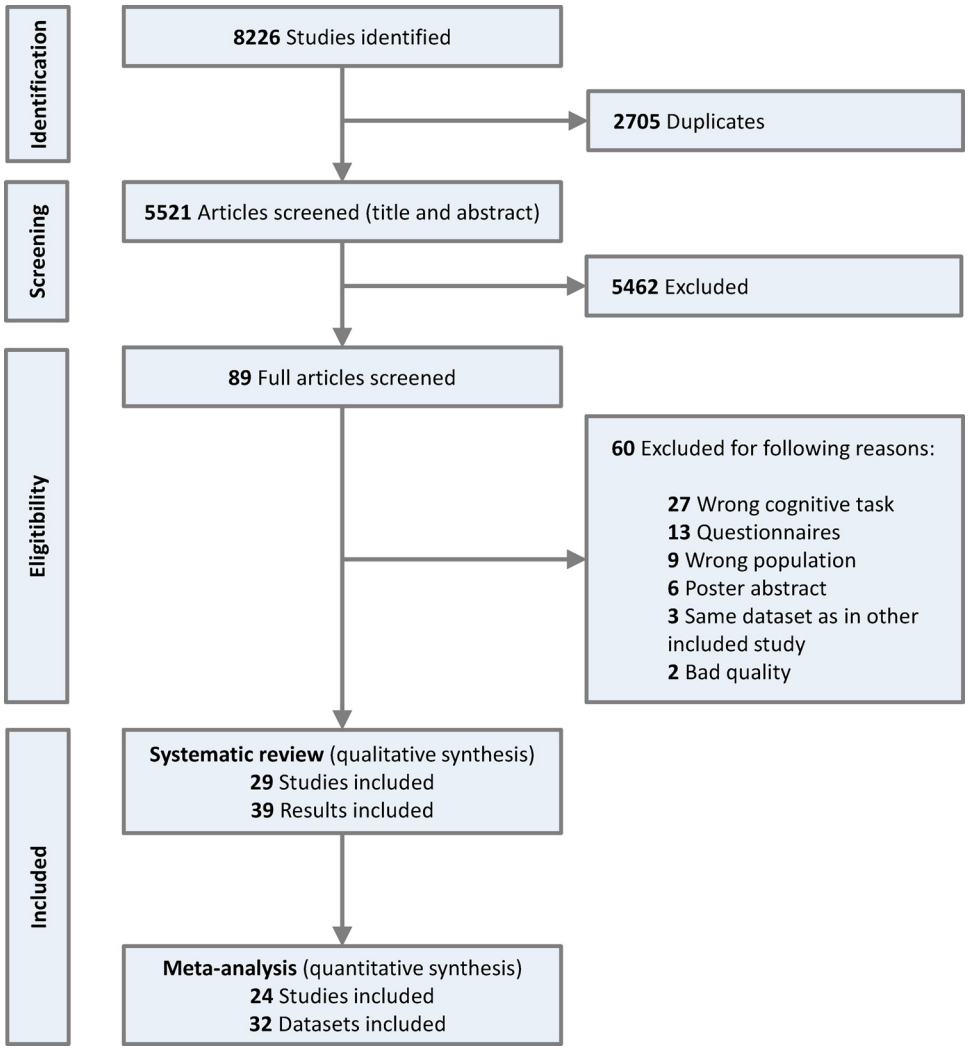

Fig. 1. Flowchart illustrating the number of articles identified and those included and excluded at each stage of the search. In some studies, multiple cognitive tasks were reported that could be included in the meta-analysis. Therefore, the number of results and datasets is higher than the number of studies.

we did not consider including tasks like the gambling-specific Stroop task or the gambling-specific Dot-Probe Task.

2.2. Eligibility criteria

Selected studies had to fulfill the following inclusion criteria: the study included human subjects aged 18–65 years; the study included DSM-5 Gambling Disorder patients, DSM-III, DSM-III-R or DSM-IV Pathological Gamblers or gamblers with a SOGS score greater than 5; the study included a healthy control group; and the study had a minimum of 10 subjects per group. Moreover, studies had to include an experimental task or paradigm to test an aspect of compulsivity, as defined by the four domains (Table 1). Original articles were included irrespective of language, publication year, publication type, or publication status. The complete list of references was exported to EndNote X7 to remove duplicates and was subsequently imported to Rayyan (Elmagarmid et al., 2014) for title and abstract screening.

2.3. Study selection

The titles and abstracts of all the identified studies were independently screened for eligibility by two authors (TvT and RJvH). Any discrepancies between the reviewer's decisions were resolved by discussion until an agreement was reached (< 1% of articles). The selected articles were subsequently read in full, to see if all inclusion criteria were met. We actively screened for duplicate publications or reuse of the same dataset and, when encountered, the latest or most complete dataset was used.

2.4. Data extraction and study quality

The following data were extracted from the selected studies: demographic and clinical characteristics of study composition (size, gender, age, clinical diagnosis, gambling severity); type of neurocognitive test used; reported outcome measure; main result of the study; primary test parameters, means and standard deviation along with other critical statistical information from which effect sizes could be computed (see Table 2–4). If primary test parameters were different from other studies using the same cognitive task, we contacted the corresponding authors. Two studies were excluded from both the systematic review and the meta-analyses because the interpretation of the reported outcome parameters was unclear and could not be clarified.

Two raters (NMS and JMK) independently rated each study for methodological quality on an 8-item validity scale assessing methodological rigor, selection and reporting bias. A previously used checklist (Thompson et al., 2013), which was based on items from the Cochrane Collaboration criteria, PRISMA recommendations, and PEDro guidelines, was adapted by removing items assessing randomization of groups and blinding procedures, as these were not applicable to studies examined in the current review (5 items). Quality levels of evidence were defined as high (6–8 points), medium (3–5 points) or low (0–2 points).

2.5. Data analysis and synthesis

Because different studies used different tests and test parameters, standardized mean differences (SMD) in effect sizes (Hedge's *g*) were calculated to assess the difference between individuals with gambling disorder and HCs across studies. This is a measure similar to Cohen's *d* but with a correction for small sample bias, and the results may be interpreted as reflecting a small (g = 0.2–0.5), medium (g = 0.5–0.8) or large (g > 0.8) effect. Hedges' *g* was coded so that positive values indicated better performance in HCs compared to individuals with gambling disorder. Effect sizes were computed using the original (unadjusted) standard deviations; if necessary, standard errors were converted to standard deviations (indicated in the corresponding tables).

As each neurocognitive task tests a different aspect of 'compulsivity' and since there is a large variation in their test parameters, meta-analyses were conducted for each task separately. To be included in the meta-analyses, a minimum of 3 studies per task was required. Due to the expected heterogeneity between study samples and methodological variation, random-effects models were used for overall between-group analyses. A significance level of $p < 0.05$ (two-tailed) was used. The presence of heterogeneity was tested using Cochran's Q and its magnitude estimated using I^2, which can be interpreted as the proportion of effect size variance due to heterogeneity. For tasks that included five or more studies, meta-regression analyses were performed with age, gender, IQ and gambling severity as covariates. We used the between-group difference of age, gender, and IQ (calculated using Cohen's *d*) as a covariate in the meta-regression analyses. All analyses were conducted using Comprehensive Meta-Analysis V2 (CMA, Bio-Englewood, New Jersey, US).

3. Results

3.1. Identified studies

The initial search identified 5521 unique studies, of which 29 could be included in this review. Fig. 1 shows a PRISMA Flow Diagram illustrating the study selection process. The number of studies excluded after full-text screen due to "Wrong cognitive task" is relatively large because studies using the Iowa Gambling Task (n = 20) were not yet excluded during abstract screening. These were excluded during full-text screening, however, because they did not fit with any of the four compulsivity-domains. Moreover, we initially wanted to include compulsivity questionnaires, so these were included in the search term and selected during title and abstract screening. However, we ultimately refrained from including self-report questionnaires in the final synthesis: questionnaires are rarely the primary outcome measure and studies often do not report the use of such questionnaires in their abstract. Therefore, the chance of missing studies which included questionnaires was high, making it impossible to include them systematically and comprehensively.

The 29 included studies comprised a total of n = 1072 individuals with gambling disorder and n = 1312 HCs. Although not all studies tested gamblers who were in therapy or obtained a formal diagnosis of gambling disorder (specified in Tables 3–5), we did only include studies which tested gamblers who scored higher than the clinical cutoff on gambling questionnaires. Therefore, we will refer to them as individuals with gambling disorder throughout the manuscript. The quality score was "medium" for three studies and "high" for 26 studies (Supplementary Table 1). In the following sections, subdivided into the four domains, we describe each task and its most common test parameters; give a qualitative summary of the findings; and present the results of the meta-analysis. Tables 2–4 provide a detailed summary of the studies included for each domain. For those neurocognitive tasks that comprised 3 or more studies, meta-analyses were conducted; individual plots are shown in Figs. 2–4.

3.2. Contingency-related cognitive flexibility

Contingency-related cognitive flexibility involves learning a rule and the subsequent adaptation of behavior after a rule change using trial-by-trial feedback. A subject thus needs to learn and unlearn contingencies flexibly. In the included studies, four tasks were identified that met this description: the Probabilistic Reversal Learning Task, the Card Playing Task, a Deterministic Reversal Learning Task and a Contingency Learning Task.

3.2.1. Probabilistic reversal learning task

In the Probabilistic Reversal Learning Task (PRLT; Cools et al., 2002), subjects choose between (usually) two stimuli and learn that one of two choices is 'good' while the other is 'bad'. The stimulus is partly predictive of the outcome (i.e. probabilistic), e.g. 70% of the time the feedback is correct and 30% of the time the feedback is false. After successfully learning to discriminate between the good and bad option, the rule changes (i.e. a reversal) and the participant needs to adapt to the new rule. Different versions of this task are used, with reversals occurring either at a fixed number of trials or after a fixed number of correct responses. Depending on the moment of reversal, perseveration can be reflected by the number of correct choices after a rule change, the total number of reversals completed or the total amount of money earned (in all measures, lower scores reflect higher perseveration).

Four studies were identified that used the PRLT in gambling disordered groups. In two studies (Boog et al., 2014; de Ruiter et al., 2009) individuals with gambling disorder showed response perseveration, whereas in the other two studies (Torres et al., 2013; Verdejo-García et al., 2015) no significant behavioral problems were observed on this task. Although different versions of the PRLT were used in each study (see Table 2), they were comparable with respect to testing 'perseverance' and therefore, all studies were included in the meta-analysis.

Data of all four studies, including a total of 77 individuals with gambling disorder and 79 HCs, were pooled and revealed no significant impairment on the PRLT between individuals with gambling disorder and HCs (effect size = 0.479; Z-value = 1.452; p = 0.144) (Fig. 2A). However, for this task, considerable heterogeneity was evidenced ($Q = 11.7$, $p < 0.01$, $I^2 = 74\%$) (Supplementary Table 2). This heterogeneity was not significantly be explained by any factors considered in the meta-regression (gender, age, IQ and gambling severity, which indeed were comparable across studies), but may reflect the fact that a different outcome measure of the PRLT was reported in each study.

3.2.2. Card playing task

In the Card Playing (or Perseveration) task (CPT; Newman et al., 1987), the participant is presented with a deck of cards and is told that a face card wins money and a number card loses money. The participant must decide, on a trial by trial basis, whether to continue playing or to quit the task. When continuing, a card is turned which results in either winning (i.e. when a face card is turned) or losing (i.e. when a number card is turned) a certain amount of money. Initially, the win-to-loss ratio is high (e.g. 90%), but this ratio decreases by 10% after every block of 10 trials, until it is 0 percent. It is thus optimal to continue to play for 40–60 trials and then quit playing. The outcome measure of this task is the number of cards turned; continuing to play when the win-to-loss ratio is clearly no longer positive (> 60 trials) indicates perseveration.

We found three studies that used the CPT in gambling disorder groups. All studies found significant differences between individuals with gambling disorder and HCs, with more individuals with gambling disorder using an (extremely) perseverative card selection strategy (Brevers et al., 2012; Goudriaan et al., 2005; Thompson and Corr, 2013). Data of all three studies, including a total of 155 individuals with gambling disorder and 123 HCs, were pooled to reveal a significant overall effect of individuals with gambling disorder being more perseverative than HCs (effect size = 0.569; Z = 3.776, p < 0.001)

Table 2
Overview included studies within Contingency-related cognitive flexibility domain.

Study	Population (♀/♂)	Age	In treatment	Clinical measure	Task	Outcome	GD vs HC	Result
Boog et al. (2014)	19 GD (5♀), 19 HC (3♀)	GD = 42.1, HC = 38.8	yes	DSM-IV; SOGS = 8.3	PRLT	number of reversals	GD < HC	GDs made less reversals
de Ruiter et al. (2009)	19 GD, 19 ND, 19 HC (♂)	GD = 34.3, HC = 34.1	yes	DSM-IV; SOGS = 8.9	PRLT	money won	GD < HC	GDs won less money than smokers and HCs
Torres et al. (2013)	21 GD (2♀), 20 CD (♂), 23 HC (2♀)	GD = 31.4, HC = 30.1	yes	DSM-IV	PRLT	overall number of correct choices	GD = HC	
Verdejo-García et al. (2015)	18 GD (2♀), 18 CD (1♀), 18 HC (1♀)	GD = 33.5, HC = 31.1	yes	DSM-IV	PRLT	hit & error rates	GD = HC	
Brevers et al. (2012)	65 GD (15♀), 35 HC (6♀)	GD = 38.9, HC = 43.2	no	DSM-IV; SOGS = 7.1	CPT	#cards played (categories)	GD < HC	More GDs used an extremely perseverative card selection strategy; perseveration correlated with SOGS score
Goudriaan et al. (2005)	48 GD (8♀), 46 AD (10♀), 47 TS (15♀), 49 HC (15♀)	GD = 39.0, HC = 35.8	yes	DSM-IV; SOGS = 13.9	CPT	#cards played (categories)	GD < HC	More GDs used a perseverative card selection strategy
Thompson and Corr (2013)	42 GD (2♀), 39 HC (20♀)	GD = 25.0, HC = 24.8	no	SOGS = 9.1	CPT	total cash won; #cards played	GD < HC	GDs played a higher amount of cards and won a smaller amount of cash, indicating perseveration
Vanes et al. (2014)	28 GD, 33 AD, 19 HC (♂)	GD = 36.6, HC = 39.1	yes	DSM-IV; SOGS = 10.6	CLT	perseverative errors	GD = HC	GDs showed some indication of perseveration in the initial phase
Janssen et al. (2015)	18 GD, 22 HC (♂)	GD = 35.2, HC = 32.2	mix	DSM-IV; SOGS = 12.3	DRLT	error rates on reversal trials; mean error rate	GD = HC	

Abbreviations: Population: GD = Gambling Disordered patients; HC = Healthy Controls; ND = Nicotine Dependent patients; CD = Cocaine Dependent patients; AD = Alcohol Dependent patients; TS = Tourette Syndrome patients; BN = Bulimia Nervosa patients; OCD = Obsessive-Compulsive Disorder patients; IAD = Internet Addiction Disorder patients; IGD = Internet Gaming Disorder patients; PrGs = Problematic Gamblers; ♂ = Male; ♀ = Female;? = gender not reported. Clinical Measure: DSM = Diagnostic and Statistical Manual of Mental Disorders; SOGS = South Oaks Gambling Screen; PGSI = Problem Gambling Severity Index; SCID = Structured Clinical Interview for the DSM; NODS = NORC Diagnostic Screen for Gambling Problems. Tasks: PRLT = Probabilistic Reversal Learning Task; CPT = Card Playing Task; DRLT = Deterministic Reversal Learning Tasks; CLT = Contingency Learning Task; WCST = Wisconsin Card Sorting Task; IED = Intra-Extra Dimensional Set Shift; TMT = Trail Making Task. Outcome measures: RT = Reaction Time; * = interference was computed as: [#items third list – ((#Words × #Colors)/(#Words + #Colors))]; TMT_B = Trail Making Test part B. GD vs HC: GD < HC reflects GD patients performing significantly worse than HCs.

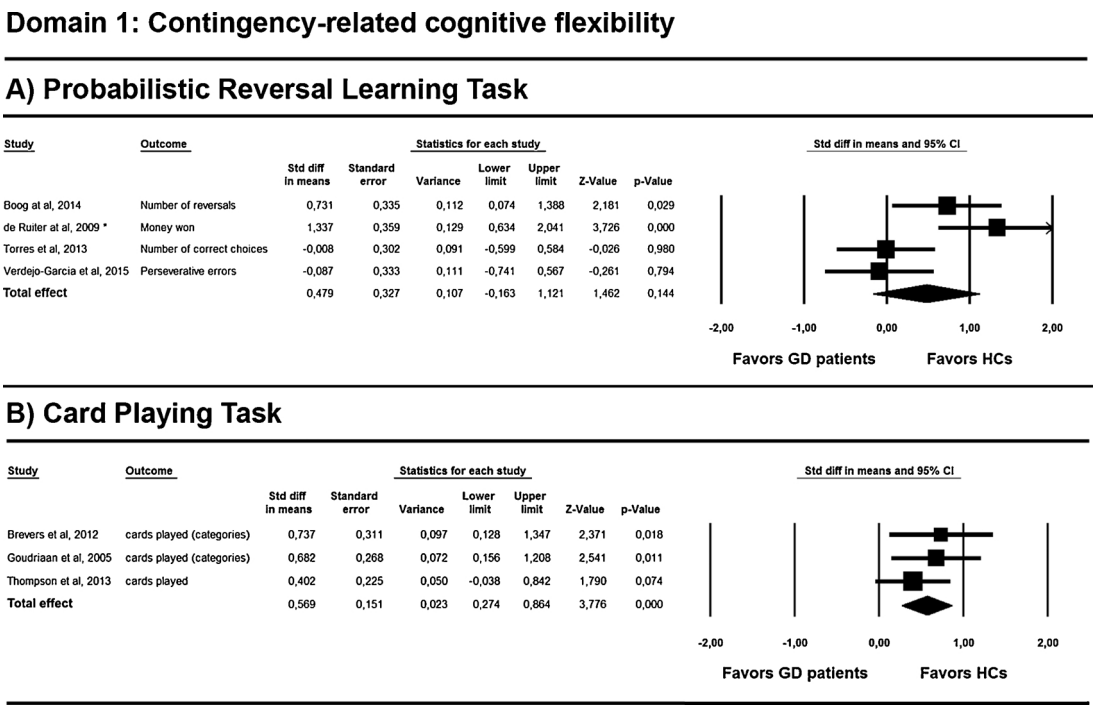

Fig. 2. Forest plot for the summary effect size of the difference on **(A)** the Probabilistic Reversal Learning Task and **(B)** the Card Perseveration Task between GD patients and HCs. *No standard deviation was reported in this study, but computed based on the Standard Error. The size of the squares reflect the relative weight of the studies for the pooled estimate. The diamond indicates the overall effect size.

(Fig. 2B). Heterogeneity was very low (Q = 1.0, p = 0.60, I^2 = 0%) (Supplementary Table 2).

3.2.3. Other tasks

Two other tasks assessing contingency-related cognitive flexibility in individuals with gambling disorder versus HCs were identified: a Deterministic Reversal Learning Task (DRLT; Janssen et al., 2015) and a Contingency Learning Task (CLT; Vanes et al., 2014).

The DRLT is similar to the PRLT but more straightforward, as the stimulus is entirely predictive of the outcome (i.e. reward or punishment) rather than probabilistic. The primary outcome measure is the error rate after reversal, with more errors after reversal indicating perseverative responding. Janssen et al. (2015) reported no behavioral performance deficits in individuals with gambling disorder versus HCs on this task.

The CLT is akin to the DRLT but includes four contingencies, only one reversal phase, and an additional extinction phase. Perseveration errors during the reversal phase are interpreted as reflecting cognitive inflexibility. Vanes et al. (2014) found no significant differences in the number of perseveration errors between individuals with gambling disorder and HCs.

3.3. Task/attentional set-shifting

Task or attentional set-shifting requires the ability to switch frequently among a set of tasks or response modes. It involves visual discrimination and attentional maintenance and shifting. Whereas contingency-related cognitive flexibility tasks contain switches within one set, task/attentional set-shifting tasks involve multiple sets (e.g. color, number or shape). This requires one to pay attention to various dimensions of the stimuli. A total of three tasks were identified within this domain: the Wisconsin Card Sorting Task, the Intra-Extra Dimensional Set-Shift and the Switch Task.

3.3.1. Wisconsin card sorting test

The Wisconsin Card Sorting Test (WCST; Heaton et al., 1981) is the most commonly used set-shifting task in humans. The participant is asked to sort response cards according to one of three classification modes (color, form, and number). The rule is acquired using the feedback provided after each response. After a fixed number of correct matches, the rule is changed and the participant must shift to a new mode of classification. Test parameters include the number of categories completed, the total number of errors and – most relevant for compulsivity – the number of perseveration errors (i.e. errors after a rule change).

A total of nine studies in individuals with gambling disorder using this task were found, of which eight studies reported significantly worse performance in individuals with gambling disorder versus HCs on at least one test parameter (not necessarily perseveration errors). Combining all studies and including a total of 274 individuals with gambling disorder and 342 HCs, a highly significant effect was found, with individuals with gambling disorder making more perseverative errors than HCs (effect size = 0.518; Z = 5.895, p < 0.001) (Fig. 3A). Heterogeneity was low (Q = 10.9, p = 0.28, I^2 = 17%) (Supplementary Table 2).

3.3.2. Intra-extra dimensional set-shift (IED)

In the Intra-Extra Dimensional Set-Shift (IED) task (Robbins et al., 1998), two stimuli are presented. One is correct and one incorrect. Using a touch screen, the participant touches one of two stimuli and is presented with feedback. After six correct trials, the stimuli and/or rule change: initially, the stimuli are composed of one ‘dimension’ (i.e. color-filled shapes) and the changes are intra-dimensional (i.e. from one color-filled shape another color-filled shape). Later, the stimuli are composed of two ‘dimensions’ (i.e. color-filled shapes and white lines) and, during the last stage, changes are extra-dimensional (i.e. from color-filled shapes to white lines). Test parameters include the number of stages completed, the number of intra-dimensional errors, the number of extra-dimensional errors and, most consistently reported in the studies here and indicative of perseverative responding, the total number of errors.

In the four studies that used the IED, three found that individuals

Table 3
Overview included studies within Task/attentional set-shifting domain.

Study	Population (♀/♂)	Age	In treatment	Clinical measure	Task	Outcome	GD vs HC	Results ($p < 0.05$)
Álvarez-Moya et al. (2010)	15 GD, 15 HC, 15 BN (♀)	GD = 44.4, HC = 35.5	yes	DSM-IV; SOGS = 11.2	WCST	perseverative errors	GD < HC	GDs made more perseverative errors than HCs
Black et al. (2013)	54 GD (35♀), 65 HC (38♀)	GD = 45.3, HC = 47.5	mix	DSM-IV; NODS = 13.7	WCST	perseverative responses	GD < HC	GDs made more perseverative errors than HCs
Boog et al. (2014)	19 GD (5♀), 19 HC (3♀)	GD = 42.1, HC = 38.8	yes	DSM-IV; SOGS = 8.3	WCST	perseverative errors	GD = HC	
Cavedini et al. (2002)	20 GD (1♀), 40 HC (22♀)	GD = 38.5, HC = 30.3	yes	DSM-IV; SOGS = 15.8	WCST	perseverative errors; categories	GD = HC	
Goudriaan et al. (2006)	49 GD (9♀), 48 AD (11♀), 46 TS (14♀), 50 HC (15♀)	GD = 37.3, HC = 35.6	yes	DSM-IV; SOGS = 11.6	WCST	perseverative responses; #categories	GD = HC; GD < HC	GDs did not make more perseverative responses compared to HCs, but completed fewer categories
Hur et al. (2012)	16 GD (♂), 31 OCD (8♀), 52 HC (16♀)	GD = 28.3, HC = 25.1	yes	DSM-IV; SOGS = 15.8	WCST	perseverative errors; non-perseverative errors	GD = HC; GD < HC	GDs did not make more perseverative responses compared to HCs, but did show more non-perseverative errors
Ledgerwood et al. (2012)	45 GD (21♀), 45 HC (23♀)	GD = 46.1, HC = 45.8	mix	DSM-IV	WCST	perseverative responses; categories	GD = HC; GD < HC	GDs did not make more perseverative responses compared to HCs, but did complete fewer categories
Rugle and Melamed (1993)	33 GD, 33 HC (♂)	GD = 41.3, HC = 40.8	yes	SOGS = 17.9	WCST	total trials	GD < HC	GDs used more trials to finish six correct sets, indicating worse perseveration
Zhou et al. (2016)	23 GD (5♀), 23 IAD (6♀), 23 HC (7♀)	GD = 29, HC = 28	yes	DSM-IV	WCST	perseverative errors; categories	GD < HC; GD < HC	GDs made more perseverative errors compared to HCs and completed fewer categories
Choi et al. (2014)	15 GD, 15 IGD, 15 ADs, 15 HC (♂)	GD = 27.5, HC = 25.3	yes	DSM-5; PGSI = 19.9	IED	total errors	GD < HC	PGs made more errors than HCs
Manning et al. (2013)	30 GD, 30 HC (♂)	GD = 37.1, HC = 37.2	yes	DSM-IV; SOGS = 13.4	IED	total errors	GD = HC	
Odlaug et al. (2011)	46 GD (23♀), 69 PrGs (16♀), 135 HC (55♀)	GD = 45.4, HC = 23.4	no	DSM-IV; SCID = 7.5	IED	total errors	GD < HC	PGs made more errors than HCs
Patterson et al. (2006)	18 GD, 20 HC (?)	GD = 45, HC = 41	yes	DSM-IV; SOGS = 14.3	IED-like	total responses	GD < HC	GDs completed fewer trials than HCs
van Timmeren et al. (2016)	26 GD, 26 HC (♂)	GD = 37.1, HC = 37.9	yes	DSM-IV; SOGS = 11.1	Switch task	switch cost; %correct switches	GD = HC	

For a complete list of abbreviations: see Table 2.

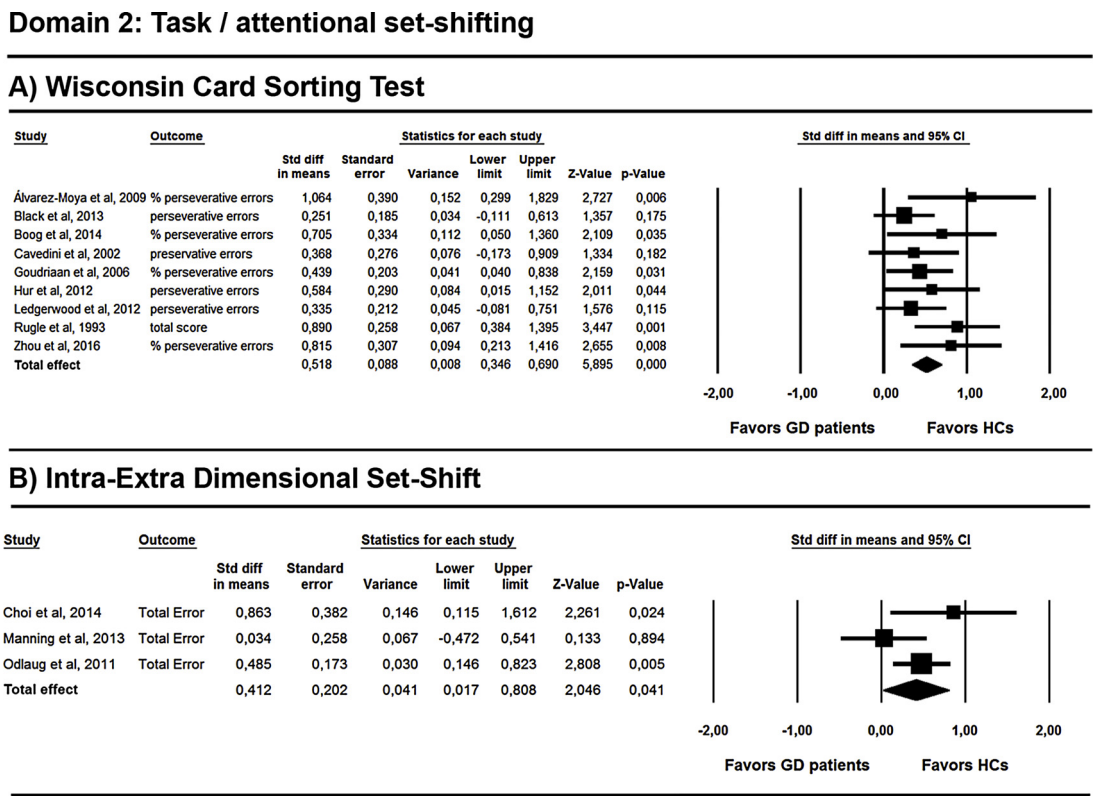

Fig. 3. Forest plot for the summary effect size of the difference on **(A)** the Wisconsin Card Sorting Task and **(B)** the Intra Extra Dimensional Set Shift between GD patients and HCs. The size of the squares reflect the relative weight of the studies for the pooled estimate. The diamond indicates the overall effect size.

with gambling disorder made significantly more errors than HCs (Choi et al., 2014; Odlaug et al., 2011; Patterson et al., 2006) and one study found no group differences (Manning et al., 2013). One study using an earlier version of the IED (Patterson et al., 2006) was not included in the meta-analysis because a different test parameter was reported. Combining the other three studies with a total of 91 individuals with gambling disorder and 180 HCs showed a significant overall impairment in individuals with gambling disorder on the IED (effect size = 0.412, Z = 2.046, p = 0.041) (Fig. 3B). Heterogeneity was relatively low (Q = 3.71, p = 0.16, I^2 = 46%) (Supplementary Table 2).

3.3.3. Switch task

In the Switch Task (Sohn et al., 2000), a letter and a digit are shown simultaneously in either red or blue. Depending on the color of these symbols, the participant is instructed to focus on the letter (red) or the digit (blue). Depending on whether the letter/number is a consonant/odd or a vowel/even, the participant needs to press left/right, respectively. Cognitive flexibility is measured by comparing accuracy and reaction time of the trials following a color switch with those after a color repeat. The only study using this task (van Timmeren et al., 2016) found no significant differences in task performance between individuals with gambling disorder and HCs.

3.4. Attentional bias/disengagement

Attentional bias or disengagement involves the ability to respond to certain environmental stimuli while ignoring others. Cognitive flexibility, here, is defined by a subject's ability to inhibit a prepotent, automatic response. Failing to inhibit such an automatic response may lead to inflexible behavior. The link between attentional bias and cognitive flexibility may be less clear than with the previous domains and is the subject of some disagreement in the literature (Izquierdo et al., 2017), as attentional bias can also depend on other executive functions. The results within this domain thus relate to compulsivity indirectly. The tasks that were included in this domain are the Stroop (Color-Word Interference) Task and the Trail Making Test.

3.4.1. Stroop task

The Stroop Task (Stroop, 1935) is a classic neuropsychological task that requires selective attention, cognitive flexibility and inhibitory control. In this task, the participant is presented with color words (e.g. red), which are either printed in the same (congruent) color or a different (incongruent) color. The participant is then asked to name the ink color of these words. The interference score is often used as a test parameter for the Stroop Task and reflects the increase in reaction time caused by seeing an incongruent word compared to a congruent word. This interference score is (at least partially) dependent on the inhibition of an automatic response to read the word. A failure to inhibit this automatic tendency can lead to inflexible behavior and this score can, therefore, be seen as a measure of cognitive flexibility. However, interference scores dependent on other cognitive processes too, such as attention and impulsive responding. Indeed, performance on the Stroop task is also thought to reflect (motor) impulsivity.

Of the 12 articles that used the Stroop task, seven found significant impairments in individuals with gambling disorder compared to HCs, whereas five did not. For the meta-analyses, three studies were excluded because only reaction times were reported and no interference index could be obtained (De Wilde et al., 2013; McCusker and Gettings, 1997; Potenza et al., 2003). For one study, the interference index could be calculated based on reported reaction times (incongruent – congruent; Lai et al., 2011). Of these four excluded studies, two reported significantly worse performances in individuals with gambling disorder, while the other two reported no significant group differences. Data of the remaining nine studies, including 337 individuals with gambling disorder and 404 HCs, were pooled and revealed a significant effect with individuals with gambling disorder showing more interference problems on the Stroop task compared to HCs (effect size = 0.331, Z = 2.575, p = 0.01) (Fig. 4A). However, there was significant

Table 4
Overview included studies within Attentional bias/disengagement domain.

Study	Population (♀/♂)	Age	In treatment	Clinical measure	Task	Outcome	GD vs HC	Result
Albein-Urios et al. (2012)	23 GD, 29 CD, 20 HC (?)	GD = 35.6, HC = 28.6	yes	DSM-IV	Stroop	interference index	GD < HC	GDs showed inhibition problems compared to HCs
Álvarez-Moya et al. (2010)	15 GD, 15 BN, 15 HC (♀)	GD = 44.4, HC = 35.5	yes	DSM-IV; SOGS = 11.2	Stroop	interference score*	GD < HC	GDs had a higher interference score than HCs
Black et al. (2013)	54 GD (35♀), 65 HC (38♀)	GD = 45.3, HC = 47.5	mix	DSM-IV; NODS = 13.7	Stroop	interference index	GD = HC	
De Wilde et al. (2013)	22 GD (2♀), 31 HC (4♀)	GD = 33,5, HC = 28.1	yes	DSM-IV; SOGS = 11.1	Stroop	RT	GD < HC	GDs were significantly slower task than HCs
Goudriaan et al. (2006)	49 GD (9♀), 48 AD (11♀), 46 TS (14♀), 50 HC (15♀)	GD = 37.3, HC = 35.6	yes	DSM-IV; SOGS = 11.6	Stroop	interference index	GD < HC	GDs showed inhibition problems compared to HCs
Hur et al. (2012)	16 GD (♂), 31 OCD (8♀), 52 HC (16♀)	GD = 28.3, HC = 25.1	yes	DSM-IV; SOGS = 15.8	Stroop	interference index	GD = HC	
Lai et al. (2011)	37 GD, 40 HC (♂)	GD = 36.4,HC = 35.6	yes	DSM-IV; SOGS = 14.3	Stroop	interference index	GD = HC	
Ledgerwood et al. (2012)	45 GD (21♀), 45 HC (23♀)	GD = 46.1, HC = 45.8	mix	DSM-IV	Stroop	interference index	GD = HC	
McCusker and Gettings (1997)	15 GD, 15 HC (♂)	GD = 33.6, HC = 23.4,	yes	–	Stroop	RT	GD = HC	
Kertzman et al. (2006)	62 GD (20♀), 83 HC (25♀)	GD = 40.6, HC = 40.4	yes	DSM-IV; SOGS > 5	Stroop	interference index	GD < HC	GDs showed inhibition problems compared to HCs
Potenza et al. (2003)	13 GD, 11 HC (♂)	GD = 35.2, HC = 29.0	yes	DSM-IV; SOGS = 12.6	Stroop	% incorrect; RT incorrect	GD = HC	
Regard et al. (2003)	21 GD (1♀), 19 HC (1♀)	GD = 33.6, HC = 34.4	yes	DSM-III	Stroop	RT; number of errors	GD = HC; GD < HC	GDs were not slower but did make more errors on the Stroop task than HCs
Black et al. (2013)	54 GD (35♀), 65 HC (38♀)	GD = 45.3, HC = 47.5	mix	DSM-IV; NODS = 13.7	TMT	TMT_B (sec)	GD = HC	
Choi et al. (2014)	15 GD, 15 IGD, 15 ADs, 15 HC (♂)	GD = 27.5, HC = 25.3	yes	DSM-5; PGSI = 19.9	TMT	TMT_B (sec)	GD = HC	
Hur et al. (2012)	16 GD (♂), 31 OCD (8♀), 52 HC (16♀)	GD = 28.3, HC = 25.1	yes	DSM-IV; SOGS = 15.8	TMT	TMT_B (sec)	GD = HC	
Rugle and Melamed (1993)	33 GD, 33 HC (♂)	GD = 41.3, HC = 40.8	yes	SOGS = 17.9	TMT	TMT_B (sec)	GD = HC	

For a complete list of abbreviations: see Table 2.

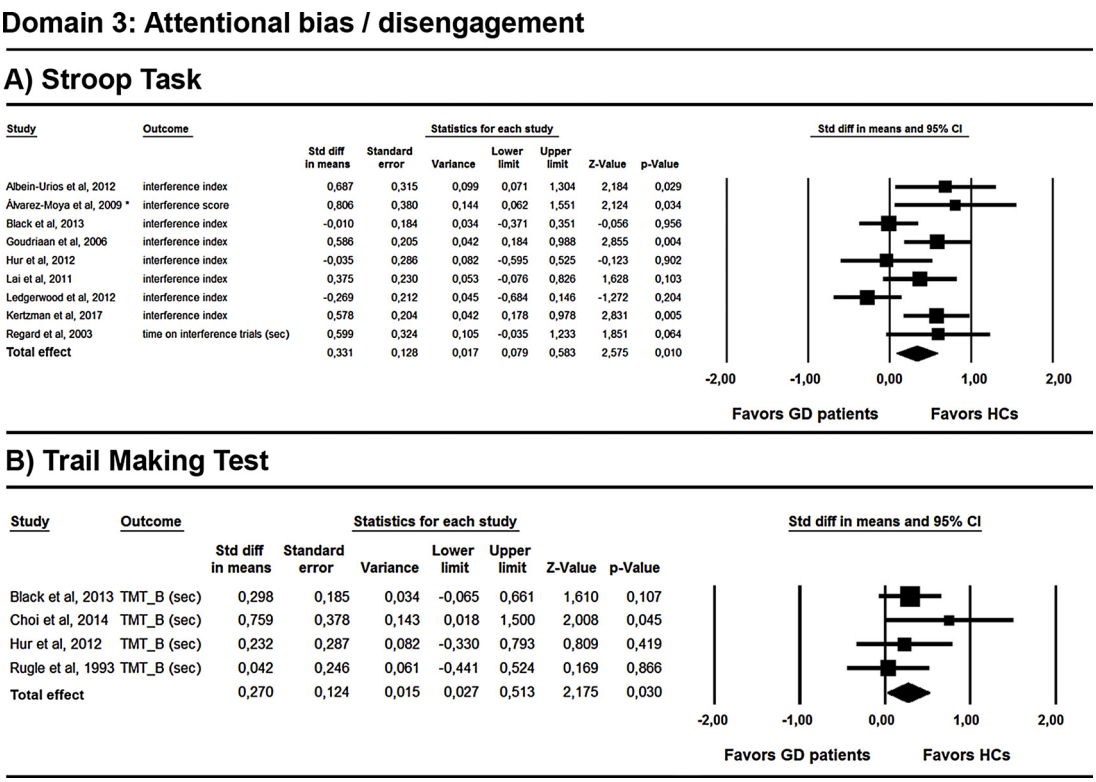

Fig. 4. Forest plot for the summary effect size of the difference on **(A)** the Stroop Task and **(B)** the Trail Making Test between GD patients and HCs. *No standard deviation was reported in this study, but computed based on the Standard Error. The size of the squares reflect the relative weight of the studies for the pooled estimate. The diamond indicates the overall effect size.

heterogeneity as represented by significant Q-scores ($Q = 19.5$, $p < 0.01$) and moderate I^2 (59%) (Supplementary Table 2). This result was not explained by any of the variables we considered in the meta-regression (all $p > 0.05$), but again may reflect inconsistent reporting of outcome measures, as it was not always reported how interference indexes were computed across studies.

3.4.2. Trail making test

The Trail Making Test (TMT; Reitan, 1992) is a paper and pencil task, in which a participant is instructed to connect a sequence of consecutive targets as quickly as possible while maintaining accuracy. It consists of two parts: during the first part (A) all targets are numbers (1, 2, 3, etc.) and the participant needs to connect the numbers in sequential order; during the second part (B) the targets are letters and numbers and the participant is instructed to sequentially connect those in alternating order (1, A, 2, B, etc.). This requires the subject to inhibit the automatic inclination to connect numbers or letters in order (1, 2, 3, or A, B, C, etc.), rather than alternating between the two. The amount of time needed to complete the second part of the test (TMT-B) reflects cognitive inflexibility and working memory problems. Although the difference score B-A is a purer indicator of cognitive flexibility (Sanchez-Cubillo et al., 2009), TMT-B was the most consistently reported score across the included studies and is, therefore, the outcome measure we used for the meta-analysis. Note that we incorporated the TMT-B in the Attentional bias/disengagement domain because solving this task requires the continuous inhibition of a prepotent response. However, attentional set shifting is also required to complete this task and therefore it could also be placed under the Task/Attentional Set-Shifting domain.

Only one of the four studies that used the TMT-B found a significant difference between individuals with gambling disorder and HCs, with gamblers performing worse. Combining these four studies in the meta-analysis, with a total of 118 individuals with gambling disorder and 165 HCs, we found that individuals with gambling disorder performed significantly worse on the TMT-B than HCs (effect size = 0.270, Z-score = 2.175, $p = 0.030$) (Fig. 4B). Heterogeneity was low ($Q = 6.26$, $p < 0.18$, $I^2 = 36\%$) (Supplementary Table 2).

3.5. Habit learning

Habit learning refers to the tendency of actions to become automatic when they are frequently repeated. According to associative learning theories, instrumental learning can be supported by goal-directed and habitual control systems (Balleine and Dickinson, 1998). In the former, actions are performed and updated depending on an outcome. Over time, the habitual system starts to render behavior automatic and actions become insensitive to the outcome, instead relying on stimulus-response contingencies. Compulsive behavior could either be a consequence of impaired goal-directed control or an overactive habit system. Assessments of habit learning should incorporate specificity regarding which of the two systems controls the behavior. Perseveration on reversal-learning paradigms, for example, also involve reward learning based on stimulus-outcome associations, but may be a consequence of both systems (Izquierdo et al., 2017). Examples of tasks that are suggested to specifically test habit learning are the fabulous fruit game (de Wit et al., 2009) and the two-step task (Daw et al., 2011).

Although habit learning is hypothesized to play an important role in the transition from goal-directed to compulsive behavior, no studies were identified assessing habit learning in gambling disorder.

4. Discussion

4.1. General discussion

We systematically reviewed the literature for and performed meta-analyses of studies testing compulsivity-related neuropsychological function in gambling disorder versus HCs. Compulsivity was divided into four separate domains representing different components of compulsive

behavior assessed with various neuropsychological tasks (Table 1). We found that individuals with gambling disorder, compared to HCs, show performance deficits in a broad range of compulsivity-related neuropsychological functions. Despite some variability between individual tasks, the available evidence consistently indicates performance deficits within all compulsivity domains in individuals with gambling disorder compared to HCs. These results will first be discussed for each compulsivity domain before discussing them in a broader context.

Within the contingency-related cognitive flexibility domain, the individual tasks showed mixed results (Fig. 2). Results from studies using the PRLT did not reveal significant behavioral inflexibility in individuals with gambling disorder; however, this could be due to the relatively small sample size. Another factor that possibly obscures these results is the diversity in test and outcome parameters between the studies, which was also reflected by the significant level of heterogeneity detected. On the CPT, a significant impairment with a medium effect size estimate was found in individuals with gambling disorder versus HC. This result may be especially relevant clinically, as impaired performance on this task has shown to be predictive of relapse in individuals with gambling disorder (Goudriaan et al., 2008) and similar performance deficits have been reported in substance use disorders (Martin et al., 2000). Interestingly, perseverative responding on this task seems to normalize when adding a 5 s feedback-response pause (Thompson and Corr, 2013). One explanation could be that compulsive responding is in part mediated by impulsive responding. Another study found that while HCs slow down in response speed after a loss, individuals with gambling disorder do not (Goudriaan et al., 2005). This, again, may be explained by the increased impulsive responding, as often reported in gambling disorder (Verdejo-García et al., 2008). The interaction between impulsive and compulsive behaviors is a topic we will return to later in the discussion.

The available studies testing task/attentional set-shifting show a highly consistent pattern: in all studies, individuals with gambling disorder perform worse than controls (Fig. 3). Results from the meta-analyses show significant performance deficits with moderate effect sizes in individuals with gambling disorder versus HCs on both the WCST and the IED. The reported test parameters on these tasks are highly consistent, which is also reflected by the low level of heterogeneity within this domain. Taken together, these results provide substantial evidence for performance deficits in cognitive flexibility in individuals with gambling disorder. This is further substantiated by a recent study using a large non-clinical sample of regular gamblers which shows a positive correlation between IED errors and various scales of gambling severity, including DSM-5 criteria (Leppink et al., 2016). However, studies trying to predict treatment outcome based on performance on the WCST in individuals with gambling disorder (Rossini-Dib et al., 2015) or substance use disorders (Aharonovich et al., 2006) have been unsuccessful.

On both tasks included within the attentional bias/disengagement domain, significant performance deficits were found in individuals with gambling disorder, with small-to-medium effect sizes (Fig. 4). The results on the Stroop task, however, should be interpreted cautiously as heterogeneity was high. This could not be explained by accounting for age, sex, IQ or gambling severity in the meta-regression analysis.

Overall, these results suggest a general tendency of individuals with gambling disorder to exhibit compulsive tendencies that are not directly related to the gambling behavior itself. These performance deficits may be associated with both the development and the maintenance of gambling symptoms. For example, the general inability to flexibly switch attention, or the tendency to perseverate on a behavior once it has been learned, may give rise to an increased risk for developing compulsive gambling behavior. Moreover, these performance deficits may be a consequence of disordered gambling. In both cases, this may be related to increased difficulties in quitting the gambling behavior, as the majority of studies tested individuals with gambling disorder who were in treatment. This potential relationship between treatment outcome and performance on those tasks has to be studied more extensively (Goudriaan et al., 2008) as this may offer possibilities for preventive and therapeutic interventions. Interestingly, a similar pattern of performance deficits on neurocognitive tasks is present in OCD patients, the prototypical disorder of compulsive behavior: a meta-analysis recently found significant deficits on the WCST, IED, the Stroop task and the TMT-B (Shin et al., 2014). Impaired performance on those tasks thus seems to generalize to other compulsive disorders too.

Neuroimaging methods have been used to investigate the neural correlates of cognitive flexibility, set-shifting and attentional disengagement tasks in healthy control subjects. Regions frequently associated with these domains include the orbitofrontal cortex (OFC), the ventrolateral (vlPFC), ventromedial (vmPFC) and dorsolateral prefrontal cortex (dlPFC) and the basal ganglia (Fineberg et al., 2010; Izquierdo et al., 2017). Conceivably, abnormal brain responses in similar regions were observed in gambling disorder when probed with tasks assessing these neurocognitive domains (recently reviewed by Moccia et al., 2017). Five studies included in this review also investigated brain functioning in individuals with gambling disorder and HCs while subjects were performing compulsivity-related tasks. During the Stroop task, individuals with gambling disorder showed decreased vmPFC activity (Potenza et al., 2003), while decreased vlPFC activity was reported during the PRLT (de Ruiter et al., 2009; Verdejo-García et al., 2015). An EEG study found abnormal feedback-evoked cortical activity in individuals with gambling disorder during the PRLT (Torres et al., 2013). Decreased structural white matter integrity between the dlPFC and the basal ganglia, a tract important for cognitive flexibility, was observed in individuals with gambling disorder (van Timmeren et al., 2016), although this was not directly related to the performance on an attentional switch task. The available neuroimaging evidence in gambling disorder testing compulsivity thus converges towards the view of individuals with gambling disorder showing decreased brain function and structure in areas that are important for cognitive flexibility, set-shifting, and attentional disengagement.

The neurochemical mechanisms contributing to compulsivity are not well understood, although dopamine and serotonin are thought to play key roles (Fineberg et al., 2010). Previous studies in both humans and animals have convincingly shown that cognitive flexibility is specifically and dissociably affected by both dopamine and serotonin. For example, baseline dopamine synthesis capacity in the human striatum predicts reversal learning performance, while the effects of dopaminergic drug administration also depend on these baseline levels (Cools et al., 2009). Prefrontal dopamine depletion in monkeys, on the other hand, does not affect reversal learning, whereas serotonin depletion specifically impairs reversal leaning and not attentional set-shifting (Clarke et al., 2007, 2005). Glutamate has also been implicated in reversal learning and other forms of cognitive flexibility, but results have been contradicting (Izquierdo et al., 2017) In gambling disorder, some studies have reported altered dopamine levels, although findings have been inconsistent (Boileau et al., 2013; van Holst et al., 2017) and little is known about neurotransmitter function in relation to neurocognitive tasks. So far, only one study has directly investigated dopamine function and its relation to reversal learning (DRLT) in individuals with gambling disorder. Janssen et al. (2015) found that, as expected, administration of a sulpride (a D2-receptor antagonist) led to impaired reward- versus punishment learning in healthy controls. In individuals with gambling disorder, however, sulpride did not have any effect on performance when compared to the placebo condition. Moreover, a pilot study found that administration of memantine, a NMDA-receptor antagonist that reduces glutamate excitability, improves cognitive flexibility (as measured by the IED) and resulted in decreased gambling (Grant et al., 2010). Considering the scarcity of studies investigating the neurochemical mechanisms contributing to compulsivity in gambling disorder, more research is needed.

4.2. Limitations and recommendations for future research

The central aim of this systematic review and meta-analysis was to summarize and integrate the evidence for neuropsychological performance deficits in gambling disorder that can be related to compulsive behavior. However, compulsivity is a complex multidimensional construct and compulsive behavior may arise for other reasons that were not assessed in this review. Known factors contributing to compulsive aspects of addiction are anxiety and distress (Koob and Le Moal, 2008); initially, the behavior may serve as a coping mechanism, then tolerance to reward may develop but the behaviors may persist as a method of reducing discomfort. Under the influence of motivational triggers, such behaviors may ultimately result in automatic, unconscious compulsions and the loss of control. We also did not assess the relationship and interaction between compulsivity and impulsivity, i.e. the tendency to act prematurely without foresight. Impulsivity is a multifaceted trait, generally associated with risk- and reward-seeking, whereas compulsivity is less reward-driven and associated with harm-avoidance (Fineberg et al., 2010). However, both concepts share the feeling of lack of control, and both may arise from failures of 'top-down' cognitive control (Dalley et al., 2011). Both factors may also interact: compulsive behavior may be predisposed by increased impulsive responding, exemplified by high trait impulsivity in rats predicting compulsive drug seeking (Belin et al., 2008). Thus, impulsivity could evolve into compulsivity and these interactions are exciting avenues for future research.

Although the measured constructs are generally regarded as traits, there could be state dependent impairments at play, caused by depressive symptoms, attentional problems, or other impairments that could be a consequence of gambling disorder. Furthermore, compulsivity itself may be state-dependent (i.e. related to illness state or stage) and therefore has been suggested to be an unstable 'moving target' that cannot be an endophenotype (Yücel and Fontenelle, 2012). On the other hand, compulsivity has been viewed as a hypothetical trait with a common underlying endophenotype (Robbins et al., 2012). Longitudinal studies are needed to address these issues.

As compulsivity was our primary domain of interest, we did not assess other, non-compulsive neuropsychological deficits in gambling disorder. Therefore, we cannot make any claims about the specificity of our effects to compulsive (versus non-compulsive) aspects of neurocognitive functioning in gambling disorder. Moreover, these neurocognitive tasks of compulsivity are also dependent on other (non-)executive cognitive processes: for example, shifting on the IED task between colors and shapes also requires visual processing (Miyake et al., 2000).

Despite its potentially crucial role as 'building block' of pathological, compulsive behavior associated with addictions (Everitt and Robbins, 2015), there is a complete lack of experimental studies investigating habit learning in gambling disorder. Thus, whether gambling disorder is characterized by aberrant habit learning is still an open question. Although most of the work relating to habit learning and addiction has come from animal studies, several studies have recently reported impairments in habit formation in substance use disordered humans. Previous studies have demonstrated an overreliance on habit-learning in e.g. alcohol (Sjoerds et al., 2013) and cocaine-dependent patients (Ersche et al., 2016). Decreased goal-directed (model-based) control has been associated with various 'disorders of compulsivity' (including binge-eating disorder, obsessive-compulsive disorder and substance use disorders; Voon et al., 2014); alcohol dependence (Sebold et al., 2014, but see Sebold et al., 2017); and with a symptom dimension comprising compulsive behavior and intrusive thought in a large sample of healthy control subjects (Gillan et al., 2016).

Our approach provides a possible means to investigate and identify the concept of compulsivity *trans*-diagnostically, which in turn may help to predict vulnerability and to target behavioral and pharmacological treatments more effectively (Robbins et al., 2012). Future studies are encouraged to make comparisons between gambling disorder and other 'disorders of compulsivity'. The CPT, WCST, and IED seem to be the most sensitive to pick up performance deficits, at least in individuals with gambling disorder. While it was beyond our scope to review this systematically, some of the studies included in this review did compare individuals with gambling disorder with substance use disorders (Albein-Urios et al., 2012; Choi et al., 2014; de Ruiter et al., 2009; Goudriaan et al., 2006, 2005; Torres et al., 2013; Vanes et al., 2014; Verdejo-García et al., 2015), behavioral addictions (Choi et al., 2014; Zhou et al., 2016) or obsessive-compulsive disorder (Hur et al., 2012). In general, these studies indicate performance deficits in those groups that are similar to (Albein-Urios et al., 2012; Goudriaan et al., 2006, 2005; Hur et al., 2012; Vanes et al., 2014; Zhou et al., 2016) or worse (Choi et al., 2014) than those in individuals with gambling disorder.

Within gambling disorder, gamblers can also be divided into subtypes. Previous studies have done this in multiple ways: based on their preferred gambling activity (e.g. slot-machine or casino gamblers; Goudriaan et al., 2005), based on comorbidity or personality traits (e.g. depressive, sensation-seeking or impulsive; Álvarez-Moya et al., 2010), or based on their motivation for gambling (e.g. coping with stress or negative emotions; Stewart et al., 2008). In relation to cognitive flexibility, one study found that casino gamblers were highly perseverative on the CPT, whereas slot-machine gamblers used an (also disadvantageous) conservative approach (Goudriaan et al., 2005). Future studies may identify clinically relevant, dimensional subgroups (within and between psychiatric disorders) by investigating the interaction of such subtypes and individual task performance. One way to both improve patient classification and understanding of the mechanisms underlying performance deficits is by using computational modeling, i.e. 'computational psychiatry' (Huys et al., 2016; Maia and Frank, 2011). To dissect multiple components of compulsivity-related cognitive functioning that cannot be picked-up using classical approaches, it might be fruitful to (re-)analyze existing data using computational models (Lesage et al., 2017).

4.3. Conclusion

In this systematic review and meta-analysis, we have investigated four neurocognitive domains that are considered to be particularly relevant to compulsive tendencies in gambling disorder. To this end, we selected behavioral tasks that measure executive functions reflecting any of these elements. Both the qualitative and quantitative results suggest that individuals with gambling disorder, in general, show performance deficits in cognitive flexibility, set-shifting, and attentional bias, while no studies investigating habit learning in gambling disorder were identified. Overall, these findings support the idea that gambling disorder is characterized by compulsivity-related neurocognitive impairments, as exemplified in perseveration and cognitive inflexibility. However, as mentioned previously, the mapping of neuropsychological tasks onto the separate domains of compulsivity is not always clear-cut. Therefore, the need remains to revise and refine the conceptual definition and classification of compulsivity, which will help to advance research in this field.

Apart from being important for gambling disorder itself, these findings may have broader implications. By viewing gambling disorder as a behavioral addiction that resembles substance use disorders without the confounding effects of drug administration, these results support the hypothesis that susceptibility for compulsivity predates addictive behaviors (Leeman and Potenza, 2012). As such, they provide a possible link between impairments in executive functions related to compulsive action and vulnerability for addiction and may contribute to establishing an endophenotype for compulsivity-related disorders (Gottesman and Gould, 2003).

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All authors critically reviewed content and approved final version for publication.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neubiorev.2017.11.022.

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