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1 Cognitive training: a new avenue in gambling disorder management?
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30 **A. Current therapeutics in gambling disorder**

31 Addictive disorders represent a major challenge in public health, with a considerable human
32 and social burden. The recent gathering in classification of disease of addiction with and
33 without substance (i.e. behavioral addiction) allowed the recognition of gambling disorder as
34 an addictive disorder ("Non-Substance-Related Disorders [312.31 (F63.0)]" within
35 "substance- Related and Addictive Disorders") (David Kupfer and TaskForce 2013). No
36 medication is currently approved for its treatment. Aside mutual help groups, most
37 interventions are motivational interventions, cognitive behavioral therapies (CBT), or a
38 combination of both (Fink, Parhami et al. 2012, Choi, Shin et al. 2017). CBT consist in the
39 analysis of problem behaviors, and corresponding thoughts and feelings. This analysis is
40 variably associated with exposure techniques, thoughts restructuring (Chretien, Giroux et al.
41 2017), emotion regulation, dealing with high-risk situations and avoidance of the problem
42 behavior, building a relapse plan. Mindfulness-based therapies aim at fostering attention and
43 self-control, and at decreasing discomfort inherent to craving and sensitivity to cues
44 (Tolchard 2017). A broad panel of modalities to dispense psychotherapeutic interventions in
45 gambling disorder has been reported, including self-help manuals, groups interventions, face
46 to face intervention, online interventions, virtual reality (Bouchard, Robillard et al. 2017).
47 Therapeutic interventions still have demonstrated a weak to moderate effect size in
48 published trials (Gainsbury and Blaszczynski 2011). Several methodological issues have
49 limited the relevance of previous CBT trials among problem gamblers (Fink, Parhami et al.
50 2012). In particular, these kind of psychological interventions are demanding as regarding
51 cognitive abilities (Kiluk, Nich et al. 2011). High impact of cognitive functioning and abilities in
52 problem gamblers could be barriers to the acquisition of coping skills from cognitive
53 behavioral therapies.

54

55

56 **B. Cognitive deficits in gambling disorder**

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

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

99 to state on non-reward based inhibition impairments in problem gamblers (Boog,
100 Hoppener et al. 2014). Sensitivity to reward has also been extensively studied. At
101 the clinical level, hypersensitivity for large monetary gains, which might reflect
102 hypersensitivity of reward system, has been described (Brevers, Koritzky et al. 2014).
103 Neurocognitive reward sensitivity could be related to self-reported overspending behavior in
104 pathological gambling (Alvarez-Moya, Ochoa et al. 2011). Other authors reported
105 differential sensitivity to monetary versus non-monetary rewards anticipation and
106 outcome in pathological gambling as compared to healthy controls. Neuroimaging
107 studies in substance use disorders suggest different neural effects between different
108 types of psychotherapeutic interventions and their components. These effects differ
109 according to their neurofunctional targets, and in particular the use of cue involving
110 the substance, monetary or non-monetary rewards.. It has been shown that these
111 different effects according to therapeutic strategies have however common targets:
112 the inhibitor control network, and the reward system.. (Zilverstand, Parvaz et al.
113 2016). Involved brain areas were the striatum, the nucleus accumbens, the ventral
114 tegmental area, the inferior frontal gyrus and the dorsal anterior cingulated cortex
115 (Zilverstand, Parvaz et al. 2016). No such neuro-imaging data are available to
116 document the impact of psychotherapies in gambling disorder, however similar brain
117 areas have been demonstrated to be implicated in the gambling disorder process
118 (Grant, Odlaug et al. 2016, Limbrick-Oldfield, Mick et al. 2017). Connectivity between
119 the reward system and the inhibitory control network has been repeatedly
120 demonstrated to be implicated in the addiction and the remission processes and in
121 the response to a medication in gambling disorder (Kayser, Vega et al. 2017).
122 Goudriaan and her team proposed to further explore relations between inhibitory
123 control, cue reactivity and motivational processes, underlining the differential
124 responses found on executive processes between gambling cues and neutral cues in
125 pathological gamblers (van Holst, van Holstein et al. 2012). These authors defined 3
126 domains impacted in gambling disorders that could be targets for cognitive training:
127 self-control, a concept including inhibition and impulsivity, cue-reactivity and reward
128 sensitivity (Goudriaan, Yucel et al. 2014).

129

130 **C. Cognitive training**

131 *Definition*

132 Cognitive rehabilitation aims to: (a) inform and provide psycho-education about cognitive
133 functions, and the problems as well as the strengths of patients, (b) improve components of
134 executive functions when possible through relearning, (c) compensate impairments if
135 relearning of functions is impossible in the case of loss of cognitive skills, (d) training people
136 to use adaptive methods for increasing independence in activities of daily living skills (Chung,
137 Pollock, Campbell, Durward, & Hagen, 2013; Koehler, Wilhelm, & Shoulson, 2012).
138 Respectively to these objectives, mechanisms of action of rehabilitation regard restoring the
139 functional loss through improving cognitive functions and stimulation of neuronal growth. If
140 restoring is not reachable, rehabilitation regards compensating or adapting to functional loss.
141 These strategies imply advanced psycho-education and collaboration with the affected
142 subject. They develop self-awareness and self-regulation of behavior.
143 Cognitive training (also called “brain training”) is currently used to improve fluid intelligence
144 (“Gf”) (and its components such as working memory, inhibitory control, etc.) in reason of its
145 supposed malleability and its relation to daily activities (Jaeggi, Buschkuhl, Jonides, &
146 Shah, 2011). Indeed, the purpose of these kind of training is to obtain transfer to non-
147 experimental and ecological situations (Karbach & Kray, 2009; Klingberg, 2010). Cognitive
148 training is referenced in brain damaged patients (Ashley, Ashley et al. 2012, Nelson,
149 Macdonald et al. 2013), aging (Anguera, Boccanfuso et al. 2013), Attention Deficit/
150 Hyperactivity Disorder (Memarmoghaddam, Torbati et al. 2016), and in some psychiatric
151 conditions, like schizophrenia (Bucci, Piegari et al. 2013) or major depression (Motter,
152 Devanand, Doraiswamy, & Sneed, 2015).

153

154 *Cognitive training in substance use disorders*

155 Few cognitive training programs have been tested and published in addictive disorders.
156 Verdejo-Garcia identified in his review 4 targets for cognitive training in substance use
157 disorders (Verdejo-Garcia 2016): cognitive bias, response inhibition, working memory, and
158 goal-directed behavior. The training trials recruited subjects with alcohol use disorder,
159 methamphetamine use disorder, stimulant use disorder or opiate use disorder. Most studies
160 used computerized programs, which are likely to be cost-effective. An early trial assessed
161 the efficacy of a 2-hours session of computer assisted cognitive training per week over a 6-
162 month period in patients with various substance use disorders with cognitive deficits: cocaine
163 (29 subjects, 40%), alcohol (18 subjects, 25%), opioids (12 subjects, 17%), stimulants (3
164 subjects, 4%), and cannabis (3 subjects, 4%) (Fals-Stewart and Lucente 1994). The program
165 remediated deficits in attention, motor skills, spatial orientation, and working memory. The
166 authors concluded that participants in the cognitive training group demonstrated a shorter
167 time to cognitive recovery during the first 2 months of treatment. Another controlled trial
168 assessed the efficacy of a 15 one-hour sessions computerized training program, in thirty-

169 eight recently detoxified alcoholics (Peterson, Patterson et al. 2002). The program targeted
170 memory, visual-motor coordination, and visual-spatial skills. The trial showed no efficacy on
171 addiction recovery despite improvement in cognitive performance following detoxification.
172 More recently, Bickel and colleagues conducted a controlled trial in 27 patients with a
173 stimulant use disorder assessing the efficacy of a training program targeting working
174 memory and found that rates of discounting of delayed rewards were significantly reduced
175 among subjects who benefited from the working memory training (Bickel, Yi et al. 2011).
176 Rupp and collaborators assessed the efficacy of a training program aiming attention,
177 executive function, and memory in 20 alcohol-dependent patients (Rupp, Kemmler et al.
178 2012). They reported a significant improvement in attention/executive function and memory
179 domains and in clinical outcomes (i.e. well-being and craving). Wiers and collaborators have
180 led several trials on alcohol-dependent subjects and heavy drinkers, targeting attention bias.
181 They reported that four brief sessions of experimental Cognitive Bias Modification, that
182 preceded regular inpatient treatment in 214 alcoholic inpatients, could change patients'
183 approach bias into an avoidance bias for alcohol. Patients trained to make avoidance
184 movements (i.e. pull for approaching and push for avoidance) in response to alcohol pictures
185 showed better treatment outcomes at one year follow-up (Wiers, Eberl et al. 2011). This
186 team is currently recruiting in another trial assessing web-based cognitive bias modification
187 for problem drinkers and gamblers (van Deursen, Salemink et al. 2013), with no available
188 data to date. A team from South Africa reported a subjective improvement of impulsivity in a
189 pilot study in methamphetamine users after a computerized cognitive training program
190 targeting working memory, with self-reported measures only and without a non-training
191 computer-based control group (Brooks, Wiemerslage et al. 2017), and changes in brain
192 volume after the same program, with no patient controlled group (Brooks, Burch et al. 2016)
193 Despite the robust documentation of inhibition deficit in addictive disorders, very few data are
194 available on the efficacy of cognitive training tasks or programs targeting inhibition skills.. In
195 a pragmatic trial, it has been found that practicing a non-specific task of self-control (i.e.
196 avoiding sweets and tightening a handgrip) could prevent relapse in smokers (Muraven
197 2010). More recently, Gamito and colleagues found, in 14 male heroin addicts, consistent
198 improvements in cognitive functioning between baseline and follow-up assessments,
199 especially for executive functions processes, sustained attention, decision making, cognitive
200 flexibility, as well as verbal memory and depressive symptoms (Gamito, Oliveira et al. 2017).
201 Loughead and colleagues found no between-group difference in 213 adult treatment-seeking
202 smokers randomized to receive, in addition of nicotine patch therapy, 12 weeks of either
203 computerized cognitive training program targeting working memory, attention, and response
204 inhibition, or computerized relaxation (Loughead, Falcone et al. 2016). Another trial studied
205 immediate effects of an inhibition training task. The active group was required to repeatedly

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

210

211

212 *Cognitive training in gambling disorder*

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

220 *Systematic search*

221 We conducted a systematic review of literature following PRISMA standards (Liberati et al.,
222 2009). A comprehensive search of the PubMed/MEDLINE database was conducted. The
223 following terms were entered and combined as keywords : ((gambling OR gambler OR
224 gamblers) AND (addiction OR disorder OR problem OR pathological) AND ("cognitive
225 training" OR "cognitive rehabilitation" OR "cognitive bias modification" OR ("inhibition" AND
226 training") OR ("working memory" AND "training")OR ("goal-directed" AND "training") OR
227 ("Go/No-Go" AND "Training ") OR ("Cogmed" AND "Training ") OR (PSSCogReHab" AND
228 "Training ") OR ("Cogpack" AND "Training ") OR ("mHealth" AND "Training ") OR (Cognitive
229 Bias Modification" AND "Training ") OR ("Goal-Management" AND " Training ")). The seven
230 last keywords were added according to Chowdhury literature review of cognitive training in
231 substance use disorder, as they are the identified programs used to date in the field.
232 Inclusion criteria for the studies were as follows: (1) studies in gambling disorders (2)
233 reporting use or efficacy data on a cognitive training intervention. There was no exclusion
234 criterion nor language restriction. The search was conducted in September 2017. The
235 selection of articles was double-checked (HJA and AL). The flow chart presented in Fig. 1
236 shows the reasons for non-including articles. A total of 9 articles were retrieved, but none
237 could be included: 7 did not regard an intervention of cognitive training, 2 did not regard
238 gambling disorder. A comprehensive search was also conducted in the clinicalTrial.gov
239 database. The following terms were entered and combined as keywords: (gambling
240 (=condition) and training OR rehabilitation OR remediation (=intervention). We screened 13
241 declared trials: 1 was a non-interventional study, 11 assessed for other intervention than
242 cognitive training. One ongoing trial currently recruiting could be identified on clinicalTrial.gov

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

254

255 **D. Discussion and perspectives**

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

275 *Is cognitive training a realistic therapeutic tool in gambling disorder?*

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

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

304 *How to build a relevant cognitive training program?*

305 There is a great temptation to build comprehensive programs covering the whole spectrum of
306 impacted or involved neurocognitive fields in addiction. Before achieving this final goal, it
307 could be of interest to demonstrate the efficacy of the separate components to include in a
308 therapeutic program, and to investigate their functioning. Most assessed interventions
309 consisted in attention bias modification, using substance-specific cues, more or less fitted to
310 the individual. More recently, there has been being an increasing enthusiasm for cognitive
311 control inhibition involvement in the physiopathology of addictions, and for its possible
312 training as a therapeutic intervention (Bari & Robbins, 2013; Lubman, Yücel, & Pantelis,
313 2004; Morein-Zamir & Robbins, 2015; Verdejo-Garcia, 2016). Some interventions have been
314 proposed as inhibition training, while using cues specific to the substance (Wiers, Eberl et al.
315 2011). However, the relevance of specific cues could be debated, as contradictory findings

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

336 *A need for controlled trials*

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

348 *How to assess cognitive training in gambling disorder?*

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

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

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

383 Cognitive training, identified as self-control network training, could be dispensed in
384 association with other strategies, particularly in those enhancing self-control. Other
385 approaches could be associated to cognitive training: mindfulness-based therapies, identified
386 as state-training strategies, transcranial magnetic stimulation (Tang, Posner et al. 2015), or
387 drugs that enhance learning abilities, particularly N-acetyl-cysteine (Bullock and Potenza
388 2013, Skvarc, Dean et al. 2017), which is already in the therapeutic pipeline for gambling
389 disorder. Treatment as usual and other used medical resources should be very precisely

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

395

396

397

398

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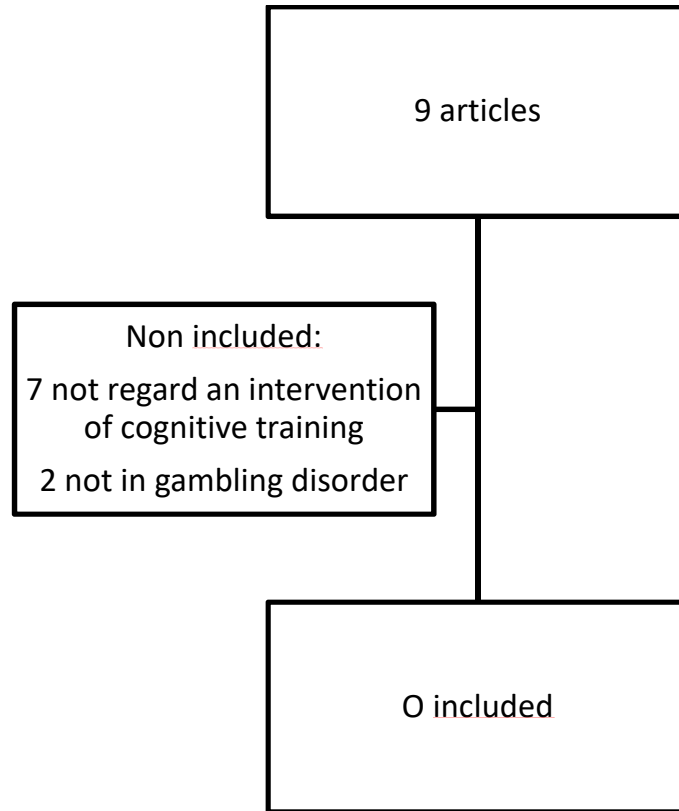
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593 Figure 1: Pubmed flow chart



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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 is 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**
-