The association between impulsivity and relapse in patients with alcohol use disorder : a literature review

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Research Report

The association between impulsivity and relapse in patients with alcohol use disorder: A literature review

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ABSTRACT

Aims: Impulsivity has been identified as a key relapse risk factor in patients with alcohol use disorder (AUD), however the inherent characteristics of this relationship has been largely understudied. The heterogeneity of AUD and variation in impulsivity constructs require careful consideration to inform future work examining the relationship. This study sought to review empirical findings examining facets of impulsivity and AUD relapse.

Methods: A systematic search strategy was employed to capture studies on impulsivity measures related to AUD relapse. Impulsivity measures were qualitatively organized in terms of 'trait impulsivity' - typically measured by self-report questionnaires - and 'behavioural impulsivity'; i.e. 'motor impulsivity', 'impulsive choice' and 'reflection impulsivity, assessed with cognitive-behavioural tasks.

Results: Seventeen peer-reviewed papers were identified. Relapse outcomes varied substantially in relation to impulsivity measures. Twelve papers included aspects of 'trait impulsivity', and 9 studies included 'behavioural impulsivity' measures, from which 5 studies dealt with the 'impulsive choice' subcategory. The Barratt Impulsivity Scale was the self-report questionnaire that was most frequently used.

Conclusions: All three included facets of impulsivity ('trait-, motor- and impulsive choice impulsivity'), were associated with AUD relapse, but none seemed to be superior to another. Research on the relation between impulsivity and AUD relapse is relatively scarce. Future research and treatment options are proposed.

Keywords: alcohol use disorder, relapse, impulsivity, endophenotype, personalized medicine

Short summary

Impulsivity measures (categorized in terms of 'trait impulsivity' and 'behavioural impulsivity') are associated with alcohol use disorder (AUD) relapse.

Research on this association is surprisingly scarce and suggests that specific facets of impulsivity are modestly associated with relapse.

Targeting impulsivity in AUD treatment may reduce relapse risk.

MANUSCRIPT

1. Introduction

1.1. Impulsivity construct

Alcohol use disorder (AUD) is a highly prevalent disorder (Rehm *et al.*, 2015; Grant *et al.*, 2017), frequently involving multiple cycles of treatment, abstinence, and relapse (McKay and Hiller-Sturmhofel, 2011). For instance, such repeated abstinence-relapse cycles have been associated with intensified withdrawal and increased psychiatric symptoms (Ooms *et al.*, 2020). Therefore, identifying distinct relapse factors is highly relevant (McKay *et al.*, 2006). Impulsivity is one potentially relevant relapse determinant that remains relatively understudied (Reyes-Huerta et al., 2018; Sliedrecht et al., 2019).

The role of impulsivity in the initiation and progression of addictive behaviours remains an important topic (Noël, Brevers, and Bechara, 2013; Noel, Brevers, and Bechara, 2014; Koob and Volkow, 2016; Uhl, Koob, and Cable, 2019). Yet, impulsivity may have an initiating role in the development and course of substance use disorder, suggesting an underlying vulnerability, or may also be a consequence of chronic substance use (Jentsch et al., 2015; Jentsch & Taylor, 1999; Wit, 2009).

On a neurobiological level, deficits in response inhibition, leading to impulsive behaviours, could originate in both frontal cortex and striatal dysfunction. An overlap was found of impulsivity and addiction aspects that may have a common neurobiological origin, i.e. an abnormal fronto-striatal connectivity (Galandra *et al.*, 2018).

On a neuro-chemical level, neurotransmitter dysfunction, particularly decreased dopamine D2 receptor function and altered serotonin receptor function, seem to play a key role in promoting impulsive behaviours (Jentsch et al., 2015; Jentsch & Taylor, 1999). Recent research also found a role for dysfunctions in glutamate, gamma aminobutyric acid, dopamine, norepinephrine, and serotonin signalling (Kozak *et al.*, 2018).

On a cognitive level, impairments in executive function have been found related to several other psychiatric disorders, like borderline personality disorder (BPD) (Linhartová *et al.*, 2019), suicidality (Liu *et al.*, 2017) and attention deficit hyperactivity disorder (ADHD) (Adler *et al.*, 2018; Linhartová *et al.*, 2019). Furthermore, a vast body of research has investigated the impulsivity- gambling disorder association (Ioannidis *et al.*, 2019). Recently, it has been advocated that impulsivity measures should be part of a standard

neuropsychological assessment set to be used in research and treatment in addictive disorders - for instance - analogous to the MATRICS model, developed for schizophrenia (Yücel *et al.*, 2019).

Impulsivity is frequently considered a multidimensional psychological construct, which is often seen as maladaptive inhibitory processes, characterized by an inability to withhold a response; often in the face of negative consequences, a preference for small immediate rewards at the expense of larger delayed rewards (i.e., delay discounting), acting without forethought, novelty/sensation-seeking, and an increased tendency to engage in risky behaviours (Bari and Robbins, 2013).

The impulsivity construct is an area of recent research interest. Over the past several years, several reviews on impulsivity and inhibition, impulsivity and emotions/arousal, and impulsivity and genetic factors have been published (Bari & Robbins, 2013; Herman et al., 2018; Kovács et al., 2017; Sanchez-Roige et al., 2019). Additionally, new research has emphasized emotional components of impulsivity in patients with substance use disorders (SUDs) (McHugh and Goodman, 2019). Importantly, the recently proposed Alcohol and Addiction Research Domain Criteria (Witkiewitz, Litten, and Leggio, 2019) has included impulsivity as a core construct within the executive function domain (Kwako *et al.*, 2019), proposing that initiation and maintenance of AUD can be partially explained by neurobiological deficits and adaptations in executive function.
Recent advances have indicated that impulsivity is a broad umbrella construct (Broos et al., 2012; Dom et al., 2007; Stevens et al., 2014). Broos and colleagues have proposed the existence of three different aspects of impulsivity in humans: self-reported impulsivity, impulsive choice, and impulsive action (Broos *et al.*, 2012). Their impulsivity constructs were based on a principal component analysis on several commonly used assessment measures of impulsivity. Meda et al. also acknowledged the multidimensional aspect of impulsivity, and based on a factor analysis identified five widely used impulsivity factors: “Self-reported Behavioural Activation, Self-reported Compulsivity and Reward/Punishment, Self-reported Impulsivity, Behavioural Temporal Discounting, and Behavioural Risk-Taking” (Meda et al., 2009, p. 390).

In addition, Stevens et al. identified two aspects within the impulsivity construct, namely impulsive choice (subdivided in ‘delay discounting’ and ‘decision making’) and ‘impulsive action’ (subdivided in ‘motor disinhibition’ and ‘cognitive disinhibition’) (Stevens et al., 2014).

Similar to the Broos et al. (2012) definition, Herman et al. compared several existing impulsivity- concepts and postulated an impulsivity- subdivision in terms of 'trait impulsivity' and 'behavioural impulsivity' (Herman *et al.*, 2018). 'Trait impulsivity' describes a somewhat stable pattern of impulsivity, grounded in the person's character, and is often assessed by the use of self-report questionnaires. 'Behavioural impulsivity' describes a behavioural pattern of impulsivity, which is often assessed by task-based measures of objective measures during variable circumstances. They also stated that the 'behavioural impulsivity' category could be further subcategorized into 'motor impulsivity', 'reflection impulsivity' and 'impulsive choice'-categories (Herman *et al.*, 2018). As described in detail below, each of these categories can be measured by the use of a variety of self-report and behavioural-task based assessment instruments (Hamilton *et al.*, 2015; Herman *et al.*, 2018). Importantly, these subdivisions are also consistent with the definitions of impulsivity proposed by Meda et al. (2009) and Stevens et al. (2014) and, thus, the Herman et al. (2018) characterization incorporates aspects from multiple contemporary definitions of impulsivity (Meda *et al.*, 2009; Broos *et al.*, 2012; Stevens *et al.*, 2014). As such, we have used this organizing framework from Herman and colleagues (2018) in the current study. Importantly, we have explicitly not included negative urgency, which is a unique dimension of impulsivity, in the current review and we refer interested readers to a recent review on negative urgency and addiction relapse (Zorrilla and Koob, 2019).

1.2 Measuring impulsivity

1.2.1 Assessment of impulsivity

Previous research has shown that impulsivity can be captured by means of several self-report scales and behavioural tasks, but correlations were found to be generally weak (Broos et al., 2012; Dom et al., 2007; Reynolds et al., 2006; Stevens et al., 2014). Others however, found a statistically significant overlap between several laboratory tasks and self-report measures (Meda *et al.*, 2009). More recently, associations between behavioural performance, self-reported impulsivity and decision making processes have been investigated (Portugal *et al.*, 2018) and impulsiveness scores (but not decision-making) were associated with actual behavioural performance.

Behavioural-task measures of impulsivity have been shown to be reliably administered and may be used to assess various facets of impulsivity as intermediate phenotypes for SUD (Gottesmann and Gould, 2003; Weafer, Baggott, and De Wit, 2013), and AUD (Kwako *et al.*,

2019). While various self-report and behavioural measures, measure different aspects of 'impulsivity', it seems none of these categories has better predictive value in regard to relapse (King *et al.*, 2014). However, in a study of impulsivity in patients with borderline personality disorder and SUD, behavioural measures were found to have a better predictive value in relation to actual behaviour (Maraz *et al.*, 2016).

1.2.2 Specific impulsivity measures

'Trait impulsivity' can be measured by several self-report scales. For example, the Barratt Impulsiveness Scale (BIS-11) is a commonly used self-report questionnaire to assess trait impulsivity (Patton et al., 1995). Other frequently used questionnaires are Zuckerman's Sensation Seeking Scale (SSS), and the Urgency, Premeditation, Perseveration and Sensation-Seeking (UPSS) scale (Herman et al., 2018). 'Behavioural impulsivity' can be measured by several behavioural tasks, like the Stop Signal Task (SST), Go/ No Go task (GNG), and several memory tasks; all measuring different aspects of 'motor impulsivity'. Also, tasks to measure 'reflection impulsivity' (whereby choices are made without consideration), have been developed. The 'behavioural impulsivity' subcategory 'impulsive choice' is often measured by using the Delay Discounting Task, the Iowa Gambling Task (IGT), and the Balloon Analogue Risk Task (BART) (Herman et al., 2018).

1.3. Impulsivity and relapse

An important question is whether cognitive deficits associated with impulsivity are relevant to clinical outcomes, i.e. treatment retention, relapse, reduction of substance use and/or craving, and quality of life (Verdejo-Garcia, Garcia-Fernandez, and Dom, 2019). A growing body of research suggests a potential link between impulsivity and relapse in substance use (Barreno et al., 2019; Stevens et al., 2015; Stevens et al., 2014). In particular, impulsive choice and impulsive action are considered key relapse determinants in AUD (Reyes-Huerta *et al.*, 2018). However, prospective studies exploring the relationship between relapse and impulsivity measures are scarce in patients with AUD. Courtney et al. tested several dimensions of impulsivity in a non-clinical sample of problematic drinkers (majority having an AUD) and found impulsive decision making to be related to the amount of alcohol use (Courtney *et al.*, 2012). Although an association between relapse and impulsivity may exist, the nature of this relationship remains inconclusive (Sliedrecht et al., 2019). Of note, research on alcohol

relapse is frequently complicated by the ambiguous and varying conceptualization of the concept of relapse. The definition of 'AUD relapse' remains a semantic indistinctness (McKay et al., 2006; Miller, 1996; Sliedrecht et al., 2019), whereby "the heuristic value of AUD relapse as currently studied is low" (Maisto et al., 2016, p. 849). Taken together, impulsivity may seriously negatively impact the clinical outcome of patients. However, which dimensions of impulsivity are the drivers, the nature of the exact mechanisms, and the magnitude of these effects remain to be explored.

1.4. The present paper

The objective of this paper was to present the results of a systematic literature search on the relationship between impulsivity and relapse in patients with AUD, followed by a qualitative review of the results. The impulsivity- subdivision of Herman et al. was used to provide an overview of the different aspects of impulsivity in terms of 'trait impulsivity' and 'behavioural impulsivity' (Herman *et al.*, 2018) (see Table 1). The findings of the review will be categorized in terms of the aforementioned subdivision.

We hypothesized that neurocognitive and behavioural measures of impulsivity would have a higher predictive value regarding AUD relapse over subjective self-report questionnaires (Gottesmann and Gould, 2003; Weafer *et al.*, 2013; Salvatore, Gottesman, and Dick, 2015; Maraz *et al.*, 2016; Kwako *et al.*, 2019).

2. Methods

2.1 Search strategy

The original search algorithm is described in a recent systematic review on AUD relapse factors (Sliedrecht et al., 2019). However, the search was updated and focused on the impulsivity-relapse association in patients with AUD, by means of using the broad MeSH search terms 'alcoholism' (which also includes terms AUD, alcohol dependence, alcohol abuse), 'recurrence' and 'impulsive behaviour' (or synonyms compatible to the search engine used), which were coupled using the Boolean search operator 'AND'. The search was commenced in PubMed, PsycInfo, the Cochrane database of systematic reviews and the DARE database on June 24, 2020, and restricted to articles in the English language and were filtered on human studies.

2.2. Statistical analyses

The outcomes were tabulated in terms of the subdivision regarding impulsivity aspects. In those cases that the design of the included study permitted comparisons (control group), the impulsivity measures of the relapsed and those regarded as 'not relapsed' (i.e.in most cases abstinent patients) were extracted and compared. Complementary to the qualitative nature of this review, the associations between impulsivity measures and relapse, mean values, standard deviation of the abstinent control group were collected from the original papers to calculate effect-sizes, by dividing the mean value differences with the standard deviation of the abstinent control group. Effect sizes were calculated derived from five of the sixteen included studies (31%) that comprised figures on the use of 9 measurement instruments.

3. **Results**

3.1. Study selection

The search yielded 149 articles, from which titles and abstracts were screened by two authors (WS & RdW). In order to be included, articles had to describe an association between AUD relapse and impulsivity in patients with AUD. Excluded were for example articles describing relapse in other substances, without measurement of impulsivity, as well as several articles that described 'craving'. Eventually, thirty-five full text articles were read for eligibility assessment and added to this, was one extra article from an earlier pilot- search. Finally, 17 peer reviewed articles describing AUD relapse in relation to impulsivity were included in this study. The quality was guarded by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method (Moher *et al.*, 2009). To visualize the selection and data extraction process see the flow chart in Figure 1.

[INSERT Figure 1]

From the included articles, the following data were extracted and tabulated in terms of study design/population, follow-up period, sample size, impulsivity measure used, and the results/statistics. In addition, the AUD relapse definition that was used in each paper was tabulated. A relationship between impulsivity and AUD relapse with $p < 0.05$ was regarded as statistically significant.

3.2. *Findings*

3.2.1. General findings

Of the 17 included studies, eleven studies were European, three came from the United States, one from Canada, one from China and one from Turkey. Sample sizes varied between 20 and 473, and in all but two (Fein, Klein, and Finn, 2004; Tucker *et al.*, 2016) cases, the sample consisted of a clinically obtained research population. Follow up period varied from several months to eight years. Most research measured 'impulsivity' by using the Barratt Impulsivity Scale (BIS-11), which is a self- report measure (Patton, Stanford, and Barratt, 1995). In half of the included studies, the impulsivity– relapse association was found to be statistically significant. An overview of included articles can be found in Table 1.

[INSERT Table 1]

3.2.2 Relapse definitions

In all included articles, the definition for AUD relapse is provided in Table 1. Relapse definitions varied greatly, from any (substance) use to number of AUD related problems. Therefore, no uniform relapse definition could be extracted from the included papers. In the current review, we examine the association between impulsivity and AUD relapse based on the impulsivity measures and AUD relapse definition as they were used in the original study.

3.2.3. Overview of included studies

Trait impulsivity

Ten out of 16 studies reported on the relationship of BIS-11 or BIS-15 self-report measures and AUD relapse, whereby most frequently the BIS- sum score was used in the analyses. In 4 studies this association was found to be statistically significant (Bowden-Jones *et al.*, 2005; Evren *et al.*, 2012; Rubio *et al.*, 2018; Wang *et al.*, 2018). However, in one study a more fine-grained analysis of the data was applied, whereas controlling for craving, showed that the BIS score appeared to be indirectly associated with relapse via craving (Evren *et al.*, 2012). In another study, an inverse relation was found, and lower trait impulsivity levels were associated with a higher probability of a lapse (Papachristou *et al.*, 2014). In five studies, findings on the BIS/ AUD relapse – association were not statistically significant (Charlet *et al.*, 2013; De Wilde *et al.*, 2013; Matheus-Roth *et al.*, 2016; Bernhardt *et al.*, 2017).

Personality based impulsivity measures were assessed by Novelty Seeking (NS) scores (Evren *et al.*, 2012) and the 'Personality research form' (Prf) (Moos and Moos, 2003). Only the Novelty Seeking subcategory 3 (NS3), was significantly associated with relapse. Impulsivity in the Prf was not associated with relapse. Also, in one study 'Trait impulsivity' was assessed by using the UPPS Impulsive Behaviour scale (Quoilin *et al.*, 2018), which was statistically significant associated with AUD relapse.

'Behavioural impulsivity'- 'motor impulsivity'

In two studies a Go/ No-Go paradigm was used, testing the response inhibition performance. Response inhibition deficits were associated with AUD relapse (Czapla *et al.*, 2016; Rupp *et al.*, 2016). In one study, to assess 'motor impulsivity', the Stop Signal Test (SST) was used, but findings in relation to AUD relapse were not statistically significant (Jakubczyk *et al.*, 2013). In a more recent study, measures of behavioural inhibition (visual reaction time (RT) task, Stop-Signal, Anti-Saccade, Number-Letter task), and neuronal motor inhibition (instructed-delay choice RT task) were all found to be statistically significant in relation to AUD relapse (Quoilin *et al.*, 2018).

'Behavioural impulsivity'- 'impulsive choice'

The outcomes on the Iowa Gambling Test (IGT), the Simulated Gambling Task (SGT) and an unnamed gambling test (Bechara *et al.*, 1994) were also investigated in relation to relapse. In two studies a statistically significant association with relapse was found (Bowden-Jones *et al.*, 2005; De Wilde *et al.*, 2013), and in one study this association was not statistically significant (Fein *et al.*, 2004).

Delay Discounting (DD) was investigated in three studies. One study showed that DD was associated with AUD relapse (Bernhardt *et al.*, 2017), and in another study this association was not statistically significant (De Wilde *et al.*, 2013). In an additional study (Tucker *et al.*, 2016), no specific data regarding relapse could be extracted.

Bernhardt et al. also investigated Probability Discounting for Gain (PDG), and Mixed Gambles (MG), which were not associated with relapse. In this latter study an association with Probability Discounting for Loss (PDL) and AUD relapse was found (Bernhardt *et al.*,

2017). In one study, the Balloon Risk Analogy Test (BART) was used and test- performance was statistically significantly associated with relapse (Wang et al., 2018).

Effect sizes

To give an impression of the strength of the impulsivity- relapse associations, we calculated effect sizes, which are displayed in Table 1. Effect sizes of 0.8 and more, are considered as 'large', as effect sizes exceeding 1.2 are considered 'very large' (Sawilowsky, 2009). However, the interpretation of these results should be done with caution, and a pooled analysis/ meta-analysis would not be proper.
In the 'trait impulsivity' category we calculated effect sizes of 0.7 (BIS-11 attention scores) , 0.4 (BIS-11 total scores (Wang *et al.*, 2018), 1.1 (Novelty Seeking subcategory 3) (Evren *et al.*, 2012), and 1.7 (Barratt Impulsiveness Scale) (Bowden-Jones et al., 2005).
In the 'behavioural impulsivity' subcategory 'motor inhibition', we found an effect size of 1.1 for the Go/ No-go inhibition paradigm, accounting for an odds ratio of 1.55 (higher impulsivity scores associated with relapse) (Rupp *et al.*, 2016). Finally, for the 'impulsive choice' subcategory effect sizes of 0.4 (BART performance) (Wang *et al.*, 2018), 0.2 (Delay Discounting) , and 0.7 (PDL) (Bernhardt *et al.*, 2017), could be calculated.
In addition, an effect size of 1.3 for an unnamed gambling task (Bowden-Jones et al., 2005) was calculated.

4. Discussion

4.1.1 General overview

The role of impulsivity related to alcohol use disorder (AUD) and other substance use disorders (SUD) is a growing area of research, but the current qualitative review on the empirical literature examining the association between impulsivity and AUD relapse suggests this literature is relatively scarce and heterogenous. Our results add new elements to an earlier systematic review on a broader spectrum of factors associated with AUD relapse (Sliedrecht et al., 2019), and indicates some promising future directions for studying the association between AUD relapse and impulsivity, as outlined below.

In the studies that used measures from the 'trait impulsivity'- category, the Barratt Impulsivity Scale was most frequently used. The results indicate a consistent association between 'trait impulsivity' and AUD relapse. However, the magnitude of this effect varied across studies.

Among the other personality-based measurement instruments that have been used we found less consistent associations between trait impulsivity and relapse. Together, findings indicated a large variability in the association between AUD relapse and the construct of 'trait impulsivity'. For instance, although the BIS was the most frequently used measurement instrument, the effect sizes varied from small to large across studies of different research populations.

To account for the impulsive reactions that may be elicited by different circumstances, the use of objective 'behavioural impulsivity' tasks, it would be tempting to suggest that these instruments would have a higher level of face validity and results would be more preferable. With respect to the concept of 'behavioural impulsivity' multiple tasks, covering a wide range of aspects of this category have been employed. For example, the 'Go/ No- Go' test is commonly used in measuring 'motor impulsivity', but even than accounts only for the 'inhibition' part (Herman et al., 2018; Vassileva and Conrod, 2019). For this 'behavioural impulsivity' subcategory, there seems to be an association with AUD relapse as well, but also in this category, various instruments are used and the strength of statistical outcomes varies. This prevents us from drawing firm conclusions.

Finally, in the 'impulsive choice' subcategory, different measurement instruments are used as well. In one out of two studies delay discounting was associated with AUD relapse, and in another study, 'Probability Discounting for Loss' (PDL) was associated with relapse. The same was true for the BART, as was shown in one study. Relatively small effect sizes and highly varying statistical outcomes could indicate that the association of this category with AUD relapse is considered weak.

As reported in Table 1, we also calculated effect sizes (based on difference of the means), which varied from small (delay discounting) to very large (BIS). Because of heterogeneity in samples and definitions used, results should be interpreted with caution and a meta-analysis was not feasible. Based on the fraction of statistically significant findings within each category and the effect sizes found, our hypotheses were not supported and the behavioural measures and self-report measures of impulsivity were globally even strongly associated with AUD relapse. We would suggest the future use of well-defined and more semantically uniform sub-aspects of impulsivity constructs and AUD relapse definitions. The use of standardized impulsivity constructs and relapse definitions, could help bridge key constructs in alcohol research to facilitate translational research (Ray *et al.*, 2020).

It was recently hypothesized that AUD relapse can especially be seen as an inability to value delayed rewards (delay discounting) and to inhibit prepotent responses (Reyes-Huerta *et al.*, 2018). In a subset of patients with AUD, impulsivity might be associated with proneness on the rewarding effects of alcohol use (Westman, Bujarski, and Ray, 2017) and higher levels of craving (Joos *et al.*, 2012a). Alternatively, deficits in impulse control may impact treatment compliance and retention, and via that way, indirectly, influence relapse in alcohol use for patients who engaged treatment. Finally, impulsivity may be considered a mediator of other factors that impact craving and relapse (e.g. stress or mood). It was recently found that the craving-relapse association, can be mediated by impulsive decision making ('rash impulsivity') (Coates *et al.*, 2020). Finally, the relation between stress and relapse might be mediated by impulsivity in the context of both cigarette smoking and alcohol use (Ansell *et al.*, 2012; Hamilton *et al.*, 2013).

Other research on impulsivity has shown that the severity of alcohol use disorders is associated with impaired behavioural control (Claus, Kiehl, and Hutchison, 2011), which may influence the risk of relapse. This imbalance in control abilities is caused by different developmental trajectories of distinct reward and regulatory brain circuitry during the maturing process (Van Leijenhorst *et al.*, 2010). Yet, it has been shown that impulsivity fluctuates not only in adolescence, but throughout the life-span, suggesting state as well as trait aspects (Mayhew and Powell, 2014). Individual variation in decrease of impulsivity was found to be linked to alcohol consumption patterns (Littlefield, Sher, and Wood, 2009; Littlefield and Sher, 2010), which also could imply reciprocal effects on the progression of addiction (Littlefield *et al.*, 2009).

According to the early Eysenckian theoretical formulations, impulsivity was considered a prominent personality trait, originally included in the extraversion dimension, but later built-in the Psychoticism dimension (Eysenck and Eysenck, 1977). Building upon Eysenck's work, psychobiological models that include impulsivity have been proposed and created by e.g. Zuckerman et al. (1979, 1991), Cloninger et al. (1981, 1994), Babor et al (1992) identifying impulsivity/disinhibition as an important risk factor for relapse and future substance abuse (Zuckerman and Neeb, 1979; Cloninger, Bohman, and Sigvardsson, 1981; Zuckerman *et al.*, 1991; Babor *et al.*, 1992; Cloninger, 1994).

In general, such impulsivity concepts are typically applied to measure long-term trait-dependent features of impulsivity and frequently measured with the Barratt Impulsiveness Scale (BIS-11), one of the most widely used self-report measures. In contrast, behavioural

tasks are considered to be more sensitive to situation-specific changes in impulsivity that e.g. encompass stressful situations, induced craving by cue-related stimuli such as alcohol, and temporal impaired emotional functioning (Moeller *et al.*, 2001; Dougherty *et al.*, 2003, 2005). Furthermore, alcohol typology could be a useful framework in identifying future targeted medication options (Leggio *et al.*, 2009), and to predict treatment retention and outcome (Foulds *et al.*, 2017).

4.1.2 Limitations

Of importance, interpretation and generalisation of the findings remains difficult given that throughout the different studies impulsivity constructs, measurement instruments, patient numbers, and follow up periods varied widely. Also, the potential role of gender, age, or psychiatric comorbidity (as a potential confounder) on the impulsivity- relapse association could not be deduced from the content of the included papers. This prevents us from drawing firm conclusions. Being aware of a 'language bias', we limited our search to papers written in English. Nevertheless, research from various countries was included. A meta- analysis of effect sizes was not feasible given the heterogeneity in study designs, instruments used, and relapse definitions. This was also found in a recent study on impulsivity and gambling, whereas meta-analyses could not be performed on impulsivity measures because of a lack of sufficient data in the included studies (Ioannidis *et al.*, 2019).

It must be noted that in the last decades several perspectives on impulsivity have been postulated. Some components of frequently used inventories (like 'venturesomeness', 'positive urgency', 'inattention' and 'non- planning' impulsivity can be categorized in the 'trait impulsivity' main- category, whereas for example the 'behavioural impulsivity' sub category 'motor impulsivity' could be further subdivided in 'stopping' and 'waiting' impulsivity. In addition, some categories with different names throughout literature are actually synonyms, like 'insensitivity to consequences' and 'delay discounting', as well as 'impulsive choice' and 'decision making'.

We did not include measures of 'urgency' in the current review because negative urgency has recently been the focus of a similar review that was recently published (Zorrilla and Koob, 2019). Overall, the field of neurocognitive research in addictions is highly in need of the implementation of a widely accepted standard test-battery probing well defined cognitive dimensions relevant for addictive disorders (Verdejo-Garcia *et al.*, 2019; Yücel *et al.*, 2019).

4.2. Future research

Results from this review suggests distinct aspects of impulsivity and AUD relapse are related. Experts in the field have indicated that impulsivity measures, i.e. impulse control, reward valuation and action selection, should be part of a standard neuropsychological assessment in addictive disorders (Yücel *et al.*, 2019) and this would assist future research examining the impulsivity and AUD relapse association.

The interpretation of the outcomes of self-report measures, like the BIS-11, should be done with caution. This accounts for distinct behavioural measures as well, such as reliability and predictive validity in relation to AUD relapse. More research is needed as has for example been done recently in relation to success in quitting smoking (McCarthy *et al.*, 2016). Our results show that we did not find evidence that behavioural measures have more predictive potential over self- report measures in relation to AUD relapse.

As identified in many publications, there is no uniform concept of relapse being used in the literature. The use of a uniform definition of AUD relapse/ remission would be critical for future comparative research.

4.3 Future treatment options

At this moment, the number of effective evidence-based treatment options specifically targeting impulsive behaviours is scant (Vassileva and Conrod, 2019). Novel treatment options are mostly experimental in nature (Vassileva and Conrod, 2019). A future step could be to initiate clinical trials that focus on potential therapeutic options for reducing impulsivity and increasing behavioural control in SUD/AUD patients.

Psychological treatments can be used to strengthen top down impulse control or weaken bottom up drive (Verdejo-Garcia *et al.*, 2019). A recent example of the former, is Goal Management Training (GMT), which is a therapist-guided cognitive remediation training that instructs participants to implement a meta-cognitive strategy to decision-making (Levine *et al.*, 2011), and has also been shown to improve executive function in alcohol and stimulant polysubstance users (Alfonso *et al.*, 2011; Valls-Serrano, Caracuel, and Verdejo-Garcia, 2016) as well as in HIV+ participants with SUDs (Casaletto *et al.*, 2016). However, in spite of the positive effects on cognitive measures, effect on alcohol and substance use reduction could not be demonstrated.

Treatment interventions can also aim at weakening the bottom-up substance use oriented drive. An example of this approach is cognitive bias modification (CBM). In a recent meta-analysis, a cognitive bias- impulsivity relationship was demonstrated, supporting the need of further research on cognitive bias modification (Leung *et al.*, 2017). In a recent review, however, a positive effect of CBM on AUD relapse rates could not be reliably confirmed (Boffo *et al.*, 2019). The use of targeted repetitive Transcranial Magnetic Stimulation (TMS) is an area of growing research interest. Several impulsivity related brain areas have shown to be successfully targeted in TMS (Ibrahim *et al.*, 2019; Vassileva and Conrod, 2019). Cognitive Enhancement Therapy may also be an effective treatment option for the 'impulsive AUD' population (Kozak *et al.*, 2018).

Finally, there is substantial evidence in preventing AUD relapse (McDonell *et al.*, 2017) and SUD relapse (Davis *et al.*, 2016) by employing contingency management (CM). Furthermore, this was confirmed (Tomko, Bountress, and Gray, 2016) in a diagnostic group (smoking, cannabis) with impulsivity characteristics ('trait impulsivity' and 'impulsive choice' measures).

Based on 'impulsivity theoretical constructs', and their neurobiological basis, several pharmacological-options ("cognitive enhancers') have recently been postulated and investigated. In a randomized placebo- controlled trial, the use of the 'cognitive enhancer' modafinil did not lead to higher abstinence rates, but there could be a positive effect in a subcategory of patients with baseline impaired response inhibition (Joos et al., 2012). Modafinil also modulated impulsive decision making (delay discounting), as was shown in a small randomized, placebo-controlled study (Schmaal *et al.*, 2014). Naltrexone is used as an anti- craving agent to prevent alcohol relapse, but seems to have the potential to modulate the neural correlates of motor inhibition as well (Nestor *et al.*, 2018). The same accounts for the anticonvulsant topiramate, which also showed some effects on 'behavioural impulsivity' (Rubio, Martínez-Gras, and Manzanares, 2009). In a placebo-controlled pilot study, the use of the antipsychotic medication quetiapine showed a significant effect on response inhibition, as measured by the Stop Signal Task (Moallem and Ray, 2012). Recent studies show a positive effect of high dosages of methylphenidate on amphetamine and cocaine use in stimulant-dependent ADHD patients (Konstenius *et al.*, 2014; Skoglund *et al.*, 2017). Interestingly, also other associated substance use in these patients, e.g., alcohol and cannabis, diminished in these trials. This finding may indicate a substance "transdiagnostic" effect of high dosed methylphenidate (Verdejo-Garcia *et al.*, 2019).

In a randomized, placebo-controlled, double-blind, crossover study with 87 healthy controls, the dopaminergic drug 'L- Dopa', attenuated risk seeking in the more impulsive individuals, but no effect on 'impulsive choice' was found (Petzold *et al.*, 2019).

At last, the prescription of the aversive anti-relapse medication disulfiram is intuitively done with much precaution in 'impulsive' patients with AUD. However, the use of supervised disulfiram in a patient population known for impulsivity (borderline personality disorder), was shown to be rather safe in a small case history study (Mutschler *et al.*, 2010).

5. Conclusions

Both 'behavioural impulsivity' (with 'motor impulsivity' and 'impulsive choice' sub-categories) and 'trait impulsivity', as measured by distinct measurement instruments, seem to be associated with AUD relapse risk. Research on the relation between distinct measures of impulsivity and AUD relapse is still relatively scarce. We found that none of the impulsivity subcategories had greater predictive value in regard to AUD relapse. Treatment options are still largely experimental, so more research is needed. The use of standardized impulsivity constructs and relapse definitions, could help bridge key constructs in alcohol research to facilitate translational research.

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