26 Cognitive Functions in Substance-Related and Addictive Disorders

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26.1 Introduction

Substance-related and addictive disorders (SRADs), including alcohol, cannabis, gambling, and stimulant use disorders, are characterized by maladaptive behaviour or dysfunctional use of a substance that leads to clinically distressing consequences (e.g. craving, health issues, interference with work, school, or personal life) [1]. SRADs are difficult to treat, and relapse remains a big issue despite available pharmacological and behavioural treatments. Crucially, cognitive deficits (e.g. cognitive biases, deficits in executive functions) can predict relapse [2]. Hence, improving cognitive functions is a promising therapeutic option for dealing with craving and relapse [2]. Cognitive deficits can be present before the onset of SRADs and worsen with chronicity [3]. Yet, not all patients with SRADs present the same cognitive profile, as they can vary across diagnoses and as a function of comorbidities [2]. More specifically, a meta-analysis found that patients with alcohol and stimulant use disorders particularly present impaired cognitive flexibility; patients with cannabis and 3,4-methylenedioxy-methamphetamine (MDMA) use disorders predominantly display impairments in complex planning and processing speed; patients with opioid use disorder mostly demonstrate reasoning impairments, and patients with cannabis and methamphetamine use disorders mainly show memory deficits [4].

Within this context, transcranial current stimulation (tCS) over the dorsolateral prefrontal cortex (DLPFC) has been successfully used to strengthen cognitive functions [5–14] and help patients resist craving and avoid relapse. Given such evidence, an overview of which cognitive functions have been successfully improved in patients with SRADs can inform clinical practice and help develop new interventions. Hence, this chapter reviews studies that examined tCS-induced effects on cognitive

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functions relevant to SRADs, namely, cognitive bias and executive functions. The relationship between cognitive functions and craving, mood, and stress is also discussed. All included studies are sham-controlled, randomized, blinded, and used transcranial direct current stimulation, unless otherwise stated (Table 26.1).

26.2 tCS Effects in Cognitive Functions in SRADs

Several studies assessed the effects of tCS on cognitive functions in SRADs. These can be divided into two main categories: studies on implicit cognitive functions, for example, cognitive bias, and studies on explicit cognitive functions, for example, executive functions (see Fig. 26.1; Table 26.1).

26.2.1 tCS Effects on Cognitive Biases in SRADs

Some patients with SRADs are aware that their addictive behaviour is detrimental, yet they still carry it out despite the negative consequences. One way to explain this behaviour is by taking into account implicit cognitive functioning such as cognitive biases. Cognitive biases are automatic, implicit, and favourable processing of certain stimuli (e.g. external cues) over others [15]. Two major forms are approach bias and attentional bias. Approach bias happens when patients are quicker to approach rather than avoid cues [15]. Attentional bias occurs when patients display biased attention towards cues, which can increase craving [16]. Seven studies assessed the effects of tCS on cognitive biases [5, 6, 13, 14, 17–19] in alcohol and methamphetamine users. Four of these studies found significant reductions in cognitive biases when targeting the bilateral DLPFC [5, 6, 13, 14], as well as the DLPFC and shoulder [6]. In particular, two studies found reduced approach biases in alcohol users when placing the anode over the right and cathode over the left DLPFC [5] and vice versa [13]. Also, one of these studies combined tCS with a cognitive bias modification protocol [13]. In addition, one study found decreased attentional biases in tobacco smokers when patients received real transcranial alternating current stimulation (tACS) paired with attentional bias modification as compared to sham tACS with attentional bias modification training, as shown by decreased time observing smoking-related stimuli measured with an eye tracker [14]. Further, a single study reported decreased attentional bias towards drug cues in abstinent, treatment-seeking patients with methamphetamine use disorder [6]. Patients performed a probe detection task before and after they received two 13-min tCS sessions. Patients were randomly assigned to one of six groups with different electrode montages: (1) anode over the left DLPFC, cathode over the right shoulder; (2) anode over the right DLPFC, cathode over the left shoulder; (3) anode over the left DLPFC, cathode over the right supraorbital ridge; (4) anode over the right DLPFC, cathode over the left supraorbital ridge; and (5) anode over the left DLPFC, cathode over the right DLPFC. Sham condition consisted of electrodes over the right and left DLPFC. Of these, two groups displayed reduced attentional bias towards cues as measured by reaction times, that is, one group receiving anodal and cathodal transcranial direct current stimulation (tDCS) over the left and right DLPFC, respectively, and one group receiving anodal and cathodal tDCS over the left DLPFC and the shoulder, respectively.

26.2.2 tCS Effects on Executive Functions in SRADs

Higher order cognitive functions such as executive functions are believed to be impaired in SRADs [2, 3]. Some researchers purport that patients with SRADs have an imbalance between implicit and explicit processes, in which executive functions fail to control implicit urges. In line with this, a series of studies attempted to increase cognitive control to reduce addictive behaviour. Several studies have assessed the effects of tCS in SRADs on a wide range of executive functions, such as cognitive flexibility, decision-making, working memory, self-regulation, and selective attention (see Fig. 26.1; Table 26.1).

Table 26.1 Transcranial current stimulation can modulate several cognitive functions in substance-related and addictive disorders

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Cognitive bias							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10 Hz, 2 mA 30 min	N/A	N/A	Observation of smoking-related and neutral stimuli with eye tracking	↓ amount of time looking at smoking-related pictures
Vanderhasselt, 2020 [5]	Randomized Double-blind Sham-controlled Crossover (37)	Alcohol	1 session/condition 2 mA 20 min	R DLPFC	L DLPFC	Rewarded Go/No-Go	↓ reward-triggered approach bias
Claus, 2019 [18]	Randomized Double-blind Sham-controlled 2 × 2 factorial (79)	Alcohol	4 sessions (once a week for 4 consecutive weeks)[a] 2 mA 2 × 10 min	R IFG	L upper arm	Approach Avoidance-Task	No significant effect
Den Uyl, 2018 [17]	Randomized Double-blind Sham-controlled 2 × 2 factorial (83)	Alcohol	4 sessions over 1 week[a] 2 mA 20 min	L DLPFC	R DLPFC	Visual probe task Implicit Association Task	No significant effect
Shahbabaie, 2018 [6]	Randomized Double-blind Sham-controlled Parallel (90)	Methamphetamine	1 session 2 mA 2 × 13 min	L DLPFC	R shoulder or R DLPFC^ Other montages were used but were not associated with significant effects on attentional bias.	Probe detection task	↓ attentional bias towards drug cues

(continued)

Table 26.1 (continued)

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Den Uyl, 2017 [13]	Randomized Double-blind Sham-controlled Parallel (91)	Alcohol	4 sessions over 1 week[a] 2 mA 20 min	L DLPFC	R DLPFC	Approach avoidance task	↓ approach bias
Den Uyl, 2016 [19]	Randomized Double-blind Sham-controlled 2 × 2 factorial (78)	Alcohol	3 sessions over 3 or 4 days[a] 1 mA 15 min	L DLPFC	R supraorbital area	Approach avoidance task Implicit association task	No significant effect
Cognitive flexibility							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Wisconsin Card Sorting Task	↓ perseverative errors ↑ completed categories
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Wisconsin Card Sorting Task	↓ perseveration errors
Decision-making							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10 Hz, 2 mA 30 min	N/A	N/A	Delay Discounting task	↓ percent of immediate choices
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Balloon Analog Risk Task	↓ adjusted value ↓ maximum pumping
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Iowa Gambling Task	↑ net score

Gorini, 2014 [9]	Randomized Single-blind Sham-controlled Crossover (18)	Cocaine	1 session/condition 1.5 mA 20 min	L/R DLPFC	L/R DLPFC	Game of Dice Task Balloon Analog Risk Task	↓ average of safe bets (anode over L DLPFC) ↑ average of safe bets (anode over R DLPFC) ↓ adjusted average pumps
Fecteau, 2014 [10]	Randomized Quadruple-blind Sham-controlled Crossover (12)	Tobacco	5 daily sessions/ condition 2 mA 30 min	R DLPFC	L DLPFC	Ultimatum Game	↑ rejected offers of cigarettes
Pripfl, 2013 [11]	Counterbalanced Sham-controlled Crossover (18)	Tobacco	1 session/condition .45 mA 15 min	L/R DLPFC	L/R DLPFC	Cold Columbia Card Task and Hot Columbia Card Task	↓ number of cards chosen in risky gamble (anode L DLPFC/cathode R DLPFC) ↓ number of cards chosen in risky gamble (anode R DLPFC/cathode L DLPFC)
Boggio, 2010 [25]	Randomized Double-blind Sham-controlled Parallel (25)	Cannabis	1 session 2 mA 15 min	L/R DLPFC	L/R DLPFC	Risk Task	↑ choice of more risky prospects
Self-regulation							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Go/No-Go	↓ reaction time ↑ accuracy go trials ↑ accuracy no-go trials
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	Flanker Task	No significant effect
Witkiewitz, 2019 [31]	Randomized Double-blind Sham-controlled Parallel (84)	Alcohol	Variable number of sessions[a,b] 2 mA 30 min	R IFG	L upper arm	Stop signal reaction time task	No significant effect

(continued)

Table 26.1 (continued)

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Lee, 2018 [12]	Open-label Single-arm (15)	Internet gaming	3 sessions a week for 4 weeks 2 mA 30 min	L DLPFC	R DLPFC	Brief self control scale	↑ self-control
Selective attention							
Xu, 2013 [33]	Counterbalanced Single-blind Sham-controlled Crossover (24)	Tobacco	1 session/condition 2 mA 20 min	L DLPFC	R supraorbital area	Visual attention task	No significant effect
Working memory							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	N-back	↓ response time ↑ accuracy
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	N-back	No significant effect
Overall executive function							
da Silva, 2013 [34]	Randomized Sham-controlled Parallel (13)	Alcohol	One session per week for 5 weeks 2 mA 20 min	L DLPFC	R supradeltoid area	Frontal Assessment Battery	No significant effect
Klauss, 2014 [35]	Randomized Double-blind Sham-controlled Parallel (33)	Alcohol	2 daily sessions for 5 consecutive days 2 mA 13 min	R DLPFC	L DLPFC	Frontal Assessment Battery	No significant effect

Some articles appear more than once since they measured more than one cognitive function

DLPFC dorsolateral prefrontal cortex, *IFG* inferior frontal gyrus, *VMPFC* ventromedial prefrontal cortex, *L* left hemisphere, *R* right hemisphere, ↑ increase, ↓ decrease

[a]Some or all subjects received a behavioural intervention as well

[b]Subjects participated in a rolling group mindfulness-based relapse prevention while receiving either active or sham tDCS; those in the active and sham groups attended 4.32 and 3.78 sessions, respectively

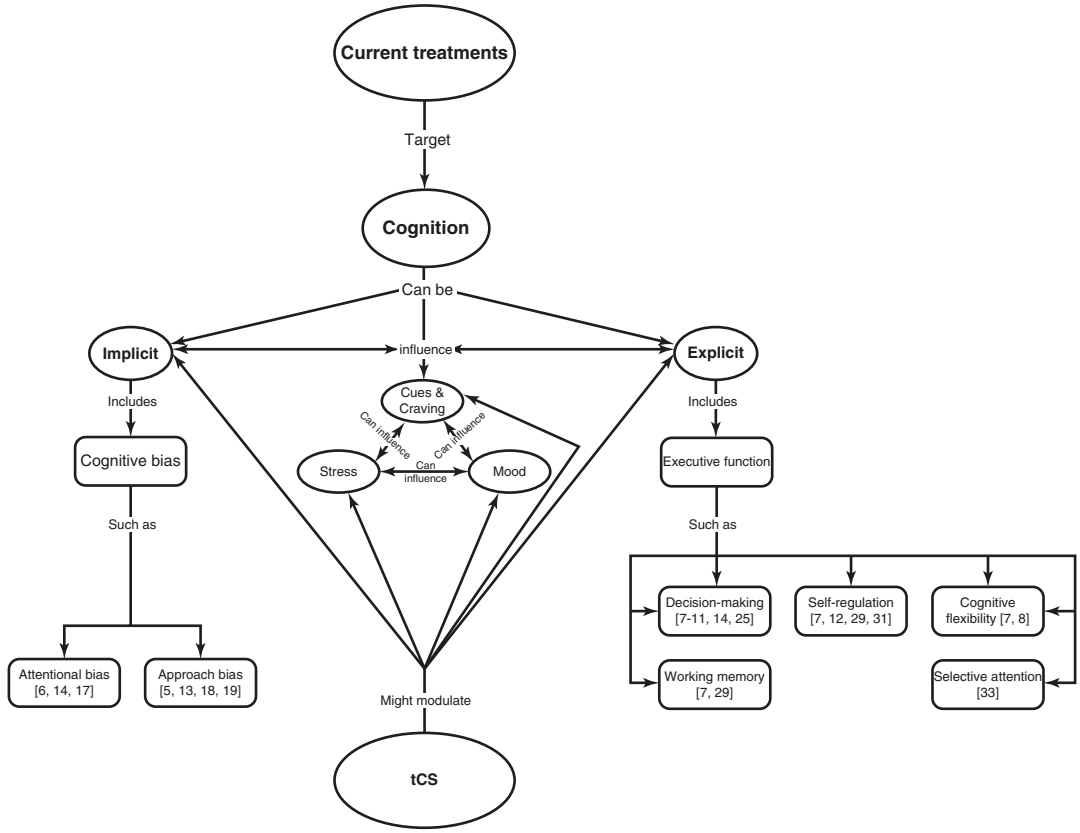

Fig. 26.1 Transcranial current stimulation and current treatments might be used to target implicit as well as explicit cognitive functions in substance-related and addictive disorders. Some other processes might be worth targeting as well, such as craving, mood, and stress, since they can influence cognitive functions and vice versa

Cognitive flexibility, also known as set-shifting, reflects the ability to adapt to different responses or situations [20]. Measuring cognitive flexibility can be a useful marker of cognitive control and possibly compulsivity [21]. Two studies reported improved cognitive flexibility following tCS over the DLPFC (anode over the left, cathode over the right DLPFC) in patients with methamphetamine use disorder [7] and gambling disorder (anode over the right, cathode over the left DLPFC) [8]. More specifically, patients showed decreased perseveration errors and/or completed categories on the Wisconsin Card Sorting Task [22].

Decision-making encompasses evaluating potential outcomes and selecting the most appropriate option [23]. This ability can be impaired in patients with SRADs, in that they show a tendency to choose immediate rewards (e.g. drug or monetary rewards) despite the possible detrimental consequences [24]. Up to now, six studies examined the effect on decision-making of tCS over the bilateral DLPFC across different SRADs, including cocaine [9], gambling [8], methamphetamine [7], tobacco [10, 11, 14], and cannabis [25] use disorders. Some studies applied the anode and cathode over the right and left DLPFC [8, 10], and vice versa [7], whereas some used both montages [9, 11, 25], and one used tACS to target both DLPFCs [14]. The first six studies reported improvements in various measures of decision-making (e.g. Balloon Analog Risk Task, Iowa Gambling Task, Game of Dice Task, Ultimatum Game, Columbia Card Task, Delay Discounting Task). The last study reported increased risky choices among patients with can-

nabis use disorder [25]. Nonetheless, this study demonstrated that these patients display different decision-making processes as compared to healthy individuals for the same task [26].

Working memory refers to the ability to store and use short-term information [3, 27] which can influence other processes, such as decision-making. For instance, working memory training decreases delay discounting in patients with stimulant use disorder [28]. Two studies evaluated the effects of tCS on working memory in patients with SRADs. The first one reported decreased response time and increased accuracy on the N-Back Task by applying tCS over the DLPFC (anode over the left and cathode over the right DLPFC) in methamphetamine use disorder [7]. The second study (which placed the electrodes over the ventromedial PFC and the DLPFC with reversed polarity) did not find significant effects on the N-Back Task [29].

Self-regulation reflects the ability to maintain ideal motivational, emotional, and cognitive arousal, including inhibition and self-control [27]. Inhibition is the ability to control actions, thoughts, behaviours, and/or emotions to overcome internal (e.g. craving) or external (e.g. cue-induced) desire [27]. Self-control reflects the ability to resist temptations and hastiness [27]. Low self-control is a hallmark of SRADs [1] as it may predispose individuals to the inability to control, reduce, or stop the addictive behaviour [30]. Four studies evaluated tCS-induced effects on response inhibition [7, 29, 31] and self-control [12]. Regarding response inhibition, one study applied tCS over the DLPFC (anode over the left DLPFC, cathode over the right DLPFC) and reported significantly increased accuracy of trials and decreased reaction time on the Go/No-Go task [7]. The other two studies were conducted in patients with tobacco use disorder [29] and heavy drinkers (98.9% of individuals displayed alcohol use disorder) [31] but they did not report significant tCS-induced effects. To note, one of these studies combined tCS with a mindfulness-based relapse prevention [31]. The effects of tCS on self-control were evaluated in a prospective study on patients with internet gaming disorder [12]. This was a single-arm, open-label study in which patients received 12 active tCS sessions (anode over the left and cathode over the right DLPFC) three times a week for 4 weeks. Patients displayed increased self-control, which correlated with decreased severity and time playing games as assessed by the Brief Self-Control Scale [12]. Interestingly, the tCS regimen was followed by a partial alleviation of the asymmetry of glucose metabolism between the two DLPFCs. Although speculative, this may reflect a better communication between the two DLPFCs, which could lead to increased self-control. Despite the promising results, randomized, sham-controlled studies are necessary to draw further conclusions.

Selective attention is demonstrated by the ability to maintain attentional focus on the environment [27]. This function is closely related to working memory and attentional biases, since both require holding attention for some time [15, 27]. In SRADs, selective attention predicts the motivation to engage in treatment [32]. Work by Xu and collaborators [33] found no effect of tCS on selective attention in patients with tobacco use disorder. The study used anodal and cathodal tCS over the left DLPFC and the right supraorbital area, respectively. The authors discussed that this may be due to spurious factors such as the fact that patients were abstinent overnight, which might influence tCS-induced effects on cortical excitability.

Two studies evaluated the effects of tCS on overall executive functions [34, 35], as assessed by the Frontal Assessment Battery, in patients with alcohol use disorder. Although the studies used different montages, neither of them found significant effects. Nevertheless, some limitations of the studies should be mentioned. For one, one study presented differences in the baseline amount of drinking between the active and sham groups [34]. Moreover, both studies had small sample sizes, which may reflect a lack of statistical power.

26.2.3 tCS Effects on Craving, Mood, and Stress in SRADs

Craving, mood, and stress also play a major role in SRADs. They can influence cognition and can be modulated by tCS [36] (see Fig. 26.1).

Craving is a complex process where individuals display a powerful urge or desire for a substance or an addictive behaviour (e.g. gambling, internet gaming) [1]. Craving can be triggered by external cues (e.g. a person, a place, or an object), as well as internal signals, such as mood or stress [37]. It is believed to play a central role in SRADs and constitutes one of the diagnostic criteria in the DSM-5 [1]. Several clinical studies confirmed that tCS over the bilateral DLPFC can decrease craving in SRADs (for reviews, see [36, 38]). Yet, it remains to be seen whether this effect is due to a direct impact of the stimulation on craving or to an indirect effect which is secondary to an improvement of cognitive control [2].

Mood can also influence SRADs, since it can reinforce addictive behaviour [39]. For instance, anxious or depressive moods can influence cognitive functions such as self-control or decision-making and trigger craving and relapse. Therefore, improving mood might be one way to improve cognitive control to resist substances. Some evidence points to the effectiveness of tCS in improving mood in patients with SRADs [33, 40]. Two studies on tobacco use disorder found reduced negative affect following (1) anodal stimulation over the right (but not the left) DLPFC and cathodal stimulation over the right DLPFC [40] and (2) anodal stimulation over the left DLPFC and cathodal stimulation over the right supraorbital area [33]. In both studies, there were differences neither in craving, nor in cigarette consumption. To note, patients were abstinent for at least 6 [40] or 10 [33] hours, possibly suggesting the pertinence of testing in sated patients. Further, a preliminary study reported that tCS increased the perception of the quality of life in patients with online gaming disorder [12] (the details of this study are described in Table 26.1 as well as in a previous section about self-control).

Stress is a psychological and phenomenological experience accompanied by a specific physiological response [41]. Stress is purported to play a role in different stages of SRADs, from the initiation of the addictive behaviour to its relapse [41]. Both stress and addictive disorders are thought to share a common neurophysiology, including a disrupted hypothalamic-pituitary-adrenal axis, as well as disrupted cognitive functions (e.g. selective attention, decision-making). In turn, both stress and addictive disorders may influence mood and cue reactivity, thereby increasing craving and probability of relapse. Furthermore, withdrawal symptoms themselves can cause stress for the individual. Thus, it is important to provide stress-coping strategies for patients with SRADs. Some evidence indicates that one session of active tCS over the DLPFC (anode over left DLPFC; cathode over right DLPFC), as compared to sham, can prevent a stress response (e.g. cortisol level) and decrease anxiety in healthy individuals that undergo psychosocial stress [42]. It remains to be seen whether tCS may be beneficial to stress reduction also in patients with SRADs.

26.3 Discussion

Taken together, there are some trends that allow us to observe a general picture. First, targeting the bilateral DLPFC appears to be the most effective tCS approach [5–10, 12–14], regardless of anode or cathode placement (see Table 26.1). This might suggest the importance of location and not laterality in SRADs [36], at least for cognitive functions. Second, decision-making was the most improved function across a variety of SRADs (tobacco, methamphetamine, gambling, cocaine use disorders, but not cannabis use disorder), which all targeted the bilateral DLPFC. Hence, there appears to be a link between targeting the

DLPFCs and ameliorated decision-making. One possible explanation is that tCS modulates the interhemispheric balance between the two DLPFCs that is needed for decision-making functions [43]. It might be interesting for future studies to examine any possible underlying mechanisms (e.g. using fMRI). Also, it might be worth examining whether tCS can modulate other cognitive functions that are impaired across different SRADs (e.g. cognitive flexibility in alcohol and stimulant use disorders, and reasoning in opioid use disorder [4]). Combining tCS with behavioural interventions such as cognitive bias modification, does not appear to lead to promising results for alcohol use disorder. This might be due to several factors, such as the motivation of the subjects (some were not treatment seeking, and therefore might not be motivated to reduce their drinking), or the study design (perhaps, there were too few sessions to induce changes). Interestingly, combining tACS with attentional bias modification decreased attentional biases, as well as improving decision-making and decreasing craving in patients with tobacco use disorder. Although this was a proof of concept study [14], it nevertheless demonstrated the potential pertinence of combining these two interventions in SRADs.

Furthermore, a series of limitations of the reviewed studies should be taken into account. First, patient characteristics such as age and sex knowingly influence tCS-induced effects [44–47] but were not always properly considered. In addition, the pattern of substance use disorders is different in men and women. For example, most studies included samples with a majority of men or even men only. It would be important to include more women in studies. Importantly, it would be imperative to determine whether there are differences between sexes in tCS responses. Second, the majority of studies included detoxified and abstinent patients, while other stages of SRADs (e.g. sated, non-treatment seekers) remain unexplored. A recent study in non-treatment-seeking tobacco smokers suggested that sated patients responded better to tCS as compared to deprived patients, as reflected by a greater deactivation of the default mode network [29]. To support, acute nicotine in sated, as compared to abstinent, patients may present greater neural plasticity [48], thus, presumably they may respond more to tCS. Third, most studies did not include patients with comorbid disorders other than tobacco use disorder. Considering that comorbidities (e.g. mood disorders) are common in SRADs [49], it might be worth examining different subgroups. Fourth, the motivation to change, which is associated with better response to tCS, remains unexplored [50]. Improving selective attention might be one way to improve motivation [32]. Also, greater motivation may relate to a better adherence to tCS regimens, which likely require several sessions in order to produce clinically meaningful improvements of symptoms [36]. Fifth, behavioural states before stimulation and individual differences in brain morphometry on the effect of tCS treatments should be considered [51]. For instance, we previously observed that behaviours and brain morphometry impacted tDCS changes on neural substrates in patients with gambling disorder. In one study, there were positive correlations between tCS-induced changes of neurotransmitter levels in prefrontal and striatal regions and gambling-related behaviours (i.e. craving, impulsivity, risk-taking) in patients with gambling disorder [52]. In another study, there were positive correlations between tDCS-induced elevations of prefrontal GABA levels and morphometry (volume and thickness) of the DLPFC in patients with gambling disorder [51]. In addition, the use of more objective and standardized outcome measures (e.g. a cue-provoked paradigm for craving) would allow more direct comparisons across studies. Finally, future work could assess whether tCS can modulate other cognitive functions that may be relevant to SRADs, such as memory bias [53] and mindfulness [54].

26.4 Conclusion

In conclusion, tCS holds a strong clinical potential to improve cognitive functions when targeting the DLPFC. Further work is needed to determine the most effective protocols. One interest-

ing therapeutic avenue might be individualized treatments based on patient characteristics such as brain morphometry, age, and sex. Future studies could aim to optimize outcomes by combining tCS with medications or behavioural interventions (e.g. cognitive behavioural therapy) in order to improve outcomes even more [36].

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