Physical activity: A promising adjunctive treatment for severe alcohol use disorder

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PHYSICAL ACTIVITY: A PROMISING ADJUNCTIVE TREATMENT FOR SEVERE ALCOHOL USE DISORDER

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ABSTRACT

Substance use disorder develops from complex interactions between socio-environmental and neurobiological factors. A neurocognitive model of addiction, the triadic model, proposes that Alcohol Use Disorder (AUD) is the result of an imbalance between the reflective and the impulsive subcomponents along with a disruption of the regulatory subcomponent. Physical activity is considered as an emerging treatment for severe AUD (sAUD). This short review examines the efficacy and mechanisms of action of physical intervention as an adjunctive treatment in severe AUD (sAUD) within the theoretical framework of the triadic model.

Physical activity is a feasible, safe, and less stigmatizing approach than classical treatments. It improves sAUD patients' mental and physical comorbidities. The key finding of this short review is that physical activity could contribute to a rebalancing of the triadic model in sAUD patients by 1) improving neuroplasticity and cognitive functioning, 2) reducing impulsivity and urgency, and improving emotional regulation, and 3) reducing craving. This rebalancing could eventually reduce the risk of relapse. However, due to methodological issues, it remains difficult to observe an effect of physical activity on drinking outcomes. At best, a trend towards a reduction in alcohol consumption was noted. The mechanisms that could explain the benefits of physical activity in sAUD patients involve multiple physiological processes such as dopaminergic or glutamatergic transmission and signaling or neuroplasticity.

Future randomized controlled trials should include neuropsychological and impulsivity assessments, in more controlled environments. Physical activity could contribute to a personalization of sAUD treatment using each subcomponent of the triadic model as a therapeutic target. Physical exercise could be an adjunctive treatment for sAUD patients, favoring the benefit of more usual treatments such as cognitive behavioral therapies. It could also be a stand-alone intervention in less severe patients.

KEYWORDS: alcohol use disorder; cognitive impairments; impulsivity; craving; physical activity ; rehabilitation

1. INTRODUCTION

Alcohol Use Disorder (AUD) is a complex disease marked by a loss of control over alcohol consumption despite negative consequences (APA DSM-5 Task force, 2013; Koob & Le Moal, 2008; Volkow & Boyle, 2018 for a review). AUD involves social, psychological, behavioral and biological dysfunction such as brain alterations (Volkow & Boyle, 2018 for a review). Severe AUD (sAUD, i.e., 6 or more DSM 5 symptoms among eleven (APA DSM-5 Task force, 2013) is associated with somatic and psychiatric comorbidities, as well as a frequent sedentary lifestyle (Linke & Ussher, 2015 for a review; World Health Organization et al., 2018). sAUD affects 25% of all AUD patients (Grant et al., 2015). Recovery from sAUD is often a long-term process requiring multiple episodes of outpatient or residential treatment, with a poor treatment retention and a high relapse rate (40 and 60% respectively) (National Institute on Drug Abuse (NIDA), 2012).

Access to standard care remains difficult for sAUD patients. A major barrier is the fear of stigmatization (Kohn et al., 2004; Probst et al., 2015). Ideally, new treatments of sAUD should have few adverse effects and improve patients' co-morbidities while promoting abstinence and preventing relapse. They should also be perceived as less stigmatizing by patients. Physical activity appears promising because it meets most of these criteria (Hallgren, Vancampfort, et al., 2018).

The existing literature supporting physical interventions for sAUD includes narrative and systematic reviews as well as meta-analyses. These studies explore physical functioning of sAUD patients and the short-term and long-term effects of physical activity on neuropsychiatric and cognitive measures, behavioral variables, and alcohol drinking outcomes (Ashdown-Franks et al., 2019; Giesen et al., 2015; Hallgren, Vancampfort, Giesen, et al., 2017; Stoutenberg et al., 2016 for reviews). Mechanisms underlying the impact of physical activity on substance use disorder, however, still need to be explored (Lynch et al., 2013 for a review).

The present review provides additional insight into the current literature by analyzing the efficacy and mechanisms of action of physical interventions for sAUD within the theoretical framework of the triadic model, a neurocognitive model of addiction. Its objectives are thus 1) to describe the neurobiological substrates of sAUD, 2) to examine the potential beneficial effects of physical activity in sAUD patients, and 3) to discuss the clinical and research perspectives of physical activity for sAUD and more generally for AUD patients.

2. NEUROCOGNITIVE MODEL OF AUD

Theoretical neurocognitive models have been proposed to better understand decision-making processes. In the dual-process model, decision-making under risk emerges from the interactions between a deliberative subcomponent underlying cognitive and analytic evaluation, and an affective subcomponent involved in an emotional evaluation (Mukherjee, 2010). The first subcomponent favors controlled decisions while the second results in automatic and impulsive responses. Distinct cerebral networks underly each subcomponent: a prefrontal network for the deliberative-reflective subcomponent (prefrontal cortex, cingulum, cerebellum), and a limbic network for the affective-impulsive subcomponent (amygdala and striatum) (Mukherjee, 2010; Noël et al., 2013). This model was adapted and largely validated in AUD (Wiers et al., 2010; Noël et al., 2013). Noël et al. highlighted the role of insula and craving, and proposed a triadic model *(Figure 1A)* (Noël et al., 2013).

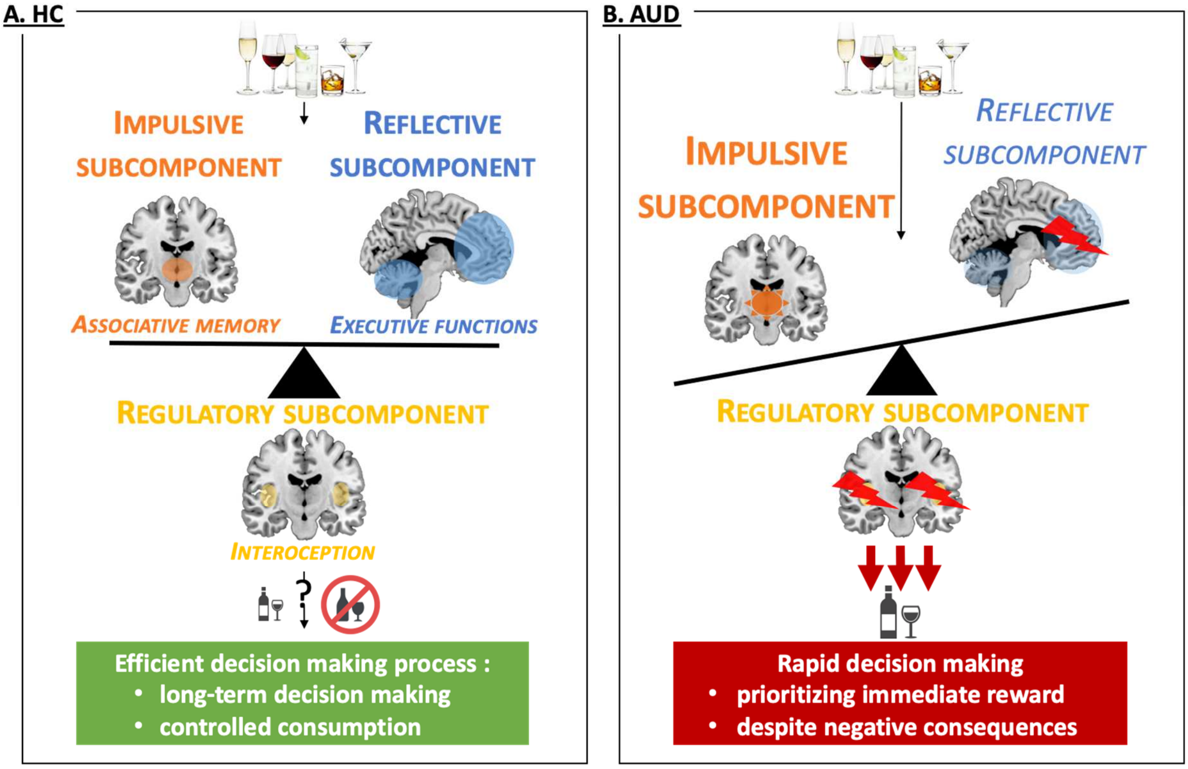

Figure 1. Triadic model adapted from Noël et al. 2013. A) In healthy controls (HC), the balanced interactions between the two main subcomponents result in adapted decision-making due to alcohol cues. B) In sAUD patients, the weakening ( ) of the reflective subcomponent, the over-activation ( ) of the impulsive subcomponent and/or the disruption ( ) of the regulatory subcomponent account for a rapid decision favoring alcohol consumption.

In this triadic model, sAUD is the consequence of an imbalance between the reflective and impulsive subcomponents with a weakening of the reflective subcomponent and/or an overactivation of the impulsive subcomponent face to alcohol and emotional stimuli *(Figure 1B)* (Noël et al., 2013; Wiers et al., 2010). The insula plays a regulatory role between these two subcomponents, by translating bottom-up, interoceptive signals into subjective outputs, such as the urge (i.e. craving) to consume alcohol (Noël et al., 2013). In response to an alcohol cue, this imbalance accounts for rapid decision-making, prioritizing short-term reward irrespective of the long-term consequences.

Reflective subcomponent. Chronic and excessive alcohol consumption is associated with gray matter shrinkage and altered white matter integrity affecting notably the frontocerebellar circuit involved in motor and executive abilities (Le Berre et al., 2017; Stavro et al., 2013 for reviews). Early in abstinence, these alterations result in impaired inhibition, updating and planning, flexibility and decision-making abilities with indirect consequences on metacognitive abilities, episodic memory, emotional processes and social cognition (Le Berre et al., 2017 for a review). Effective treatment requires efficient cognitive functioning in order to learn new skills and strategies to prevent relapse (Bates et al., 2013 for a review). Executive abilities are needed to achieve awareness, to resolve ambivalence towards problematic behaviors and to promote the motivation to change (Le Berre et al., 2013). Maintaining changes in behavior regarding alcohol is also a costly cognitive challenge because it requires inhibiting habits or routines as well as considering and planning new behaviors without alcohol. In a 6-month follow-up study, Czapla et al. found that deficits in response inhibition observed early in abstinence were a significant relapse predictor, in conjunction with the number of previous detoxifications (Czapla et al., 2015).

Impulsive subcomponent. Impulsivity is defined as a tendency to react rapidly or in unplanned ways to stimuli without proper regard for consequences or risks (Lejuez et al., 2010 for a review). It is viewed as a multidimensional construct related to personality traits, emotional or motivational dispositions, but also to cognitive functioning, particularly executive functions (Shin et al., 2012 for a review). Impulsivity is high in sAUD patients and increases the risk for initial use, development of dependence, and relapse (Evren et al., 2012; Lejuez et al., 2010; Shin et al., 2012 for reviews). The impulsive subcomponent is mainly associated with the amygdala and striatum (Noël et al., 2013). Decision-making deficits observed in sAUD patients may also result from impairment in emotional networks (Czapla et al., 2015; Le Berre et al., 2014). Emotional impairments, associated with alterations of the limbic system, have been repeatedly reported in individuals with sAUD: alexithymia, impaired perception of emotions on faces or prosody, altered humor processing, empathy, and theory-of-mind (Le Berre, 2019; Oscar-Berman et al., 2014; Uekermann & Daum, 2008 for reviews). Moreover, sAUD patients experience increased sensitivity with higher automatic processing and attentional biases to alcohol-related cues (Field et al., 2008; Lannoy et al., 2014). Thus, when sAUD patients decide to abstain or reduce their alcohol consumption, they are confronted with habitual reflexes and alcohol-approach biases, especially in emotional contexts for which alcohol is often a coping strategy.

Regulatory subcomponent. Craving has become one of the cardinal symptoms of AUD in the most recent nosography (APA DSM-5 Task force, 2013). Craving results from a conflict between the need to drink alcohol and the desire not to do so (Naqvi et al., 2014). According to Naqvi's model, the insula is integrated with the rest of the goal-directed system, when automatic drug seeking is interrupted by a negative consequence or by the availability of a better alternative (Naqvi et al., 2014). Imaging studies show that activity of the insula correlates with subjects' rating of urge for cigarettes, cocaine, alcohol, and heroin (APA DSM-5 Task force, 2013; Noël et al., 2013).

Each subcomponent of the triadic model (executive functions, impulsivity/emotion, craving) is a therapeutic target in sAUD treatment. Several treatments, such as mindfulness meditation, cognitive remediation or cognitive behavioral therapy, have shown their effectiveness on some of these subcomponents (Coates et al., 2018; Garland & Howard, 2018; Rupp et al., 2012). Physical activity appears very promising since it has the potential to simultaneously target all three subcomponents.

3. PHYSICAL ACTIVITY IN sAUD TREATMENT

3.1. Definition and current clinical guidelines

Physical activity is defined as “planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Caspersen et al., 1985). Despite promising and growing scientific data, clinical guidelines on sAUD treatment have until now rarely mentioned physical exercise, and when they do so, it is mainly considered as a recreational activity *(Figure 2)*. For example, English, Australian and French clinical guidelines only mention physical exercise as a “recreational group proved to be beneficial in terms of engaging in other non-drinking-related activities”, a “simple way to relax”, and “body-mediated activity” respectively (Haber et al., 2009; National Collaborating Centre for Mental Health Staff, 2011; Société Française d’Alcoologie, 2015). A recent update of the American NIDA guidelines for drug addiction treatment points out that physical activity is increasingly being used in clinical practice for people with addictions and could be a promising adjunctive treatment (National Institute on Drug Abuse (NIDA), 2012).

National guidelines on AUD			**Exhaustive list of mentions concerning physical activity**
National Institute on Drug Abuse (NIDA)	Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition)	Updated January 2018	« <u>Can exercise play a role in the treatment process?</u> Yes. **Exercise** is increasingly becoming a component of many treatment programs and has proven effective, when combined with cognitive- behavioral therapy, at helping people quit smoking. **Exercise** may exert beneficial effects by addressing psychosocial and physiological needs that nicotine replacement alone does not, by reducing negative feelings and stress, and by helping prevent weight gain following cessation. Research to determine if and how exercise programs can play a similar role in the treatment of other forms of drug abuse is under way. » *p.29*
U.S. Department of Health & Human Services	Facing addiction in America The Surgeon General’s Report on Alcohol, Drugs, and Health	2016	« <u>Acute Stabilization and Withdrawal Management</u> (…) Most periods of withdrawal are relatively short (3 to 5 days) and are managed with medications combined with vitamins, **exercise**, and sleep. One important exception is withdrawal from alcohol and sedatives/ tranquilizers, especially if the latter are combined with heavy alcohol use. Rapid or unmanaged withdrawal from these substances can be protracted and can produce seizures and other health complications. » *p. 4.12*
National Institute for Health & Clinical Excellence (NICE)	Alcohol-use disorders The nice guideline on diagnosis, assessment and management of harmful drinking and alcohol dependence	Updated August 2019	« <u>Experience of treatment setting – inpatient</u> Bacchus (1999) carried out a study about opinions on inpatient treatment for drug and alcohol dependence. (…) Recreational groups (for example, art therapy, **exercise** and cookery) also proved to be beneficial in terms of engaging in other non-drinking-related activities. » *p.74*
Australian Government Department of Health and Ageing	Guidelines for the Treatment of Alcohol Problems	2009	« <u>Getting through alcohol withdrawal: A guide for patients and carers</u> Everyone has simple ways to relax – watching television, videos, listening to music, warm baths, **light exercise**, reading – do whatever works for you. » *p.177*
Société Française d’Alcoologie (SFA)	Mésusage de l’alcool : dépistage, diagnostic et traitement Recommandation de bonne pratique *Alcohol abuse: screening, diagnosis and treatment Recommendation for good practice*	2015	« <u>What is the place of non-pharmacological and non-psychotherapeutic interventions?</u> (…) We can distinguish different types of workshops: - Body-mediated activities: **physical activity**, different methods of relaxation (…) Regular **physical activity** is often considered effective in increasing commitment to change and improving self-esteem, but there is a lack of data to support this belief. (…) The interventions that have shown the best evidence of effectiveness in reducing anxiety associated with alcohol misuse are **physical activity**, relaxation techniques and bibliotherapy. » *p.48*

Figure 2. Comprehensive list of references to physical activity or exercise in the American, English, Australian and French clinical guidelines for the treatment of addictions and Alcohol Use Disorder (Haber et al., 2009; National Collaborating Centre for Mental Health Staff, 2011; National Institute on Drug Abuse (NIDA), 2012; Société Française d'Alcoologie, 2015; Substance Abuse and Mental Health Services Administration (US) & Office of the Surgeon General (US), 2016).

Physical activity is already being used in psychiatric disorders to improve psychiatric symptoms and physical health of patients. A recent review examined the efficacy of physical activity across numerous classes of mental disorders, including alcohol and substance use disorder (Ashdown-Franks et al., 2019). Physical activity had a significant effect on symptoms of depression, anxiety and schizophrenia with few side effects (Stubbs et al., 2018 for a review).

3.2. Effects of physical activity in the treatment of sAUD

3.2.1. Physical and mental health

Most sAUD patients have a sedentary lifestyle but remain interested in physical activity, which is often preferred compared to pharmacological treatments (Abrantes et al., 2011). Several recent reviews conducted in sAUD patients indicate that moderate-to-vigorous intensity physical activity could be an adjunctive non-pharmacological treatment (Ashdown-Franks et al., 2019; Giesen et al., 2015; Hallgren, Vancampfort, Giesen, et al., 2017). Physical activity is a feasible and safe therapeutic approach in sAUD treatment. It has been related to a reduction in sedentary lifestyle and an improvement of poor physical health (Abrantes et al., 2011; Hallgren, Vancampfort, Schuch, et al., 2017). It improves sAUD patients' comorbidities such as somatic issues (metabolic syndrome, cardiovascular diseases, diabetes) or mental health problems (depression, anxiety, sleep disorder) (Giesen et al., 2015). A systematic review published by Giesen et al. included 14 controlled exercise interventions conducted in sAUD. It highlighted the beneficial effects of physical activity (aerobic exercise and strength training) on physical fitness, resting heart rate, physical activity level, and strength, with no adverse events reported (Giesen et al., 2015). Hallgren et al. performed a systematic review and meta-analysis of physical activity in sAUD patients (21 studies; n=1204). Exercise programs involved moderate intensity aerobic exercise (n=13), combination of aerobic exercise and strength training (n=5) or yoga/stretching (n=3). Exercise programs were 2 to 52 weeks long, and the mean exercise session duration was 43 minutes. Most of the programs were supervised (n=17). Hallgren et al. reported a significant reduction in depressive symptoms and a significant improvement in physical fitness (Hallgren, Vancampfort, Giesen, et al., 2017). Other benefits can be expected including an improvement of social abilities, appetite and sleep, quality of life, and self-efficacy (Giesen et al., 2015; Stoutenberg et al., 2016).

3.2.2. Drinking outcomes

Giesen et al. reported "inconsistent effects with a slight trend toward a positive effect" on drinking behavior (abstinence rate, alcohol use frequency and total amount consumed) or craving in their systematic review (Giesen et al., 2015). Another narrative review by Manthou et al. reported that physical activity had a positive impact on alcohol consumption, abstinence rates, or the urge to drink in 6 out of the 11 studies reviewed (Manthou et al., 2016). Wang et al. performed a meta-analysis on physical activity in substance use disorder. Only 3 studies specifically examined sAUD, and 3 others focused on alcohol use in polydrug abusers (Wang et al., 2014). Results indicated that physical activity can significantly increase the abstinence rate in subjects with sAUD. Of the 21 studies included in Hallgren's meta-analysis, only five studies adequately reported data on alcohol drinking outcomes (number of standard drinks consumed per day, or per week, number of heavy drinking days, AUDIT total score, alcohol urge/craving) (Hallgren, Vancampfort, Giesen, et al., 2017). Long-term exercise (3 studies described the use of moderate intensity aerobic exercise, and 2 the use of yoga) was associated with nonsignificant reductions of alcohol consumption and of the risk level associated with alcohol consumption.

Three randomized controlled trials have been conducted more recently and are thus not included in the previous reviews or meta-analyses. Roessler et al (2017) examined the effects of a 6-month moderate exercise intervention in sAUD patients. The interventions were as follows: treatment as usual (TAU), TAU and supervised physical activity, TAU and individual and autonomous physical activity with only a written training program. A moderate level of physical activity was protective against excessive drinking whatever the intervention, with a "dose-response" effect. In each intervention group, participants with moderate level physical activity (using the International Physical Activity Questionnaire IPAQ categories of physical activity intensity in everyday life (Craig et al., 2003)) had better drinking outcomes than participants with low level physical activity. The amount of alcohol consumed in each intervention group decreased by 4% for each increased exercising day (Roessler et al., 2017). In a 2-arm randomized controlled trial, Georgakouli et al. (2017) investigated changes in drinking behavior and biochemical response to exercise. Eleven heavy drinkers performed an 8-week supervised moderate exercise training (50-60% HRR, Heart Rate Reserve i.e. the difference between maximum heart rate and resting heart rate). The intervention resulted in a significant reduction of alcohol consumption and fitness improvement in heavy drinkers but did not significantly change hormonal responses (in particular in the hypothalamic-pituitary-adrenal axis involved in stress adaptation). Finally, Jensen et al. (2018) randomly assigned 105 sAUD patients to two groups. The experimental group underwent a treatment as usual combined with running and brisk walking for 30–45 min twice a week in small supervised groups or individually. The control group consisted of a treatment as usual only. Drinking outcomes were assessed after 6 and 12 months of training. Training was estimated of moderate intensity (78% HRR) with no difference between supervised groups or individual practice. A significant reduction in training frequency was observed in both groups after the first month. Alcohol intake significantly decreased (219 to 41 units of pure alcohol per 30 days) for the entire sample of patients with no significant difference between groups.

The idea that physical activity may be an efficient strategy in sAUD treatment is not new; it has been demonstrated that physical activity is a safe and acceptable intervention with benefits on physical fitness and mental health of sAUD patients. However, the literature indicates that it remains difficult to observe changes in drinking outcomes with, at best, a trend toward a reduction in alcohol consumption. The absence of consensus regarding the effect of physical activity on drinking outcomes can be explained by several factors: the heterogeneity of the patients included in the mentioned studies, the diversity in study designs, the limited number of randomized and controlled trials, and the still imprecise criteria for personalizing physical activity for sAUD patients. A combined approach using physical activity as an adjunctive treatment, in addition to behavioral therapies and medications, is particularly pertinent for sAUD. Patients often suffer from poor physical and mental health, cognitive and emotional impairments, high impulsivity and cognitive biases, and craving, all of which require specialized intervention. Physical activity could participate in the rebalancing of the three subcomponents in the triadic model of sAUD.

3.3. How can physical activity rebalance the triadic model of sAUD ?

3.3.1. Reflective subcomponent

Considering the pro-cognitive effect of physical activity in various adult populations (including mental disorder or regular tobacco smokers), Hallgren et al. suggested that physical activity may have a beneficial cognitive effect in sAUD patients (Hallgren, Vancampfort, et al., 2018). In their recent systematic review and meta-analysis, they point the lack of relevant cognitive assessments in the studies conducted so far (Hallgren, Vancampfort, Giesen, et al., 2017). However, data from other clinical populations appear promising and highlight the potential role of physical activity programs as an adjunct to current cognitive rehabilitation strategies.

Studies conducted in both animals and humans suggest that physical activity has a facilitating effect on neuroplasticity and may improve cognitive functioning (Costa et al., 2019; Hötting & Röder, 2013 for reviews). Meta-analyses report a significant positive effect of regular physical training in sedentary adults, healthy older adults, or in psychiatric populations on several cognitive functions, including executive abilities, attention and processing speed, memory, and on different related cerebral networks (Firth et al., 2016; Hötting & Röder, 2013; Knöchel et al., 2012; Smith et al., 2010). In schizophrenia, a review conducted on the pro-cognitive mechanisms of physical exercise described the use of aerobic exercise using cycle ergometers or treadmills, bodyweight exercises, interactive videogames or free-weights sometimes associated with resistance-based training such as muscle strengthening (Firth et al., 2016 for a review). Exercise programs included in this meta-analysis were on the average 12,2 weeks long (ranging from 4 to 24 weeks) with 2,9 sessions per week on average (ranging from 2 to 4 sessions), of 20 to 60 minutes in duration. Control conditions were table football, occupational therapy, treatment as usual or relaxation training. Exercise was associated with improvement in global cognition, in particular for supervised interventions by physical activity professionals. Exercise significantly improved working memory functioning, social cognition, attention and vigilance, but not processing speed, verbal and visual memory, or reasoning and problem solving. In sedentary adults, exercise programs involved aerobic exercise comprising endurance programs (running, walking, cycling, or swimming), ranging from a few weeks up to one year in duration (Hötting & Röder, 2013 for a review). Control interventions were light stretching and toning programs, or waiting list. Benefits were mostly observed for executive functions associated with frontal brain regions. In healthy older adults (Smith et al., 2010 for a review), exercise programs lasted between 6 weeks to 18 months and focused on moderate aerobic exercise such as brisk walking and/or jogging, combined or not with strength training intervention. Control conditions were stretching and toning, health education, relaxation, or waiting-list. Combined aerobic exercise and strength training interventions seemed to improve attention and processing speed to a greater extent than aerobic exercise alone. Longer or higher intensity programs were not associated with better improvements in neurocognition.

In patients with an altered reflective subcomponent, physical activity could be combined with cognitive stimulation. In effect, physical activity may "prepare" the brain to respond to cognitive stimulation. Cognitive changes induced by physical activity could thus be potentiated by this combination (Hötting & Röder, 2013 for a review). Patients with alcohol-related cognitive impairments require specific supervision because feelings of fatigue and self-defeating thoughts demand inhibitory control so that patients continue to be motivated for exercising (Costa et al., 2019 for a review). Self-selected exercise (e.g. by giving patients a choice of different types of moderate intensity group aerobic exercise) is preferable to reduce self-defeating thoughts, promote adherence to the exercise and train self-assessment abilities. Decision-making is highly mobilized to arbitrate between perceived effort, feelings, and internal conversations (Costa et al., 2019 for a review).

3.3.2. Impulsive subcomponent

Physical activity has been successfully used in attention deficit hyperactivity disorder (ADHD) (Christiansen et al., 2019). ADHD is characterized by symptoms of inattention, hyperactivity and impulsivity, along with deficits in executive functions, emotional regulation and motivation (APA DSM-5 Task force, 2013). ADHD is highly comorbid with sAUD

(Zulauf et al., 2014). Regular physical activity significantly reduced ADHD subjects' impulsivity and hyperactive behaviors (Abramovitch et al., 2013; Christiansen et al., 2019).

Two components of impulsivity that are particularly implicated in sAUD could be targeted by physical activity: sensation seeking and urgency, or the tendency to act rashly to regulate emotions, in particular negative emotions (Shin et al., 2012 for a review). Physical activity could be useful to decrease urgency and improve emotional regulation. Reed et al. performed a meta-analysis that examined the effect of acute aerobic exercise (such as aerobic dance, walking, jogging, running, swimming, and cycling) on self-reported positive affect (focusing on the positive subscale such as "energy" or "joy"). Dose of exercise was estimated as the product of exercise intensity (%Vo2R i.e. % of oxygen uptake reserve) and duration. Physical activity was associated with increased positive affect, which could last up to 30 minutes post-exercise, especially in individuals with low affective pre-exercise scores, and even for low to moderate doses. No threshold could be found for intensity or duration to be considered as having a significant effect on affect. Physical activity could thus be a self-regulatory strategy to improve "feelings of energy" and increase positive affect (Reed & Ones, 2006; Stoutenberg et al., 2016). It could also be considered as a safe way to activate the reward system, thus "competing" with drinking behavior (Brené et al., 2007; Lynch et al., 2013 for reviews). Finally, in a randomized counter balanced cross-over study (brisk walking i.e. moderate aerobic exercise versus 15 minutes of passive seating) conducted in 20 abstaining (at least 3 days of abstinence) excessive alcohol drinkers, Taylor et al showed that a single session of exercise could reduce automatic attentional bias towards alcohol-related images and alcohol urge (Taylor et al., 2013).

In patients with an overactive impulsive subcomponent, it seems safer to avoid high-intensity exercise, which has been associated with negative affective states and lower pleasure during exercise in sedentary individuals, causing an increase in the dropout rate (Costa et al., 2019 for a review). High-intensity exercise could also mimic the brain effects of alcohol drinking on the reward circuit and increase vulnerability to substance abuse and excessive exercise (Hausenblas et al., 2017; Lynch et al., 2013 for reviews). Moderate intensity exercise should be preferred, ideally in supervised but open-access exercise sessions, to avoid absenteeism and abandonment.

3.3.3. Regulatory subcomponent

Exercise has been shown to be associated with decreased craving for smoking, or marijuana use (Stoutenberg et al., 2016 for a review). In sAUD, two of the studies included in the meta-analysis of Hallgren et al. explored the acute effects of physical activity in sAUD patients (Hallgren, Vancampfort, Giesen, et al., 2017). In the first randomized trial (Ussher et al., 2004), craving intensity was significantly reduced in sAUD inpatients immediately following moderate intensity cycling lasting 10 minutes, compared to patients undergoing 10 minutes of very light intensity cycling. However, the decrease was short-lived with a significant decline in alcohol urges for the experimental condition versus control during exercise but not at any measurement point following (immediately after the exercise, and 5 and 10 minutes following exercise). In the second study (Jamurtas et al., 2014), 9 sAUD inpatients and 9 healthy controls exercised for 30 minutes at a low intensity. There was a 17%, but nonsignificant, decrease of alcohol urge in sAUD inpatients tested before and immediately after exercising. Authors pointed the very small sample size of their study and the low initial alcohol urge levels of the patients. In the Taylor et al. study, the short bout of moderate aerobic exercise (brisk walking) reduced significantly craving compared to passive seating when evaluated immediately after the exercise, and 5 and 10 minutes after (Taylor et al., 2013). In a more recent study, Brown et al described a decrease in alcohol craving in 26 patients following a 20- to 40-minute moderate intensity exercise program that was conducted once a week, over 12 weeks. This decrease in craving was significantly more pronounced than the one observed in patients who received only physical activity advice (a single session of brief advice for autonomous practice) (Brown et al., 2016). Taken together, these results indicate that exercise should be at least of moderate intensity to reduce craving. It seems relevant to consider short and easily achievable sessions several times a week and early after detoxification when the control of sudden craving is targeted.

3.4. Mechanisms underlying the impact of physical activity on sAUD

A better understanding of the potential numerous mechanisms of action of physical activity would help improve its effectiveness for each sAUD patient. Physical activity might be positive not only on a psychological (e.g. stress and mood regulation, self-efficacy) or social level (e.g. social reinforcement, change in lifestyle that encourages more healthy behaviors including better diet or sleep) but also on a neurobiological and neurocognitive level (Costa et al., 2019; Giesen et al., 2015; Hallgren, Vancampfort, Giesen, et al., 2017; Stoutenberg et al., 2016 for reviews).

Neurobiological mechanisms involved in the development of AUD include a dysregulation of the reward function via dopamine and opioid peptide deficits and increased brain stress system activity via corticotropin-releasing factor and dynorphin. It also involves a dysregulation of glutamatergic and GABAergic networks (Koob & Volkow, 2016). sAUD is associated with brain alterations and dysfunction (in particular prefrontal cortex, limbic system and cerebellum), neuroinflammation, altered neurogenesis and neuroplasticity, and abnormal neurotransmission. These abnormalities account for cognitive and emotional processing impairments (Le Berre, 2019; Oscar-Berman et al., 2014; Perry, 2016). Neurobiological mechanisms induced by physical activity in sAUD involve multiple signaling pathways and systems (Costa et al., 2019; Lynch et al., 2013). Physical activity may favor the regulation of the neurotransmission, and a protective and restorative effect against the neurotoxicity of alcohol (Perry, 2016 for a review). In effect, physical activity results in neuroplasticity, possibly through a stimulation of cerebral circulation (Mandolesi et al., 2018 for a review), as well as neurogenesis and synaptogenesis, possibly through an increase in neurotrophins expression (such as Brain-Derived Neurotrophic Factor BDNF) (Hötting & Röder, 2013; Perry, 2016 for reviews). Increased neurogenesis, decreased neuroinflammation and oxidative stress, and moderation of glucocorticoid release in the stress axis could compensate for the harmful effects of alcohol in sAUD (Perry et al. 2016 for review). Moriarty et al. demonstrated that the level of exercise intensity may influence prefrontal cortex oxygenation during cognitive testing using functional near infrared spectroscopy (fNIR) (Moriarty et al., 2019). The fNIR device was used to measure hemoglobin difference changes between pre-exercise baseline and post-exercise cognitive assessment. Four conditions were compared in height healthy and physically active volunteers: non-exercise control, moderate intensity aerobic exercise, high intensity aerobic interval exercise, and mind-body yoga exercise. Activation (using oxygenated/deoxygenated hemoglobin changes as an indirect marker of neural activation) was higher after moderate intensity aerobic exercise compared to high intensity, yoga or control. But prefrontal cortex activation did not correlate with cognitive performance. In addition, a negative relationship was found between cognitive abilities and exercise intensity, indicating that exhausting exercise could be cognitively prejudicial. Even though the sample size remains small and the experiment only included single exercise sessions, these findings suggest that repeated moderate activity may improve brain oxygenation and cognitive functioning.

Lynch et al. proposed that the efficacy of physical activity in sAUD may vary across individuals (age or sex in particular) and depend on the stage of the addiction process as well as the exercise modalities (Lynch et al., 2013 for a review). Through facilitation of dopaminergic transmission and adaptations in dopaminergic signaling, moderate physical activity could prevent drug use by introducing an alternative reward. By its own reinforcing properties, physical activity could also prevent the development of addiction and reduce the risk of relapse through the normalization of glutamatergic and dopaminergic signaling or the blockage of changes in chromatin via epigenetic regulation of BDNF caused by chronic exposure to alcohol and repeated withdrawal (Costa et al., 2019; Lynch et al., 2013 for reviews).

Other physiological systems involved in the initiation and development of sAUD could also be impacted by both short-term and long-term physical activity : norepinephrine, serotonin, endocannabinoids (Hallgren, Vancampfort, Giesen, et al., 2017; Lynch et al., 2013; Stoutenberg et al., 2016 for reviews).

4. LIMITS AND PERSPECTIVES

4.1. Research considerations

To our knowledge, no studies evaluated the effects of physical activity on each of the 3 sub-components of the triadic model simultaneously. Future protocols investigating the mechanisms explaining the efficacy of physical activity in sAUD should include repeated neuropsychological assessments and neuroimaging examinations, but also a comprehensive evaluation of impulsivity and craving.

It is very difficult to investigate the efficacy of physical activity in sAUD in a real-world setting since many environmental factors can interfere with the effect of exercise programs (e.g. alcohol exposure, stressors, lack of social support or resources, etc.). Stoutenberg et al. (2016) claimed that a highly controlled environment (i.e., residential treatment programs) is crucial to determine the efficacy of exercise training in sAUD and its optimal modalities (dose, frequency, intensity) before determining its effectiveness in a real-world setting (Stoutenberg et al., 2016). Exercise programs should also take the heterogeneity of sAUD patients into account, in order to determine an optimal and personalized exercise intervention. The impact of demographical or clinical factors (e.g. impulsivity, craving levels, cognition, but also age, comorbidities and physical condition, gender, stage and severity of AUD, social status and skills, co-addictions, etc.) on the effectiveness of physical activity should be investigated more precisely (Lynch et al., 2013, 2017; Sari et al., 2017; Wang et al., 2014).

Moreover, there is only a limited number of randomized controlled trials and previous studies are very heterogeneous regarding the nature of the interventions and measurements (in particular concerning alcohol consumption), as well as limited sample sizes with a high drop-out rate. For example, in Hallgren et al meta-analysis (10 studies, 1204 participants), 40,3% of sAUD patients dropped out from physical activity programs. This dropout rate was noticeably higher than in other populations with mental illness, such as depression or schizophrenia. However, this dropout rate was not significantly different from the control conditions (Hallgren, Vancampfort, Giesen, et al., 2017). Supervision of physical activity by a qualified trainer and motivational strategies was associated with a decrease in the dropout rates (Hallgren, Vancampfort, Giesen, et al., 2017).

The implementation of physical activity in sAUD treatment programs could also enable us to deepen our understanding of this triadic neurocognitive model. The fact that each subcomponent is potentially affected in a different way by physical activity or requires specific adaptation of exercise programs reinforces their theoretical autonomy. On the contrary, a global effect of physical activity would rather suggest a direct relationship between the subcomponents, which is also suggested by the bidirectional relationship between cognitive and affective/impulsive regulation during physical activity (Costa et al., 2019 for a review). This review therefore encourages rethinking the nature of the relationships between the three subcomponents.

4.2. Clinical considerations

4.2.1. Physical activity as a personalized intervention for sAUD patients

Each subcomponent of the triadic model of sAUD constitutes a therapeutic target for physical activity. It might be useful to evaluate each of the three subcomponents in clinical practice. Physical activity could be adjusted with regard to each individual's triadic subcomponent configuration (Figure 3).

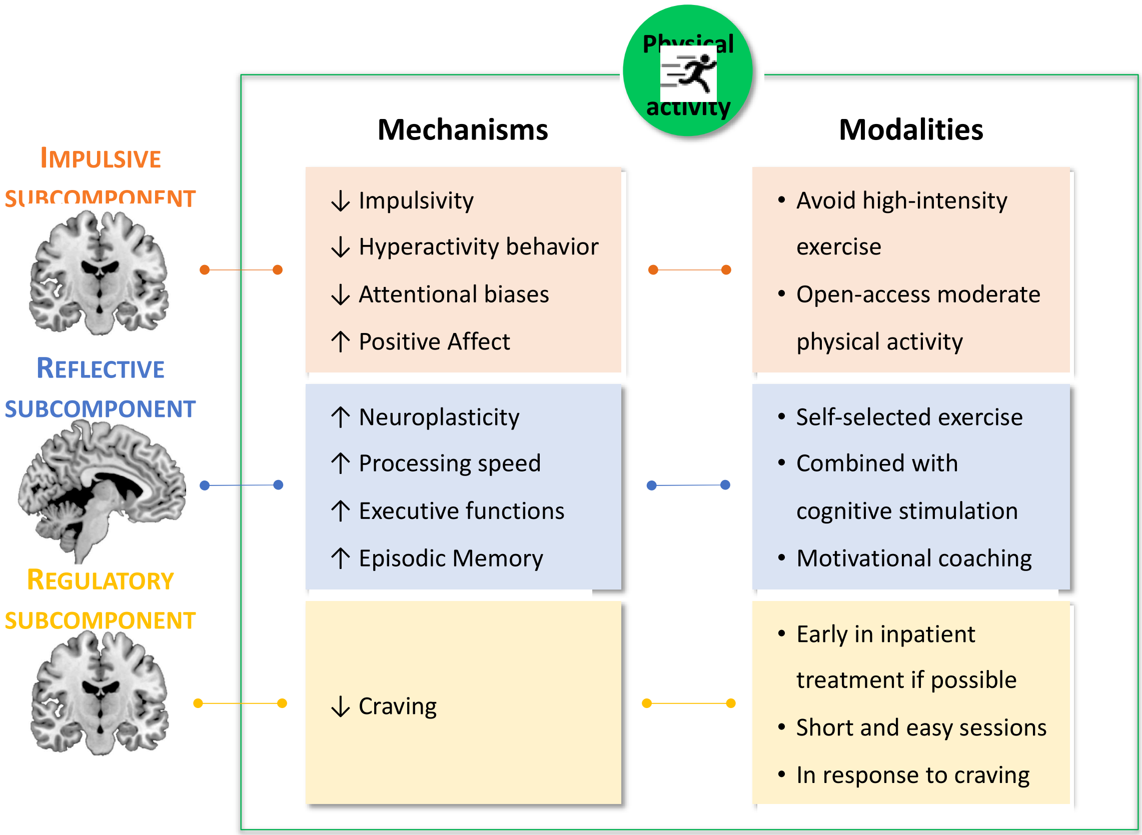

Figure 3. Potential effects and mechanisms of physical activity on each subcomponent of the triadic model. Suggestions of physical activity specifically targeting each subcomponent.

The physical activity proposed to sAUD patients could range from yoga to different kinds of aerobic or non-aerobic exercises, from low to vigorous intensity. It could be a single session or routine exercise and could be performed individually or in groups (Costa et al., 2019; Hallgren, Vancampfort, Giesen, et al., 2017). Clinical guidelines for patients with severe mental illness propose that the "intervention consists of 2-3 sessions of supervised aerobic and/or aerobic and resistance training exercise a week of 45-60 minutes duration of moderate (to vigorous) intensity" (Stubbs et al., 2018 for a review). Further clinical research is required to specify the ideal modalities of physical interventions in sAUD depending on which subcomponent is especially affected, on the patients' comorbidities or physical limitations, their lack of exercise experience, and their exercise preferences and expectations. sAUD patients expect physical exercise to improve their health, to be an accomplishment, to make them feel stronger, be physically fit, and to increase their self-confidence and their confidence in staying sober (Abrantes et al., 2011; Stoutenberg et al., 2015). However, structural (type of exercise, timing, transportation/equipment issues, cost), social (need for accountability and unsupportive relations) and emotional (fear, guilt, shame, negative affect, laziness, lack of motivation) barriers can be identified and they could result in high dropout rates in physical activity programs (Abrantes et al., 2011; Stoutenberg et al., 2015). To maximize participation, sAUD patients should be given motivational coaching, and psychosocial and cognitive support, with the goal of identifying an enjoyable physical activity. Reduction of the dropout rate is crucial and could be achieved by individualizing the physical activity proposed to each patient (Hallgren, Vancampfort, et al., 2018; Williams, 2008).

In sum, physical exercise programs conducted in sAUD should be progressive and supervised to increase motivation and engagement, reduce failure, and improve self-efficacy and empowerment. Programs should provide diversified range of moderate intensity aerobic exercise, taking the participants' expectancies and limitations into account. These programs should be offered early in the therapeutic program, on a long-term basis, with several sessions per week, and as a first line treatment to reduce stigma. Craving could be specifically targeted by short and easily achievable physical exercise. The French "physical activity on prescription" program is an interesting model. Enshrined in law in 2016, this free program emphasizes that “As part of the care pathway for patients with chronic diseases, the attending physician may prescribe physical activity adapted to the pathology, physical abilities and mental risk of the patient”. Exercise could be incorporated into usual sAUD cares, in particular in cognitive behavioral therapy and cognitive remediation programs.

4.2.2. Physical activity as an adjunctive treatment

With the exception of patients with severe withdrawal syndrome (e.g. delirium tremens or seizure), light and supervised physical activity could even be proposed from the very beginning of the residential treatment in order to attenuate withdrawal symptoms and ease anxiety symptoms (Hallgren, Vancampfort, Giesen, et al., 2017; Wang et al., 2014).

For sAUD patients, physical activity could be implemented in sedentary patients by adapting physical activities and providing specialized motivational support in medically-prescribed programs (Hallgren, Vancampfort, et al., 2018). Existing psychosocial and neurocognitive rehabilitation programs could integrate physical activity advices, or at best supervised physical activity modules including empowerment strategy.

We can also speculate that physical activity could improve the efficacy of the behavioral therapies recommended in sAUD treatment. First, physical activity could improve cognitive abilities (in particular episodic memory and executive functions), which would result in increased awareness of the consequences of the disease and better learning processes, abilities to project into the future and to implement relapse prevention strategy. These skills are crucial in cognitive behavioral therapy. Second, improvements in physical and mental health could increase the motivation to pursue sAUD treatment. In a motivational interview approach, the perception of short and middle-term benefits could help maintain a change in drinking behavior. A cognitive behavioral therapy approach could also encourage patients to challenge their own irrational beliefs about alcohol thanks to physical activity benefits (e.g. from “ I need alcohol to feel well” to “I could exercise to feel well”).

4.2.3. Physical activity as a stand-alone intervention?

Although this review focuses on sAUD patients, who require specific care and for whom physical activity would be an adjunctive treatment, physical activity could be seen as a less stigmatizing entry point into addiction care for mild-to-moderate AUD subjects (e.g. patient who do not require pharmacological treatment or hospital care) (Hallgren, Vancampfort, et al., 2018). In this specific context, physical activity could be used as a stand-alone intervention. This hypothesis is currently examined in a Swedish RCT that compared, in 210 mild-to-moderate AUD patients, the effect of a 12-week intervention (treatment as usual ; yoga ; aerobic training) on alcohol outcomes (Hallgren, Andersson, et al., 2018). Physical activity could also be useful after a brief screening intervention in primary care settings or as a preventive measure, because craving is described at all stages of AUD, and impulsivity can be very strong, even in non-sAUD individuals. Findings from prevention studies showed that drug prevention programs that include physical activity effectively reduced rates of initiation and use of alcohol (Lynch et al., 2013 for a review).

In sum, physical activity is a promising adjunctive treatment for sAUD. The triadic model provides a theoretical framework 1) to better understand the mechanisms of physical activity efficacy, 2) to evaluate which of the three components is affected and 3) to target the subcomponent affected by adapting and personalizing exercise programs in order eventually to rebalance the triadic model of AUD.

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