Cognitive training: A new avenue in gambling disorder management?

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A. Current therapeutics in gambling disorder

Addictive disorders represent a major challenge in public health, with a considerable human and social burden. The recent gathering in classification of disease of addiction with and without substance (i.e. behavioral addiction) allowed the recognition of gambling disorder as an addictive disorder ("Non-Substance-Related Disorders [312.31 (F63.0)]" within "substance- Related and Addictive Disorders") (David Kupfer and TaskForce 2013). No medication is currently approved for its treatment. Aside mutual help groups, most interventions are motivational interventions, cognitive behavioral therapies (CBT), or a combination of both (Fink, Parhami et al. 2012, Choi, Shin et al. 2017). CBT consist in the analysis of problem behaviors, and corresponding thoughts and feelings. This analysis is variably associated with exposure techniques, thoughts restructuring (Chretien, Giroux et al. 2017), emotion regulation, dealing with high-risk situations and avoidance of the problem behavior, building a relapse plan. Mindfulness-based therapies aim at fostering attention and self-control, and at decreasing discomfort inherent to craving and sensitivity to cues (Tolchard 2017). A broad panel of modalities to dispense psychotherapeutic interventions in gambling disorder has been reported, including self-help manuals, groups interventions, face to face intervention, online interventions, virtual reality (Bouchard, Robillard et al. 2017). Therapeutic interventions still have demonstrated a weak to moderate effect size in published trials (Gainsbury and Blaszczynski 2011). Several methodological issues have limited the relevance of previous CBT trials among problem gamblers (Fink, Parhami et al. 2012). In particular, these kind of psychological interventions are demanding as regarding cognitive abilities (Kiluk, Nich et al. 2011). High impact of cognitive functioning and abilities in problem gamblers could be barriers to the acquisition of coping skills from cognitive behavioral therapies.

B. Cognitive deficits in gambling disorder

Cognitive deficits in gambling disorder are indeed increasingly studied. Research in this addiction without substance appears to be a tremendous opportunity to further understand the cognitive dysfunctions linked to the addiction process itself, free from the toxicity of a substance use (Volkow, Fowler et al. 2004). Reported impaired functions are planning (Ledgerwood, Orr et al. 2012), decision making, including decision making that involves risk (Tanabe, Thompson et al. 2007), social decision making, delay discounting (Petry 2001, Cosenza, Griffiths et al. 2017), reward process (Gardner 2011, Brevers, Koritzky et al. 2014), executive control and

inhibition (Smith, Mattick et al. 2014) (Noel, Van der Linden et al. 2013). Moreover, problematic gamblers have been shown to have decreased social cognition responses (e.g. empathy) and lower performance at a visuospatial perspective-taking task (Tomei, Besson, & Grivel, 2017). Most of these deficits correspond to documented deficits in substance use disorders. (Petry 2001, Tanabe, Thompson et al. 2007, Hulka, Eisenegger et al. 2013, Noel, Brevers et al. 2013). However, some dissimilarity has been reported, and it has been recently underlined that problem gamblers did not seem to present a generalized executive impairment, and had better performances than a group of healthy controls on some executive functions such as flexibility, sustained attention and working memory (n=24 and 21) (Kapsomenakis, Simos et al. 2018), contrarily to findings in substance use disorder (Bickel, Moody et al. 2014). The most explored cognitive deficits in gambling disorder correspond to the cognitive facets of behavioral impulsivity. Impulsivity is defined as a state or trait tendency in automatic, rapid and unreflective behavioral responses. Generally, the neurocognitive conception of impulsivity can be divided into impulsive choices, related to delay discounting and impulsive decision making, and impulsive actions, related to motor disinhibition, interference and cognitive disinhibition and personality trait (Stevens, Verdejo-Garcia et al. 2014). High levels of automaticity, impaired cognitive inhibition, lack of self-control, and maladaptive self-regulation appear to be the common cognitive substrates of behavioral impulsivity (Brooks, Lochner et al. 2017), involved in gambling disorder. Chowdhury and colleagues identified in a systematic review that motor impulsivity and its underlying motor disinhibition could be one of the main features of pathological gamblers psychopathology (Chowdhury, Livesey, Blaszczynski, & Harris, 2017). At the clinical level, Billieux and colleagues demonstrated that, if impulsivity is known to be high in gambling disorder in a general way, different impulsive patterns could be identified. Indeed, gamblers were characterized by high level of selective components of impulsivity (i.e. at the affective, motivational and neurocognitive levels), suggesting different underlying cognitive processes leading to close but not overlapping phenotypes of pathological gamblers (Billieux, Lagrange et al. 2012). Similarly, Mallorqui and co. could distinguish 2 clusters in a sample of problem gamblers, with one older, with a later age of onset, and global neuropsychological, including poor inhibition, working memory and cognitive flexibility functioning than the other (Mallorqui-Bague, Tolosa-Sola et al. 2017). Inconsistent results have been reported

to state on non-reward based inhibition impairments in problem gamblers (Boog, Hoppener et al. 2014). Sensitivity to reward has also been extensively studied. At the clinical level, hypersensitivity for large monetary gains, which might reflect hypersensitivity of reward system, has been described (Brevers, Koritzky et al. 2014). Neurocognitive reward sensitivity could be related to self-reported overspending behavior in pathological gambling (Alvarez-Moya, Ochoa et al. 2011). Other authors reported differential sensitivity to monetary versus non-monetary rewards anticipation and outcome in pathological gambling as compared to healthy controls. Neuroimaging studies in substance use disorders suggest different neural effects between different types of psychotherapeutic interventions and their components. These effects differ according to their neurofunctional targets, and in particular the use of cue involving the substance, monetary or non-monetary rewards.. It has been shown that these different effects according to therapeutic strategies have however common targets: the inhibitor control network, and the reward system.. (Zilverstand, Parvaz et al. 2016). Involved brain areas were the striatum, the nucleus accumbens, the ventral tegmental area, the inferior frontal gyrus and the dorsal anterior cingulated cortex (Zilverstand, Parvaz et al. 2016). No such neuro-imaging data are available to document the impact of psychotherapies in gambling disorder, however similar brain areas have been demonstrated to be implicated in the gambling disorder process (Grant, Odlaug et al. 2016, Limbrick-Oldfield, Mick et al. 2017). Connectivity between the reward system and the inhibitory control network has been repeatedly demonstrated to be implicated in the addiction and the remission processes and in the response to a medication in gambling disorder (Kayser, Vega et al. 2017). Goudriaan and her team proposed to further explore relations between inhibitory control, cue reactivity and motivational processes, underlining the differential responses found on executive processes between gambling cues and neutral cues in pathological gamblers (van Holst, van Holstein et al. 2012). These authors defined 3 domains impacted in gambling disorders that could be targets for cognitive training: self-control, a concept including inhibition and impulsivity, cue-reactivity and reward sensitivity (Goudriaan, Yucel et al. 2014).

C. Cognitive training

Definition

Cognitive rehabilitation aims to: (a) inform and provide psycho-education about cognitive functions, and the problems as well as the strengths of patients, (b) improve components of executive functions when possible through relearning, (c) compensate impairments if relearning of functions is impossible in the case of loss of cognitive skills, (d) training people to use adaptive methods for increasing independence in activities of daily living skills (Chung, Pollock, Campbell, Durward, & Hagen, 2013; Koehler, Wilhelm, & Shoulson, 2012). Respectively to these objectives, mechanisms of action of rehabilitation regard restoring the functional loss through improving cognitive functions and stimulation of neuronal growth. If restoring is not reachable, rehabilitation regards compensating or adapting to functional loss. These strategies imply advanced psycho-education and collaboration with the affected subject. They develop self-awareness and self-regulation of behavior.

Cognitive training (also called “brain training”) is currently used to improve fluid intelligence (“Gf”) (and its components such as working memory, inhibitory control, etc.) in reason of its supposed malleability and its relation to daily activities (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). Indeed, the purpose of these kind of training is to obtain transfer to non-experimental and ecological situations (Karbach & Kray, 2009; Klingberg, 2010). Cognitive training is referenced in brain damaged patients (Ashley, Ashley et al. 2012, Nelson, Macdonald et al. 2013), aging (Anguera, Boccanfuso et al. 2013), Attention Deficit/ Hyperactivity Disorder (Memarmoghaddam, Torbati et al. 2016), and in some psychiatric conditions, like schizophrenia (Bucci, Piegari et al. 2013) or major depression (Motter, Devanand, Doraiswamy, & Sneed, 2015).

Cognitive training in substance use disorders

Few cognitive training programs have been tested and published in addictive disorders. Verdejo-Garcia identified in his review 4 targets for cognitive training in substance use disorders (Verdejo-Garcia 2016): cognitive bias, response inhibition, working memory, and goal-directed behavior. The training trials recruited subjects with alcohol use disorder, methamphetamine use disorder, stimulant use disorder or opiate use disorder. Most studies used computerized programs, which are likely to be cost-effective. An early trial assessed the efficacy of a 2-hours session of computer assisted cognitive training per week over a 6-month period in patients with various substance use disorders with cognitive deficits: cocaine (29 subjects, 40%), alcohol (18 subjects, 25%), opioids (12 subjects, 17%), stimulants (3 subjects, 4%), and cannabis (3 subjects, 4%) (Fals-Stewart and Lucente 1994). The program remediated deficits in attention, motor skills, spatial orientation, and working memory. The authors concluded that participants in the cognitive training group demonstrated a shorter time to cognitive recovery during the first 2 months of treatment. Another controlled trial assessed the efficacy of a 15 one-hour sessions computerized training program, in thirty-

eight recently detoxified alcoholics (Peterson, Patterson et al. 2002). The program targeted memory, visual-motor coordination, and visual-spatial skills. The trial showed no efficacy on addiction recovery despite improvement in cognitive performance following detoxification. More recently, Bickel and colleagues conducted a controlled trial in 27 patients with a stimulant used disorder assessing the efficacy of a training program targeting working memory and found that rates of discounting of delayed rewards were significantly reduced among subjects who benefited from the working memory training (Bickel, Yi et al. 2011). Rupp and collaborators assessed the efficacy of a training program aiming attention, executive function, and memory in 20 alcohol-dependent patients (Rupp, Kemmler et al. 2012). They reported a significant improvement in attention/executive function and memory domains and in clinical outcomes (i.e. well-being and craving). Wiers and collaborators have led several trials on alcohol-dependent subjects and heavy drinkers, targeting attention bias. They reported that four brief sessions of experimental Cognitive Bias Modification, that preceded regular inpatient treatment in 214 alcoholic inpatients, could change patients' approach bias into an avoidance bias for alcohol. Patients trained to make avoidance movements (i.e. pull for approaching and push for avoidance) in response to alcohol pictures showed better treatment outcomes at one year follow-up (Wiers, Eberl et al. 2011). This team is currently recruiting in another trial assessing web-based cognitive bias modification for problem drinkers and gamblers (van Deursen, Salemink et al. 2013), with no available data to date. A team from South Africa reported a subjective improvement of impulsivity in a pilot study in methamphetamine users after a computerized cognitive training program targeting working memory, with self-reported measures only and without a non-training computer-based control group (Brooks, Wiemerslage et al. 2017), and changes in brain volume after the same program, with no patient controlled group (Brooks, Burch et al. 2016) Despite the robust documentation of inhibition deficit in addictive disorders, very few data are available on the efficacy of cognitive training tasks or programs targeting inhibition skills.. In a pragmatic trial, it has been found that practicing a non-specific task of self-control (i.e. avoiding sweets and tightening a handgrip) could prevent relapse in smokers (Muraven 2010). More recently, Gamito and colleagues found, in 14 male heroin addicts, consistent improvements in cognitive functioning between baseline and follow-up assessments, especially for executive functions processes, sustained attention, decision making, cognitive flexibility, as well as verbal memory and depressive symptoms (Gamito, Oliveira et al. 2017). Loughead and colleagues found no between-group difference in 213 adult treatment-seeking smokers randomized to receive, in addiction of nicotine patch therapy, 12 weeks of either computerized cognitive training program targeting working memory, attention, and response inhibition, or computerized relaxation (Loughead, Falcone et al. 2016). Another trial studied immediate effects of an inhibition training task. The active group was required to repeatedly

inhibit a response towards smoking cues (100%), while the control group was required to inhibit a response towards smoking and neutral cues with equal frequency (50%). No between group differences was found, indicating possible positive effect of the control program inhibiting neutral and smoking cues (Adams, Mokrysz et al. 2017).

Cognitive training in gambling disorder

After reviewing the cognitive impairments and therapeutic strategies targeted on cognitive functioning, we decided to investigate this thematic in the growing field of behavioral addiction. More precisely, we sought to explore existing literature in gambling disorder which represents a new clinical framework for psychological interventions based on neurocognitive approach of problematic behaviors. Following this goal, we conducted a systematic search aiming at identifying any use or efficacy data on cognitive training intervention in gambling disorders.

Systematic search

We conducted a systematic review of literature following PRISMA standards (Liberati et al., 2009). A comprehensive search of the PubMed/MEDLINE database was conducted. The following terms were entered and combined as keywords : ((gambling OR gambler OR gamblers) AND (addiction OR disorder OR problem OR pathological) AND ("cognitive training" OR "cognitive rehabilitation" OR "cognitive bias modification" OR ("inhibition" AND" training") OR ("working memory" AND "training")OR ("goal-directed" AND "training") OR (“Go/No-Go” AND “Training ") OR (“Cogmed” AND “Training ") OR (PSSCogReHab” AND “Training ") OR (“Cogpack” AND “Training ") OR (“mHealth” AND “Training ") OR (Cognitive Bias Modification” AND “Training ") OR (“Goal-Management” AND “ Training “)). The seven last keywords were added according to Chowdhury literature review of cognitive training in substance use disorder, as they are the identified programs used to date in the field. Inclusion criteria for the studies were as follows: (1) studies in gambling disorders (2) reporting use or efficacy data on a cognitive training intervention. There was no exclusion criterion nor language restriction. The search was conducted in September 2017. The selection of articles was double-checked (HJA and AL). The flow chart presented in Fig. 1 shows the reasons for non-including articles. A total of 9 articles were retrieved, but none could be included: 7 did not regard an intervention of cognitive training, 2 did not regard gambling disorder. A comprehensive search was also conducted in the clinicalTrial.gov database. The following terms were entered and combined as keywords: (gambling (=condition) and training OR rehabilitation OR remediation (=intervention). We screened 13 declared trials: 1 was a non-interventional study, 11 assessed for other intervention than cognitive training. One ongoing trial currently recruiting could be identified on clinicalTrial.gov

with the keyword gambling and (training or rehabilitation or remediation of modification) (NCT01528982 assessing a cognitive training intervention compared to a mindfulness based intervention). Grey literature search with keywords "cognitive training" AND gambling AND "efficacy" reported 5 first pages (50 results) on Google gave no result regarding efficacy data, but identified several projects: two ongoing or planned trials (Wiers and al. and our team Luquiens and al.), and one lab project (Yüccel and al.). The first ongoing trial involved alcohol and gambling disorders, and aimed to assess attention bias modification and motor inhibition response specific to gambling cues. The second planned trial aimed to assess a cognitive training program targeting cognitive control unspecific to gambling. We presented anticipated methodological difficulties based on available data in the other fields and particularly in substance use disorders."

D. Discussion and perspectives

Despite increasing literature regarding cognitive deficits in gambling disorder and on cognitive training in mental health, no use or efficacy data of cognitive training in gambling disorder is yet available. This lack of exploitable result is indeed a limit for a systematic search. However, as negative results from clinical trials have demonstrated to deliver valuable information (Teixeira da Silva 2015), the absence of available data on our topic is informative in itself. Numerous reviews recommend the development of cognitive training programs in gambling disorders, mainly based on existing literature on cognitive training in substance use disorders, and on the psychophysiology of the disorders considered as close to the one of substance use disorders (Chowdhury et al., 2017; Ersche et al., 2012; Grant & Chamberlain 2014; Karim & Chaudhri, 2012; Yau & Potenza, 2015), even though the evidence of efficacy of this therapeutic line is mixed in substance use disorders (Cristea, Kok et al. 2016) . The publication of a review with a close topic during the process of revision of the present article demonstrates the interest of clinicians and researchers in the field (Challet-Bouju, Bruneau et al. 2017). Studies assessing cognitive training in gambling disorder are being conducted and first results should be upcoming. This delay is an opportunity to learn from trials in close fields such as substance use disorder, in order to produce robust and rapidly applicable efficacy data on candidate programs. Existing data on cognitive training raised a number of methodological issues, which should be taken into account in the future initial trials in the field of gambling disorder.

Is cognitive training a realistic therapeutic tool in gambling disorder?

Main general challenges for cognitive training regard neuroplasticity through (1) possible limitations in underlying 'learning machinery' due to pathophysiology, (2) possibly resistant 'overlearned' maladaptive patterns of neural functioning (Vinogradov, Fisher et al. 2012).

However, the substance –free nature of gambling disorder allows being optimistic as compared to results in fields where cognitive training comes to compensate brain damages due to trauma, stroke or toxicity of a substance use. In another hand, data from cognitive training in substance use disorder and the robust evidence of cognitive impairments in gambling disorder subjects are a plausible basis for applying this treatment technique and for designing controlled studies in the field. Some studies surprisingly reported an even higher level of impairment in some executive functions and particularly in decision making in people with gambling disorder than with alcohol use disorder (Kovacs, Richman et al. 2017). Moreover, the substance-free nature of gambling addiction should give reason for particular optimism about the potential for progression through cognitive training programs. Correlation between cognitive impairments and clinical cognitive distortions retrieved in the literature reinforce this plausibility (Del Prete, Steward et al. 2017). Nonetheless, improving a specific performance related to a training session is not always sustained and does not necessarily translate in daily life functioning in an ecological transfer. Verbruggen and colleagues questioned the long-lasting potential of inhibition training on decision making while gambling. They suggested a carryover effect more than an increase of the function. This would mean that training could lead to establishment of strategies to complete a task more than restoring a skill (Verbruggen, Adams et al. 2013). However, their demonstration was based on experimental tasks in healthy volunteers. Restoring an impaired function is rather different from improving an already efficient function. Moreover, the finality of training is to improve daily life functioning, requiring the possibility of generalization of acquired skills and their ecological transfer. Several studies supported the possibility of generalization of skills trained during cognitive rehabilitation programs after the sessions, especially in early interventions, in dementia (Savage, Piguet et al. 2014) or schizophrenia (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014; Saperstein & Kurtz, 2013).

How to build a relevant cognitive training program?

There is a great temptation to build comprehensive programs covering the whole spectrum of impacted or involved neurocognitive fields in addiction. Before achieving this final goal, it could be of interest to demonstrate the efficacy of the separate components to include in a therapeutic program, and to investigate their functioning. Most assessed interventions consisted in attention bias modification, using substance-specific cues, more or less fitted to the individual. More recently, there has been being an increasing enthusiasm for cognitive control inhibition involvement in the physiopathology of addictions, and for its possible training as a therapeutic intervention (Bari & Robbins, 2013; Lubman, Yücel, & Pantelis, 2004; Morein-Zamir & Robbins, 2015; Verdejo-Garcia, 2016). Some interventions have been proposed as inhibition training, while using cues specific to the substance (Wiers, Eberl et al. 2011). However, the relevance of specific cues could be debated, as contradictory findings

were found with such programs in real life and in lab conditions (Verdejo-Garcia, 2017). Specific cues are confronted to the artificial lab-environment of the experiment (Hudson, Gough et al. 2017). In gambling, it seems that specificity for the individual of a gambling cue could be difficult to reach in an experimental design *ex vivo* (Leyton and Vezina 2012). On the contrary, It has been shown that gambling cues could "hijack" cognitive resources due to high incentive-salience (Brevers, Bechara et al. 2013). It could then be interesting to target functions without gambling cues, and then work on transfer of the acquired skills in daily life including in the gambling context. However, the feasibility of transfer of benefits from training using unspecific exercises (i.e. unrelated to the substance or behavior involved in the addictive process) is still to be documented. Emotion regulation is interlaced with executive functioning that are seen as a cognitive substrate of the adaptation (Aron, 2007; Dennis & Chen, 2007; Thoma et al., 2011). Future training programs may integrate this component during the training process (Estevez Gutierrez, Herrero Fernandez et al. 2014, Navas, Contreras-Rodriguez et al. 2017). Finally, cognitive training is a learning process; it is thus needed to integrate motivational components to optimize learning abilities. E-health and computerized programs could be a tremendous opportunity to implement cognitive training interventions, in this difficult to reach gamblers population, characterized by a high treatment gap. Modalities of implementation are still to be discussed and assessed, as guidance seems to enhance adherence in active treatment seeking addicts, but could be aversive in screened non initially treatment seeking ones (Luquiens, Tanguy et al. 2016).

A need for controlled trials

Learning from the other fields that are more advanced in cognitive training (Brooks, Wiemerslage et al. 2017), rigorous designs and control groups should be implemented in the future very first trials assessing efficacy of cognitive training programs in gambling disorder. As any time-involving strategy, the control group can't reasonability be a waiting list or any less time-involving intervention. A proper control group with similar modalities is needed in any trial assessing the efficacy of a cognitive training program. Some authors used neutral cue tasks as controls of specific cues, i.e. related to the substance or behavior (Wiers, Rinck et al. 2010); it could seem hazardous, as training unspecific to the addictive behavior is in the pipeline too. Pseudo-training may be an alternative as to ensure that the control intervention is not active e.g. an. inactive computerized program to control a candidate computerized cognitive training program.

How to assess cognitive training in gambling disorder?

Understanding of mechanisms of action of therapeutic programs requires to characterize the relationship between an individual patient's characteristics at baseline including genetic factors, developmental stage, possible neurophysiologic biosignatures, and neurocognitive profile and their ability to make and retain benefits from neuroplasticity-based cognitive

training (Vinogradov, Fisher et al. 2012). However, it is unclear if commonly used neuropsychological tasks are sensible enough to detect slight improvements expected in pathological gamblers. Demonstration of efficacy of a program should neither be limited to neuropsychological assessments, nor to clinical functioning. Neuropsychological assessments and clinical functioning have indeed been reported to be correlated, and their joined assessment could inform on mechanisms of actions of treatment strategies. For instance, in this perspective, cognitive distortions have been shown to be correlated with affect- or motivation-driven aspects of impulsivity (urgency and sensation seeking), but not with cognitive impulsivity (lack of premeditation and lack of perseverance) (Del Prete, Steward et al. 2017). Assessment of efficacy should then be transversal, randomized clinical trials should integrate neural, neuropsychological outcome alongside clinical ones and a complete characterization of patients' profiles. Moreover, resistant impairments, which do not improve after an intervention, could constitute, paradoxically, impairments to target specifically, in a perspective of increasing remission rates. Given the current debate on clinical tools to assess change in gambling behavior in clinical trials in gambling disorder, it appears interesting to assess clinically the different axes identified by the Banff consensus: measures of gambling behaviour - the net expenditure each month, the frequency with which gambling takes place, and the time spent thinking about or engaged in the pursuit of gambling each month, but also measures of problems caused by gambling in the different impacted areas of life (Walker, Toneatto et al. 2006). If the "abstinence versus moderation" debate is not as accurate in gambling disorder as in substance use disorders, it could be of interest to precisely explore the association between non-abstinent clinical outcomes and motor and cognitive inhibition, to help in interpreting neuropsychological outcomes. Time of assessments should reflect maintenance of the acquired skills and of clinical improvements, but should be long enough to take into account clinical episodic forms of gambling disorder (David Kupfer and TaskForce 2013). Combining clinical assessments and neuropsychological ones could avoid misunderstanding an improvement or a lack of improvement for the patient at a particular timepoint, and help in understanding global clinically relevant evolution.

Cognitive training: an add-on treatment or a strategy by its own?

Cognitive training, identified as self-control network training, could be dispensed in association with other strategies, particularly in those enhancing self-control. Other approaches could be associated to cognitive training: mindfulness-based therapies, identified as state-training strategies, transcranial magnetic stimulation (Tang, Posner et al. 2015), or drugs that enhance learning abilities, particularly N-acetyl-cysteine (Bullock and Potenza 2013, Skvarc, Dean et al. 2017), which is already in the therapeutic pipeline for gambling disorder. Treatment as usual and other used medical resources should be very precisely

documented, in order to avoid any interpretation bias. Personalized strategies could be drawn and will have to demonstrate efficacy. However, given the very large treatment gap in gambling disorder (Gainsbury, Hing et al. 2014), computerized cognitive training as a single and non face-to-face strategy could also be interesting on its own, and could, if effective, present an interesting cost-efficacy profile.

References

Adams, S., C. Mokrysz, A. S. Attwood and M. R. Munafo (2017). "Resisting the urge to smoke: inhibitory control training in cigarette smokers." R Soc Open Sci **4**(8): 170045.

Alvarez-Moya, E. M., C. Ochoa, S. Jimenez-Murcia, M. N. Aymami, M. Gomez-Pena, F. Fernandez-Aranda, J. Santamaria, L. Moragas, F. Bove and J. M. Menchon (2011). "Effect of executive functioning, decision-making and self-reported impulsivity on the treatment outcome of pathologic gambling." J Psychiatry Neurosci **36**(3): 165-175.

Anguera, J. A., J. Boccanfuso, J. L. Rintoul, O. Al-Hashimi, F. Faraji, J. Janowich, E. Kong, Y. Larraburo, C. Rolle, E. Johnston and A. Gazzaley (2013). "Video game training enhances cognitive control in older adults." Nature **501**(7465): 97-101.

Ashley, M. J., J. Ashley and L. Kreber (2012). "Remediation of information processing following traumatic brain injury: a community-based rehabilitation approach." NeuroRehabilitation **31**(1): 31-39.

Bickel, W. K., L. Moody and A. Quisenberry (2014). "Computerized Working-Memory Training as a Candidate Adjunctive Treatment for Addiction." Alcohol Res **36**(1): 123-126.

Bickel, W. K., R. Yi, R. D. Landes, P. F. Hill and C. Baxter (2011). "Remember the Future: Working Memory Training Decreases Delay Discounting Among Stimulant Addicts (English)." Biological psychiatry (1969) **69**(3): 260-265.

Billieux, J., G. Lagrange, M. Van der Linden, C. Lancon, M. Adida and R. Jeanningros (2012). "Investigation of impulsivity in a sample of treatment-seeking pathological gamblers: a multidimensional perspective." Psychiatry Res **198**(2): 291-296.

Boog, M., P. Hoppener, V. D. W. BJ, A. E. Goudriaan, M. C. Boog and I. H. Franken (2014). "Cognitive Inflexibility in Gamblers is Primarily Present in Reward-Related Decision Making." Front Hum Neurosci **8**: 569.

Bouchard, S., G. Robillard, I. Giroux, C. Jacques, C. Loranger, M. St-Pierre, M. Chretien and A. Goulet (2017). "Using Virtual Reality in the Treatment of Gambling Disorder: The Development of a New Tool for Cognitive Behavior Therapy." Front Psychiatry **8**: 27.

Brevers, D., A. Bechara, A. Cleeremans, X. Noël, V. S. Chandrasekhar Pammi and J. Linnet (2013). "Iowa Gambling Task (IGT): twenty years after - gambling disorder and IGT." Frontiers in Psychology **4**: 1.

Brevers, D., G. Koritzky, A. Bechara and X. Noel (2014). "Cognitive processes underlying impaired decision-making under uncertainty in gambling disorder." Addict Behav **39**(10): 1533-1536.

Brooks, S. J., K. H. Burch, S. A. Maiorana, E. Cocolas, H. B. Schioth, E. K. Nilsson, K. Kamaloodien and D. J. Stein (2016). "Psychological intervention with working memory training increases basal ganglia volume: A VBM study of inpatient treatment for methamphetamine use." Neuroimage Clin **12**: 478-491.

Brooks, S. J., C. Lochner, S. Shoptaw and D. J. Stein (2017). "Using the research domain criteria (RDoC) to conceptualize impulsivity and compulsivity in relation to addiction." Prog Brain Res **235**: 177-218.

Brooks, S. J., L. Wiemerslage, K. H. Burch, S. A. Maiorana, E. Cocolas, H. B. Schioth, K. Kamaloodien and D. J. Stein (2017). "The impact of cognitive training in substance use disorder: the effect of working memory training on impulse control in methamphetamine users." Psychopharmacology (Berl).

Bucci, P., G. Piegari, A. Mucci, E. Merlotti, M. Chieffi, F. De Riso, M. De Angelis, W. Di Munzio and S. Galderisi (2013). "Neurocognitive individualized training versus social skills individualized training: a randomized trial in patients with schizophrenia." Schizophr Res **150**(1): 69-75.

Bullock, S. A. and M. N. Potenza (2013). "Update on the Pharmacological Treatment of Pathological Gambling." Curr Psychopharmacol **2**(3): 204-211.

Challet-Bouju, G., M. Bruneau, I. Group, C. Victorri-Vigneau and M. Grall-Bronnec (2017). "Cognitive Remediation Interventions for Gambling Disorder: A Systematic Review." Front Psychol **8**: 1961.

Choi, S. W., Y. C. Shin, D. J. Kim, J. S. Choi, S. Kim, S. H. Kim and H. Youn (2017). "Treatment modalities for patients with gambling disorder." Ann Gen Psychiatry **16**: 23.

Chretien, M., I. Giroux, A. Goulet, C. Jacques and S. Bouchard (2017). "Cognitive restructuring of gambling-related thoughts: A systematic review." Addict Behav **75**: 108-121.
Cosenza, M., M. D. Griffiths, G. Nigro and M. Ciccarelli (2017). "Risk-Taking, Delay Discounting, and Time Perspective in Adolescent Gamblers: An Experimental Study." J Gambl Stud **33**(2): 383-395.
Cristea, I. A., R. N. Kok and P. Cuijpers (2016). "The Effectiveness of Cognitive Bias Modification Interventions for Substance Addictions: A Meta-Analysis." PLoS One **11**(9): e0162226.
David Kupfer and D. S. M. TaskForce (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).
Del Prete, F., T. Steward, J. F. Navas, F. Fernandez-Aranda, S. Jimenez-Murcia, T. P. Oei and J. C. Perales (2017). "The role of affect-driven impulsivity in gambling cognitions: A convenience-sample study with a Spanish version of the Gambling-Related Cognitions Scale." J Behav Addict **6**(1): 51-63.
Estevez Gutierrez, A., D. Herrero Fernandez, I. Sarabia Gonzalvo and P. Jauregui Bilbao (2014). "[Mediating role of emotional regulation between impulsive behavior in gambling, Internet and videogame abuse, and dysfunctional symptomatology in young adults and adolescents]." Adicciones **26**(4): 282-290.
Fals-Stewart, W. and S. Lucente (1994). "The effect of cognitive rehabilitation on the neuropsychological status of patients in drug abuse treatment who display neurocognitive impairment." Rehabilitation Psychology **39**(2): 75-94.
Fink, A., I. Parhami, R. J. Rosenthal, M. D. Campos, A. Siani and T. W. Fong (2012). "How transparent is behavioral intervention research on pathological gambling and other gambling-related disorders? A systematic literature review." Addiction **107**(11): 1915-1928.
Gainsbury, S. and A. Blaszczynski (2011). "A systematic review of Internet-based therapy for the treatment of addictions." Clin Psychol Rev **31**(3): 490-498.
Gainsbury, S., N. Hing and N. Suhonen (2014). "Professional help-seeking for gambling problems: awareness, barriers and motivators for treatment." J Gambl Stud **30**(2): 503-519.
Gamito, P., J. Oliveira, P. Lopes, R. Brito, D. Morais, C. Cacoete, A. Leandro, T. Almeida and H. Oliveira (2017). "Cognitive Training through mHealth for Individuals with Substance Use Disorder." Methods Inf Med **56**(2): 156-161.
Gardner, E. L. (2011). "Addiction and brain reward and antireward pathways." Adv Psychosom Med **30**: 22-60.
Goudriaan, A. E., M. Yucel and R. J. van Holst (2014). "Getting a grip on problem gambling: what can neuroscience tell us?" Front Behav Neurosci **8**: 141.
Grant, J. E., B. L. Odlaug and S. R. Chamberlain (2016). "Neural and psychological underpinnings of gambling disorder: A review." Prog Neuropsychopharmacol Biol Psychiatry **65**: 188-193.
Hudson, A., K. Gough, S. Yi, M. Stiles, P. Davis MacNevin and S. H. Stewart (2017). "Examining the effects of gambling-relevant cues on gambling outcome expectancies." International Gambling Studies **17**(2): 236-250.
Hulka, L. M., C. Eisenegger, K. H. Preller, M. Vonmoos, D. Jenni, K. Bendrick, M. R. Baumgartner, E. Seifritz and B. B. Quednow (2013). "Altered social and non-social decision-making in recreational and dependent cocaine users." Psychol Med: 1-14.
Kapsomenakis, A., P. G. Simos, G. Konstantakopoulos and D. S. Kasselimis (2018). "In Search of Executive Impairment in Pathological Gambling: A Neuropsychological Study on Non-treatment Seeking Gamblers." J Gambl Stud.
Kayser, A. S., T. Vega, D. Weinstein, J. Peters and J. M. Mitchell (2017). "Right inferior frontal cortex activity correlates with tolcapone responsivity in problem and pathological gamblers." Neuroimage Clin **13**: 339-348.
Kiluk, B. D., C. Nich and K. M. Carroll (2011). "Relationship of cognitive function and the acquisition of coping skills in computer assisted treatment for substance use disorders." Drug Alcohol Depend **114**(2-3): 169-176.
Kovacs, I., M. J. Richman, Z. Janka, A. Maraz and B. Ando (2017). "Decision making measured by the Iowa Gambling Task in alcohol use disorder and gambling disorder: a systematic review and meta-analysis." Drug Alcohol Depend **181**: 152-161.

Ledgerwood, D. M., E. S. Orr, K. A. Kaploun, A. Milosevic, G. R. Frisch, N. Rupcich and L. H. Lundahl (2012). "Executive function in pathological gamblers and healthy controls." J Gambl Stud **28**(1): 89-103.
Leyton, M. and P. Vezina (2012). "On cue: striatal ups and downs in addictions." Biol Psychiatry **72**(10): e21-22.
Limbrick-Oldfield, E. H., I. Mick, R. E. Cocks, J. McGonigle, S. P. Sharman, A. P. Goldstone, P. R. Stokes, A. Waldman, D. Erritzoe, H. Bowden-Jones, D. Nutt, A. Lingford-Hughes and L. Clark (2017). "Neural substrates of cue reactivity and craving in gambling disorder." Transl Psychiatry **7**(1): e992.
Loughead, J., M. Falcone, E. P. Wileyto, B. Albelda, J. Audrain-McGovern, W. Cao, M. M. Kurtz, R. C. Gur and C. Lerman (2016). "Can brain games help smokers quit?: Results of a randomized clinical trial." Drug Alcohol Depend **168**: 112-118.
Luquiens, A., M. L. Tanguy, A. Benyamina, M. Lagadec, H. J. Aubin and M. Reynaud (2016). "Tracking online poker problem gamblers with player account-based gambling data only." Int J Methods Psychiatr Res **25**(4): 333-342.
Mallorqui-Bague, N., I. Tolosa-Sola, F. Fernandez-Aranda, R. Granero, A. B. Fagundo, M. Lozano-Madrid, G. Mestre-Bach, M. Gomez-Pena, N. Aymami, I. Borras-Gonzalez, J. Sanchez-Gonzalez, M. Bano, A. Del Pino-Gutierrez, J. M. Menchon and S. Jimenez-Murcia (2017). "Cognitive Deficits in Executive Functions and Decision-Making Impairments Cluster Gambling Disorder Sub-types." J Gambl Stud.
Memarmoghaddam, M., H. T. Torbati, M. Sohrabi, A. Mashhadi and A. Kashi (2016). "Effects of a selected exercise programon executive function of children with attention deficit hyperactivity disorder." J Med Life **9**(4): 373-379.
Muraven, M. (2010). "Practicing self-control lowers the risk of smoking lapse." Psychol Addict Behav **24**(3): 446-452.
Navas, J. F., O. Contreras-Rodriguez, J. Verdejo-Roman, A. Perandres-Gomez, N. Albein-Urios, A. Verdejo-Garcia and J. C. Perales (2017). "Trait and neurobiological underpinnings of negative emotion regulation in gambling disorder." Addiction **112**(6): 1086-1094.
Nelson, L. A., M. Macdonald, C. Stall and R. Pazdan (2013). "Effects of interactive metronome therapy on cognitive functioning after blast-related brain injury: a randomized controlled pilot trial." Neuropsychology **27**(6): 666-679.
Noel, X., D. Brevers and A. Bechara (2013). "A neurocognitive approach to understanding the neurobiology of addiction." Current Opinion In Neurobiology **23**(4): 632-638.
Noel, X., M. Van der Linden, D. Brevers, S. Campanella, P. Verbanck, C. Hanak, C. Kornreich and F. Verbruggen (2013). "Separating intentional inhibition of prepotent responses and resistance to proactive interference in alcohol-dependent individuals." Drug Alcohol Depend **128**(3): 200-205.
Peterson, M. A., B. Patterson, B. M. Pillman and M. A. Battista (2002). "Cognitive recovery following alcohol detoxification: A computerised remediation study." Neuropsychological Rehabilitation **12**(1): 63-74.
Petry, N. M. (2001). "Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls." Psychopharmacology (Berl) **154**(3): 243-250.
Petry, N. M. (2001). "Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates." J Abnorm Psychol **110**(3): 482-487.
Rupp, C. I., G. Kemmler, M. Kurz, H. Hinterhuber and W. W. Fleischhacker (2012). "Cognitive remediation therapy during treatment for alcohol dependence." J Stud Alcohol Drugs **73**(4): 625-634.
Savage, S. A., O. Piguet and J. R. Hodges (2014). "Giving Words New Life: Generalization of Word Retraining Outcomes in Semantic Dementia." J Alzheimers Dis.
Skvarc, D. R., O. M. Dean, L. K. Byrne, L. Gray, S. Lane, M. Lewis, B. S. Fernandes, M. Berk and A. Marriott (2017). "The effect of N-acetylcysteine (NAC) on human cognition - A systematic review." Neurosci Biobehav Rev **78**: 44-56.
Smith, J. L., R. P. Mattick, S. D. Jamadar and J. M. Iredale (2014). "Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis." Drug Alcohol Depend.

Stevens, L., A. Verdejo-Garcia, A. E. Goudriaan, H. Roeyers, G. Dom and W. Vanderplasschen (2014). "Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders." J Subst Abuse Treat **47**(1): 58-72.

Tanabe, J., L. Thompson, E. Claus, M. Dalwani, K. Hutchison and M. T. Banich (2007). "Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making." Hum Brain Mapp **28**(12): 1276-1286.

Tang, Y. Y., M. I. Posner, M. K. Rothbart and N. D. Volkow (2015). "Circuitry of self-control and its role in reducing addiction." Trends Cogn Sci.

Teixeira da Silva, J. A. (2015). "Negative results: negative perceptions limit their potential for increasing reproducibility." J Negat Results Biomed **14**: 12.

Tolchard, B. (2017). "Cognitive-behavior therapy for problem gambling: a critique of current treatments and proposed new unified approach." J Ment Health **26**(3): 283-290.

van Deursen, D. S., E. Salemink, F. Smit, J. Kramer and R. W. Wiers (2013). "Web-based cognitive bias modification for problem drinkers: protocol of a randomised controlled trial with a 2x2x2 factorial design." BMC Public Health **13**: 674.

van Holst, R. J., M. van Holstein, W. van den Brink, D. J. Veltman and A. E. Goudriaan (2012). "Response inhibition during cue reactivity in problem gamblers: an fMRI study." PLoS One **7**(3): e30909.

Verbruggen, F., R. C. Adams, F. van 't Wout, T. Stevens, I. P. McLaren and C. D. Chambers (2013). "Are the effects of response inhibition on gambling long-lasting?" PLoS One **8**(7): e70155.

Verdejo-Garcia, A. (2016). "Cognitive training for substance use disorders: Neuroscientific mechanisms." Neurosci Biobehav Rev **68**: 270-281.

Vinogradov, S., M. Fisher and E. de Villers-Sidani (2012). "Cognitive training for impaired neural systems in neuropsychiatric illness." Neuropsychopharmacology **37**(1): 43-76.

Volkow, N. D., J. S. Fowler and G. J. Wang (2004). "The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies." Neuropharmacology **47 Suppl 1**: 3-13.

Walker, M., T. Toneatto, M. N. Potenza, N. Petry, R. Ladouceur, D. C. Hodgins, N. el-Guebaly, E. Echeburua and A. Blaszczynski (2006). "A framework for reporting outcomes in problem gambling treatment research: the Banff, Alberta Consensus." Addiction **101**(4): 504-511.

Wiers, R. W., C. Eberl, M. Rinck, E. S. Becker and J. Lindenmeyer (2011). "Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome." Psychol Sci **22**(4): 490-497.

Wiers, R. W., M. Rinck, R. Kordts, K. Houben and F. Strack (2010). "Retraining automatic action-tendencies to approach alcohol in hazardous drinkers." Addiction **105**(2): 279-287.

Zilverstand, A., M. A. Parvaz, S. J. Moeller and R. Z. Goldstein (2016). "Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms." Prog Brain Res **224**: 285-304.

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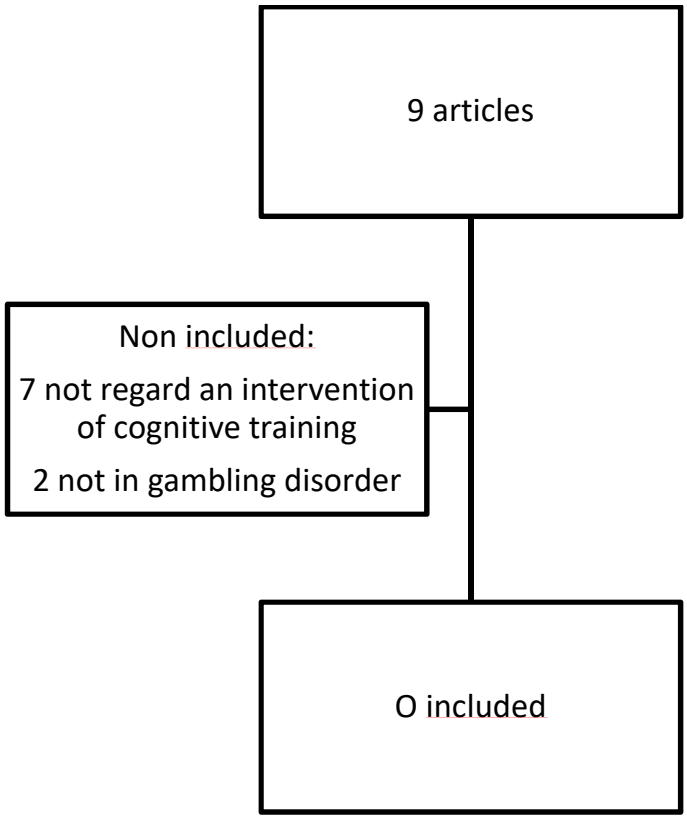

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Table 1. Methodological challenges in the development and efficacy assessment of cognitive training programs in gambling disorder

• **Choice of cognitive function targeted: multiple functions, one function in isolation. Can a cognitive function be trained in isolation?**
• **Choice of cue and environment of training: specific, neutral. What it the level of specificity of gambling cues?**
• **How should training be provided?? Individual vs. group? Supervised?**
• **How to integrate emotional components affecting cognitive abilities?**
• **Choice of endpoints: clinical, neuropsychological, neuro-imaging**
• **Are commonly used neuropsychological tasks sensible enough to pick up cognitive improvements?**
• **Follow up duration: what is a sustained effect? How to take into account the episodic types of gambling?**
• **What should be the control group? Can a neutral cue be used as a relevant control of a specific cue? What if the neutral cue is active?**
• **Should cognitive training be conceived as an add-on intervention? With what other treatment could the training be associated**

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