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DISSERTATION

Zielorientierte Entscheidungsfindung bei regelmäßigem Alkoholkonsum

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Inhaltsverzeichnis

1. Zusammenfassung der Publikationen

In sogenannten Zwei-System-Theorien wird die Entstehung und Aufrechterhaltung von Abhängigkeitserkrankungen als Resultat einer veränderten Balance zwischen einem (überaktiven) Belohungssystem und einem (dysfunktionalen) Kontrollsystem verstanden. In der vorliegenden Publikationspromotion wurde die Beteiligung beider Systeme an Entscheidungen für Alkoholkonsum, an der Entstehung von Suchtdruck und kognitiver Kontrollfähigkeit sowie an der Wirksamkeit eines neuartigen suchtdruckreduzierenden Therapieansatzes, des Cognitive Bias Modification Trainings (CBM), untersucht. Hierfür kam funktionelle und strukturelle Magnetresonanztomographie zum Einsatz. Es fand sich ein überaktives Belohnungssystem im Zusammenhang mit Entscheidungen für den Alkoholkonsum, sowie im Zusammenhang mit subjektivem Suchtdruck. Diese Überaktivierung konnte durch CBM erfolgreich reduziert werden. Eine reduzierte kognitive Kontrollfähigkeit war bei alkoholabhängigen Patienten mit einer zunehmenden Atrophie inferiorer frontaler Hirnareale assoziiert. Die präsentierten Arbeiten unterstreichen die Bedeutung eines überaktiven Belohnungssystems für die Entstehung von Suchtdruck und suchttypischem Entscheidungsverhalten und damit auch als potenzielle Zielpathologie für innovative Therapiekonzepte.

Dual system theories state an altered interaction between an (overactive) reward and a (dysfunctional) control system in substance use disorders. In the present work, the role of both systems is investigated regarding pro-alcohol decisions, craving and cognitive control as well as the effect mechanism of new craving-reducing treatment strategies (cognitive bias modification training, CBM). To this end, functional and structural magnet resonance imaging was used. We found an association between craving, decisions in favor of alcohol and an hyperactivation of reward-associated circuits. This hyperactivation was shown to be successfully reduced by cognitive bias modification training. Growing atrophy of the inferior frontal gyrus was related to increasing disinhibition in alcohol-dependent patients. Hence, the results underscore the importance of an hyperactivated reward system for the development of craving and addictive decision behavior. Targeting automatic tendencies and associated hyperactivations of reward areas may therefore be a promising direction for future therapies in alcohol use disorder.

1.1 Einleitung

Alkoholabhängigkeit äußert sich durch wiederholte Entscheidungen für Alkoholkonsum bei konkreten Trinkgelegenheiten. Charakteristischerweise erfolgen diese Entscheidungen entgegen einem Wunsch, den Alkoholkonsum zu reduzieren oder ganz zu beenden: Ein typisches Verhaltensmuster, das für sich bereits Eingang in die DSM-5-Kriterien zur Diagnose von Suchterkrankungen gefunden hat ("Worrying about stopping or consistently failed efforts to control one’s use", (1)).

Sogenannte Zwei-System-Theorien von Entscheidungsfindung und Abhängigkeitsentstehung (2, 3) ermöglichen zwei verschiedene kognitive Erklärungen für dieses Verhaltensmuster. In diesen Modellen werden Entscheidungen als Resultat der Interaktion zweier kognitiv wie anatomisch unterscheidbarer Systeme, eines Belohnungs- und eines Kontrollsystems, konzipiert. Bezogen auf Abhängigkeitserkrankungen lässt sich für Betroffene, die mit einer Konsumgelegenheit konfrontiert werden, entsprechend eine Überaktivierung des Belohnungssystems, eine insuffiziente Aktivierung des Kontrollsystems oder eine Kombination aus beidem postulieren, die letztlich in dem beschriebenen Verhalten (Konsum trotz anders lautender Vorsätze) münden. Tatsächlich dokumentieren zahlreiche Verhaltens- und Bildgebungsstudien abhängigkeitsspezifische Veränderungen beider Systeme, die im Folgenden kurz zusammengefasst werden sollen.

Alkoholabhängige Menschen zeigen subjektiven Suchtdruck ("craving") (4) und automatische Annährungstendenzen ("approach bias") (5, 6), wenn sie mit suchtbezogenen Reizen konfrontiert werden. FMRT-Studien legen eine Verbindung zwischen diesen Verhaltensmustern und einem überaktiven Belohnungssystem nahe. In Untersuchungen zur sogenannten "cue reactivity", d.h. zu spezifischen Aktivierungen des Gehirns in Reaktion auf alkoholische im Vergleich zu nicht-alkoholischen Stimuli (Bilder oder Geschmacksproben), konnten insbesondere verstärkte Aktivierungen von Amygdala, ventralem Striatum und ventromedialem Präfrontalkortex nachgewiesen werden, sowohl für alkoholabhängige Patienten (7-14) als auch für Menschen mit starkem Alkoholkonsum ("heavy drinker", (15-17)). Die Aktivität von Amygdala und ventralem Striatum scheint darüber hinaus direkt mit subjektiven Suchtdruck beim Betrachten alkoholischer Stimuli zu korrelieren (14, 18). Es liegt also nahe, in einer überschießenden alkoholbezogenen Aktivierung von Belohnungsarealen eine Ursache für pro-Alkohol-Entscheidungen bei Abhängigen

zu suchen ("Hypothese eines überschießenden Belohnungssignals").

Auf der anderen Seite existieren zahlreiche Vorarbeiten, die dysfunktionale Kontrollsysteme als (Mit-)Ursache für die Aufrechterhaltung von Abhängigkeitserkrankungen nahe legen. Dies zeigt sich auf der Verhaltensebene - auch ohne Einsatz alkoholbezogener Stimuli - in einer Vernachlässigung langfristig lohnenswerterer Entscheidungsoptionen zugunsten kleinerer, aber kurzfristiger Belohnungen bei Patienten mit Alkoholabhängigkeit (19). Außerdem findet sich ein tendenziell riskanteres Entscheidungsverhalten (20) und ein schlechteres Abschneiden in Aufgaben, die inhibitorische Kontrolle erfordern (z.B. Go-NoGo-Task, Stop-Signal-Task, (21) für eine Übersicht). Bildgebungsstudien verweisen auf einen Zusammenhang mit verringerten Aktivierungen derjenigen Areale, die mit dem (erfolgreichen) Ausüben kognitiver Kontrolle in Verbindung gebracht werden. Dies trifft vor allem für den lateralen Präfrontalkortex und insbesondere dessen dorsalen Part (DLPFC) zu, dessen Aktivierung in Gesunden mit der Wahl langfristig lohnenswerter Entscheidungsstrategien zusammen zu hängen scheint (22-24). Passend hierzu begünstigt umgekehrt die Ausschaltung des DLPFC durch Läsionen oder interventionell mittels repetitiver transkranieller Magnetstimulation (rTMS) ein impulsives Entscheidungsverhalten (25, 26). Vergleicht man Personen mit und ohne Abhängigkeitserkrankungen bezüglich ihrer DLPFC-Aktivierung während Aufgaben, die inhibitorische Kontrolle erfordern, finden sich signifikant reduzierte Aktivierungen in der Gruppe der Abhängigen (27, 28). Aus diesen Befunden motiviert sich die Hypothese, dass ein dysfunktionales kognitives Kontrollsystem für Entscheidungen für den Alkoholkonsum gegen den eigenen Vorsatz verantwortlich sein könnte ("Hypothese dysfunktioneller Kontrollsysteme").

Eine experimentelle Überprüfung dieser pathophysiologischen Hypothesen ist von Interesse auch für die Entwicklung abhängigkeitsspezifischer Therapiestrategien, die zur Zeit hauptsächlich auf eine Stärkung kognitiver Kontrolle gegenüber der "Verlockung" des Substanzkonsums abzielen. Eine mögliche Alternative hierzu stellt das sogenannte "Cognitive Bias Modification Training" dar, in dem unbewusste Belohnungs- und Annährungsautomatismen reduziert werden sollen: Hierfür drücken die Patienten mit einem Joystick wiederholt Bilder alkoholischer Getränke von sich weg. Die Wirksamkeit dieser Therapieverfahren wird inzwischen in mehreren Studien dokumentiert (6, 29), unklarer sind bislang hingegen die neurokognitiven Substrate dieser Wirksamkeit.

Die in dieser Dissertation vorliegenden Studien testen den Einfluss eines überschießenden

Belohnungssignals ebenso wie eines dysfunktionellen Kontrollsystems auf Entscheidungen für Alkoholkonsum in einem eigens hierfür entwickelten Entscheidungsparadigma. Außerdem werden Aktivitätsveränderungen in entsprechenden Arealen des Belohnungs- und Kontrollsystems als potenzielle neurophysiologische Korrelate der Wirkung des Cognitive Bias Modification Training sowie alkoholspezifische strukturelle Hirnveränderungen und ihr Zusammenhang zu kognitiven Kontrollprozessen untersucht.

1.2 Methodik

Studie 1: Achtunddreißig männliche Teilnehmer mit unterschiedlich ausgeprägtem Alkoholkonsum, quantifiziert durch den "Alcohol Use Disorders Identification Test" (AUDIT, Fragebogen der WHO) entschieden sich in einer neu entwickelten Entscheidungsaufgabe wiederholt während einer fMRT-Messung zwischen zwei Getränken. Eines der gewählten Getränke wurde zufällig selektiert und den Probanden am Ende des Experiments serviert, wodurch die getroffenen Entscheidungen einen realen Charakter bekamen. Die präsentierten Getränkepaare konnten entweder ein alkoholisches und ein nicht-alkoholisches ("Alkohol-Kondition") oder aber aber zwei nicht-alkoholische Getränke enthalten ("Nicht-Alkohol-Kondition"). In jedem Fall enthielten die Paare aber - basierend auf vor der MRT-Sitzung durchgeführten Ratings der Probanden für jedes Getränk - jeweils ein Getränk, das von den Probanden als begehrter und eins, das von ihnen als gesünder eingeschätzt wurde. Auf dieser Basis konnten vier verschiedene Entscheidungstypen in den Analysen unterschieden werden:

1. Entscheidungen für das begehrtere (alkoholische) Getränk in Alkohol-Konditionen - auch als gescheiterte Selbstkontrolle im Alkoholbereich bezeichnet

2. Entscheidungen gegen das begehrtere (alkoholische) Getränk in Alkoholkonditionen (und damit für das weniger begehrte, aber gesündere nicht-alkoholische Getränk) - auch als erfolgreiche Selbstkontrolle im Alkoholbereich bezeichnet

3. Entscheidungen für das begehrtere (nicht-alkoholische) Getränk in Nicht-Alkohol-Konditionen - auch als gescheiterte Selbstkontrolle im Nicht-Alkoholbereich bezeichnet

4. Entscheidungen gegen das begehrtere (nicht-alkoholische) Getränk in Nicht-Alkoholkonditionen (und damit für das weniger begehrte, aber gesündere nicht-alkoholische

Getränk) - auch als erfolgreiche Selbstkontrolle im Nicht-Alkoholbereich bezeichnet

Die fMRT-Aufnahmen wurden zunächst mittels "Statistical Parametric Mapping" , Version 8, (SPM8) vorverarbeitet, d.h. für unterschiedliche Aufnahmezeitpunkte der einzelnen Schnitte korrigiert ("slice timing"), für Bewegungen während der Aufnahmen korrigiert ("realignment"), in den standardisierten MNI-Raum (Montreal Neurological Institute) räumlich normalisiert ("coregistration" und "normalization") und schließlich geglättet ("smoothing").

Anschließend wurde die Hirnaktivität während Entscheidungen für alkoholische Getränke mit derjenigen für begehrtere nicht-alkoholische Getränke verglichen und somit Aktivierungsunterschiede ermittelt, die spezifisch für pro-Alkohol-Entscheidungen sind. Um Unterschiede zu identifizieren, die mit dem jeweiligen Schweregrad des Alkoholkonsums zusammen hängen, wurde dieser Aktivierungsunterschied mit der jeweiligen AUDIT Punktzahl als Maß der Trinkschwere korreliert. Hierdurch werden Areale identifiziert, die während pro-Alkohol-Entscheidungen eine zunehmende Aktivierung mit steigender Trinkschwere zeigen: Dies sollten, der "Hypothese eines überschießenden Belohnungssignals" zufolge, belohnungsassoziierte Areale sein. Umgekehrt wurden auch Areale gesucht, die während pro-Alkohol-Entscheidungen eine *abnehmende* Aktivierung mit steigender Trinkschwere zeigen. Dies sollten, der "Hypothese dysfunktioneller Kontrollsysteme" zufolge, kontrollassoziierte Areale sein. Um auszuschließen, dass es sich bei den in dieser Analyse gefundenen Unterschieden um einen reinen Effekt des Zeigens von Alkohol handelt (es wurden Entscheidungen für ein alkoholisches Getränk mit Entscheidungen für ein begehrtes Getränk im nicht-alkoholischen Bereich, also ohne zur Auswahl stehenden Alkohol verglichen), wurde zusätzlich eine weitere Analyse gerechnet, die eine maximale Spezifität für *gescheiterte Selbstkontrolle* im Alkoholbereich garantieren soll. Hierfür wurde vom oben ausgeführten Kontrast (Entscheidung für ein begehrtes alkoholisches versus Entscheidung für ein begehrtes nicht-alkoholisches Getränk) der analoge Kontrast für Entscheidungen mit erfolgreicher Selbstkontrolle abgezogen: Der resultierende Kontrast berechnet also Aktivierungen bei Entscheidungen für das begehrtere alkoholische Getränk versus Entscheidungen für das begehrtere nicht-alkoholische Getränk verglichen mit Entscheidungen *gegen* das begehrtere alkoholische Getränk vs. Entscheidungen *gegen* das begehrtere nicht-alkoholische Getränk (Interaktionskontrast zwischen Alkohol- vs. Nicht-Alkoholkondition und gescheiterter vs. erfolgreicher Selbstkontrolle). Er korrigiert damit für Effekte, die auf die bloße Präsenz eines

alkoholischen Getränks in den Entscheidungspaaren zurückzuführen sind, indem Aktivierungen während erfolgreicher Selbstkontrolle im alkoholischen Bereich abgezogen werden.

Diese Analysen wurden in hypothesengeleiteten a priori regions of interest durchgeführt, die, angelehnt an eine hauseigene Vorstudie (8), das ventrale Striatum, den medialen Präfrontalkortex und die Amygdala als belohnungsassoziierte Areale und den dorsolateralen Präfrontalkortex als kontrollassoziiertes Areal beinhalteten. Innerhalb dieser Regionen erfolgte eine Korrektur für multiples Testen mittels "family-wise-error"-Algorithmus (FWE).

Studie 2: Zweiunddreißig abstinente, alkoholabhängige Patienten wurden über drei Wochen mit sechs Einheiten eines Cognitive Bias Modification Training (CBM) trainiert, in dem sie Bilder je nach Format (Hoch- oder Querformat) mit einem Joystick zu sich hin ziehen oder von sich wegdrücken mussten. Unterschieden wurden ein Scheintraining, in dem zu 50% Bilder von alkoholischen Getränken und zu 50% Bilder von nicht-alkoholischen Getränken weggedrückt, bzw. herangezogen wurden und ein echtes Training, in dem zu 90% Bilder von alkoholischen Getränken weggedrückt wurden (durch eine entsprechend häufigere Präsentation alkoholischer Bilder im wegzudrückenden Bildformat). Die Patienten wurden diesen Gruppen randomisiert zugewiesen.

Jeweils vor und nach den drei Wochen mit CBM- oder Scheintraining wurden automatische alkoholspezifische Annährungstendenzen (alcohol approach bias) quantifiziert, indem zunächst der Unterschied in den Reaktionszeiten von den trials, in denen die Getränke per Joystick zu sich hingezogen wurden mit derjenigen von trials, in denen die Getränke weggedrückt wurden, verglichen wurde (approach bias). Indem man diesen Unterschied zwischen Annäherung und Abwehr wiederum zwischen alkoholischen und nicht-alkoholischen Getränken vergleicht, erhält man ein Maß für die Stärke *alkoholspezifischer* automatischer Annährungstendenzen (alcohol approach bias). Desweiteren wurde vor und nach dem Training eine fMRT-Messung der alcohol cue reactivity (Hirnaktivierung als Reaktion auf alkoholische im Vergleich zu nicht-alkoholischen Stimuli) durchgeführt. Die Vorverarbeitung der Bilder umfasste, analog zu Studie 1, slice timing, realignment, coregistration, normalization und smoothing. Anschließend wurden Aktivitätsunterschiede in der cue reactivity vor und nach dem Training ermittelt und zwischen der Scheintraining- und der echten Trainingsgruppe verglichen. Hierfür kamen hypothesengeleitete a priori regions of interest (ventrales Striatum und Amygdala als belohnungsassoziierte Areale) und

erneut eine FWE-Korrektur für multiples Testen zum Einsatz.

Studie 3: Zweiundzwanzig abstinente alkoholabhängige Patienten und 21 gesunde Kontrollen wurden auf regionale Volumenunterschiede in ihrer grauen Hirnsubstanz mittels einer "voxel-based morphometry" (VBM) - Analyse (auf Basis von anatomischen T1-MRT-Aufnahmen) untersucht. Außerdem wurde als Test für inhibitorische Kontrollfähigkeit ein sogenannter "stop-signal task" in der Gruppe der Alkoholabhänigen durchgeführt. In dieser Aufgabe sollen die Patienten möglichst schnell die Richtung eines kurz präsentierten Pfeils angeben ("go trial"). In manchen Fällen ändert der Pfeil kurzfristig seine Richtung und es soll keine Antwort gegeben werden ("stop trial"). Hierfür muss die bereits vorbereitete motorische Antwort kurzfristig unterbrochen werden, weswegen die Perfomance in diesen trials als Hinweis auf die Inhibitionsfähigkeit gewertet wird.

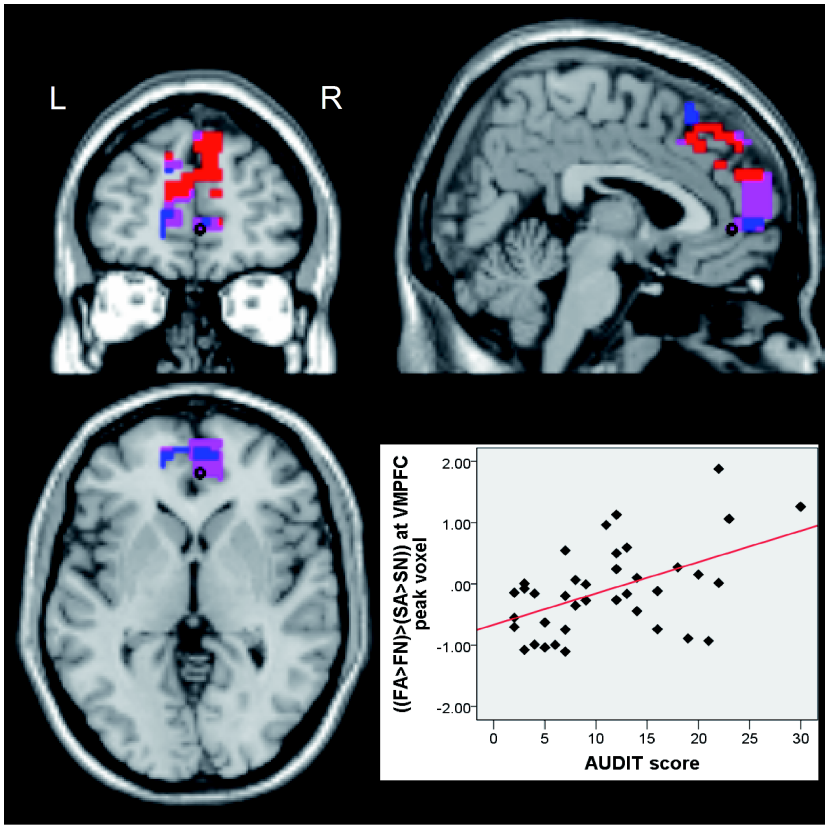
Das Volumen der grauen Substanz wurde probandenweise mittels der VBM8 Toolbox für SPM8 bestimmt. Hierzu wurden die hochauflösenden T1-Aufnahmen mit Hilfe des DARTEL-Algorithmus (30) in den MNI-Raum normalisiert. Anschließend wurden zum einen Areale mit relativer Atrophie in alkoholabhängigen Patienten im Vergleich zu gesunden Probanden gesucht. Hierfür wurde ein F-Test auf Gruppenunterschiede gerechnet und für multiples Testen mittels FWE-Korrektur ($p < 0.05$) ohne a priori ROIs korrigiert ("whole-brain-Korrektur"). Zum anderen wurde überprüft, ob Zusammenhänge zwischen diesen Atrophien und der Inhibitionsfähigkeit der jeweiligen Probanden (stop-signal task) bestehen. Hierfür wurde das Volumen derjenigen Areale mit signifikantem Volumen-Unterschied zwischen alkoholabhängigen Patienten und gesunden Kontrollen probandenweise extrahiert und auf Korrelationen mit den individuellen Ergebnissen des stop-signal-tasks untersucht.

1.3 Ergebnisse

Studie 1: Auf der Verhaltensebene fand sich eine positive Korrelation zwischen der Trinkschwere (AUDIT scores) und der Anzahl der Entscheidungen für begehrtere alkoholische, verglichen mit nicht-alkoholischen Getränken, außerdem eine negative Korrelation mit der Reaktionszeit von Entscheidungen für begehrtere alkoholische, verglichen mit nicht-alkoholischen Getränken. Das

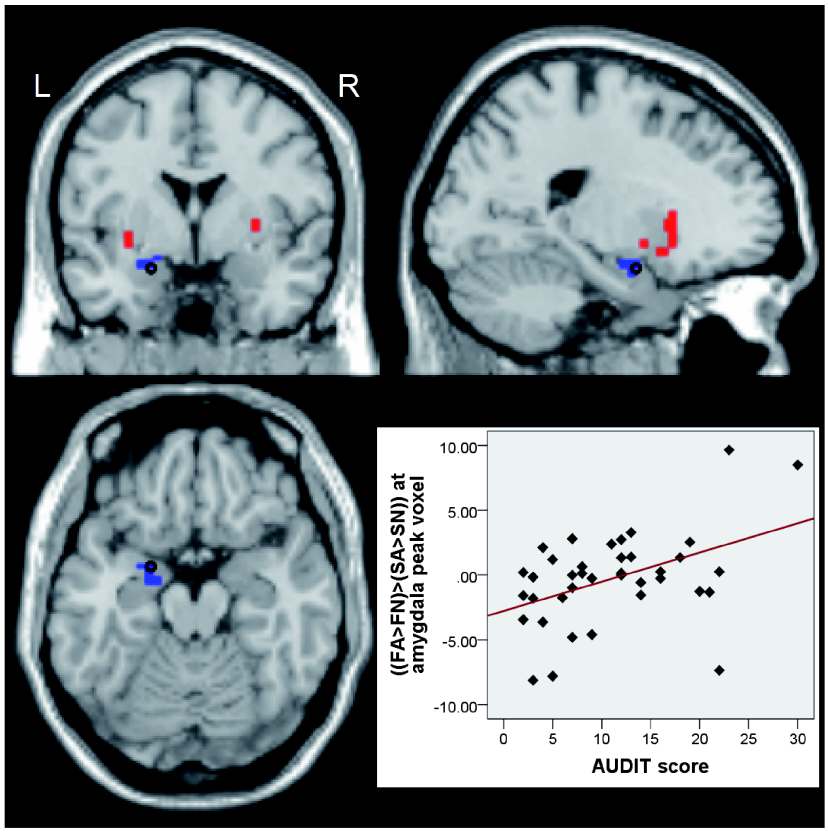
heißt, dass sich mit steigender Trinkschwere häufiger und schneller für alkoholische Getränke entschieden wurde.

In der Bildgebung korrespondierte dem eine mit zunehmender Trinkschwere ansteigende Aktivierung von belohnungsassoziierten Arealen (Amygdala, ventrales Striatum, ventromedialer Präfrontalkortex, Test der Hypothese eines überschießenden Belohnungssignals) während Entscheidungen für alkoholische Getränke verglichen mit Entscheidungen für nicht-alkoholische Getränke, beziehungsweise im Interaktionskontrast, bei dem zusätzlich Aktivierungen während erfolgreicher Selbstkontrolle abgezogen wurden (Abbildung 1, $p < 0{,}05$ FWE-korrigiert für a priori regions of interest). Die umgekehrte Analyse, die auf Areale zielte, die während pro-Alkohol-Entscheidungen eine sinkende Aktivität mit steigender Trinkschwere zeigen (negative Korrelation zwischen AUDIT Punktzahl und Aktivität, Test der Hypothese dysfunktionaler Kontrollsysteme), ergab keine signifikanten Areale.



(a)

Abbildung 1: Mit steigender Trinkschwere ansteigende Aktivierungen in belohnungsassoziierten Arealen während Entscheidungen für alkoholische Getränke verglichen mit nicht-alkoholischen Getränken (a für den medialen Präfrontalkortex; b für Amygdala und ventrales Striatum). Rot: Areale mit signifikanter Korrelation von AUDIT Punktzahl und Aktivierungsunterschieden zwischen Entscheidungen für das begehrtere alkoholische Getränk vs. Entscheidungen für das begehrtere nicht-alkoholische Getränk. Blau: Areale mit signifikanter Korrelation zwischen AUDIT Punktzahl und



(b)

Aktivierungsunterschieden zwischen Entscheidungen für das begehrtere alkoholische Getränk vs. Entscheidungen für das begehrtere nicht-alkoholische Getränk verglichen mit Entscheidungen *gegen* das begehrtere alkoholische Getränk vs. Entscheidungen *gegen* das begehrtere nicht-alkoholische Getränk (Interaktionskontrast zwischen Alkohol- vs. Nicht-Alkoholkondition und gescheiterter vs. erfolgreicher Selbstkontrolle).

Studie 2: Auf Verhaltensebene fand sich für die CBM-Trainingsgruppe eine signifikante Reduktion des alcohol approach bias und des alkoholbezogenem Suchtdrucks nach durchgeführtem CBM-Training im Vergleich zu vorher. In der Schein-Trainingsgruppe trat ein solcher Therapieeffekt nicht auf.

In den Bildgebungsergebnissen zeigte sich vor dem Training zunächst in beiden Gruppen eine bilaterale Amygdalaaktivierung als Reaktion auf alkoholische im Vergleich zu nicht-alkoholischen Getränken (alcohol cue reactivity), zudem eine Korrelation zwischen Aktivität in der Amygdala und subjektivem Suchtdruck. In der Gruppe mit echtem CBM-Training schwächte sich die alcohol cue reactivity in der Amygdala nach erfolgtem Training signifikant ab, während sich in der Gruppe mit Schein-Training kein Effekt zeigte. Interessanterweise korrelierte der Grad dieser trainingsassoziierten Aktivitätsreduktion der Amygdala wiederum mit der Reduktion des Suchtdrucks durch das Training, was den Zusammenhang zwischen Wirksamkeit des Trainings und Reaktivität der Amygdala auf alkoholische Reize unterstreicht.

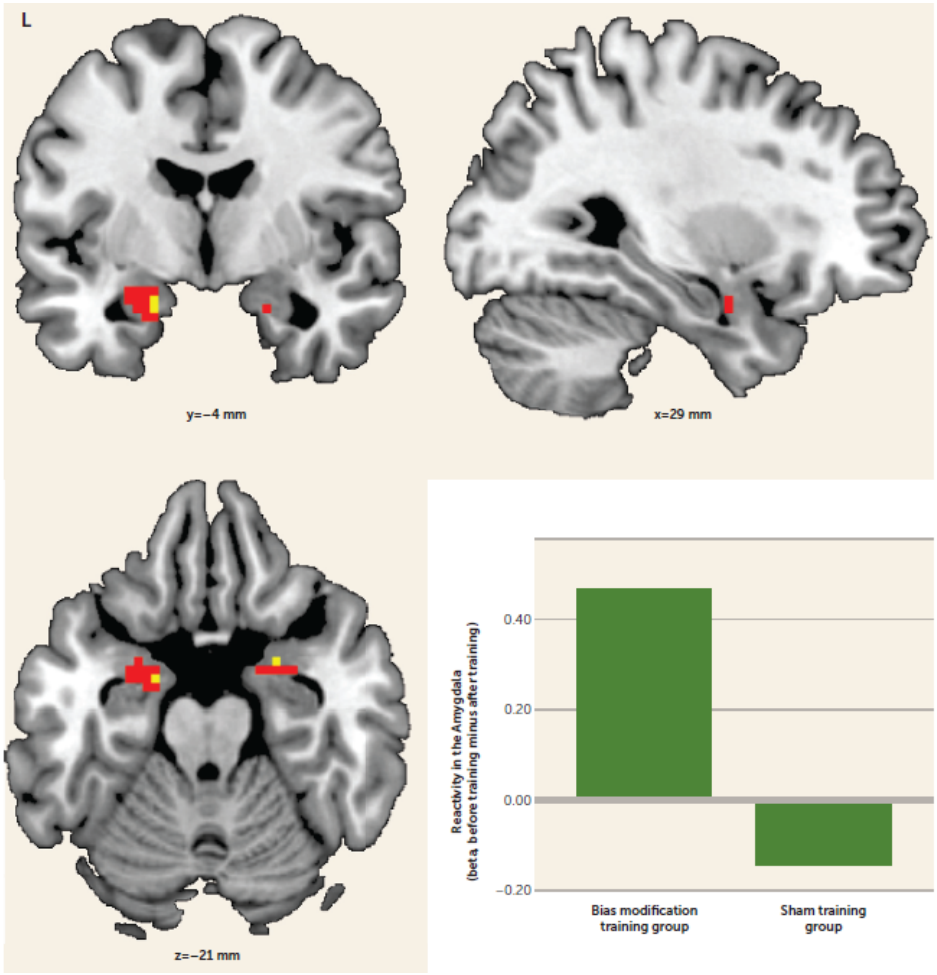
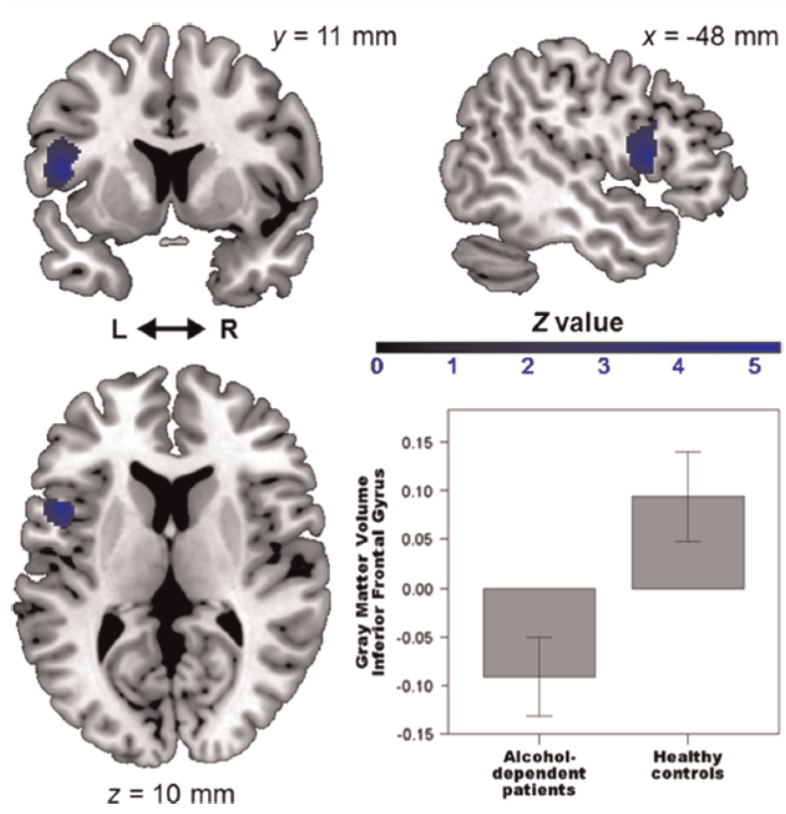
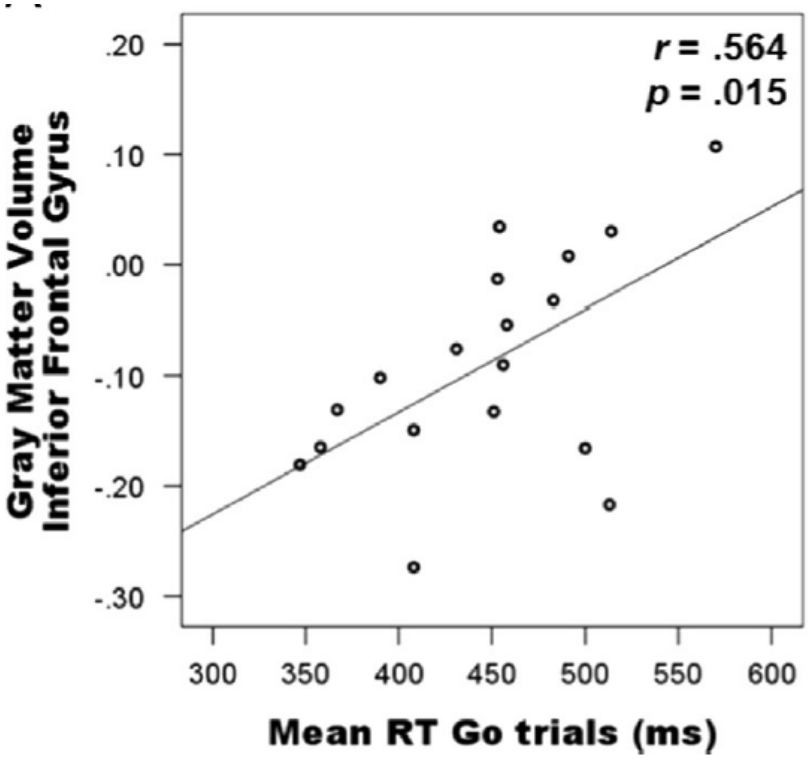


Abbildung 2: Reduktion der Reaktivität der Amygdala auf alkoholische Reize durch echtes CBM verglichen mit Scheintraining

Studie 3: Im linken inferioren frontalen Gyrus (IFG) zeigte sich eine signifikante Volumenreduktion der grauen Substanz in alkoholabhängigen Patienten verglichen mit gesunden Kontrollen (FWE-korrigierte Analyse ohne a priori region of interest, Abbildung 3a). Das Volumen dieses Areals korrelierte in der Gruppe der alkoholabhängigen Patienten zudem signifikant positiv mit der Reaktionsgeschwindigkeit in den go trials des stop-signal tasks, was einen Hinweis auf eine disinhibiertere Antwortstrategie darstellen könnte (schnellere go-Reaktion mit abnehmendem Volumen des IFG, Abbildung 3b). Zwischen der Reaktionsgeschwindigkeit in den stop-trials des stop-signal-task und dem Volumen dieses Areals fand sich jedoch kein signifikanter Zusammenhang.



(a)



(b)

Abbildung 3: (a) Durchschnittliches Volumen des inferioren frontalen Gyrus in alkoholabhängigen Patienten verglichen mit gesunden Kontrollen und (b) Korrelation dieses Volumens mit Reaktionszeiten in go-trials des stop-signal-tasks in alkoholabhängigen Patienten

1.4 Diskussion

1.4.1 Neuronale Korrelate von Suchtdruck, automatischen Annährungstendenzen und pro-Alkohol- Entscheidungen

In Studie 2 konnten Vorbefunde, denen zufolge Suchtdruck ebenso wie automatische alkoholbezogene Annährungstendenzen mit einer Aktivierung belohnungsassoziierter Areale einhergehen (7-18), für die Amygdala reproduziert und damit noch einmal die Bedeutung des Belohnungssystems für die Aufrechterhaltung von Alkoholabhängigkeit unterstrichen werden.

Studie 1 demonstriert passend dazu erstmals, dass auch *Entscheidungen* für alkoholische Getränke mit zunehmender Trinkschwere mit steigender Aktivität von belohnungsassoziierten Arealen (Amygdala, ventrales Striatum und medialer Präfrontalkortex), nicht aber mit abnehmender Aktivität von kontrollassoziierten Arealen (dorsolateraler Präfrontalkortex) einhergehen. Sie liefert damit weitere Evidenz für die Hypothese einer überschießenden Aktivierung von Belohnungssystemen als physiologischem Ausdruck von Suchtdruck, automatischen Annährungstendenzen und schließlich auch tatsächlicher Entscheidungen für den Alkoholkonsum. Für die konkurrierende Hypothese einer verminderten Aktivierung von Kontrollsystemen fand sich indes kein Korrelat in den Bildgebungsergebnissen.

Um den Entscheidungen einen realeren Charakter zu geben, wurde eines der gewählten Getränke, also potenziell auch Alkohol, im Anschluss an das Experiment an die Teilnehmer ausgehändigt: Hierdurch verbietet sich selbstverständlich der Einschluss von Probanden mit manifester Abhängigkeitserkrankung. Die in dieser Studie präsentierten Ergebnisse sind entsprechend dimensionaler Natur, d.h. sie bezeichnen nicht kategoriale Unterschiede zwischen Gruppen (alkoholabhängige Probanden versus Kontrollprobanden), sondern graduelle Zusammenhänge zwischen dem Schweregrad des Alkoholkonsums und der Aktivität von Hirnarealen während Entscheidungen für Alkoholkonsum. Dieser Ansatz ist kompatibel zu einer Neubetrachtung von Abhängigkeitserkrankungen, in der diese nicht als dichotom aufgefasst werden, sondern vielmehr als Kontinuum, das vom beginnenden Alkoholmissbrauch zur manifesten schweren Abhängigkeit reicht (diese Neubetrachtung hat auch Eingang in das neue

DSM-5 gefunden). Ob die Ergebnisse tatsächlich auf Fälle ausgeprägter Abhängigkeit übertragbar sind, müsste dennoch in weiterführenden Studien geklärt werden.

1.4.2 Überschießende Amygdalaaktivierung als Zielpathologie des Cognitive Bias Modification Training

Die in Studie 1 nahegelegte Bedeutung des Belohnungssystems für pro-Alkohol-Entscheidungen kann als Hinweis auf die Sinnhaftigkeit von Therapiestrategien gelesen werden, die statt auf eine Stärkung kognitiver Kontrolle auf eine Reduktion automatischer Belohnungsprozesse abzielen. Eine solche Therapiestrategie stellt das sogenannte Cognitive Bias Modification Training dar. Die Wirksamkeit dieses Trainings auf Suchtdruck ebenso wie auf automatische Annährungstendenzen konnte in Studie 2 im Vergleich zu einem placeboartigen Schein-Training demonstriert und entsprechende Vorbefunde (6, 29) repliziert werden.

Erstmalig konnten - im Sinne von Hirnaktivitätsunterschieden vor und nach dem Training - auch neuronale Korrelate dieser Wirksamkeit beleuchtet werden. Diese wurden in erster Linie für die Amygdala nachgewiesen, was die Bedeutung dieser Struktur für die Aufrechterhaltung von Abhängigkeit unterstreicht, gerade weil auch in Studie 1 die Amygdala als Areal identifiziert werden konnte, dessen ansteigende Aktivität mit zunehmender Trinkschwere pro-Alkohol-Entscheidungen begünstigt.

Diese Ergebnissen passen zu einer Rekonzeptualisierung der Rolle der Amygdala in Emotionsregulation und Belohnung, die sich durch zahlreiche jüngere Forschungsergebnisse motiviert. Während Aktivierungen der Amygdala klassischerweise mit negativem Affekt, Aversion und Angst in Verbindung gebracht wurden (31), belegen neuere Studien mit verschiedenster Methodik die Prozessierung von Belohnungen und Positivreizen in der Amygdala. Eine Kernstudie konnte durch Einzelzellableitungen in Affen eine Neuronenpopulation in der Amygdala nachweisen, die explizit auf stimulusbezogene konditionierte *Belohnungen* reagiert (32). Passend hierzu verlieren Affen und Ratten durch Läsionen der Amygdala die Fähigkeit, Zusammenhänge zwischen Stimuli und Belohnungen zu lernen (33, 34). Auch in Menschen konnte per fMRT eine entsprechende Aktivierung der Amygdala als Grundlage der Assoziation von Stimuli und

Belohnungen nachgewiesen werden (35). Vor diesem Hintergrund lassen sich die Ergebnisse unserer Studien als Evidenz für eine amydgalavermittelte Verknüpfung von substanzbezogenen Reizen (z.B. von Bildern alkoholischer Getränke) und Belohnungsempfinden interpretieren, die eine zentrale Rolle in der Aufrechterhaltung von Suchterkrankungen spielen könnte. Die in Studie 2 nachgewiesenen nachlassenden Amygdalaktivierungen bei erfolgreicher therapeutischer Auflösung dieser Reiz-Belohnungs-Assoziationen erweitern in dieser Perspektive analoge Vorbefunde (35) auf den Bereich der Abhängigkeit. Davon unbenommen unterstreicht gerade Studie 1 auch die Bedeutung „klassischer“ dopaminerger Belohnungsareale wie dem ventralen Striatum: Die intensiven Verbindungen zwischen Amygdala und ventralem Striatum sprechen in diesem Zusammenhang für eine Interaktion beider Areale bei der Prozessierung von Belohnungen (36).

1.4.3 Hirnanatomische Korrelate von Alkoholabhängigkeit und reduzierter Inhibitionsfähigkeit

Mit dem Nachweis einer relativen Atrophie des inferioren frontalen Gyrus in alkoholabhängigen Patienten im Vergleich zu gesunden Kontrollen konnten auch in Studie 3 zunächst Vorbefunde bestätigt werden (37, 38). Darüber hinaus wurde erstmalig gezeigt, dass eine Atrophie dieses Areals auch von einem tendenziell disinhibierten Entscheidungsverhalten in einem stop-signal task flankiert wird. Zu bemerken ist allerdings, dass hier nur schnellere Reaktionszeiten in go trials, aber nicht verlängerte Reaktionszeiten in stop trials vorlagen, die bei einer beeinträchtigten Impulsinhibition eigentlich auch zu erwarten wären. Zudem wurde in dieser Studie die Performance im stop-signal-task nur in der Patienten-, nicht aber in der Kontrollgruppe erfasst, so dass auf dieser Grundlage keine Aussagen über Gruppenunterschiede in der (behavioralen) Inhibitionsfähigkeit getroffen werden können. Inhibitionsdefizite in alkoholabhängigen Patienten sind allerdings vorbefundlich beschrieben (21, 39).

1.4.4 Schlussfolgerung

Die vorliegenden Studien betrachten die Rolle von belohnungs- und kontrollassoziierten Arealen in Alkoholabhängigkeit. Vor allem die Bedeutung von überschießender Aktivierung von Belohnungsarealen konnte dokumentiert werden, sowohl für Suchtdruck und automatische Annährungstendenzen, als auch für reale Entscheidungen für Alkoholkonsum. Eine therapeutische Konsequenz dieser Erkenntnisse wäre eine verstärkte Fokussierung auf Belohnungs- statt auf Kontrollprozesse, wie sie im Cognitive Bias Modification stattfindet: Für diese Therapiestrategie konnte eine wirksame Reduktion von Suchtdruck und der entsprechenden überschießenden Amygdalaaktivierung demonstriert werden.

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2. Anteilserklärung

Eidesstattliche Versicherung

„Ich, Heiner Stuke, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: "Zielorientierte Entscheidungsfindung bei regelmäßigem Alkoholkonsum" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Heiner Stuke hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Stuke, H., S. Gutwinksi, C.E. Wiers, T.T. Schmidt, S. Gropper, J. Parnack, C. Gawron, C.H. Attar, S. Spengler, H. Walter, A. Heinz, and F. Bermpohl, To drink or not to drink: Harmful drinking is associated with hyperactivation of reward areas rather than hypoactivation of control areas in men. J Psychiatry Neurosci, 2016. 41(3): p. 150203.
Beitrag im Einzelnen (bitte kurz ausführen): Substantielle Mitwirkung am Studiendesign, Beteiligung an 80% der fMRT-Untersuchungen, statistische Auswertung, Schreiben des Manuskriptentwurfes und substantielle Mitwirkung an der Anfertigung der Publikation in der vorliegenden Form.

Publikation 2: Wiers, C.E., C. Stelzel, T.E. Gladwin, S.Q. Park, S. Pawelczack, C.K. Gawron, H. Stuke, A. Heinz, R.W. Wiers, M. Rinck, J. Lindenmeyer, H. Walter, and F. Bermpohl, *Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence.* Am J Psychiatry, 2015. 172(4): p. 335-43.
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Publikation 3: Wiers, C.E., C.K. Gawron, S. Gropper, S. Spengler, H. Stuke, J. Lindenmeyer, H. Walter, and F. Bermpohl, *Decreased gray matter volume in inferior frontal gyrus is related to stop-signal task performance in alcohol-dependent patients*. Psychiatry Res, 2015. 233(2): p. 125-30.
Beitrag im Einzelnen (bitte kurz ausführen): Beteiligung an 30% der MRT-Messungen, Beteiligung an der statistischen Auswertung, substantielle Mitwirkung an Entwurf und Anfertigung der Publikation in der vorliegenden Form.

Unterschrift des Doktoranden/der Doktorandin

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3. Druckexemplare der ausgewählten Publikationen

3.1 To drink or not to drink: Harmful drinking is associated with hyperactivation of reward areas rather than hypoactivation of control areas in men

Research Paper

To drink or not to drink: Harmful drinking is associated with hyperactivation of reward areas rather than hypoactivation of control areas in men

Heiner Stuke, MD; Stefan Gutwinski, MD; Corinde E. Wiers, PhD; Timo T. Schmidt; Sonja Gröpper, MD; Jenny Parnack, MD; Christiane Gawron, MD; Catherine Hindi Attar, PhD; Stephanie Spengler, PhD; Henrik Walter, MD, PHD; Andreas Heinz, MD, PhD; Felix Bermpohl, MD, PhD

Background: The maintenance of harmful alcohol use can be considered a reiterated decision in favour of alcohol in concrete drinking occasions. These decisions are often made despite an intention to quit or reduce alcohol consumption. We tested if a hyperactive reward system and/or an impaired cognitive control system contribute to such unfavourable decision-making. **Methods:** In this fMRI study, men with modest to harmful drinking behaviour, which was measured using the Alcohol Use Disorders Identification Test (AUDIT), repeatedly made decisions between alcoholic and nonalcoholic drinks. Based on prior individual ratings, decision pairs were created with an alcoholic decision option considered more desirable but less beneficial by the participant. By correlating AUDIT scores with brain activation during decision-making, we determined areas explicitly related to pro-alcohol decisions in men with greater drinking severity. **Results:** Thirty-eight men participated in our study. Behaviourally, we found a positive correlation between AUDIT scores and the number of decisions for desired alcoholic drinks compared with beneficial nonalcoholic drinks. The fMRI results show that AUDIT scores were positively associated with activation in areas associated with reward and motivation processing (i.e., ventral striatum, amygdala, medial prefrontal cortex) during decisions favouring a desired, nonbeneficial alcoholic drink. Conversely, we did not find hypoactivation in areas associated with self-control (dorsolateral prefrontal cortex). These effects were not present when participants chose a desired, nonbeneficial, nonalcoholic drink. **Limitations:** The men participating in our study had to be abstinent and would potentially consume an alcoholic drink at the end of the experiment. Hence, we did not define manifest alcohol dependence as an inclusion criterion and instead focused on less severely affected individuals. **Conclusion:** Our results indicate that with growing drinking severity, decisions for alcoholic drinks are associated with increasing activity in reward-associated neural systems, rather than decreasing activity in self-control–associated systems.

Introduction

The maintenance of harmful alcohol use implies reiterated decisions to consume alcohol in concrete drinking occasions. These decisions are often made despite an intention to quit or reduce alcohol consumption. Although there is quite a large body of evidence on neural responsivity to alcohol cues or neural mechanisms of general decision-making capacities in individuals with alcohol use disorders, the neural processes during real drinking decisions remain largely unclear.

Dual-process models of addiction[1,2] state the importance of 2 distinct but interacting systems during decisions for and against alcohol consumption. On the one hand, a reward system (also referred to as an impulsive, motivational, or reflexive system) has been implicated in the immediate emotional assessment of stimuli and automatic (approach) behaviour. On the other hand, a cognitive control system (also referred to as a deliberative or reflective system) that modulates this primary assessment by integration of higher-order considerations, such as long-term effects of a possible decision, has been suggested. In theory, both a hyperactive reward system and an impaired control system may contribute to addictive behaviour. Indeed, behavioural and neuroimaging data suggest alterations in both systems in individuals with substance use disorders.

Alcohol-dependent or heavily drinking individuals show subjective craving[3] and automatic approach tendencies[4,5] when confronted with alcoholic drinks, and a substantial body of literature suggests that such addiction-related behaviour is

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associated with an overactive reward system. Specifically, fMRI studies have consistently linked alcohol cue reactivity (i.e., brain responses to the presentation of alcohol stimuli) with the amygdala, ventral striatum and ventromedial prefrontal cortex (VMPFC) in both alcohol-dependent patients[6–14] and heavy drinkers.[15–17]

Moreover, alcohol-dependent patients showed activation of the ventral striatum and VMPFC when approaching versus avoiding alcohol compared with fruit juice in a joystick task,[18] and activation of the amygdala and ventral striatum has been reported to correlate with subjective craving in alcohol-dependent patients.[14,18] Thus, hyperactivity in reward-associated neural systems appears to play a role in craving and approach behaviour. Conversely, this enhanced response to alcohol-related stimuli may be accompanied by an attenuated response to nonalcoholic rewarding stimuli.[12,18] This neuroimaging finding is behaviourally paralleled by a loss of interest in activities that are not related to alcohol consumption.

On the other hand, previous findings suggest impaired self-control function in alcohol-dependent or heavily drinking individuals. At the behavioural level, these individuals show a preference for short-term rather than long-term rewards,[19] as well as for riskier decision options.[20] At the neural level, this may correspond to attenuated activity of the second system in dual system models of decision-making. This control system supposedly modifies automatic behaviour by integrating goals related to long-term benefits.

In healthy individuals, dorsolateral prefrontal cortex (DLPFC) activation has been associated with a preference for long-term over short-term rewards,[21,22] whereas disruption of the DLPFC by repetitive transcranial magnetic stimulation (rTMS) has been shown to promote impulsive decision behaviour.[23] In an fMRI study on healthy dieters choosing between a tastier and a healthier food product, decisions in favour of the healthier product were correlated with increased DLPFC activation.[24] In line with this finding, lesions of the DLPFC led to the inability to change dysfunctional decision patterns.[25] In indivdiuals with substance use disorders, neuroimaging studies have shown attenuated DLPFC activity during inhibitory control tasks.[26,27] Furthermore, the DLPFC was more active in smokers when using cognitive strategies to suppress craving.[28] Taken together, these findings suggest that functional and structural alterations in self-control areas could lead to the inability to resist craving despite the intention to quit drinking.

Behavioural and neuroimaging data suggest that alterations in the reward as well as in the control system contribute to addictive behaviour. An overwhelming desire (associated with hyperactivation of reward-associated circuits) as well as impaired control processes (associated with hypoactivation in control-associated areas) may contribute to the maintenance of substance use despite awareness of its harmful consequences. The aforementioned fMRI studies either focused on passive exposure to alcohol-related stimuli (thus studying responsivity of the reward system to alcohol cues, independent of actual decision-making situations) or on general decision-making tasks, such as the Iowa Gambling Task[29] or the Monetary Delayed Discounting Task[30] (thus studying control processes independent of alcohol stimuli). Hence, these studies mainly focused either on reward or control processes in addiction. The present study addressed the question of how both systems interact during real-life drinking decisions and how this interplay is altered with increasing drinking severity.

For this purpose, we used an fMRI task where individuals with widely differing drinking severity decided between alcoholic and nonalcoholic drinks. The decision options were individually designed in a way that participants experienced a conflict between the desire and benefit associated with the respective drinks. We implemented a real-world decision by scheduling scanning sessions on Friday or Saturday evenings and by serving one of the chosen drinks directly after scanning. By this means, the paradigm established by Hare and colleagues[24] was adopted to elucidate the neural mechanisms of decisions for desired, nonbeneficial alcoholic drinks. Specifically, we tested if increased activity of reward areas (hypothesis of overwhelming desire), decreased activity of self-control areas (hypothesis of impaired control processes) or a combination of both promotes harmful pro-alcohol decisions.

Methods

Participants

We recruited men between 20 and 60 years old through advertising for participation in the study. Exclusion criteria were withdrawal symptoms when abstinent, cannabis consumption 4 weeks before participation and substance dependence other than alcohol and/or nicotine. Participants were told before they enrolled in the study that there would be urine toxicology tests on a random basis. In practice, this random screening was not performed, and we relied on the participants' self-disclosure instead. In addition, to be eligible for participation, individuals were required to have no other DSM-IV Axis-I disorders and no history of head trauma or neurologic disorders. To guarantee a general awareness of health issues, participants were asked about eating habits and health awareness in the screening interview.

Participants were screened for DSM-IV criteria for alcohol abuse and alcohol dependence using the Mini-International Neuropsychiatric Interview (M.I.N.I.).[31] As participants received real drinks at the end of the experiment, we did not include abstinent or immediately treatment-seeking participants to avoid the risk of provoking relapses. After the experiment, all participants were given information on addiction counselling centres and treatment possibilities.

Participants completed the following questionnaires concerning drinking behaviour: the Alcohol Use Disorders Identification Test[32] (AUDIT; assessing harmful drinking on a scale of 0 to 40), the Obsessive Compulsive Drinking Scale[33] (OCDS) and the Alcohol Dependence Scale[34] (ADS). The AUDIT was used as the main variable modelling severity of harmful drinking.

We collected the following additional information to allow strict control over confounding variables and potential psychiatric comorbidities. Handedness was assessed using the Edinburgh Handedness Inventory[35] (EHI), and the Matrix Reasoning Test of the Wechsler Adult Intelligence Scale[36]

(WAIS) was used as a proxy of general intelligence. We assessed depressive symptoms using the Beck Depression Inventory (BDI), anxiety using the State-Trait Anxiety Inventory[37] (STAI) and impulsiveness using the Barratt Impulsiveness Scale[38] (BIS) and the Monetary Choice Questionnaire[39] (MCQ). The Lifetime Drinking History (LDH[40]) was used to assess the participants' drinking behaviour over the lifespan.

The study was approved by the Ethical Committee of the Charité, Universitätsmedizin Berlin. After complete description of the study, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Experimental setting

Participants were instructed not to drink anything for 2 hours before the scanning session to ensure a basic level of thirst. Because participants arrived at the scanning site 90 min before the fMRI session to perform the ratings and fill out consent forms and questionnaires, we can say for certain that they did not drink within this timeframe. Moreover, every session was scheduled for evenings before either weekends or public holidays to guarantee drinking willingness. Before the experiment, a minibar with drinks was presented to the participant in a room near the scanning room, and the participants were told that 1 of the decisions made during the experiment would be implemented after the experiment.

Ratings

Prior to scanning, participants rated 120 photographs depicting alcoholic drinks (e.g., beer, wine, liquor) as well as a variety of nonalcoholic drinks (e.g., lemonade, milk, juice) with regard to desire and beneficence. The wording of the 2 questions was (translated from German) "In your honest opinion, how great is your desire to have this drink right now?" for the desire rating and "How beneficial/harmful would it be to have this drink?" for the benefit rating. In both cases, the scale reached from –4 to 4, with 0 as a neutral value (Fig. 1). The drinks were presented using high-resolution colour pictures matched for luminance and size between alcoholic and nonalcoholic items. We used the ratings to create conflicting pairs of a more beneficial and a more desired drink in the decision task. The image set's suitability to create such conflicting pairs was investigated beforehand and optimized in a behavioural pilot study involving 8 participants.

Decision task

In the decision task, 2 images of drinks were presented simultaneously, followed by a fixation cross (Fig. 2). Within a 4-s interval, participants chose (by button press) between 2 nonalcoholic drinks or between an alcoholic and a nonalcoholic drink. The decisions involving an alcoholic drink are hereafter referred to as "alcohol trials," and those with 2 nonalcoholic drinks are refferred to as "nonalcohol" trials. Decision options were presented in such a way that they induced a conflict within the participant between the desire and the benefit associated with the consumption of the respective drinks. That is, based on the prescan ratings, decision options were presented where 1 drink was considered more beneficial and the other more desirable by the participant. Moreover, "close" conflict pairs that differed by only 1 point on both scales were excluded from analysis.

Depending on the participants' prior ratings and the real decision, each trial was subsumed under 1 of 4 conditions that were defined as follows (Fig. 1):

- SA: successful self-control in an alcohol–nonalcohol conflict (e.g., choosing the less desired, more beneficial nonalcoholic item),
- FA: failed self-control in an alcohol–nonalcohol conflict (e.g., choosing the more desired, less beneficial alcoholic item),
- SN: successful self-control in a nonalcohol–nonalcohol conflict (e.g., choosing the less desired, more beneficial nonalcoholic item), and
- FN: failed self-control in a nonalcohol–nonalcohol conflict (e.g., choosing the more desired, less beneficial nonalcoholic item).

The decision task was split into 4 runs of 50 trials each. For 12 of the participants, the ratings did not allow us to create the 200 conflicting stimulus pairs, so fewer trials were tested (range 50–192 decisions per participant). The reason for this was a correlation between desire and benefit ratings in these participants, which led to a reduced number of pairs with conflict between benefit and desire of the drinks and — because only pairs with this conflict were shown to the participant — to a reduced number of decisions. However, a confounding effect of this imbalance is unlikely since the number of trials per participant was not correlated with our variable of interest, the AUDIT scores ($p = 0.77$).

The general functionality of the task and the stimulus set was tested with a proof-of-concept analysis comparing blood-oxygen level–dependent (BOLD) responses between alcohol and nonalcohol trials (FA + SA) > (FN + SN). As expected, this analysis yielded strong effects in the posterior and anterior cingulate cortex and the medial prefrontal cortex (inter alia, family-wise error [FWE]–corrected whole brain analysis). Because of their replicative character, these results are not reported in the Results section.

FMRI data acquisition and preprocessing

We used a Siemens Trio 3 T scanner equipped with a 12-channel head coil to acquire MRI volumes. T_2*-weighted gradient-echo echo-planar images (EPI) containing 36 axial slices (3.5 mm thick, interleaved) without interslice gap were acquired with the following imaging parameters: repetition time (TR) 2250 ms, echo time (TE) 30 ms, flip angle 80°, matrix size 64 × 64 and field of view (FOV) 134 mm, resulting in a voxel size of 3.5 × 3.5 × 3.5 mm. Images were acquired in an oblique orientation of 30° to the anterior commissure–posterior commissure line. High resolution T_1-weighted structural data were collected for anatomic localization, with TR 900 ms, TE 2.52 ms, matrix size 256 × 256, FOV 256 mm, 192 slices (1 mm thick) and flip angle 9°.

We preprocessed functional scans using SPM8 software.[41] Functional images were corrected for slice-acquisition time (using sinc interpolation), realigned and unwarped. The high-resolution T_1 image was coregistered with the mean EPI image and subsequently segmented. Images were normalized using DARTEL and the segmented grey and white matter maps. Finally, images were spatially smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

First-level analyses

After preprocessing, individual data analysis was performed using SPM8. For each participant, we used the onsets of presentation of the decision options to generate regressors for the 4 conditions (SA, FA, SN, FN) in an event-related design (see the Decision task section and Fig. 1). We used the realignment parameters of the motion correction as covariates

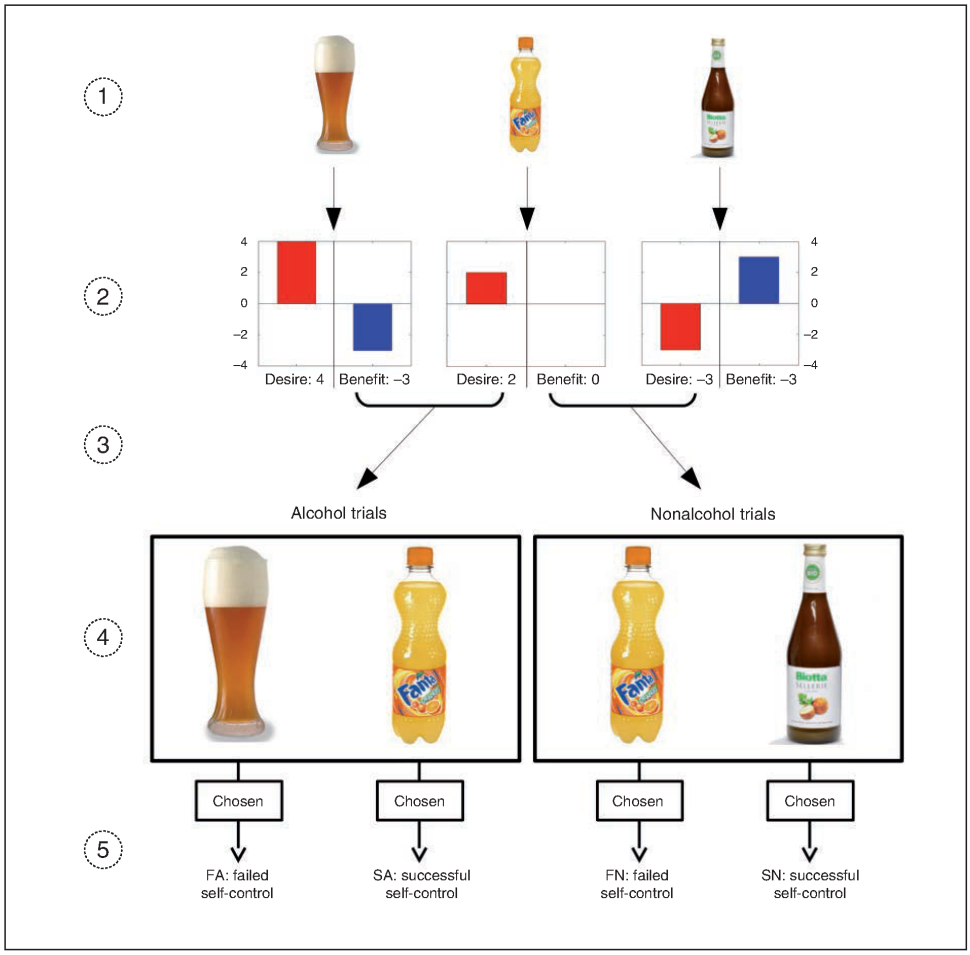

Fig. 1: Stimulus set, ratings and conditions of the decision task. (**1**) The stimulus set comprised images of 120 alcoholic and nonalcoholic drinks. (**2**) These drinks were rated by the participant in terms of desire to drink and beneficence of the drink. (**3**) Pairs of drinks inducing a conflict between desire and benefit were generated based on the individual ratings. (**4**) During the fMRI session, the participant chose between the 2 drinks. (**5**) All decisions made by participants during the decision task were assigned to 1 of 4 conditions: successful self-control in an alcohol–nonalcohol conflict (SA; e.g., choosing the nonalcoholic item), failed self-control in an alcohol–nonalcohol conflict (FA; e.g., choosing the alcoholic item), successful self-control in a nonalcohol–nonalcohol conflict (SN; e.g., choosing the less desired, more beneficial nonalcoholic item), and failed self-control in a nonalcohol–nonalcohol conflict (FN; e.g., choosing the less beneficial, more desired nonalcoholic item).

of no interest. Subsequently, specific t contrast images (see the Contrast testing section) were created and entered into the second-level group analyses.

Second-level analyses

For every contrast image created in the first-level analyses, we performed a group-level correlation analysis between AUDIT scores and contrast-specific brain activation using the Multiple Regression Design of SPM (see the "Contrast testing" section). Because there was an association between AUDIT scores and age ($r = 0.27$, $p = 0.10$), we included age as a covariate of no interest to preclude a confounding influence of age differences. For this analysis, we used a priori regions of interest (ROIs) for small-volume α error adjustment. Based on prior studies on neural correlates of alcohol-related cue reactivity, craving and approach behaviour, we included the amygdala, striatum and MPFC as ROIs to test our hypothesis of overwhelming desire. These ROIs are hereafter referred to as "reward-associated areas," although this wording certainly does not cover all cognitive processes previously proposed for these areas. Conversely, we used the DLPFC as an ROI to test our hypothesis of impaired control processes ("control-associated area"). The striatum, amygdala and MPFC were defined as described by Beck and colleagues[7] using a combination of anatomic hypotheses and previous fMRI findings regarding alcohol cue reactivity. As the DLPFC is anatomically not clearly defined and has not been reported in cue reactivity studies, a functionally defined ROI was downloaded from an online atlas.[42] All imaging results are presented with a significance threshold of $p < 0.05$, small volume–corrected for the amygdala, striatum, MPFC and DLPFC ROIs and using FWE correction to account for multiple testing.

Contrast testing

To study how brain activation during pro-alcohol decisions varies with drinking severity, we correlated AUDIT scores with specific BOLD contrasts obtained during the decision task. We aimed to identify 2 types of brain regions: areas whose activation was positively correlated with drinking severity during pro-alcohol decisions (reward-associated areas according to the hypothesis of overwhelming desire) and areas whose activation was negatively correlated with drinking severity (control-associated areas according to the hypothesis of impaired control processes).

To ensure the specificity of our findings for alcohol trials, we used decisions for more desired drinks in nonalcohol trials (FN trials) as a control condition (resulting in the contrast AUDIT × [FA – FN]). To further ensure the specificity for trials with a failure in self-control (i.e., to preclude a sole alcohol effect causing activations in AUDIT × [FA – FN]), we then subtracted the analogous contrast for successful self-control trials. This calculation yielded the interaction contrast AUDIT × [(FA – FN) – (SA – SN)], which represents the impact of growing drinking severity on activation during decisions for the more desired alcoholic drink compared with both decisions for the more desired nonalcoholic drink and decisions against the alcoholic drink. Thus, the contrasts AUDIT × (FA – FN) and AUDIT × [(FA – FN) – (SA – SN)] can be used to test the hypothesis of overwhelming desire (enhanced activation of reward areas during pro-alcohol decisions with growing drinking severity). Analogically, the inverse correlations –AUDIT × (FA – FN) and –AUDIT × [(FA – FN) – (SA – SN)] were computed indicating which areas show decreasing activations during pro-alcohol decisions with growing drinking severity (test for hypothesis of impaired control processes).

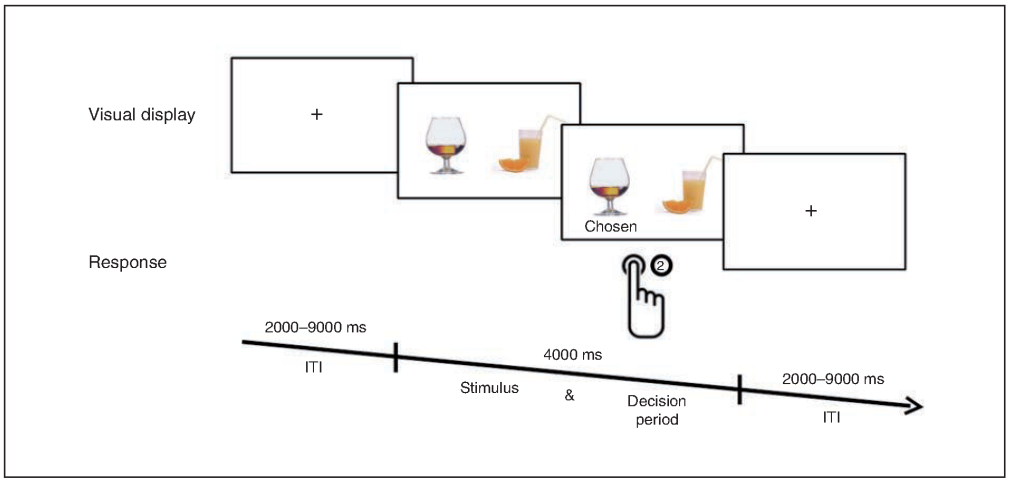

Fig. 2: Test sequence in the decision task. Two drinks were presented simultaneously. Participants had to choose 1 of the drinks within 4000 ms by pressing a button. After pressing the button, a fixation cross was presented for a variable intertrial interval (ITI) lasting 2000–9000 ms.

Behavioural analyses

For the 4 conditions SA, FA, SN and FN, we calculated the number of trials per condition and subject-wise mean response times. To check the validity of the AUDIT scores, we computed Pearson correlations between AUDIT scores and other alcohol-related measures (OCDS, ADS).

As a proxy of general impulsiveness, we correlated AUDIT scores with the general proportion of failed self-control trials (all failed self-control trials ÷ by all trials). As a measure of tendency to more likely fail in alcohol trials, we computed the ratio of failed self-control rates between alcohol and non-alcohol trials, referred to as "alcohol-specific failed self-control." It was correlated with AUDIT scores to check if this alcohol-specific failed self-control was more likely to occur in participants with more severe drinking.

We compared mean response times (RTs) between the different conditions as another measure of impulsive decision making. Analogous to contrast testing of imaging data, the interaction contrast of response times ([FAReact – FNReact] – [SAReact – SNReact]) was used to ensure the highest possible specificity for failed self-control decisions in favour of alcohol.

Results

Participants

We recruited 44 men to participate in the study. Five of them had to be excluded from the analysis for technical reasons, and 1 was excluded because of an incidental finding, leaving 38 men for data analysis. All participants were right-handed. Seventeen participants fulfilled DSM-IV criteria for alcohol abuse and 2 further fulfilled the criteria for alcohol dependence. Table 1 summarizes the final sample's demographic and behavioural features.

Behavioural results

To check the validity of AUDIT measures, we computed correlations between AUDIT, OCDS, ADS and LDH scores. These analyses revealed a significant correlation between AUDIT and OCDS ($r = 0.768$, $t_{36} = 7.19$, $p < 0.001$), AUDIT and ADS ($r = 0.828$, $t_{36} = 8.86$, $p < 0.001$) and AUDIT and alcohol consumption per month ($r = 0.561$, $t_{36} = 4.06$, $p < 0.001$) as well as for the entire life ($r = 0.513$, $t_{36} = 3.59$, $p = 0.001$) as measured

Table 1: Sample characteristics and behavioural results

Characteristic*	No. participants	Range	Mean ± SD	Pearson *R*
Age, yr	38	23 to 49	32.53 ± 7.13	0.27
Age at first drunken stupor, yr	38	12 to 18	15.16 ± 1.59	0.19
Alcohol Dependence Scale Score	36	25 to 54	32 ± 7.04	0.83†
Alcohol-specific failed self-control (ratio of failed self-control rates between alcohol and nonalcohol trials)	37	0.07 to 3.25	1.18 ± 0.56	0.41‡
AUDIT score	38	2 to 30	11.08 ± 7.05	—
No. drinking d/wk in the last mo	38	0.25 to 6	2.98 ± 2.04	0.48†
No. of drinks per drinking d in the last mo	38	3 to 12	8.16 ± 2.95	0.54†
Barratt Impulsiveness Scale score	38	42 to 171	69.43 ± 25.37	0.13
Beck Depression Inventory score	35	21 to 119	27.94 ± 16.27	0.11
Edinburgh Handedness Inventory quotient	38	10 to 100	81.75 ± 19.53	0.05
Interaction effec in response times [(FA – FN) – (SA –SN)]	37	–848.53 to 876.82	–5.7 ± 401.14	0.37‡
IQ	34	70.00 to 115.00	96.91 ± 10.87	0.14
Lifetime Drinking History alcohol intake per mo, g	38	82 to 9465	1762 ± 1774	0.56†
Lifetime Drinking History total alcohol intake, g	38	4861 to 2 754 299	390 481 ± 524 030	0.51†
Response time for FA trials, ms	38	972.57 to 2354.06	1499.08 ± 287.90	0.36‡
Response time for FN trials, ms	38	934.76 to 2303.95	1536.92 ± 316.19	0.19
Response time for SA trials, ms	37	996.96 to 3063.50	1811.08 ± 479.95	–0.22
Response time for SN trials, ms	38	994.33 to 3031.50	1864.11 ± 438.21	0.20
Monetary Choice Questionnaire — Discounting Index score	38	0.0003 to 69	0.019 ± 0.019	0.20
Obsessive Compulsive Drinking Scale score	35	2 to 28	11.09 ± 6.16	0.77†
Proportion of failed self-control trials in all trials	38	0.11 to 0.98	0.72 ± 0.22	0.03
State-Trait Anxiety Inventory score	38	45 to 52	48.92 ± 1.81	0.01
Total abstinence, mo	36	0 to 7	1.45 ± 1.95	0.16
Total drinking, yr	38	5 to 34	16 ± 7	0.30
Education, yr	38	10 to 22	16.36 ± 2.79	–0.15

AUDIT = Alcohol Use Disorders Identification Test; FA = failed self-control in an alcohol–nonalcohol conflict; FN = failed self-control in a nonalcohol–nonalcohol conflict; SA = successful self-control in an alcohol–non-alcohol conflict; SD = standard deviation; SN = successful self-control in a nonalcohol–nonalcohol conflict.
*Eighteen participants were smokers and 20 were not ($p = 0.21$, 2-sample t test).
†Significant at a threshold of $p < 0.01$.
‡Significant at a threshold of $p < 0.05$.

with LDH. There was a positive correlation between drinking severity, as reflected in the AUDIT scores, and our behavioural measure of alcohol-specific failed self-control (see the Behavioural analyses section; $r = 0.41$, $t_{36} = 2.70$, $p = 0.012$). That is, with increasing AUDIT scores, participants failed more often in alcohol than in nonalcohol trials. Moreover, with increasing AUDIT scores, participants made significantly faster decisions in alcohol trials than in nonalcohol trials in failed compared with successful self-control (interaction effect for response times AUDIT × [(FAResp – FNResp) – (SAResp – SNResp)] ($r = –0.371$, $t_{36} = –2.40$, $p = 0.024$).

There was no significant correlation between AUDIT scores and EHI scores, intelligence (matrices subtest of WAIS), BDI scores, years of education, STAI scores and impulsiveness (general proportion of failed self-control, BIS, MCQ), excluding these variables as possible confounders (Table 1).

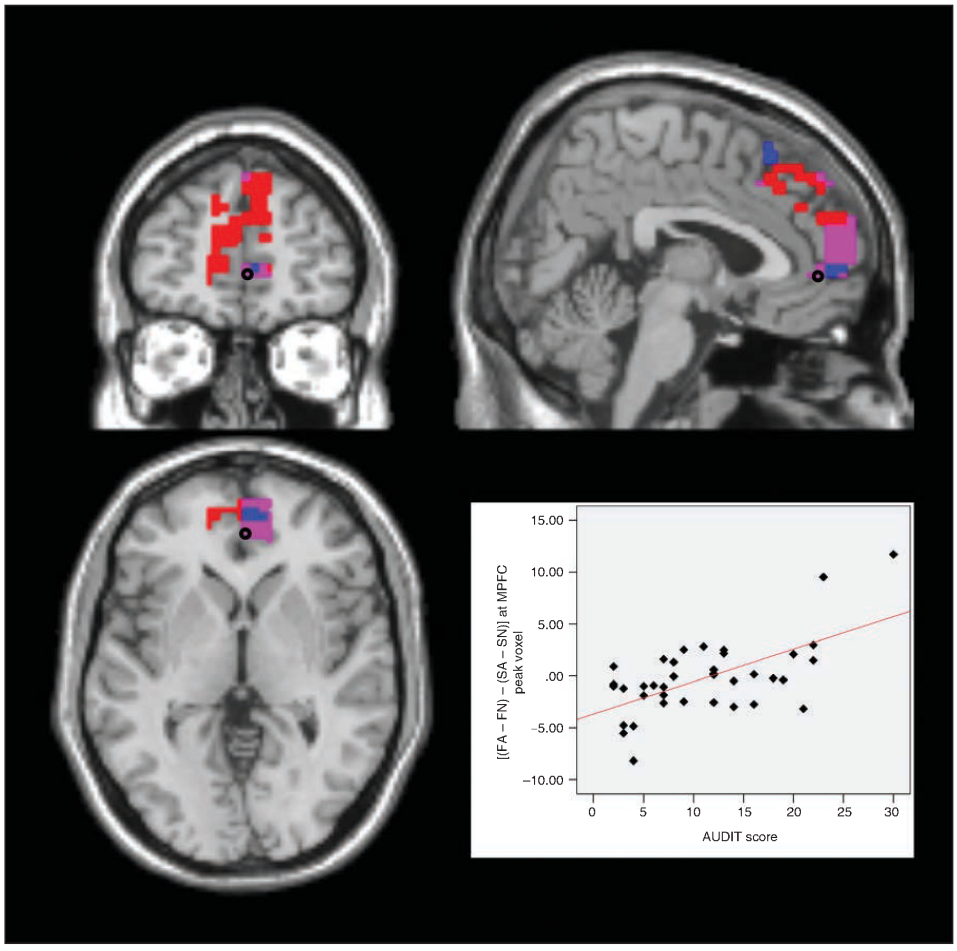

Fig. 3: Failed self-control in alcohol trials — medial prefrontal cortex (MPFC). Section views showing significant clusters for AUDIT × (FA – FN) and AUDIT × [(FA – FN) – (SA – SN)] within the MPFC at a threshold of $p < 0.05$, family-wise error–corrected. Custers are presented at a threshold of $p < 0.005$, uncorrected. Red: MPFC cluster with higher activity in participants with higher drinking severity in failed self-control in alcohol compared with nonalcohol trials (AUDIT × [FA – FN]) Blue: MPFC cluster with higher activity in participants with higher drinking severity in failed compared with successful self-control in alcohol compared with nonalcohol trials (AUDIT × [(FA – FN) – (SA – SN)]) Violet: overlap between these 2 clusters. Plot: effect of interaction contrast (FA – FN) – (SA – SN) at the marked peak voxel (Montreal Neurological Institute space: $x, y, z = 4, 49, 0$) plotted subject-wise against AUDIT score. AUDIT = Alcohol Use Disorders Identification Test; FA = failed self-control in an alcohol–nonalcohol conflict; FN = failed self-control in a nonalcohol–nonalcohol conflict; SA = successful self-control in an alcohol–non-alcohol conflict; SN = successful self-control in a nonalcohol–nonalcohol conflict.

Imaging results

To study the effect of increasing drinking severity on brain activation during failed self-control in favour of alcohol (pro-alcohol decisions), we correlated AUDIT scores with activation during failed self-control in alcohol compared with failed self-control in nonalcohol trials.

Hyperactivated areas during pro-alcohol decisions

According to the hypothesis of overwhelming desire, reward-associated areas should show enhanced activation during pro-alcohol decisions, and this hyperactivation should increase with growing drinking severity.

The corresponding analysis testing positive correlations between drinking severity and brain activation during pro-alcohol decisions (i.e., AUDIT × [FA – FN]) revealed significant results in the bilateral striatum (peak left in Montreal Neurological Institute [MNI] space: $x, y, z = -4, 7, 4$, $t_{35} = 4.34$, $p_{FWE} = 0.013$, extent = 9; peak right: $x, y, z = 35, -18, -7$, $t_{35} = 3.81$, $p_{FWE} = 0.046$, extent = 9; clusters were localized in the ventral striatal parts), in the bilateral MPFC (peak left: $x, y, z = 0, 60, 18$, $t_{35} = 4.29$, $p_{FWE} = 0.018$, extent = 82; peak right: $x, y,$

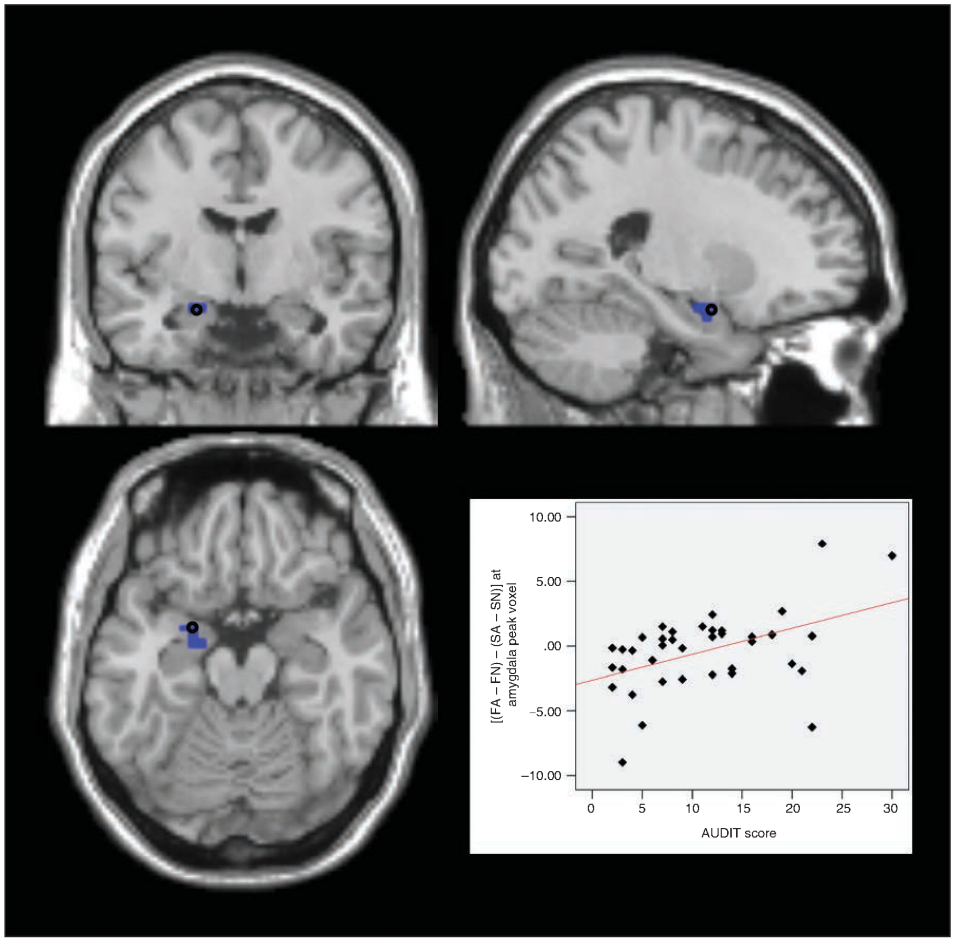

Fig. 4: Failed self-control in alcohol trials — amygdala. Section views showing significant clusters for AUDIT × (FA – FN) and AUDIT × [(FA – FN) – (SA – SN)] within the amygdala at a threshold of $p < 0.05$, family-wise error–corrected. Clusters are presented at a threshold of $p < 0.005$, uncorrected. Blue: amygdala cluster with higher activity in participants with higher drinking severity in failed compared with successful self-control in alcohol compared with nonalcohol trials (AUDIT × [(FA – FN) – (SA – SN)]). Plot: effect of interaction contrast (FA – FN) – (SA – SN) at the marked peak voxel (Montreal Neurological Institute space: $x, y, z = -21, 0, -18$) plotted subject-wise against AUDIT score. AUDIT = Alcohol Use Disorders Identification Test; FA = failed self-control in an alcohol–nonalcohol conflict; FN = failed self-control in a nonalcohol–nonalcohol conflict; SA = successful self-control in an alcohol–non-alcohol conflict; SN = successful self-control in a nonalcohol–nonalcohol conflict.

z = 4, 56, 18, t_{35} = 4.71, p_{FWE} = 0.005, extent = 105), and in the left DLPFC (peak: x, y, z = –18, 18, 60, t_{35} = 4.87, p_{FWE} = 0.002, extent = 50). Notably, these correlations were driven by both a positive AUDIT × FA correlation and a negative AUDIT × FN correlation (Appendix 1, Figs. S1–S3, available at jpn.ca), indicating enhanced activation of reward-associated areas during decisions in favour of alcohol as well as attenuated activation during decisions in favour of desirable nonalcoholic drinks.

To preclude a sole alcohol effect causing the activations in AUDIT × (FA – FN), we then subtracted the analogous activation for successful self-control trials from the above contrast. For the resulting analysis, AUDIT × [(FA – FN) – (SA – SN)], we found significant results in the left amygdala (peak: x, y, z = –21, 0, –18, t_{35} = 3.64, p_{FWE} = 0.011, extent = 3) and in the left DLPFC (peak: x, y, z = –28, 11, 63, t_{35} = 4.14, p_{FWE} = 0.014, extent = 9) as well as the bilateral MPFC (peak left: x, y, z = 0, 56, 4, t_{35} = 4.45, p_{FWE} = 0.012, extent = 56; peak right: x, y, z = 4, 49, 0, t_{35} = 4.52, p_{FWE} = 0.008, extent = 60). That is, with growing drinking severity, these areas showed increasing activations in failed compared with successful self-control in alcohol compared with nonalcohol trials (Fig. 3, Fig. 4, Fig. 5, Fig. 6).

Hypoactivated areas during pro-alcohol decisions

According to the hypothesis of impaired control, the

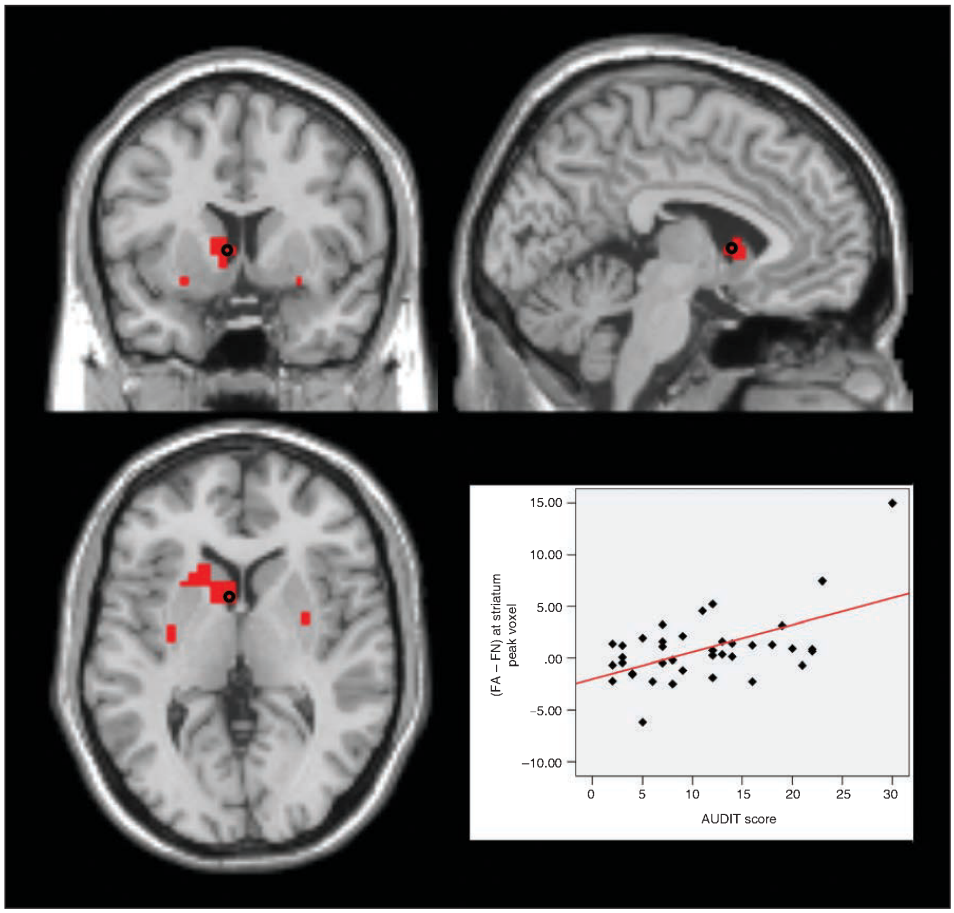

Fig. 5: Failed self-control in alcohol trials — striatum. Section views showing significant clusters for AUDIT × (FA – FN) within the striatum at a threshold of $p < 0.05$, family-wise error–corrected. Clusters are presented at a threshold of $p < 0.005$, uncorrected. Red: striatal clusters with higher activity in participants with higher drinking severity in failed self-control in alcohol compared with nonalcohol trials (AUDIT × [FA – FN]).Plot: effect of contrast (FA – FN) at the marked peak voxel (Montreal Neurological Institute space: x, y, z = –4, 7, 4) plotted subject-wise against AUDIT score. AUDIT = Alcohol Use Disorders Identification Test; FA = failed self-control in an alcohol–nonalcohol conflict; FN = failed self-control in a nonalcohol–nonalcohol conflict.

control-associated areas should show attenuated activation during pro-alcohol decisions, and the activation of these areas should further decrease with growing drinking severity.

The analysis testing negative correlations between drinking severity and brain activation during pro-alcohol decisions (i.e., –AUDIT × [FA – FN]) revealed no significant results, even after lowering the significance threshold to $p < 0.001$, uncorrected. Likewise, the more specific contrast –AUDIT × [(FA – FN) – (SA – SN)] revealed no significant results, even after lowering the threshold to $p < 0.001$, uncorrected. That is, there were no areas showing decreasing activations with growing drinking severity in failed compared with successful self-control in alcohol compared with nonalcohol trials.

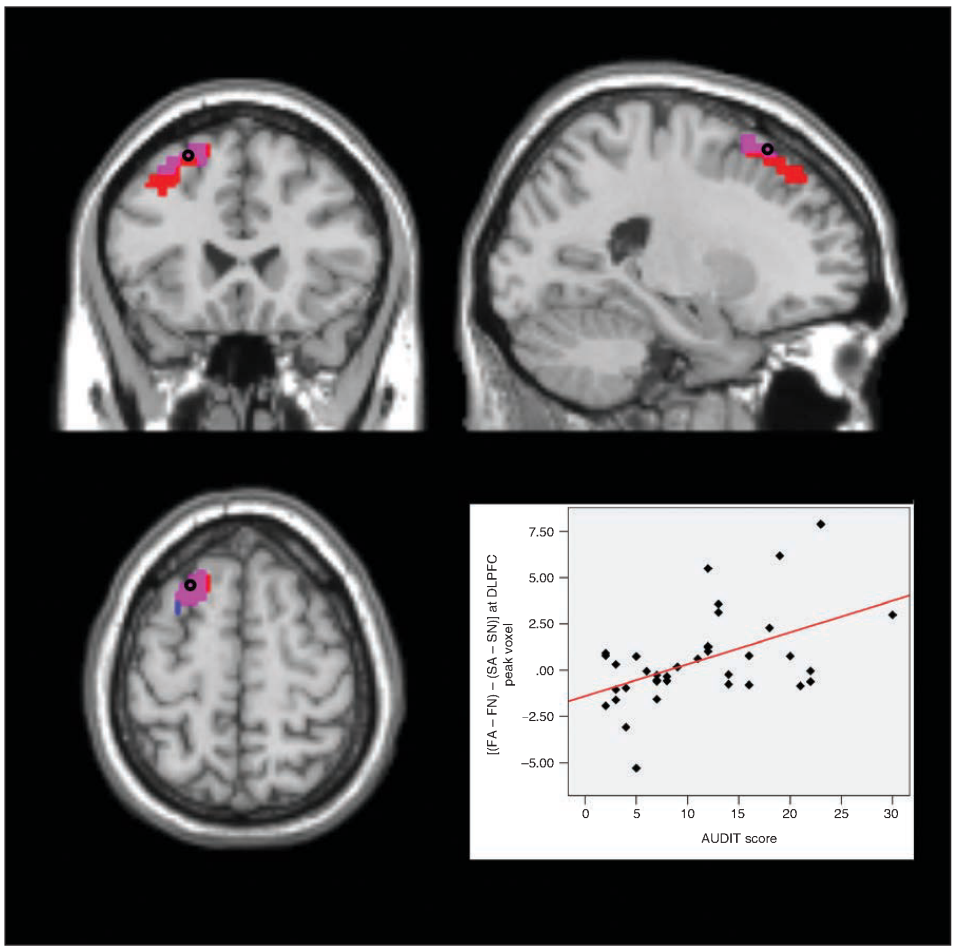

Fig. 6: Failed self-control in alcohol trials — dorsolateral prefrontal cortex (DLPFC). Section views showing significant clusters for AUDIT × (FA – FN) and AUDIT × [(FA – FN) – (SA – SN)] within the DLPFC at threshold of $p < 0.05$, family-wise error–corrected. Clusters are presented at a threshold of $p < 0.005$, uncorrected. Red: DLPFC cluster with higher activity in participants with higher drinking severity in failed self-control in alcohol compared with nonalcohol trials (AUDIT × [FA – FN]). Blue: DLPFC cluster with higher activity in participants with higher drinking severity in failed compared with successful self-control in alcohol compared with nonalcohol trials (AUDIT × [(FA – FN) – (SA - SN)]). Violet: overlap between these 2 clusters Plot: effect of interaction contrast (FA – FN) – (SA – SN) at the marked peak voxel (Montreal Neurological Institute space: *x*, *y*, *z* = –28, 11, 63) plotted subject-wise against AUDIT score. AUDIT = Alcohol Use Disorders Identification Test; FA = failed self-control in an alcohol–nonalcohol conflict; FN = failed self-control in a nonalcohol–nonalcohol conflict; SA = successful self-control in an alcohol–nonalcohol conflict; SN = successful self-control in a nonalcohol–nonalcohol conflict.

Discussion

We used fMRI to study the so-called reward and control networks during real-life decisions for and against alcohol. For this purpose, participants with widely differing drinking severity made decisions between more beneficial and more desired alcoholic and nonalcoholic drinks. We found that with increasing drinking severity, participants showed enhanced activations in the bilateral ventral striatum and MPFC as well as in the left amygdala and DLPFC during pro-alcohol decisions (failed self-control in alcohol trials). The specificity of our findings for failed self-control in alcohol trials is documented by the interaction contrast AUDIT × [(FA – FN) – (SA – SN)] that precludes a sole alcohol effect as well as a sole effect of failed self-control. Behaviourally, our fMRI finding was paralleled by an alcohol-related decision bias: with increasing drinking severity, participants failed more frequently and responded significantly faster in alcohol compared with nonalcohol trials.

Earlier studies in individuals with alcohol use disorders have implicated the striatum, amygdala and MPFC in reward processing and have linked activation in these areas to craving and approach behaviour.[7–12,15–17,43] However, to our knowledge, this is the first study to demonstrate that a hyperactivation of these reward-associated areas is associated not only with the development of craving, but also with real decisions in favour of alcoholic drinks.

Besides enhanced responses of the reward system, we hypothesized that areas of the control system would be hypoactive during failed self-control, resulting in pro-alcohol decisions. However, contrary to our hypotheses, we found that these decisions were associated with hyperactivation in the DLPFC, a brain area related to self-control processes.[22–24,26,27,44] This unexpected finding may represent compensatory processes (i.e., enhanced though insufficient self-control efforts in harmful drinkers when confronted with alcohol). This would be in accordance with the clinical observation that individuals with alcohol use disorders tend to choose alcoholic drinks despite their awareness of the risks involved and the intention to quit or reduce drinking. Moreover, similar ineffective hyperactivations of control-associated areas have previously been reported in abstinent alcohol-dependent patients.[45]

In addiction research, there is an ongoing debate on whether harmful decisions for alcohol are due to enhanced responses in reward/motivation areas (overwhelming desire) or to a hypoactive self-control system (impaired control processes).[1,2,46] Our results suggest that decisions for alcohol consumption are linked to a hyperactivation of the reward system (reflected in activations in the striatum, amygdala and MPFC) rather than a hypoactivation of the control system. Notably, we found not only increasing activation of reward areas in pro-alcohol trials with growing drinking severity, but also decreasing activation in nonalcohol trials (Appendix 1). These findings are in line with the "hijacking" hypothesis of the reward system, stating that individuals with addiction show both enhanced responses to addiction-related stimuli and attenuated responses to non–addiction-related rewards.[18] Our findings suggest that both effects may play a role when individuals with harmful drinking behaviour choose between alcoholic and nonalcoholic drinks.

While we refer to the striatum, amygdala and MPFC as reward-associated areas in this article, we acknowledge that for each of these brain areas a variety of distinct psychological functions has been proposed. Although these proposed functions are mostly related to reward-processing, particular functional roles may be considered for each brain region. Specifically, the activation of the ventral striatum has been shown to be related to the occurrence of prediction errors and, therefore, to the guidance of learning processes. Altered activity in the ventral striatum and connectivity with the DLPFC (resulting in altered teaching signals) has been linked to the maintenance of harmful alcohol consumption.[47] Thus, the reported association between drinking severity and activation in the ventral striatum during pro-alcohol decisions may be related to malfunction of prediction error signalling and consequently to altered learning processes.

Our study aimed to transfer the paradigm of Hare and colleagues[24] from decisions between healthier and more desired food items in dieters to the context of (desired but unhealthy) alcohol consumption. Analogous to the study by Hare and colleagues, we distinguished between failed and successful self-control trials. A critical assumption in this type of paradigm is that study participants face a conflict between the desire to consume an attractive but nonbeneficial item and the awareness of the negative consequences of consumption. Because the decision options always consisted of a more desirable and a more beneficial item (as indicated by the participants' individual ratings of the drinks), we believe that participants indeed experienced such conflict in our study; the awareness for nonbeneficial effects of the drinks was reinforced by the prescan ratings that required the participants to reflect on the drinks' harmfulness. Because participants were screened for health considerations during the recruitment for the study and because all participants chose the less desired, more beneficial item in the self-control trials, we assume a general willingness to exert self-control among our study participants. Furthermore, the hyperactivation of the self-control–associated DLPFC indicates enhanced though unsuccessful self-control efforts during decisions for alcohol. In summary, there are good reasons to believe that pro-alcohol decisions in our fMRI study implied reduced self-control. That is, participants chose the desired alcoholic drink, although they were aware of the nonbeneficial effects that the consumption of this particular drink would have on their own health.

Limitations

Participants in our study had to be abstinent at the beginning and would potentially consume an alcoholic drink at the end of the experiment. Because we wanted to avoid inducing withdrawal symptoms or relapse in alcohol-dependent individuals, we did not recruit patients from our department for the study and did not define manifest alcohol dependence as an inclusion criterion. Instead, we focused on less severely affected individuals, assessing drinking severity as a

continuous variable (AUDIT scores). Accordingly, we do not provide categorical comparisons between clinically defined groups (e.g., alcohol-dependent patients v. healthy controls), but rather regression analyses on individuals with a wide range of AUDIT scores. This means our study included indivduals showing different severities of alcohol-drinking behaviour, ranging from normal to riskful to abusive to even dependent alcohol consumption. In doing so, we followed current concepts of dependence and abuse that tend to abandon dichotomous classifications (e.g., "addicted" v. "healthy") in favour of a more gradual concept of alcohol use disorders (DSM-5). However, with only 2 participants fulfilling the DSM-IV criteria for alcohol dependence, further research is required to confirm the validity of our results in a larger sample of more severely affected individuals.

Another limitation might be that, especially in small-sized regions of interest like the amygdala and the ventral striatum, we obtained significant results only in a small number of contiguous voxels. Further studies including a larger number of participants might help to also tackle the challenge of achieving larger effect sizes.

Finally, participants were told before they enrolled in the study that there would be urine toxicology tests on a random basis. In practice, this random screening was not performed, and we relied on the participants' self-disclosure instead. Thus, drug consumption among participants cannot completely be excluded.

Conclusion

Taken together, our data suggest that failed self-control in decisions for alcohol in harmful drinkers is associated with a hyperactive reward system rather than a hypoactive control system. This result is in accordance with clinical findings suggesting that cognitive approaches in psychotherapy attempting to strengthen self-control processes show only moderate effects on relapse rates.[45] The question arises how psychotherapeutic interventions could specifically address the strong automatic, implicit response of the reward system to alcohol-related cues. Cognitive bias modification therapy (CBMT) may represent such a treatment strategy. Recent studies investigated the therapeutic effects of this retraining of automatic approach tendencies and the associated hyperactivation of reward systems. In these studies, CBMT successfully reduced relapse rates 1 year later[5,48] as well as craving-related alcohol cue reactivity in the amygdala.[13] Targeting automatic tendencies rather than control processes may therefore be a promising direction for future therapies in individuals with alcohol use disorders.

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3.2 Effects of Cognitive Bias Modification Training on Neural Alcohol Cue Reactivity in Alcohol Dependence

Effects of Cognitive Bias Modification Training on Neural Alcohol Cue Reactivity in Alcohol Dependence

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Objective: In alcohol-dependent patients, alcohol cues evoke increased activation in mesolimbic brain areas, such as the nucleus accumbens and the amygdala. Moreover, patients show an alcohol approach bias, a tendency to more quickly approach than avoid alcohol cues. Cognitive bias modification training, which aims to retrain approach biases, has been shown to reduce alcohol craving and relapse rates. The authors investigated effects of this training on cue reactivity in alcohol-dependent patients.

Method: In a double-blind randomized design, 32 abstinent alcohol-dependent patients received either bias modification training or sham training. Both trainings consisted of six sessions of the joystick approach-avoidance task; the bias modification training entailed pushing away 90% of alcohol cues and 10% of soft drink cues, whereas this ratio was 50/50 in the sham training. Alcohol cue reactivity was measured with functional MRI before and after training.

Results: Before training, alcohol cue-evoked activation was observed in the amygdala bilaterally, as well as in the right nucleus accumbens, although here it fell short of significance. Activation in the amygdala correlated with craving and arousal ratings of alcohol stimuli; correlations in the nucleus accumbens again fell short of significance. After training, the bias modification group showed greater reductions in cue-evoked activation in the amygdala bilaterally and in behavioral arousal ratings of alcohol pictures, compared with the sham training group. Decreases in right amygdala activity correlated with decreases in craving in the bias modification but not the sham training group.

Conclusions: These findings provide evidence that cognitive bias modification affects alcohol cue-induced mesolimbic brain activity. Reductions in neural reactivity may be a key underlying mechanism of the therapeutic effectiveness of this training.

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Alcohol dependence is a chronic relapsing disorder, characterized by high levels of craving and the continuation of drinking despite the awareness of negative consequences (1). During the transition from voluntary to impulsive and ultimately habitual drinking, cues associated with alcohol are hypothesized to increase in salience as a result of Pavlovian drug-cue learning (2, 3). As a consequence, alcohol cues engender motivational responses in alcohol-dependent patients, which are triggered relatively automatically (4). Motivational reactivity to alcohol cues has been demonstrated repeatedly in physiological and behavioral studies and is thought to be a key underlying mechanism involved in alcohol craving and alcohol relapse, even after years of abstinence (5).

Incentive-sensitization models of addiction suggest that fronto-limbic dopaminergic neuroadaptations underlie the brain physiology of alcohol cue reactivity. Alcohol intake has been shown to release dopamine in the ventral tegmental area via interactions with opioid and GABA-ergic neurotransmission, which further projects to mesolimbic structures, such as the nucleus accumbens and the basolateral amygdala, as well as frontal areas (5, 6). Since dopamine signals motivational relevance, it has been hypothesized to be a key neurobiological substrate of drug-cue learning. For example, neuroimaging studies have shown that when alcohol-dependent patients are exposed to alcohol cues, activation in reinforcement-related mesolimbic areas is evoked (5, 7). Reactivity in these areas has been positively related to craving (8–10), to reward processing (11–13), and to alcohol consumption after relapse (7, 14, 15). Although mesolimbic neuroadaptations have been hypothesized to be sustained after years of abstinence (2, 3), studies suggest that only a few weeks of behavioral and/or pharmacological therapy may

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decrease cue-evoked activation in the nucleus accumbens (16, 17) and amygdala (18) in alcohol-dependent individuals. Thus, training effects on nucleus accumbens and amygdala activity may be of particular importance for the ability of interventions to change neural cue reactivity.

Behaviorally, alcohol-dependent patients show an automatic approach bias for alcohol cues, that is, a tendency to more quickly approach than avoid these cues on an approach-avoidance task (9, 19, 20). In this task, participants push and pull pictorial cues with a joystick according to an irrelevant feature such as the format of the cue, and patients have been shown to pull faster than they push alcohol cues (9, 19, 20). The approach bias may reflect an impulsive response toward drug cues and has been positively associated with drug craving (21). Recently, the approach-avoidance task has been adapted into a cognitive bias modification training in which subjects implicitly learn to push away and hence avoid alcohol cues. In heavy drinkers, cognitive bias modification training has been shown to decrease the approach bias and reduce posttraining alcohol intake (22). Moreover, in two recent randomized controlled studies, cognitive bias modification training reduced alcohol craving and relapse rates up to 13% in alcohol-dependent patients, compared with a sham training in which patients pushed and pulled alcohol cues at an equal rate (19) and a non-training group (19, 23). Although these findings show the clinical potential of bias modification in alcohol dependence, it is as yet unclear how bias modification affects brain function. For instance, bias modification could directly reduce the incentive salience of alcohol cues and neural alcohol cue reactivity (2, 24). Understanding the mechanisms underlying cognitive bias modification training can help to further enhance its efficacy and thus further improve the treatment of alcohol dependence.

In this study, using a double-blind randomized design with a sham-training control condition, we examined the effects of cognitive bias modification training on neural reactivity evoked by alcohol cues in alcohol-dependent patients. Patients were randomly assigned to receive either bias modification or sham training, and they performed the approach-avoidance task for 3 weeks. The bias modification group pushed away 90% of alcohol cues, whereas this rate was 50% in the sham training group. Before and after training, neural cue reactivity was measured in functional MRI (fMRI) scans. We expected to find, first, that alcohol cue reactivity would be enhanced in the amygdala and nucleus accumbens across all subjects before training; second, that cue reactivity would decrease in the amygdala and nucleus accumbens as a result of cognitive bias modification; and third, that changes in cue reactivity in these regions would covary with changes in craving.

METHOD

Participants

The Ethical Committee of the Charité–Universitätsmedizin Berlin approved the study, and participants provided written informed consent after receiving a complete description of the study. Thirty-six male alcohol-dependent inpatients were recruited from the Salus Clinic in Lindow, Germany. Exclusion criteria for all patients were a history of neurological dysfunction, DSM-IV axis I psychiatric disorders other than alcohol dependence (assessed with the Mini International Neuropsychiatric Interview [25]), abstinence from alcohol for >4 months before participation, and intake of psychoactive medication, as tested by urine drug screening. Patients had to be free of psychoactive medication and other drugs for at least 6 months before participation.

Patients were randomly assigned to receive bias modification training or sham training. Two patients did not complete the training (one in each group), and two patients could not be present on the second day of testing for administrative reasons (both in the bias modification group). The final sample consisted of 15 men in the bias modification training group and 17 in the sham training group. Participants completed the Alcohol Dependence Scale to assess severity of dependence (26), the matrix reasoning subtest of the WAIS as a proxy for general intelligence (27), and the State-Trait Anxiety Inventory (28). The groups did not differ significantly in age, years of education, intelligence scores, or clinical variables (Table 1) or in number of smokers (12 in the bias modification group [80%] and 15 in the sham training group [88%]). Smokers were abstinent from tobacco for at least 1.5 hours before scanning.

Experimental Tasks

Approach-avoidance task. The approach-avoidance task was used to measure approach bias before and after training (29). In response to the format of the cue (landscape or portrait), participants pushed and pulled pictures with a joystick, which increased and decreased the size of the cue, respectively; participants had to respond to a cue within 2 seconds. Twenty practice trials were followed by 80 test trials (20 alcohol push, 20 alcohol pull, 20 soft drink push, 20 soft drink pull) that were presented over two blocks. Picture format to response assignment was counterbalanced, and response type assignment did not differ between the two groups. A set of 40 alcohol and 40 soft drink images was used (9).

fMRI cue reactivity. For the fMRI paradigm, the same 80 pictures that were used in the approach-avoidance task were presented over eight blocks per stimulus category. Each block consisted of five stimuli, each presented for 4 seconds. To check whether participants were focused on the task, four oddball blocks were added, containing four alcohol or soft drink stimuli and an oddball cue—a picture of an animal; in these cases, participants had to press a button with their right index finger. The duration of the task was approximately 6 minutes.

Picture rating and craving. After both scanning sessions, pictures were rated for arousal and valence on a 5-point Likert scale, and alcohol craving was assessed with the Desire for Alcohol Questionnaire (30).

Cognitive Bias Modification Training

The cognitive bias modification training scheme, which was an adapted version of the approach-avoidance task, consisted of six training sessions over 3 weeks, each consisting of 400 trials (200 alcohol and 200 soft drink) (19, 23). The experimental bias modification group pushed away 90% and pulled 10% of the alcohol cues (and the reverse for soft drink cues: 10% push and 90% pull). These ratios were 50/50 in the sham training group. Twenty cues were used for training (10 alcohol and 10 soft drink) (19, 23). To test for effects on cue reactivity based on stimulus category (alcohol versus soft drink) rather than on specific pictures, pictures in the training were different but comparable to cues used before and after training in the avoidance task and fMRI cue reactivity.

TABLE 1. Demographic and Clinical Characteristics of Patients Who Received Bias Modification Training or Sham Training

Characteristic	Bias Modification Training		Sham Training		p
	Mean	SD	Mean	SD	
Age (years)	45.33	6.84	42.88	8.31	0.37
Education (years)	10.60	1.45	10.47	1.33	0.79
Wechsler Adult Intelligence Scale score	15.57[a]	5.20	14.06	5.09	0.42
Duration of abstinence (days)	36.87	27.01	57.35	39.87	0.10
Duration of dependence (years)	17.53	9.74	13.06[b]	6.88	0.14
Number of detoxifications	5.87[c]	8.59	3.59[d]	7.20	0.42
Alcohol intake before admission (grams/day)	332.55	213.65	244.15	164.19	0.20
Alcohol Dependence Scale score	17.87	9.63	14.50	5.45	0.24
Trait Anxiety score	35.21	8.42	34.47	7.42	0.80
State Anxiety score	32.67	8.10	33.82	8.02	0.69

[a] N=14.
[b] Range, 2–30.
[c] Range, 0–26.
[d] Range, 0–30.

fMRI acquisition and preprocessing. Scanning was done in a 3-T whole-body MRI scanner (Magnetom Trio Tim, Siemens, Germany) equipped with a 12-channel head coil. A standard T_2-weighted echo planar imaging sequence was used with the following parameters: sequential descending acquisition, repetition time=2 seconds, echo time=25 ms, flip angle=80°, 64×64 pixels in-plane resolution, 34 slices, slice thickness=3 mm, voxel dimensions=3×3×3 mm^3, 0.75-mm gap between slides, field of view=192×192 mm^2, 140 images per session.

Functional data analysis was performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Scans were spatially realigned, slice-time corrected, and normalized to the standard echo planar imaging template. Smoothing was performed with an 8-mm full width at half maximum Gaussian kernel. Participants did not move more than 2 mm or 2 degrees.

Statistical Analysis

For the approach-avoidance task, responses that were missed or incorrect and response times longer than three standard deviations above the mean were discarded based on each participant's performance. Alcohol approach bias scores were calculated by subtracting median reaction times ([alcohol push − pull] − [soft drink push − pull]). Two-by-two mixed analyses of variance on alcohol approach bias, craving, and picture ratings were calculated, with time (before versus after training) as a within-subject factor and group (bias modification versus sham) as a between-subject factor. Post hoc group comparisons were performed with two-sample t tests at an alpha of 0.05.

Three fMRI regressors—alcohol, soft drink, and oddball blocks (20 seconds each)—were built for every subject and were convolved with the hemodynamic response function with default temporal filtering of 128 seconds. On the single-subject level, two contrasts were calculated. Contrast 1 was alcohol cue reactivity before training: ([alcohol > soft drink] before training); and contrast 2 was alcohol cue reactivity before and after training: ([alcohol > soft drink] before training) − ([alcohol > soft drink] after training). On the second level, t tests were used to calculate alcohol cue reactivity before training in both groups and between-group alcohol cue reactivity before and after training. Post hoc t tests were used in our a priori regions of interest to explore directions of the interaction of time by group.

Based on our hypotheses, anatomically defined left and right nucleus accumbens and amygdala were chosen as regions of interest (5, 9, 14, 31, 32) and were used for small-volume correction of the results, with a significance threshold of 0.05, family-wise error corrected. Exploratory whole-brain analyses are presented in the data supplement that accompanies the online edition of this article.

Behavioral approach bias scores, craving, and alcohol picture ratings before training were correlated with blood-oxygen-level-dependent (BOLD) contrast 1 (alcohol cue reactivity before training) using our regions of interest. For behavioral variables showing a positive correlation in our regions of interest before training, we computed difference scores for before and after training and correlated these with significant activations in BOLD contrast 2 (alcohol cue reactivity before and after training).

RESULTS

Behavioral Effects of Cognitive Bias Modification Training

Approach-avoidance task. Alcohol approach bias scores before and after training, as well as difference scores, were distributed normally in both groups (Kolmogorov-Smirnov test, all p values >0.62). Mean error rates were 3.04% (SD=3.22) before training and 2.65% (SD=3.83)

after training, collapsed across the groups. There were no main effects of group or time and no interaction effect of group by time.

For the alcohol approach bias scores, there was no significant interaction effect of group by time, and there were no main effects. Exploratory t tests showed that the groups did not differ before and after training and that a decrease in mean reaction time approached significance in the cognitive bias modification training group (before training, mean=11.90, SD=64.01; after training, mean=−25.53, SD=55.80; t=1.18, df=14, p=0.091) but not in the sham training group (before training, mean=−9.35, SD=122.21; after training, mean=21.50, SD=99.89; t=−0.64, df=16, p=0.53).

Subjective alcohol craving and picture ratings. For craving scores, there was a main effect of time (F=9.32, df=1, 30, p=0.005; η^2=0.23). In both groups, craving scores were higher before training (bias modification group, mean=15.20, SD=6.95; sham training, mean=12.29, SD=5.01) than after (bias modification group, mean=12.33, SD=6.20; sham training, mean=10.36, SD=3.62). There was no significant interaction effect of group by time for craving scores. Exploratory paired t tests showed that the groups did not differ before and after training, but craving scores significantly decreased in the bias modification group (t=3.86, df=14, p=0.002) but not in the sham training group.

There was a significant interaction effect of group by time for arousal ratings of alcohol pictures (F=4.19, df=1, 30, p=0.05; η^2=0.12), with arousal ratings having a nearly significant decrease in the bias modification training group (before training, mean=1.02, SD=0.40; after training, mean=0.88, SD=0.51; t=2.01, df=14, p=0.064) but not in the sham training group (before training, mean=0.98, SD=0.34; after training, mean=1.04, SD=0.38; t=0.82, df=16, p=0.43). There were no significant effects of group by time for valence ratings. Before and after training, the groups did not differ in arousal and valence.

Cue-Evoked Brain Activation Within and Between Groups

All patients paid attention to the cue reactivity task, as shown by their responses to all four oddball cues, before and after training.

Before training, subjects pooled across both groups showed alcohol cue-evoked activity in the amygdala bilaterally (peak Montreal Neurological Institute coordinates, left side: −21, −7, −14; t=4.98, df=31, p<0.001; right side: 21, −7, −17; t=2.87, df=31, p=0.052) while viewing alcohol cues compared with viewing soft drink cues. In this contrast, the right nucleus accumbens was also activated, although the effect fell short of significance (peak coordinates: 8, 8, −11; t=2.48, df=31, p=0.057). Figure 1 illustrates the pretraining activations in the amygdala and nucleus accumbens. (See Table S1 in the online data supplement for whole brain activations showing no relevant between-group differences before training.)

In the assessment of group differences in alcohol cue reactivity before and after training, the bias modification group showed significantly greater reductions in alcohol cue-evoked activation in the amygdala bilaterally (peak coordinates, left side: −15, −1, −23; t=2.97, df=30, p<0.05; right side: 27, 2, −20; t=3.08, df=30, p<0.05) compared with the sham training group (Figure 2). This effect was not present for the nucleus accumbens, even at a more liberal threshold of p<0.005 uncorrected. After training, the bias modification group had significantly lower activation in the left amygdala than the sham training group (peak coordinates: −15, −1, −26; t=3.86, df=30, p<0.05). (See Table S1 in the online data supplement for whole brain activations.)

Post hoc t tests on cue reactivity before and after training within groups demonstrated a significant reduction of left and right amygdala activity in the bias modification group (peak coordinates, left side: −27, 2, −17; t=3.58, df=14, p<0.05; right side: 24, 2, −20; t=2.88, df=14, p<0.05). However, this was not the case for the sham training group, even at p<0.005 uncorrected.

Correlations With Behavioral Measures

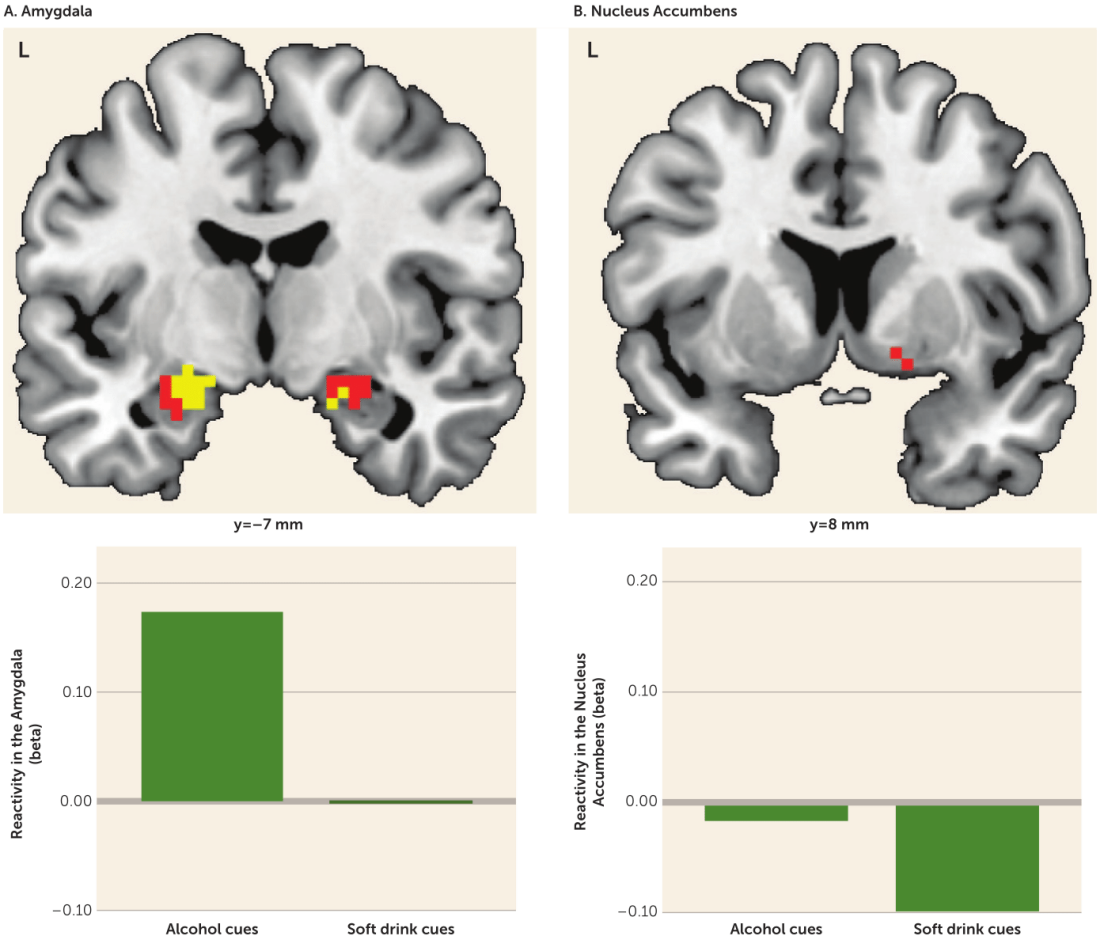
Before training, both groups' craving scores significantly correlated with alcohol cue-induced amygdala activity bilaterally (coordinates, left side: −18, −7, −17; t=6.15, df=31, p<0.001); right side: 21, −4, −23; t=3.88, df=31, p<0.01). Craving scores were correlated with activity in the right nucleus accumbens, but the effect fell short of significance (peak coordinates: 15, 11, −8; t=2.15, df=31, p=0.057). Arousal ratings also correlated with cue reactivity in the left and right amygdala (coordinates, left side: −27, −4, −20; t= 3.67, df=31, p=0.01; right side: 21, −1, −14; t=3.46, df=31, p<0.05), and in the right nucleus accumbens, although again falling just short of significance (peak coordinates: 18, 8, −11; t=2.51, df=31, p=0.052). Alcohol approach bias scores and valence ratings did not correlate with alcohol cue-induced activations in our regions of interest.

In the bias modification group, the difference in right amygdala activity before and after training correlated positively with the decrease in alcohol craving (peak coordinates: 30, 2, −17; t=3.44, df=14, p<0.05), but not in the sham training group. Moreover, when the correlation slopes of cue reactivity and craving before and after treatment were compared between the two groups, there was an effect in the right amygdala (peak coordinates: 30, 2, −17; t=3.85, df=30, p<0.01), providing stronger evidence for a greater correlation in bias modification (Figure 3). There were no significant correlations between decreases in arousal ratings and decreases in amygdala activation. See Table S2 in the online data supplement for exploratory analyses of alcohol cue reactivity and relapse rates 1 year after training.

DISCUSSION

Our aim in this study was to examine the effects of cognitive bias modification training on neural alcohol cue reactivity. The results provide first evidence that cognitive bias modification training can affect cue-induced amygdala activity, an

FIGURE 1. Baseline Alcohol Cue Reactivity in the Amygdala and Nucleus Accumbens in Alcohol-Dependent Patients[a]

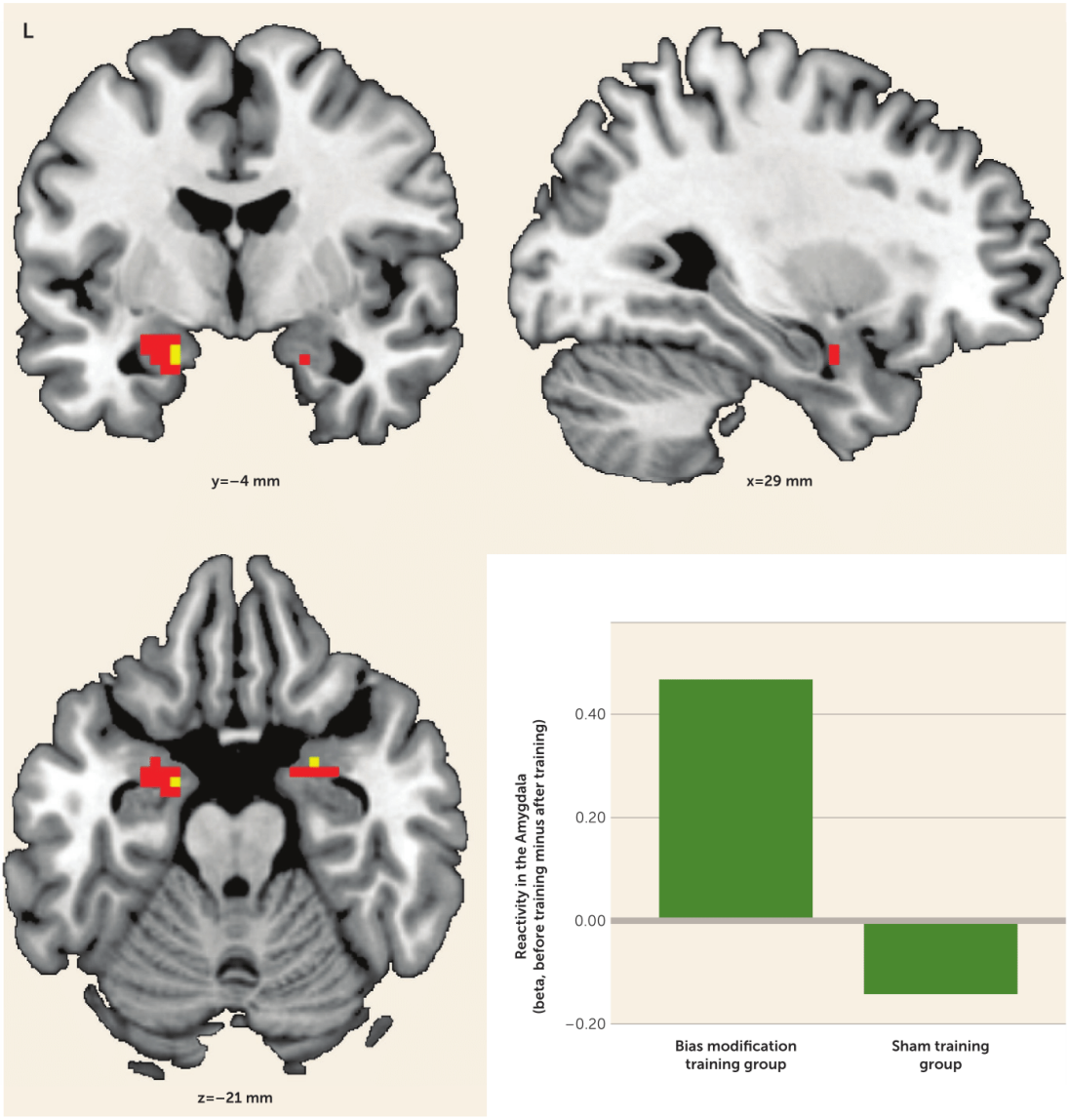


[a] Before training, both groups of alcohol-dependent patients showed significant alcohol cue reactivity (alcohol − soft drink) in the left and right amygdala (panel A; $p<0.05$, family-wise error corrected, small-volume corrected), as well as reactivity approaching significance in the right nucleus accumbens (panel B; $p=0.057$, family-wise error corrected, small-volume corrected). For graphical purposes, significance levels of 0.05 (red) and 0.005 (yellow) uncorrected were used to plot activations. Activations in both areas correlated with alcohol craving scores and arousal ratings of alcohol cues.

area previously associated with alcohol cue reactivity, alcohol craving, and relapse prediction (5, 7–9, 12, 14, 15, 17). Before training, both groups showed alcohol cue reactivity in the amygdala and in the nucleus accumbens (although the latter fell short of significance), which correlated positively with craving scores and arousal ratings of alcohol cues. These findings replicate previous studies of alcohol dependence and suggest that alcohol cue reactivity may be related to clinical severity of dependence (5, 7–9, 12, 33). When comparing alcohol cue-evoked brain reactivity before and after training, amygdala activity differed between the two groups: while amygdala activity decreased in the bias modification group, this effect was not observed in the sham training group. Moreover, the decrease in right amygdala activity correlated with a decrease in alcohol craving scores in the bias modification group, but not in the sham training group. Therefore, reduction of alcohol cue-induced amygdala activity may be an important underlying mechanism contributing to the previously reported therapeutic effectiveness of cognitive bias modification training (19, 23) and may serve as a biomarker for reductions in clinically relevant alcohol craving.

The amygdala has been shown to play a central role in Pavlovian conditioned learning, the modulation of incentive salience to reward cues, and the formation and consolidation of emotional memories (12, 34). In recent work, a function of

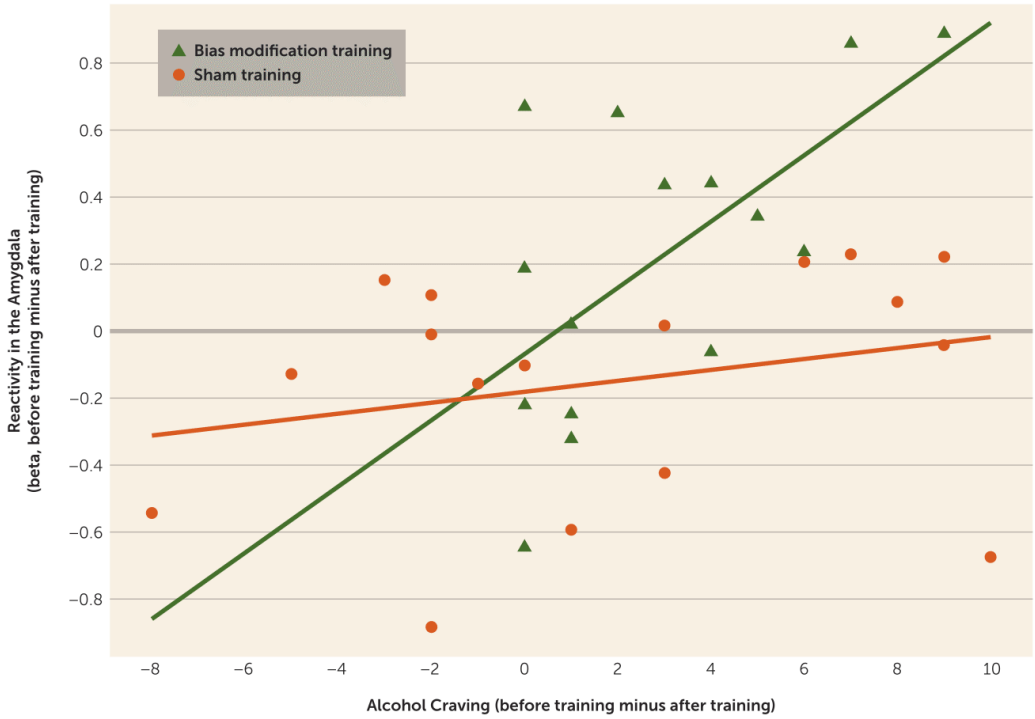
FIGURE 2. Change in Cue Reactivity in Alcohol-Dependent Patients Who Received Bias Modification Training or Sham Training[a]



[a] While amygdala activation decreased bilaterally over the course of training in the bias modification training group ($p<0.05$, family-wise error corrected, small-volume corrected), there was no reduction in the sham training group, even at $p<0.005$ uncorrected. For graphical purposes, significance levels of 0.05 (red) and 0.005 (yellow) uncorrected were used to plot activations.

the amygdala has been described as the processing of the personal motivational salience of stimuli (35). The region has been associated with craving while passively viewing drug cues in drug-dependent patients (12, 36) and in approaching versus avoiding alcohol cues on the approach-avoidance task (9), and two recent studies found that increased alcohol cue reactivity in the amygdala was predictive of alcohol relapse after abstinence (14, 15). A study by Schneider et al. (18) showed that the combination of pharmacological and behavioral therapy reduced amygdala activity when smelling alcohol in alcohol-dependent patients, whereas a healthy comparison group did not show reductions in amygdala activation over the same period. Although the Schneider et al. study could not distinguish whether the effect was due

FIGURE 3. Correlation of Alcohol Craving and Change in Cue Reactivity of the Right Amygdala After Bias Modification Training or Sham Training in Alcohol-Dependent Patients[a]



[a] The graph shows the correlation of the amygdala cue reactivity change before and after training with scores on the Desire for Alcohol Questionnaire in the two groups. In the bias modification training group, the difference between right amygdala activations before and after treatment correlated significantly with the decrease in alcohol craving ($p<0.05$, family-wise error corrected, small-volume corrected), whereas this was not the case for the sham training group, even at $p<0.005$ uncorrected. Beta values of activations were extracted per subject at $p=0.005$ uncorrected.

to behavioral or pharmacological interventions, it showed that the amygdala can be flexibly modulated over time with respect to alcohol-induced cue reactivity. Moreover, it has recently been shown (37) that emotional cue-evoked amygdala activity can be modulated by attentional bias modification in anxious individuals. A possible interpretation of our results, in which bias modification was found to reduce amygdala cue reactivity, is that bias modification reduces the motivational salience of alcohol cues. In line with this interpretation, we found that bias modification reduced arousal ratings of alcohol cues. Moreover, bias modification-induced reductions in right amygdala activation correlated with reductions in alcohol craving.

How might cognitive bias modification cause such a reduction in salience? It may be that this effect is related to findings on inhibition training (38–40). These studies have shown that the inhibition of responses to initially positively valenced stimuli results in a devaluation of that stimulus category. Hypothetically, the requirement to consistently perform incongruent actions in approach/avoidance modification (i.e., actively and habitually avoid previously desired alcohol cues) causes a similar effect: patients could solve the avoid-alcohol problem by reducing the overall salience of alcohol cues (24) and hence reduce behavioral biases associated with them. It therefore may be that reducing overall salience is easier to achieve than changing the automatic response bias without reducing salience. Additional research is needed to provide evidence for or against the hypothesis that the mediating mechanism of cognitive bias modification involves, at least partially, reductions in the salience of alcohol cues.

Despite significant effects of cognitive bias modification on neural cue reactivity, its correlation with craving, and behavioral effects on arousal ratings, we could not replicate the interaction effect of group by time on approach bias scores found by Eberl et al. (23) and Wiers et al. (19, 22). Since effects of bias modification on approach bias and alcohol craving are in the hypothesized direction—we observed a reduction in approach bias (falling short of significance) as well as a significant reduction in craving in the bias modification training group but not in the sham training group—it is likely that the lack of effect is due to the relatively small sample size in this study. Although behavioral effects of

training have been observed in sample sizes of 200 to 500 (19, 23), sample sizes of around 15 alcohol-dependent patients have been shown to be sufficient to measure alcohol cue-evoked neural activity (7, 16) and reductions in cue reactivity over time (16–18). Moreover, to allow training effects to generalize to general alcohol stimuli, patients were trained on different cues than those used for behavioral and neural assessments. This was not the case in previous studies, and this conservative approach may have led to less power for the behavioral effect. Nevertheless, our results show that the effects of bias modification generalize to other, nontrained stimuli, at least in terms of neural effects and in arousal ratings of alcohol cues. Furthermore, we scanned patients after 1 month of abstinence on average, which may have reduced the likelihood of detecting effects of training on behavior and brain activation. This may explain the weak initial activation of the nucleus accumbens before training and the fact that we did not observe the hypothesized difference in reductions in the nucleus accumbens between groups. Another limitation is that our study assessed craving as a clinical outcome measure but was not designed to detect between-group differences in relapse. We assessed relapse 1 year after our assessment of abstinence (reported in the online data supplement), but our study was underpowered to detect cue reactivity effects for relapse. Nevertheless, behavioral craving (10) and amygdala cue reactivity have been shown to predict relapse in alcohol dependence (14, 15), providing further evidence that alcohol cue-induced amygdala reactivity is important for clinical success in alcohol dependence. Studies with larger sample sizes are needed to explore whether the neural effects of cognitive bias modification training in the amygdala are not only associated with alcohol craving, but also can predict relapse status.

In conclusion, we show here for the first time that cognitive bias modification training affects alcohol cue reactivity, which was associated with reductions in alcohol craving. These results suggest that bias modification can reduce the motivational salience of drug cues encoded in the amygdala. Such findings can help us better understand the underlying mechanisms of the clinical effects of cognitive bias modification, which can lead to improved training schemes. Furthermore, fMRI measurements may prove useful in predicting whether cognitive bias modification will be effective for individual patients.

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3.3 Decreased gray matter volume in inferior frontal gyrus is related to stop-signal task performance in alcohol-dependent patients

Wiers CE, Gawron CK, Gropper S, Spengler S, Stuke H, Lindenmeyer J, et al. Decreased gray matter volume in inferior frontal gyrus is related to stop-signal task performance in alcohol-dependent patients. Psychiatry research. 2015;233(2):125-30.doi:http://dx.doi.org/10.1016/j.pscychresns.2015.05.006

Wiers CE, Gawron CK, Gropper S, Spengler S, Stuke H, Lindenmeyer J, et al. Decreased gray matter volume in inferior frontal gyrus is related to stop-signal task performance in alcohol-dependent patients. Psychiatry research. 2015;233(2):125-30.doi:http://dx.doi.org/10.1016/j.pscychresns.2015.05.006

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4. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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5. Vollständige Publikationsliste

5.1 Publikationen

1. Hildebrandt, H., F. Fink, P. Eling, H. Stuke, J. Klein, M. Lentschig, A. Kastrup, C. Thiel, and T. Breckel, *Neural correlates of stimulus response and stimulus outcome shifting in healthy participants and MS patients.* Brain Cogn, 2012. **81**(1): p. 57-66.
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3. Wiers, C.E., C. Stelzel, T.E. Gladwin, S.Q. Park, S. Pawelczack, C.K. Gawron, H. Stuke, A. Heinz, R.W. Wiers, M. Rinck, J. Lindenmeyer, H. Walter, and F. Bermpohl, *Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence.* Am J Psychiatry, 2015. 172(4): p. 335-43.
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11. Weilnhammer, V.A., Stuke, H., Hesselmann, G., Sterzer, P., Schmack, K., *Evidence for a Predictive Coding Account of Bistable Perception.* Submitted, 2016.

5.2 Vorträge und Präsentationen

1. Stuke, H., Gutwinski, S., Gröpper, S., Parnack, J., Wiers, C., Bermpohl, F. *Veränderte Entscheidungsprozesse bei Personen mit missbräuchlichem Alkoholkonsum.* Posterpräsentation am 05.10.2012 auf dem Deutschen Suchtkongress
2. *To drink or not to drink: neural correlates of harmful pro-alcohol decisions*. Workshop-Talk am 29.08.2015 auf der 14th Charité Conference on Psychiatric Research: Emotional Neuroscience

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