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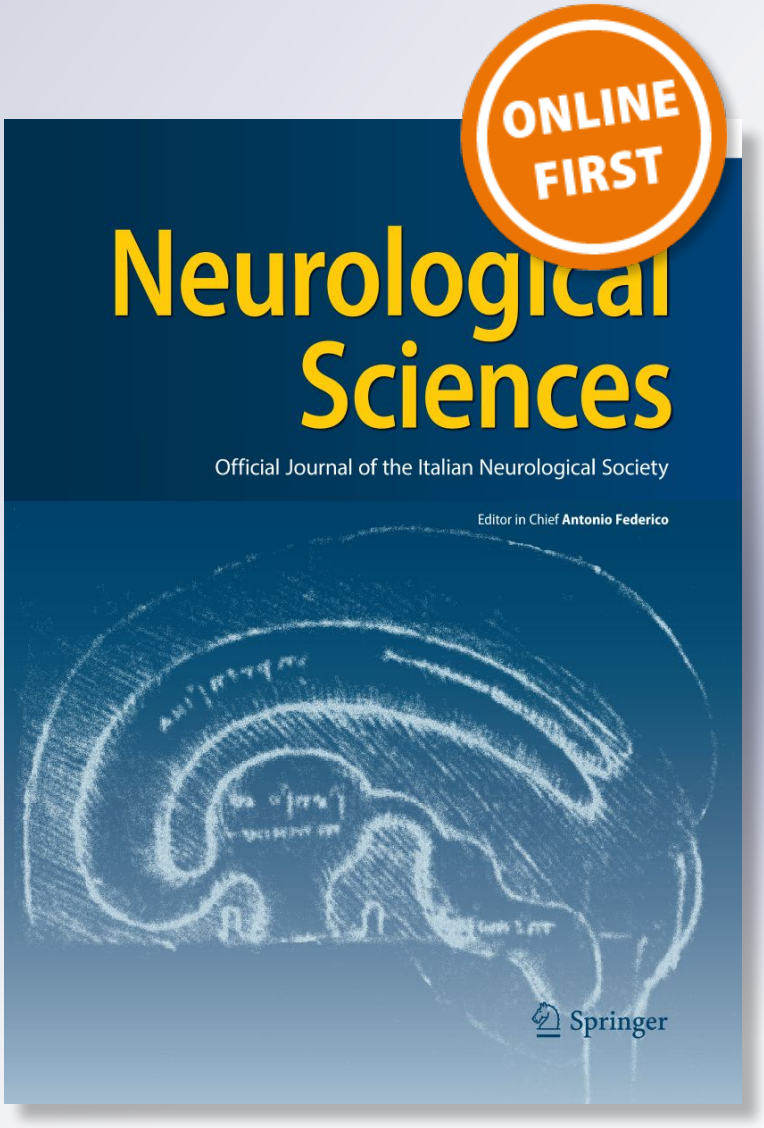

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REVIEW ARTICLE

The alcoholic brain: neural bases of impaired reward-based decision-making in alcohol use disorders

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Abstract

Neuroeconomics is providing insights into the neural bases of decision-making in normal and pathological conditions. In the neuropsychiatric domain, this discipline investigates how abnormal functioning of neural systems associated with reward processing and cognitive control promotes different disorders, and whether such evidence may inform treatments. This endeavor is crucial when studying different types of addiction, which share a core promoting mechanism in the imbalance between impulsive subcortical neural signals associated with immediate pleasurable outcomes and inhibitory signals mediated by a prefrontal reflective system. The resulting impairment in behavioral control represents a hallmark of alcohol use disorders (AUDs), a chronic relapsing disorder characterized by excessive alcohol consumption despite devastating consequences. This review aims to summarize available magnetic resonance imaging (MRI) evidence on reward-related decision-making alterations in AUDs, and to envision possible future research directions. We review functional MRI (*f*MRI) studies using tasks involving monetary rewards, as well as MRI studies relating decision-making parameters to neurostructural gray- or white-matter metrics. The available data suggest that excessive alcohol exposure affects neural signaling within brain networks underlying adaptive behavioral learning via the implementation of prediction errors. Namely, weaker ventromedial prefrontal cortex activity and altered connectivity between ventral striatum and dorsolateral prefrontal cortex likely underpin a shift from goal-directed to habitual actions which, in turn, might underpin compulsive alcohol consumption and relapsing episodes despite adverse consequences. Overall, these data highlight abnormal fronto-striatal connectivity as a candidate neurobiological marker of impaired choice in AUDs. Further studies are needed, however, to unveil its implications in the multiple facets of decision-making.

Keywords Alcohol use disorder · Decision-making · Reward · Neuroeconomics · *f*MRI · Brain morphometry

Introduction

Alcohol use disorders (AUDs) are chronic relapsing disorders characterized by excessive alcohol consumption despite its devastating consequences, loss of control in limiting intake and experience of negative emotional states when access to alcohol is prevented [1]. To define AUDs, the DSM-V combined dependence and abuse, previously conceptualized as two separate and hierarchical disorders, into one single construct ranging from mild to moderate to severe. In particular, diagnostic criteria for AUDs emphasize an impairment in *behavioral control*. Namely, the main hallmark of AUDs is not just alcohol use in itself, but rather the struggle to control its consumption. At the neuropsychological level of analysis, such impairment may be analyzed within a framework involving several cognitive domains, from the evaluative processes underlying decision-making, to executive functioning and cognitive control. These aspects need to be disentangled from the complex pattern of neuropsychological consequences of the toxic effect of alcohol and related comorbidities (nutritional deficiencies, metabolic dysfunctions, additional dependencies, etc.) [2], which contribute to chronic cognitive dysfunction up to the level of dementia [3].

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To date, two (not mutually exclusive) theories have been proposed to account for a basic decision-making disorder.

On one side, *control-related deficit* theories describe addictions as resulting from the imbalance between the so-called impulsive and reflective systems, i.e., two separate but interacting brain networks associated with oppositely valenced mechanisms of behavioral control [4, 5]. The hyperactivity of the impulsive system, associated with bottom-up affective states mediated by limbic reward-related structures such as amygdala and striatum [6], would lead to overestimate the impact of the immediate choice prospects [7]. Conversely, the hypo-activity of the reflective system, involving the anterior cingulate and prefrontal cortex, would lead to underestimate the impact of future prospects, such as the negative consequences of alcohol use. The combination of these two abnormal mechanisms might impair top-down cognitive control processes associated with the medial prefrontal cortex [8, 9]. This imbalance may thus bias decision-making processes towards bottom-up impulsive signals, at the expenses of top-down goal-driven attentional resources needed to exert behavioral control over alcohol search and consumption.

The so-called *reward-related deficit* theories highlight the role played by a motivational brain network energizing behavior via the processing of (anticipated or experienced) rewarding vs. stressing stimuli/events [10, 11]. In this perspective, the development of addiction reflects a progression from impulsivity to compulsivity mainly driven by negative reinforcement, i.e., by the need to escape the aversive state associated with the craving for alcohol. In turn, the latter is considered to reflect the dysregulation of specific neurochemical elements within several limbic structures such as amygdala and the ventral striatum, leading to decreased activity of the reward system and increased activity of the stress system. The latter, indeed, is thought to be activated by acute excessive drug intake and sensitized during repeated withdrawal. The persistence of this abnormal functioning into protracted abstinence would then contribute to the compulsivity of alcoholism [12].

In recent years, novel insights into the neural basis of decision-making impairments in AUDs are coming from neuroeconomics, an interdisciplinary research field combining notions and methods from behavioral economics and cognitive neuroscience to identify the neural bases of adaptive behavioral learning in normal and pathological conditions [13]. In the neuropsychiatric domain, this translational discipline aims to investigate how the relationship between neural systems associated with reward processing and cognitive control promotes the development and/or maintenance of disorders, and whether neurocognitive evidence may predict relapses and inform treatments. In particular, an abnormal functioning of the meso-cortico-limbic reward brain system is considered a possible biomarker or endophenotype for several neuropsychiatric disorders [14]. The reward dopaminergic pathway, indeed, is the core brain system in decision-making, activated by a variety of primary [15] and secondary rewards, including monetary [16] or social [17] ones.

Here we review and discuss such evidence by adopting a well-established distinction [18] among three key stages of decision-making processes, i.e., outcome anticipation, outcome experience, as well as outcome evaluation resulting in behavioral adaptations to past experience (learning). The former process entails the evaluation of potential outcomes before making a decision, and is referred to as "decision utility" in the case of a pure anticipation, i.e., with no expectation of knowing the actual outcome [19, 20]. When the latter is known, instead, the decision-maker can evaluate the actual consequences of her/his choices, which are automatically compared with expectations. Such comparison results in a "prediction error" signal (either in outcome magnitude, probability, or timing), shaping adaptive behavioral learning in subsequent choices [21, 22]. While different facets of this process engage specific structures within the meso-cortico-limbic pathway, they all seem to share the involvement of the striatum [18]. The latter displays an asymmetric bidirectional response of activation for anticipated gains and deactivation for anticipated losses [19, 20, 23], with the steeper degree of deactivation vs. activation reflecting individual differences in the typical tendency to overweigh potential losses relative to gains (i.e., loss aversion) [24].

This review aims to provide a concise summary of available magnetic resonance imaging (MRI) evidence on reward-related decision-making alterations in AUDs, to identify gaps in a growing literature and to envision possible future directions. Due to our focus on decision-making processes, we will review functional MRI (fMRI) studies using mostly tasks involving monetary rewards, as well as MRI studies relating choice-related parameters to neurostructural gray- or white-matter metrics. Since our aim is to draw connections between impaired decision-making and abnormal activity of the reward brain system, we will exclude studies without a healthy control group (see Table 1). Moreover, given the focus on chronic alcohol abuse, we will exclude studies on young individuals. The Altered reward-related brain activity in AUDs section summarizes available evidence on abnormal brain activity associated with alterations in the three decision-making stages described above. In the Neurostructural alterations in AUDs section, we address neurostructural changes (involving both gray- and white-matter) in AUDs, while in Conclusions section, we discuss current gaps in the literature and possible future research directions.

Table 1 Summary of the reviewed studies

Authors (year)	Subjects	Right handedness	Abstinence	Smoke	Psychoactive medications	Other substance	Diagnosis
Warse et al., (2007)	16 pt.-16 hc (only males)	Y	5 days	Y	N	N	ICD-10 DSM-IV
Bjork et al., (2008a)	23 pt.-23 hc	Y	6 days	23 pt. 3 hc	N	Y	DSM-IV
Bjork et al., (2008)	17 pt.-17 hc	Y	1 week	Not reported	Not reported	Y	DSM-IV
Beck et al., (2009)	19 pt.-19 hc	Y	1 week	19 pt. 13 hc	*N* (at least 4 days before the study)	N	ICD-10 DSM-IV
van Holst et al., (2014)	19 pt.-19 hc	Y	2 week	18 pt. 4 hc	N	N	DSM-IV
Hagele et al., (2015)	26 pt.-54 hc	Y	Not reported	25 pt. 26 hc	N	N	ICD-10 DSM-IV
Romanczuk-Seiferth et al., (2015)	15 pt.-17 hc (only males)	Y	1 week	Y	Not reported	N	ICD-10 DSM-IV
Zhu et al., (2016)	16 pt.-34 hc	Y	Not reported	15 pt. 6 hc	Not reported	Not reported	DSM-IV
Bjork et al., (2012)	29 pt.-23 hc	Y	1 week	Y	N	Y	DSM-IV
Forbes et al., (2014)	24 pt.-24 hc	Y	2 weeks	12 pt. 12 hc	Not reported	N	DSM-IV
Park et al., (2010)	20 pt.-16 hc, only males	Y	1 week	Y	N	Not reported	ICD-10 DSM-IV
Deserno et al., (2015)	13 pt.-14 hc, only male	Y	Not reported	Not reported	N	N	ICD-10 DSM-IV
Gilman et al., (2015)	18 pt.-17 hc	Y	6 days	18 pt.-1 hc	N	Y	DSM-IV
Ames et al., (2013)	17 heavy drinking 15 light drinking	Y	24 h	Y	N	N	AUDIT
Sjoerds et al., 2013	31 pt.-19 hc	28 pt. and 16 hc	24 h	18 pt	Y	N	DSM-IV
Reither et al., (2016)	43 pt.-35 hc	33 pt. and 32 hc	8 days	33 pt.-16 hc	N	N	ICD-10; DSM-IV
Beylergil et al., (2017)	34 pt.-26 hc, only male	Y	7 days	25 pt.-11 hc	N	N	ICD-10; DSM-IV
Sebold et al., (2017)	37 abstainers 53 relapser 96 hc	Y	21 days (mean)	75% pt. and 65% hc	N	N	ICD-10 DSM-IV
Fein et al., (2006)	43 pt.-58hc	Not reported	6 months	Not reported	DSM-IV	N	Average alcohol dose and duration of alcohol Use
Le Berre et al., (2014)	30 pt.-2 hc groups (45 hc for the gambling task and 27 hc for the neuroimaging study)	Not reported	7 days	Not reported	N	N	DSM-IV
Zorlu et al., (2013)	17 pt.-16 hc, only male	Y	2 weeks	17 pt.-16 hc	N	N	DSM-IV
Zorlu et al., (2014)	12 pt.-13 hc, only male	Y	6 months	12 pt.-13 hc	N	N	DSM-IV

Table 1 (continued)

Authors (year)	DM Task			Psychological/cognitive assessment	(f)MRI findings (PT vs. HC)	Behavioral findings (PT vs. HC)
	Ant	Out	Learn			
Warse et al., (2007)	MID			ADS OCDS HAMD	Reduced VS activity in gain anticipation, correlating with alcohol craving.	Stronger alcohol craving.
Bjork et al., (2008a)	MID			IQ NEO-PR-R	VS activation during gain/loss anticipation in both groups, but stronger VS activity during reward notification in alcoholics.	Significantly faster responses to targets; enhanced fearfulness elicited by non-incentive cues. Higher NEO-neuroticism and impulsiveness scores.
Bjork et al., (2008)	RTT			NEO-PR-R RT	Striatal hypersensitivity to anticipated reward; under-recruitment of PMC conflict-monitoring circuitry when reward entails potential penalties.	Higher NEO-neuroticism, extroversion and impulsivity scores and lower agreeableness and conscientiousness scores. Higher anxiety in motor-control and non-penalty trials. Higher self-reported measures of happiness in both motor-control and high-penalty trials. Effect of penalty-size on risk-taking only in hc.
Beck et al., (2009)	MID			ADS OCDS STAI HAMD BIS-10 vIQ	During gain anticipation, reduced VS activity and significant association between impulsiveness and R VS and L ACC. No significant group differences during outcome experience.	Stronger alcohol craving, depression severity and anxiety, as well as negative correlation between impulsivity and depression. Higher scores in the total, motor and cognitive scores of the BIS-10.
van Holst et al., (2014)	Card-guessing task			AUDIT IQ BIS-10	Stronger activity in the L caudate and L putamen for gain anticipation and outcome magnitude evaluation, respectively. No significant group differences during loss anticipation or probability evaluation. No correlation with impulsivity traits.	Higher AUDIT and BIS-10 scores. Significant interaction between group and probability, with lower rating of winning expectation in alcoholics.
Hagele et al., (2015)	MID			BDI STAI OCDS ADS	Reduced R VS activity during gain anticipation, negatively correlated with the severity of depressive symptoms. No significant group differences in brain activity associated with loss anticipation.	No significant group differences.
Romanczuk-Seiferth et al., (2015)	MID			BDI-II BIS-10 Matrices test	Reduced loss avoidance, as well as reduced VS activation during anticipation of both gains and losses.	Higher depression severity and BIS-10 scores.
Zhu et al., (2016)	RTT				In both groups, stronger activity at anticipation of risky vs. safe decisions. In pt., additional stronger engagement of ACC, insula, basal ganglia, as well as	No significant group differences in risk tolerance, as measured by the number of busted trials or time between first and second press (See [25]).

Table 1 (continued)

Authors (year)	DM Task			Psychological/cognitive assessment	(f)MRI findings (PT vs. HC)	Behavioral findings (PT vs. HC)
	Ant	Out	Learn			
					regions involved in motor and executive control.	
Bjork et al., (2012)	MID			NEO-PI-R	No significant group differences.	In both groups, (a) positive correlation between the amount of potential reward and both happiness and excitement; (b) negative correlation between RT and incentive magnitudes. Higher NEO-IF scores in pt.
Forbes et al., (2014)		Card-guessing task		ADS	Reduced activity in lOFC, mPFC, dlPFC, and VS during win vs. loss trials. Stronger neg-FC between the nAcc and lOFC, mPFC and dlPFC. Relationship between drinking characteristics and both the intensity of mPFC activation and its connectivity with nAcc.	No significant group differences.
Park et al., (2010)		Reward-guided dm task		AUQ vIQ	In win vs. loss trials, significant group differences in FC (related to learning rate and magnitude of craving) between VS and R dlPFC, with pt. showing no feedback-related modulation. No significant group differences in PEs-related activity in midbrain, bilateral VS, OFC, ACC, and dlPFC.	No significant group differences in general intelligence. Larger numbers of trials needed to meet learning criteria. No significant group differences concerning model fit to subject's behavior.
Deserno et al., (2015)		Reversal learning task		ADS OCDB LDH IQ WCST D2-Test	In both groups, significant relationship between PEs computation and bilateral VS activity. In pt., negative correlation between R VS activity underlying PEs computation and craving (not chronic alcohol intake).	No significant group differences in the WCST and D2-Test scores. In patients, reduced ability to meet learning criteria (see [26]).
Gilman et al., (2015)	Lane risk-taking task			IQ BIS-11 NEO-PI-R	Anticipation: significant interaction between group and cue-type (risky vs. safe) in the L SFG, with pt. showing weaker activation. Decision: significantly greater modulation by cumulative reward in the bilat caudate, putamen, thalamus, and R STG. Choice: positive correlation between earnings and activity in the L caudate and putamen, PCC and occipital gyrus. Feedback: effect of modulation by earnings in the L putamen and caudate, particularly during receipt of "wins."	Higher impulsivity and neuroticism scores. No significant group differences in the numbers of safe or risky choices.
Ames et al., (2013)			Alcohol-IAT	Working memory		

Table 1 (continued)

Authors (year)	DM Task			Psychological/cognitive assessment	(f)MRI findings (PT vs. HC)	Behavioral findings (PT vs. HC)
	Ant	Out	Learn			
				AUQ RT	Enhanced activity in compatible vs. incompatible trials in the L putamen and R insula. Stronger L OFC activity in both compatible and incompatible trials in light, compared with heavy, drinkers. Significant main effect for condition in the dlPFC during incompatible trials.	Stronger positive implicit associations towards alcohol. No significant group differences in error rates. Relationship between drinker status and alcohol use in the past 3 years. Significant correlation between alcohol urges and working memory capacity in the sample.
Sjoerds et al., 2013			Instrumental learning task	AUDIT BAI IDS	Enhanced activity in the posterior putamen during instrumental learning. Reduced vmPFC activity during goal-directed actions in pt., related to disease duration. Stronger activation of the posterior putamen during habit learning.	In the discrimination training phase, main effect of trial type in both groups, with worse performance on incongruent, compared with congruent and standard trials. In the outcome-devaluation phase, significant group effect, with worse performance regardless of trial type.
Reither et al., (2016)			Reward-guided decision-making task	TLFB OCDS ACQ AUDIT Digit-Span Digit-Symbol-Substitution-Test Matrices Test vIQ TMT(A-B)	No significant group differences in the neural signature of classical PEs. Reduced fictive PEs-related activity in the mPFC and PCC.The reduced mPFC activity correlates positively with disadvantageous choices behaviors and negatively with OCDS scores.	Significant group differences on the win-stay (with alcoholics showing less stay behaviors after win), and in the repetition behaviors (with patients showing more reiterated disadvantageous choices).
Beylergil et al., (2017)			Reward-guided decision-making task	ADS OCDS LDH	In both groups significant positive correlation between punishment sensitivity and R insula/inferior PFC activity. Significant group differences in the PEs-related activity in the bilat dlPFC, bilat dorsal premotor cortex, R IPS. Significant group differences in the negPEs-related activity in the L	

Table 1 (continued)

Authors (year)	DM Task			Psychological/cognitive assessment	(f)MRI findings (PT vs. HC)	Behavioral findings (PT vs. HC)
	Ant	Out	Learn			
						dlPFC, and in the posPEs-related activity in the R dlPFC. Significant correlation between negPEs-related activity in the L dlPFC and ADS scores.
No significant group differences in the task-related variables (i.e., learning rate).						
Sebold et al., (2017)			Two-step task	AEQ	No significant group differences in the neural signature of the classical PEs. Significantly lower model-based PEs signals in the mPFC for relapsers compared to abstainers and hc.	Correlation between the model-based control variable and AEQ scores (positive for hc, negative for relapsers and absent for abstainers).
Fein et al., (2006)			IGT	LDH MMPI-2(pd) CPI(So)	Bilateral GM reduction in the amygdala. No significant correlation between GM reduction and IGT performance.	More disadvantageous choices on the IGT, with better performance in women compared with men.
Le Berre et al., (2014)			IGT	MMSE BDI STAI	Diffuse GM volume reduction. Significant correlation between the severity of decision-making deficits and the degree of GM volume reduction in the vmPFC, dACC, and hippocampal formation.	Significantly impaired performance in the last 20 choices of the IGT.
Zorlu et al., (2013)			IGT	No Psychological/cognitive assessment	Significantly lower FA values in the CC, as well as parietal, occipital and frontal tracts.	No significant group differences in total IGT net score, despite a trend for worse performance (particularly in block 5) in pt. No correlation with WM integrity.
Zorlu et al., (2014)			IGT	No Psychological / Cognitive assessment	Significantly higher RD and AD values, but normal FA values, in frontal, temporal and parietal tracts.	No significant group differences in the IGT.

DM, decision making; *Pt*, patients; *Hc*, healty controls; *N*, no; *Y*, yes; *MID*, monetary incentive delay task; *RTT*, risk-taking task; *Alcohol-IAT*, alcohol-implicit association task; *IGT*, Iowa gambling task; *ADS*, Alcohol Dependence Scale; *OCDS*, Obsessive Compulsive Drinking Scale; *HAMD*, Hamilton Depression Rating Scale; *IQ*, intelligence quotient; *vIQ*, verbal intelligence quotient; *NEO-PI-R*, NEO Personality Inventory; *NEO-IF*, NEO personality inventory–impulsiveness factor; *RT*, reaction times; *STAI*, State Trait Anxiety Inventory; *BIS-10*, Barratt Impulsiveness Scale – Version 10; *BIS-11* Barratt Impulsiveness Scale – Version 11; *AUDIT*, Alcohol Use Disorder Identification Test; *BDI-II*, Beck Depression Inventory; *AUQ*, Alcohol Urge Questionnaire; *LDH*, Lifetime Drinking History; *WCST*, Wisconsin Card Sorting Test; *IDS*, Inventory of Depressive Symptomatology; *TLFB*, Time-Line Follow Back score for addiction severity; *ACQ*, Alcohol Craving Questionnaire; *TMT (A-B)*, Trail Making Test (A B); *AEQ*, Alcohol Expectation Questionnaire; *MMSE*, mini mental state examination; *MMPI-2(Pd)*, Minnesota Multiphasic Personality Inventory (Psychopathic deviance); *CPI(So)*, California Psychological Inventory(Socialization Scale); *PEs*, prediction errors; *R*, right; *L* left; *PMC*, PreMotor cortex; *VS*, ventral striatum; *PCC*, posterior cingulate cortex; *ACC*, anterior cingulate cortex; *dACC*, dorsal anterior cingulate cortex; *lOFC*, lateral orbitofrontal cortex; *OFC*, orbitofrontal cortex; *PFC*, prefrontal cortex; *mPFC*, medial prefrontal cortex; *vmPFC*, ventromedial prefrontal cortex; *dlPFC*, dorsolateral prefrontal cortex; *nAcc*, nucleus accumbens; *SFG*, superior frontal gyrus; *STG*, superior temporal gyrus; *IPS*, intraparietal sulcus; *GM*, gray matter; *WM*, withe matter; *FC*, functional connectivity; *FA*, fractional anisotropy; *AD*, axial diffusivity; *RD*, radial diffusivity; *CC*, corpus callosum

Altered reward-related brain activity in AUDs

Outcome anticipation

Outcome anticipation entails estimating the magnitude and/or probability of available choice options. Most theoretical approaches to decision-making, from expected utility theory [27] to prospect theory [24] and reinforcement learning [28], share the notion that choices require the integration of such attributes into a single "expected value" signal. The latter represents the overall subjective value assigned to each available option, which in principle should drive choices. In fact, longstanding evidence in behavioral economics highlights large inter-individuals differences in the value which risk-averse vs. risk-seeking individuals assign to the presence of risk (as compared with certainty) or to the amount of risk (the variance of the distribution of positive vs. negative outcomes). By unveiling neural signals reflecting these choice variables, in the past decade neuroimaging studies have highlighted distinct but interactive brain systems for the processing of subjective expected value and risk [29]. Overall, these studies have shown that gain anticipation recruits the striatum and anterior cingulate cortex [19, 20], while anticipated losses engage the amygdala and insular cortex [16, 19]. The medial orbitofrontal cortex seems to integrate these two anticipatory drives into an expected value signal [30, 31], and to process the amount of risk inherent in the choice [22].

There is evidence for an unbalanced activity within this neural circuity, and particularly in the ventral striatum, C during outcome anticipation. The observed findings, however, are not completely consistent and seem to be largely dependent on the use of different tasks tapping specific facets of anticipatory processes. Several studies employed the monetary incentive delay task (MID), or its modified versions in which reward delivery requires variable efforts, to study the neural processing of subjective expected value during *gain/loss anticipation* in both detoxified and alcoholic patients. After seeing cues indicating that they may win or lose money, participants wait for a variable anticipatory delay period, and finally respond to a rapidly presented target to try to either win, or avoid losing, money [16]. Decreased ventral striatal activity has been frequently reported in AUD patients compared with controls in this task [32–35]. Moreover, in patients, the degree of such reduction correlates with the severity of craving [32], impulsivity [33], and depressive symptoms [34]. Other studies, however, have reported opposite results, i.e., increased activity of ventral and dorsal striatum during gain/loss anticipation by alcoholic patients [36]. The observation of the latter pattern in trials characterized by low effort demand, but not in those requiring stronger effort [36], suggests a possible impairment in the computation of expected value. These results, however, were not replicated by Bjork et al. [37, 38], who failed to observe differences in ventral striatal activity between AUD patients and controls during gain/loss anticipation. This inconsistency may depend on intrinsic features of the different variants of the task, including the possibility to lose money, the smaller number of trials or the longer average interstimulus interval.

Van Holst et al. [39] used a modified version of a card-guessing task to investigate possible group differences in coding *expected value* for gains vs. losses, while also distinguishing the effect of outcome magnitude and probability. The latter are made available for both possible gains and losses, but the outcomes are obtained passively, i.e., with no requirement for an instrumental response. Compared with controls, alcoholic patients displayed stronger neural responses to the anticipation of both gain-related expected value in the left caudate and its outcome magnitude component in the left caudate and left putamen. Instead, no group difference was found neither for loss-related expected value nor for its outcome probability component.

During risk-taking paradigms, alcoholic patients seem to lack the clear segregation, displayed by controls, between the brain networks associated with making safe vs. risky decisions, which suggests a general imbalance of the conflict-monitoring neural circuitry underlying decision-making under risk [25, 40, 41]. In risky trials, patients additionally showed stronger anticipatory activity in brain networks associated with motor and executive control, as well as in the insula, anterior cingulate cortex and basal ganglia [25, 41]. Although the lack of significant differences in choice behavior suggested a preserved detection of risk, such an altered recruitment of related brain networks might reflect a defective switch between neural systems associated with decision-making in safe vs. risky situations. This hypothesis may account for the alcoholics' failure to inhibit drinking behavior despite its consequences.

To summarize, the available evidence of abnormal ventral striatal activity during outcome anticipation, particularly for gains, seems to reflect altered computations of expected value and risk in alcoholic patients. The partial inconsistency of such results, however, highlights the need of further in-depth investigations.

Outcome experience

Attending the outcome of own choices is a critical stage of decision-making, in which the comparison with expectations generates reward prediction errors (PEs), i.e., learning signals promoting behavioral adaptations in subsequent choices [21, 28]. Outcome experience thus provides novel, often emotionally connotated [42], information either confirming expectations or prompting their update.

Neuroimaging studies have highlighted the crucial role of prefrontal cortex and ventral striatum in processing outcomes and computing PEs in healthy individuals [43, 44], with the

medial and lateral sectors of orbitofrontal cortex responding, respectively, to rewarding and punishing outcomes [45]. There is evidence that the ventromedial prefrontal cortex (vmPFC) is involved in the processing of the contextual features of reward [46], while the dorsolateral prefrontal cortex (dlPFC)—and particularly its frontopolar sector—mediates the switch to explorative choice when the utility associated with the current choice falls below a given threshold [47–49]. Outcome experience and ensuing adaptive behavioral learning are thus likely to depend on fronto-striatal connectivity. Different studies have reported inconsistent findings on brain activity underlying the experience of non-drug rewards in alcoholics compared with controls. Namely, while some studies highlighted increased activity in the ventral striatum (nucleus accumbens) and anterior insula [37], others reported no group difference during such feedback evaluation [33, 36, 38, 40].

The growing interest in brain functional connectivity has prompted novel lines of inquiry concerning possible alterations of feedback evaluation in AUDs. In particular, psycho-physiological-interaction (PPI) [50] analyses have been used to investigate fronto-striatal functional connectivity during outcome experience. Compared with controls, alcoholic patients exhibited altered functional connectivity in response to monetary rewards, but not losses, between the bilateral ventral striatum and different sectors of the prefrontal cortex, i.e., lateral orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC) and dlPFC [26, 51]. Both the intensity of medial prefrontal activity and its connectivity with the nucleus accumbens were associated with drinking characteristics (i.e., years drinking, number of drinks per use, frequency and severity [51], magnitude of alcohol craving [26]), suggesting that the altered functioning of the fronto-striatal reward circuitry may represent an endophenotype of AUDs.

In spite of abnormal activity underlying outcome evaluation, however, the ability to compute classical PEs seems to be preserved in alcoholic patients [26, 52–55]. Different studies, using reward-guided decision-making paradigms, found no group difference in the correlation between individually generated trial-wise PEs and the activity of the regions underlying outcome evaluation described above, i.e., ventral striatum alongside orbitofrontal, anterior cingulate, or PFC [26, 52–55].

Overall, the consistent evidence of abnormal fronto-striatal connectivity in the processing of positive feedbacks by alcoholic patients thus suggests that decision-making impairments may reflect an altered *implementation* of PEs in subsequent choices.

Outcome evaluation and behavioral learning

The formation of an alcohol habit may be considered a form of reinforced learning, with sustained alcohol use resulting in the strengthening of associative links between consumption and either rewarding experiences or the lack of aversive experiences (i.e., respectively, positive and negative reinforcement). Reinforcement learning theory [28] states that such associations underlie the agents' ability to learn from experience, i.e., to adapt to past action-outcome contingencies via different computational routines.

In classical behavioral learning, PEs arise from comparisons between factual states, associated with affective experiences such as delusion and gloating for outcomes worse or better than expected, respectively [21]. Increasing evidence, however, shows that agents also process the foregone—*counterfactual*—outcomes of discarded options [56]. In this case, the difference between factual and *counterfactual* states (i.e., a "fictive" PE) shapes the valence and intensity of complex emotions such as regret and relief for outcomes worse or better than the foregone ones [57–59]. Two reinforcement learning models, i.e., model-free and model-based, have been proposed to ground these different computations [60, 61]. In the framework of neuroeconomics, several evidences suggest that these models are associated with two different behavioral control processes, i.e., habitual and goal-directed. The latter, associated with model-based reinforcement learning mechanism, are engaged under volitional control. Habitual responses, instead, are directly triggered by environmental cues even when the outcomes have lost their goal value, and are associated with model-free mechanism leading to achieve desirable outcomes (positive reinforcement) or to avoid/escape from aversive outcomes (negative reinforcement) [60, 61]. While goal-directed actions (flexible, but also slow to acquire) are associated with the activation of the vmPFC and dorsal caudate, habitual responses (inflexible but quick and automatic) involve the posterior putamen [62–64].

In AUDs, chronically compulsive alcohol seeking may thus be considered to reflect a gradual shift from goal-directed towards habitual control [65]. To address this hypothesis, some authors have assessed the possible imbalance of the two control processes in AUDs via learning tasks allowing to distinguish between goal-directed vs. habitual actions, i.e., instrumental learning [66] or reward-guided decision-making tasks [26, 52–55]. A bias towards the automatic process, in alcoholic patients compared with controls, is suggested by weaker activations in the vmPFC and anterior putamen during goal-directed behavior, and stronger activation in the posterior putamen during habitual behavior. Supporting the close connection between such imbalance and the disease progression, the decrease of vmPFC activity during goal-directed behavior is positively associated with AUD duration, but not with age [66].

In addition, despite the patients' preserved ability to compute classical PEs [26, 52; see Outcome experience], abnormal brain activity associated with the computation of fictive PEs has been observed in the mPFC, posterior cingulate

cortex (PCC) [53, 55], bilateral dlPFC and bilateral dorsal premotor areas, as well as the right intraparietal sulcus (IPS) [54].

There is, thus, multi-faceted evidence of impaired implementation, in AUDs, of experienced PEs in subsequent choices (i.e., behavioral learning). First, alcoholic patients display a strong correlation between the degree of alteration of fronto-striatal connectivity (particularly between ventral striatum and dlPFC) and the decrease of learning rate, as indexed by a larger number of trials needed to reverse behavior [52]. In addition, model-based evidence highlighted, in patients, a decrease of PFC activity which was both associated with impaired learning from fictive PEs [53–55], and correlated with the observed behavioral deficit in updating alternative choices as well as with obsessive compulsive drinking habits [53]. Finally, the severity of alcohol dependence is related to the decrease of activity in the same dlPFC activity tracking negative PE signals, which suggests a critical role of this region in adapting to contingency changes via the extinction of behaviors that are no longer rewarding [55]. Overall, this evidence may explain the frequent observation of impaired flexible behavior in alcoholics [52], which once again supports the shift from goal-directed to habitual behaviors as a possible hallmark of impaired behavioral control in AUDs.

Moreover, in alcoholic patients, the ability to learn from past experiences is also more strongly modulated by cumulative earnings than in healthy individuals. Unlike controls, patients display heightened activity (related to impulsivity measures) in the caudate, putamen, and insula as earnings *increase*, particularly during risky choices [40]. The enhancing effect of cumulative earnings on striatal activation in AUDs may be indicative of their heightened sensitivity to risky choices after the experience of positive outcomes.

Overall, these results converge on the hypothesis of abnormal fronto-striatal connectivity as a neural marker of altered reinforcement learning in AUDs, driving a maladaptive shift from goal-directed to automatic (i.e., stimulus-response) consumption behaviors [65–67]. Like other types of addiction, AUDs seem, thus, to reflect a maladaptive behavioral learning processes, promoted by associative links between alcohol consumption and the achievement of rewarding, or the escape from punishing, behavioral states.

The strength of such alcohol-relevant associations in AUDs has been recently addressed with an "alcohol implicit association task" (alcohol-IAT) [68]. In its original form, the IAT allows to highlight implicit attitudes by measuring, in terms of response time, the differential strength of the mental association of two concepts ("target" and "contrast" concepts) with a given attribute [69]. In this case, alcohol and mammal are, respectively, the target and contrast concepts to be assessed with respect to "positive" and "neutral" attributes. The critical index of implicit attitude is represented by the differential response time measured in so-called normatively compatible (e.g., "alcohol positive" and "mammal neutral") vs. incompatible (e.g., "mammal positive" and "alcohol neutral") pairs. Heavy drinkers displayed stronger positive implicit associations towards alcohol compared with a control group of light drinkers. At the neural level, they also showed greater activity in the left putamen and right insula during compatible trials, and weaker activity in the left OFC regardless of trial type. Interestingly, both groups revealed significant bilateral dlPFC activity during incompatible trials. This latter result suggests that also in alcoholics, the categorization of these trials requires an effortful and controlled processing of information.

Neurostructural alterations in AUDs

The evidence summarized so far has prompted the investigation of possible structural changes, in AUDs, in the brain networks in charge of decision-making, and their possible relationship with choice processes.

Preliminary evidence highlighted, in alcoholics compared with controls, a reduction of gray-matter volume—related to working-memory scores—in key nodes of these networks, such as the right anterior insula, right nucleus accumbens, and left amygdala, as well as right dorsolateral prefrontal cortex [70]. The positive correlation between the length of abstinence and gray-matter volume of nucleus accumbens and anterior insula highlights the potential recovery of structural deficits in AUDs. Available studies, however, provided inconsistent evidence relating altered decision-making abilities with brain structural changes. Le Berre et al. [71] highlighted in alcoholics a widespread GM atrophy (correlating with the severity of decision-making deficits) in key nodes of the reward system such as vmPFC, dorsal portion of the anterior cingulate cortex, and hippocampal formation. Conversely, via region-of-interest analyses Fein and colleagues [72] reported, in patients vs. controls, a bilateral gray-matter (GM) volume reduction in the amygdala (but not in the vmPFC), and no relationship with decision-making deficits. Importantly, this type of investigation is complicated by the fact that, as mentioned in the Introduction, structural brain changes may actually depend on factors other than toxic alcohol effects, possibly contributing to chronic cognitive dysfunction [2].

To date, instead, little is known about a possible relationship between decision-making impairments and abnormal white-matter integrity in AUDs. Again, the possible contribution for additional factors (e.g., vascular damage) needs to be considered. Different white-matter profiles have been found in early vs. long-term abstainers. The former group is characterized by worse performance on the Iowa gambling task, a widely used test assessing the ability to adapt choice behavior to novel reward and punishment contingencies [73]. Although suggestive of impaired reversal learning, such abnormal performance did not reflect in the observed reduction of axonal

integrity, i.e., lower fractional anisotropy (FA), in the corpus callosum, parietal, occipital, and frontal tracts [74]. After long-term abstinence, instead, neither decision-making abilities nor fractional anisotropy was found to differ between patients and controls. Detoxified alcoholics, however, show significant changes in axial and radial diffusivity in specific frontal, parietal, and temporal clusters [75]. The higher axial diffusivity observed in long-term abstinent patients compared with healthy controls is suggestive of compensatory repair processes of axonal injuries. Nevertheless, even after a long period of abstinence alcoholics still show increased radial diffusivity values, suggestive of alcohol-related myelin degradation.

Further evidence is thus needed to understand whether a recovery of white-matter integrity parallels the improvement in decision-making skills with abstinence, as well as the underlying neurobiological processes.

Conclusions

The neurocognitive bases of a decision-making impairment in AUDs represent a growing topic in neuroeconomics. Although the evidence reviewed here calls for further in-depth investigations, the available data suggest that excessive alcohol exposure affects neuroplasticity and neural signaling within brain networks in charge of reward processing and adaptive behavioral learning. In particular, abnormal ventral striatal activity and fronto-striatal connectivity in response to a variety of rewarding stimuli may represent a hallmark of maladaptive decision-making in AUDs. Although most published studies provided evidence of abnormal *outcome anticipation* (particularly for gains), the extent to which other, more specific, facets of reward processing are impaired is a matter of debate and should be pursued further. In particular, the possible relationship between abnormal ventral striatal activity and altered processing of value and risk in AUDs is controversial. Moreover, some studies reported abnormal computations of fictive PEs in alcoholics, highlighting the role of altered fronto-striatal connectivity while processing action feedback during *outcome experience*. A defective ability to *learn from past experience*, reported by several studies, likely underpins compulsive alcohol consumption and relapsing episodes despite negative consequences. This maladaptive form of behavioral learning seems to reflect a shift from goal-directed to habitual actions promoted both by weaker vmPFC activity and altered connectivity between ventral striatum and both dorsolateral and medial prefrontal cortex.

Overall, these data highlight abnormal fronto-striatal connectivity as a candidate neurobiological marker of impaired choice in AUDs. Further studies are needed, however, to unveil its implications in the multiple facets of decision-making.

The evidence on neurostructural changes associated with decision-making impairments in AUDs is nowadays limited. While different studies reported a reduction of gray-matter volume in key nodes of the meso-cortico-limbic network associated with adaptive behavioral learning, such as bilateral amygdala, vmPFC, dorsal portion of the anterior cingulate cortex, and hippocampal formation, the connection between such structural alterations and defective decision-making is weak. Stronger evidence links abnormal decision-making performance and a reduction of white-matter integrity associated with excessive alcohol exposure. Moreover, preliminary evidence supports the notion that both behavioral and white-matter alterations are at least partially reversed by long-term abstinence.

In sum, while growing evidence suggests a neurophysiological basis of a variety of behavioral alterations in alcoholic patients, current gaps in this growing literature highlight novel directions for further interdisciplinary investigations of the neural underpinnings of decision-making impairments and behavioral control in AUDs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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