Neurokognition, Hirnfunktion und Psychopathologie bei beginnenden MDMA- und Amphetaminkonsumenten

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Präambel

Die vorliegende Arbeit ist gemäß der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf in kumulativer Weise – basierend auf wissenschaftlichen Publikationen in wissenschaftlichen Publikationsorganen mit anerkanntem Begutachtungsverfahren (peer review) verfasst. Sie besteht aus einem Begleittext zur Einordnung der eingereichten Publikationen in einen größeren wissenschaftlichen Kontext und aus Kopien der eingereichten, beziehungsweise veröffentlichten Publikationen.

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Ich versichere an Eides statt, dass die Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.

Erklärung

Diese Dissertation wurde keiner anderen Fakultät vorgelegt.

Düsseldorf, den 22.02.2013

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Zusammenfassung

Bislang ist unklar, ob die beobachteten kognitiven, hirnfunktionellen und psychopathologischen Auffälligkeiten, die mit dem Konsum von 3,4-Methylendioxy-N-methylamphetamin (MDMA, „Ecstasy“) und Amphetamin (D-Amphetamin, „Speed“) assoziiert sind, in Folge des Konsums auftreten oder bereits vor Beginn des Konsums bestehen. Desweiteren wurde der Rolle verschiedener konfundierender Variablen, wie dem Konsum anderer Substanzen und dem Gesundheitsverhalten, bislang nur wenig Beachtung geschenkt. Um diesen Umständen Rechnung zu tragen, wurde eine prospektive Studie bei beginnenden MDMA- und Amphetaminkonsumenten durchgeführt. Die Rekrutierung erfolgte in der Kölner Club- und Rave-Szene. Probanden wurden zur Untersuchung zugelassen falls sie erste Erfahrungen mit Ecstasy und/oder Amphetaminen gemacht haben (mindestens eine Einnahme einer der beiden Stoffklassen), jedoch noch keinen regelmäßigen Konsum dieser Drogen aufwiesen (insgesamt maximal je fünf Einnahmen). Auch ansonsten durften die Probanden keine weiteren Drogen mit der Ausnahme von Cannabis konsumieren. Die Probanden wurden zwei Mal im Abstand von einem Jahr hinsichtlich neurokognitiver Performanz (Testbatterie mit Lern- und Gedächtnistests, sowie Tests zu frontalen exekutiven Funktionen), Hirnfunktion (fMRT mit Paradigma zum assoziativen Gedächtnis) und selbstberichteter Psychopathologie untersucht. Hinsichtlich der neurokognitiven Performanz zeigten sich signifikante Effekte bei einer Paar-Assoziations-Lern-Aufgabe zwischen MDMA-Konsumenten und Kontrollen. Auf hirnfunktioneller Ebene wurden spezifische Effekte des MDMA-Konsums hinsichtlich hippocampaler Funktion aufgezeigt. Zudem konnte ein Zusammenhang zwischen selbstberichteter Psychopathologie zum Beginn der Studie und nachfolgendem Amphetaminkonsum festgestellt werden. Zusammenfassend weisen die Ergebnisse auf spezifische Risiken des MDMA-Konsums auch nach verhältnismäßig geringem Konsum und darauf, dass ein global erhöhtes psychopathologisches Profil einen Risikofaktor für den späteren Konsum von Amphetamin darstellen könnte.

Summary

It is still unclear whether cognitive impairments, psychopathological abnormalities and alterations of brain activity associated with the consumption of 3,4-Methylendioxy-N-methylamphetamin (MDMA, „Ecstasy“) and amphetamine (d-Amphetamine, “Speed”) are a consequence of use or existed before the initiation of use. Furthermore, the influence of several confounding variables like polydrug use and health-related behavior is barely investigated. To account for these limitations, a prospective study with new users of MDMA and amphetamine was conducted. Beginning users of MDMA and amphetamine were recruited in the club and rave scene of Cologne. Subjects were included if they used at least one unit of MDMA or amphetamine but not more than five units in total. Another exclusion criterion was the ingestion of any other illicit psychotropic substance besides cannabis on more than five occasions before the day of the first examination. Subjects were tested twice with a follow-up duration of 12 months in order to investigate cognitive performance (neuropsychological test battery including measures of learning, memory, and frontal executive functions), memory-related hippocampal functioning (fMRI with an associative memory task) and self-reported psychopathology. Concerning cognitive performance, significant effects of a visual paired associates learning task between MDMA users and controls were found. The memory-related fMRI task revealed specific effects of MDMA consumption on hippocampal functioning. Additionally, self-reported psychopathological abnormalities at the beginning of the study were associated with subsequent amphetamine consumption. In conclusion, the findings may raise concerns with regard to MDMA use, even in recreational amounts over a relatively short time period. Furthermore the results suggest that a globally increased psychopathological profile could form a risk factor for the later use of amphetamine.

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Inhaltsverzeichnis

1. Einleitung

3,4-Methylendioxy-N-methylamphetamin (MDMA, „Ecstasy“) und Amphetamin (D-Amphetamin, „Speed“) sind nach Cannabis und neben Kokain die beiden am häufigsten konsumierten illegalen Drogen (1). Beide Substanzen sind Derivate von β-Phenylethylamin und teilen chemische und pharmakologische Ähnlichkeiten (2). Die Lebenszeitprävalenz für den Konsum von Amphetamin in der Altersgruppe der 18-64-jährigen liegt bei 3,7% (3). Insbesondere in der deutschen Techno-Szene ist die Lebenszeitprävalenz des Amphetaminkonsums in der Altersgruppe der 12-25-jährigen mit 46,1% jedoch deutlich höher (4). Amphetamin kann auf verschiedenste Weise konsumiert werden (z.B. mittels Inhalation, Injektion oder oraler Einnahme), wobei der intranasale Konsum innerhalb der europäischen Union am häufigsten praktiziert wird (2). Nach der Einnahme treten in Abhängigkeit von Dosierung und Konsumform prototypische Effekte wie gesteigerter Antrieb, Hypervigilanz, gesteigerter Kommunikationsdrang, Euphorie, vermindertes Hunger- und Durstgefühl aber auch dysphore Stimmung, Agitation und Aggression auf (2). Die Lebenszeitprävalenz für den Konsum von MDMA ist mit 2,4% innerhalb der Altersgruppe der 18-64-jährigen und mit 44,6% bei den 12-25-jährigen innerhalb der deutschen Techno-Szene vergleichbar mit der Prävalenz des Konsums von Amphetamin (4). MDMA wird üblicherweise in Form von Tabletten konsumiert. Die akuten psychischen Effekte von MDMA dauern über einen Zeitraum von drei bis fünf Stunden und sind gekennzeichnet durch Entspannung, Empathie, Euphorie und gesteigertem Wohlbefinden, zusammen mit Amphetamin-ähnlichen Effekten, sowie einer veränderten Wahrnehmung und leichten halluzinogenen Effekten (2, 5). MDMA und Amphetamin wirken jeweils in erster Linie auf serotonerge, dopaminerge und noradrenerge Neuronen im zentralen Nervensystem (ZNS). Die Freisetzung von Dopamin erfolgt insbesondere durch Blockierung und Umkehrung der Dopamin-Wiederaufnahmetransporter (DAT) (6). Die erhöhte Freisetzung von Serotonin und Norepinephrin erfolgt analog zu der von Dopamin durch Blockierung und Umkehrung am Serotonin-Wiederaufnahmetransporter

(SERT), beziehungsweise am Norepinephrin-Wiederaufnahmetransporter (NET) (7-9). Ein Vergleich der pharmakologischen Eigenschaften von MDMA und Amphetamin zeigt, dass durch MDMA deutlich mehr Serotonin als Dopamin freigesetzt wird, während Amphetamin deutlich mehr Dopamin als Serotonin freisetzt (10). Tierexperimentelle Studien aus den 1980er Jahren legen nahe, dass MDMA zu einer neurotoxischen Degeneration an serotonergen Axonendigungen führt und diese mit einer verminderten Serotoninkonzentration im ZNS einhergehen (2). Derartige persistierende Folgewirkungen von MDMA-Exposition wurden über einen Zeitraum von mehreren Jahren beobachtet (11, 12). Studien aus dem Humanbereich mit Messungen der Serotonin-Transporterdichte mittels der nuklearmedizinischen Positronen-Emissions-Tomographie (PET) legen nahe, dass das in Tierversuchen evidente neurotoxische Potenzial von MDMA gleichermaßen für menschliche Konsumenten relevant sein könnte (2). Bedingt durch die Beteiligung von Serotonin als Neuromodulator an vielfältigen Funktionen des ZNS, wäre ein neurotoxischer Effekt von MDMA hinsichtlich kognitiver Funktionen, psychopathologischen Auffälligkeiten und Veränderungen der neuronalen Aktivitätsmuster möglich. Bislang liegen kaum Befunde hinsichtlich der Langzeitfolgen des Amphetaminkonsums vor. Verschiedene Studien zum starken Konsum des allerdings viel potenteren Methamphetamin zeigen mittels Positronen-Emissions-Tomographie (PET), Einzelphotonen-Emissionscomputertomographie (SPECT) und Magnetresonanztomographie (MRT) einen möglicherweise über einen längeren Zeitraum bestehenden neurotoxischen Effekt (13-18).

2. Folgewirkungen des Konsums von MDMA und Amphetamin

2.1. Kognitive Folgewirkungen

In Übereinstimmung mit den zuvor beschriebenen hirnmorphologischen Folgewirkungen bei MDMA-Konsumenten, zeigen sich in den kognitiven Domänen Auffälligkeiten, die mit frontalen, temporalen und parietalen Hirnarealen in Verbindung gebracht werden (19, 20).

Eine Reihe von Quer- und Längsschnittuntersuchungen konnte vornehmlich Defizite in den Domänen Arbeitsgedächtnis, Assoziationsgedächtnis, kognitive Flexibilität und Planungsfähigkeit feststellen (21-26). Diese kognitiven Defizite zeigen, in Verbindung mit den konsistenten Ergebnissen aus bildgebenden Studien, vulnerable Domänen für die serotonerge Neurotoxizität von MDMA. Studien zu neurokognitiven Tests bei ausschließlichen Amphetaminkonsumenten liegen nach derzeitigem Kenntnisstand noch nicht vor. Eine Vielzahl der Studien zu neurokognitiven Folgewirkungen wird, analog zu bildgebenden und psychopathologischen Studien, eingeschränkt durch methodische Probleme hinsichtlich des Polydrogenkonsums der Probanden und der damit einhergehenden mangelnden Differenzierbarkeit der Effekte der einzelnen Substanzen. Daneben wurden in einigen Untersuchungen mögliche bereits vor dem Konsum existierende Gruppenunterschiede außer Acht gelassen.

2.2. Hirnfunktionelle Folgewirkungen

Innerhalb der letzten Jahre konnten verschiedene Studien mittels funktionaler Magnetresonanztomographie (fMRT) veränderte neuronale Aktivität bei MDMA- und Amphetaminkonsumenten nachweisen. MDMA-Konsumenten wiesen dabei primär anormale Aktivität in dem für das assoziative Gedächtnis relevanten hippocampalen Netzwerk auf (27, 28). Daneben wurden auch veränderte neuronale Aktivitätsmuster in frontalen Hirnarealen bei Konsumenten von MDMA und Amphetamin festgestellt. Frontale Hirnareale sind, neben anderen exekutiven Funktionen, bedeutsam für das Arbeitsgedächtnis. Eine Reihe von Studien konnte bei MDMA-Konsumenten, im Vergleich zu Kontrollprobanden, während der Ausführung einer Arbeitsgedächtnisaufgabe eine veränderte neuronale Aktivität in frontalen, parietalen, limbischen und temporalen Hirnarealen beobachten (29-31). Eine andere Studie, die Konsumenten von MDMA und Amphetamin mittels klassischer Magnetresonanztomographie (MRT) untersuchte, konnte bei MDMA-Konsumenten eine

Volumenreduktion des Hippocampus nachweisen im Vergleich zu Kontrollprobaden mit einem ähnlichen Konsum von Amphetamin (32).

2.3. Psychopathologische Folgewirkungen

Regelmäßiger MDMA-Konsum wird mit psychopathologischen Symptomen wie Angst, Depression und Exekutivfunktionsstörung, Impuls-Kontrollstörungen und Psychosen in Verbindung gebracht (33-35). Psychotische Symptome beziehen sich im Kontext des Amphetaminkonsums primär auf paranoides Denken, visuelle und auditive Halluzinationen, Impulsivität und aggressive Verhaltensweisen. Es besteht jedoch Unklarheit, ob der langfristige Konsum von MDMA psychopathologische Symptome verursacht oder ob psychopathologische Auffälligkeiten den Konsum von MDMA prädestinieren. Eine Studie von Medina und Mähen (36) konnte nachweisen, dass der Konsum von MDMA häufig nach der Entwicklung einer Achse I Erkrankung in den Domänen Depression oder Angst aufgenommen wird. Außerdem wird davon ausgegangen, dass an einer Psychose erkrankte Personen ein erhöhtes Risiko aufweisen, Rauschmittel zu konsumieren (37). Ferner wird angenommen, dass der Konsum ein Schlüsselrisikofaktor für eine psychotische Rezidiverkrankung ist (38). Außerdem wurde beobachtet, dass Personen, welche an einer Psychose erkrankt sind, einer erhöhten Gefahr ausgesetzt sind, eine Substanzabhängigkeit zu entwickeln als gesunde Menschen (39). Eine Vielzahl von Kritiken an den gegenwärtigen Studien weisen auf einen möglichen unspezifischen Einfluss von begleitendem Cannabiskonsum hin, welcher bei den Konsumenten von MDMA üblich ist (36, 40). Eine Studie von Zweben, Cohen und Christen (41) konnte nachweisen, dass etwa 25 % der Amphetaminkonsumenten (insbesondere Methamphetaminkonsumenten) eine erhöhte psychopathologische Symptomatik aufweisen. Ferner konnte gezeigt werden, dass durch Amphetaminkonsum induzierte Psychosen ein Schlüsselmerkmal von starkem Amphetaminkonsum sind. Eine andere Studie legt Depressionen als verbreitete Nebenerkrankung von substanzabhängigen Erwachsenen nahe (42).

3. Fokus der vorgelegten Studien

Die Mehrzahl der bereits existierenden Studien bezüglich der Langzeitfolgen von MDMA und Amphetamin weisen methodische Mängel unterschiedlicher Art auf. Wie bereits zuvor dargelegt, besteht Unkenntnis über die spezifischen Effekte von MDMA und Amphetamin aufgrund von nicht erfassten Konsumparametern und Polydrogenexposition der Konsumenten. Zusätzliche Unklarheit besteht hinsichtlich möglicher bereits vor dem Drogenkonsum existierender Gruppenunterschiede. Um diesen methodischen Einschränkungen entgegenzutreten wurde in den vorgelegten Studien ein prospektiver Ansatz gewählt. In einer ersten Studie wurde untersucht, inwieweit sich die neurokognitive Performanz von beginnenden Konsumenten von MDMA in Abhängigkeit der Konsumparameter innerhalb von 12 Monaten verändern. In einer zweiten Studie wurde untersucht, inwiefern sich die hippocampale Aktivität während einer Gedächtnisaufgabe über einen Zeitraum von 12 Monaten bei beginnenden Konsumenten von MDMA und Amphetamin verändert. In einer dritten Studie wurde schließlich die Entwicklung selbstberichteter Psychopathologie von beginnenden Konsumenten von MDMA und Amphetamin innerhalb eines Zeitraums von 24 Monaten untersucht.

4. Zusammenfassung der durchgeführten Studien

Insgesamt liegen der vorliegenden Dissertationsschrift drei Publikationen zu Grunde, die im Folgenden zusammengefasst dargestellt werden. Unter Punkt 7 sind die vollständigen Arbeiten aufgeführt und angehängt.

4.1. Eine prospektive Studie zu exekutiven Funktionen, Lernen und Gedächtnis bei beginnenden MDMA-Konsumenten

Wie einleitend dargestellt, bestand in vergangenen Studien Unklarheit darüber, inwiefern kognitive Defizite bei MDMA-Konsumenten bereits vor dem Konsum bestanden. Zusätzlich

besteht Ungewissheit bezüglich des Einflusses von möglichen moderierenden Variablen. Die vorliegende Studie wurde durchgeführt um den Zusammenhang zwischen MDMA-Konsum und möglichen kognitiven Folgewirkungen zu untersuchen und methodische Einschränkungen früherer Studien zu überwinden. Insgesamt wurden 149 beginnende MDMA-Konsumenten zum ersten Messzeitpunkt dieser prospektiven Studie untersucht. An der nach 12 Monaten folgenden Follow-up Untersuchung nahmen 109 MDMA-Konsumenten teil. Während des 12 Monatsintervalls konsumierten 43 Probanden, abgesehen von Cannabis, keine illegalen Substanzen, während 23 Probanden mehr als 10 Tabletten MDMA konsumierten. Bei diesen beiden Gruppen wurden mittels der Berechnung von Change Scores die Veränderung von verschiedenen kognitiven Parametern (Auditiv-Verbaler Lerntest (AVLT), Lern- und Gedächtnistest (LGT), Digit Span Test, Digit Symbol Test, Stroop Test, Trail-making Test) innerhalb des 12 Monatsintervalls erfasst. Zusätzlich wurden weitere möglicherweise relevante Variablen erhoben wie Alter, allgemeine Intelligenz, der Konsum von Cannabis, Alkohol und Tabak, medizinische Behandlungen, sportliche Aktivität, Ernährung, Schlaf und subjektives Wohlbefinden. Die erhobenen Daten wurden schließlich mittels einer multivariaten Varianzanalyse ausgewertet. Die Auswertung zeigte einen signifikanten Unterschied der sofortigen und der verzögerten Abrufleistung eines visuellen Paar-Assoziations-Lerntests zwischen den beiden Konsumentengruppen. Weitere signifikante Unterschiede hinsichtlich der verbleibenden kognitiven Parameter wurden nicht gefunden. MDMA schein somit das visuelle Paar-Assoziations-Lernen von Konsumenten zu beeinträchtigen, möglicherweise aufgrund einer serotonergen Dysfunktion hippocampaler Hirnareale infolge des MDMA-Konsums.

4.2. Hippocampale Aktivität von Konsumenten von MDMA und Amphetamin bei einer Gedächtnisaufgabe

Freizeitkonsum von MDMA wurde, wie zuvor dargestellt, wiederholt mit Defiziten der Gedächtnisleistung assoziiert. Studien mittels fMRT konnten veränderte hippocampale

Aktivitätsmuster bei MDMA- Polydrogenkonsumenten nachweisen. Inwiefern diese Veränderungen auf bereits bestehende Gruppenunterschiede zurückzuführen sind und welchen Einfluss Amphetaminkonsum hat, ist unklar. Eine prospektive Studie wurde durchgeführt um die spezifischen Effekte der MDMA- Exposition bei beginnenden Konsumenten zu eruieren. Mittels fMRT wurden 40 beginnende MDMA- und/oder Amphetaminkonsumenten, mit einer maximalen Lebenszeitdosis von bis zu fünf Tabletten MDMA oder 5 Gramm Amphetamin, bei der Bearbeitung einer Aufgabe zur Gedächtnisleistung untersucht. Nach 12 Monaten unterzogen sich die Probanden erneut der fMRT-Untersuchung. Zusätzlich wurden die Probanden zu ihrem Konsumverhalten innerhalb der vergangenen 12 Monate befragt. Eine Varianzanalyse mit Messwiederholung zeigte, dass sich die Aktivität im linken parahippocampalen Gyrus änderte. Die Aktivität in dieser Hirnregion nahm bei Konsumenten zu, welche innerhalb des 12 Monatsintervalls keine Amphetamine konsumierten, wobei sie bei den Probanden, welche ihren Konsum innerhalb des 12 Monatsintervalls fortsetzten, abnahm. Ein Effekt von Amphetamin auf die Aktivität im linken parahippocampalen Gyrus konnte nicht festgestellt werden. Die Ergebnisse legen spezifische Langzeiteffekte des MDMA-Konsums auf gedächtnisbezogene Aktivität der hippocampalen Hirnareale nahe.

4.3. Eine prospektive Studie zur Psychopathologie bei beginnenden MDMA- und Amphetaminkonsumenten

Einige Studien berichten diverse psychopathologische Auffälligkeiten bei Konsumenten von MDMA und Amphetamin. Es wurde bislang jedoch nicht untersucht, inwieweit psychopathologische Auffälligkeiten bereits vor dem Konsum von MDMA oder Amphetamin bestanden. Die vorliegende Studie ging daher mittels eines prospektiven Designs der Frage nach, ob psychopathologische Auffälligkeiten vor dem Konsum existieren oder ob sich diese erst durch den Konsum manifestieren. Insgesamt 96 beginnende MDMA- und/oder

Amphetaminkonsumenten nahmen an zwei psychopathologischen Untersuchungen im Abstand von 24 Monaten teil. Während des 24-Monatsintervalls konsumierten 31 Probanden weder MDMA noch Amphetamin, während 37 Probanden zwischen einer und 14 Tabletten MDMA konsumierten (Mittelwert: 5,18). Schließlich konsumierten 33 Probanden während des 24-Monatsintervalls 15 oder mehr Einheiten MDMA (Mittelwert: 43,73). Weiterhin konsumierten 33 Probanden innerhalb des Intervalls zwischen einem und 14 Gramm Amphetamin (Mittelwert: 4,46), während 32 Probanden 15 Gramm oder mehr (Mittelwert: 64,52) konsumierten. Die Veränderung der psychopathologischen Parameter dieser Probandengruppen innerhalb des Untersuchungszeitraumes wurde mittels einer multivariaten Varianzanalyse ausgewertet. Es wurden keine signifikanten Veränderungen der Psychopathologie zwischen den Konsumentengruppen gefunden. Jedoch wurde ein signifikanter Zusammenhang zwischen höheren psychopathologischen Werten zu Beginn der Studie und anschließendem Amphetaminkonsum gefunden. Die Ergebnisse legen nahe, dass eine global erhöhte Psychopathologie nachfolgenden Amphetaminkonsum begünstigt.

5. Diskussion

5.1. Kritische Einordnung der Ergebnisse

Defizite des visuellen-assoziativen Lernens bei Konsumenten von MDMA wurden bereits mehrfach - allerdings noch nie in einem prospektiven Design – beschrieben (20, 31, 43-45). Angesichts des Befundes, dass keine anderweitigen Veränderungen neurokognitiver Variablen mit dem Konsum von MDMA assoziiert waren, deuten die Ergebnisse der vorliegenden Arbeit auf einen spezifischen Effekt von moderatem MDMA-Konsum auf das visuelle Paar-Assoziationslernen. Dieser Befund ist konsistent mit den Ergebnissen von Brown und Mitarbeitern (46), welche ebenfalls ausschließlich eine eingeschränkte Assoziations-Lernleistung bei MDMA-Konsumenten nachweisen konnten. Ob ein möglicher Effekt von

MDMA auf andere kognitive Variablen über einen längeren Zeitraum hin besteht, bleibt unklar und stellt eine spannende Fragestellung für zukünftige Studien dar.

Angesichts des Polydrogenkonsums in der hier untersuchten Stichprobe besteht Unklarheit bezüglich der Frage, ob die nachgewiesene Verminderung der Gedächtnisleistung ausschließlich auf den Konsum von MDMA oder auch auf den begleitenden Amphetaminkonsum zurückzuführen ist. Diesbezüglich konnten Gouzoulis-Mayfrank und Mitarbeiter (20) bei einer ähnlichen Stichprobe, mittels einer schrittweisen linearen Regressionsanalyse, Beeinträchtigungen der Gedächtnisleistung auf den MDMA-Konsum zurückführen. Demnach scheint es wahrscheinlich, dass die Beeinträchtigungen der visuell-assoziativen Gedächtnisleistung eine Folgewirkung des Konsums von MDMA sind, nicht aber eine Folgewirkung des Polydrogenkonsums von MDMA und Amphetamin. Weiterhin konnte eine multiple Regressionsanalyse unter Einbeziehung des Konsums anderer Substanzen in einer Studie von Schilt und Mitarbeitern (23) dosisabhängige Einschränkungen der verbalen Gedächtnisleistung bei MDMA-Konsumenten nachweisen.

Da der Hippocampus eine fundamentale Rolle bei der assoziativen Gedächtnisleistung einnimmt (47), unterstützen die Ergebnisse der durchgeführten Studie die Hypothese, dass eine hippocampale Dysfunktion den neurokognitiven Effekten von MDMA-Konsum zugrunde liegt. Tierexperimentelle Studien zeigen einen selektiven und persistierenden Effekt von MDMA auf serotonerge Axonendigungen (12, 48-51). Speziell der Hippocampus und der Parahippocampus weisen nach MDMA-Exposition serotonerge Denervierung auf (48). Ferner spielt Serotonin eine zentrale Rolle bei der hippocampalen Neurogenese, welche Lern- und Gedächtnisleistungen inhärent ist (52). Gouzoulis-Mayfrank und Mitarbeiter (20) gehen somit davon aus, dass hippocampale Hirnareale sensitiver für eine Serotonin-Depletion sind als neokortikale Hirnregionen. Zusätzlich ist diese Hypothese konsistent mit neurokognitiven Befunden aus dem Bereich Lern-und Gedächtnisleistung im Vergleich zu anderen, von neokortikalen Hirnarealen abhängigen, neurokognitiven Funktionen.

Die zugrunde liegenden molekularen Mechanismen dieser Langzeiteffekte des MDMA-Konsums sind nicht hinreichend bekannt. Tierexperimentelle Studien legen eine durch oxidativen Stress verursachte Neurotoxizität durch MDMA-Exposition nahe (53, 54). Zudem wurden eine mitochondriale Dysfunktion und Hyperthermia mit der Verabreichung von MDMA und der Schädigung serotonerger Axonendigungen in Verbindung gebracht. Ebenfalls werden inflammatorische Zytokine, das Ubiquitin-Proteasom-System, Umwelt-bedingter Stress, neurotrophe Faktoren und Apoptose als potentielle moderierende Variablen der neurotoxischen Folgewirkungen von MDMA-Exposition vermutet. Allerdings liegen auch Hinweise vor, dass anstatt einer Neurodegeneration, neuroregulatorische Prozesse der MDMA-induzierten serotonergen Dysfunktion zugrunde liegen könnten (55). Zukünftige Untersuchungen sind notwendig, um weitere Erkenntnisse über diese molekularen Prozesse zu gewinnen.

Hinsichtlich der bildgebenden Ergebnisse sind neben einem Effekt von MDMA alternative Erklärungen denkbar. Zum einen wird der Konsum von Cannabis mit einer veränderten hippocampalen Aktivität bis zu sieben Tage nach dem letzten Konsum in Verbindung gebracht (56-59). Konsumenten in der vorliegenden Studie, welche ihren Konsum von MDMA und Amphetamin fortgesetzt haben, konsumierten, im Vergleich zu den anderen Konsumentengruppen, während der Follow-up Periode mehr Cannabis. Konfundierende (subakute) Effekte des Cannabiskonsums auf die hippocampale Hirnaktivität können somit nicht vollständig ausgeschlossen werden. Allerdings blieb der Gruppeneffekt in der durchgeführten Studie auch nach statistischer Kontrolle bezüglich des Cannabiskonsums signifikant. Ferner zeigte sich, dass sich bereits zum ersten Testzeitpunkt die hippocampale Aktivität der zukünftig abstinenten Probanden und die der zukünftig ihren Konsum fortsetzenden Probanden signifikant unterschieden. Unterschiede der individuellen Abstinenz vor Beginn der Studie könnten diesem Befund zu Grunde liegen. Die Konsumenten berichteten vor Beginn der Studie jedoch über ähnlich lange Abstinenzperioden, somit sind auch andere

Ursachen nicht auszuschließen. Die Gruppenunterschiede der hippocampalen Aktivität zu Beginn der Studie könnten schließlich auch einen Faktor darstellen, der zukünftigen Konsum begünstigt.

In Übereinstimmung mit bisherigen Querschnittsuntersuchungen moderater MDMA-Konsumenten (20, 60, 61), konnten in der vorliegenden Studie keine signifikanten Einschränkungen hinsichtlich der Gedächtnisleistung festgestellt werden. Jedoch konnte in Übereinstimmung mit bisherigen Untersuchungen (31, 62), eine verringerte parahippocampale Aktivität in der den Konsum fortsetzenden Probandengruppe gefunden werden. Die Verringerung der parahippocampalen Aktivität stand in Zusammenhang mit dem während des Testintervalls konsumierten MDMA, ein Zusammenhang mit Amphetamin- oder Cannabiskonsum bestand nicht. Somit konnten frühere Studienergebnisse (63) bezüglich der Auswirkungen von Amphetaminkonsum auf die parahippocampale Aktivität nicht bestätigt werden. Diese Inkonsistenz könnte durch die Verschiedenheit des Untersuchungsdesigns und der Stichprobe verursacht sein. Während frühere Querschnittstudien mittels multipler Regressionsanalysen MDMA- oder Amphetaminspezifische Effekte zu eruieren versuchten, bedient sich die hier vorliegende Studie eines prospektiven Designs. Zudem konsumierten die Probanden in der früheren Studie wesentlich mehr MDMA und Amphetamin im Vergleich zu dem relativ moderaten Konsum in der hier durchgeführten Studie. Denkbar ist zudem, dass MDMA-spezifische Effekte bereits bei geringem Konsum evident sind, während Amphetamin-spezifische Effekte erst bei hohen kumulativen Dosierungen messbar werden. Der Zusammenhang zwischen dem Interimkonsum von MDMA und Veränderungen der neuronalen Aktivität war in der vorliegenden Studie relativ schwach ausgeprägt. Wegen der geringen Anzahl an konsumierten MDMA-Tabletten war die Varianz innerhalb der Stichprobe relativ gering. Daneben können Störfaktoren wie die Reinheit des konsumierten MDMA und fehlerhafte Konsumangaben insbesondere bei kleineren Stichproben mit moderatem

Konsummuster zu Verzerrungen führen. Zukünftige Studien sind somit notwendig um die hier vorgestellten Ergebnisse zu validieren.

Im Gegensatz zu vorherigen Untersuchungen unserer Arbeitsgruppe und anderen Forschungsgruppen (64-67) konnte die vorliegende Studie keinen Zusammenhang zwischen MDMA-Konsum und einer Dysfunktion frontal-parietaler Hirnregionen finden. Auch dies könnte durch den relativ moderaten MDMA-Konsum in der untersuchten Stichprobe begründet sen. Eine derartige Dysfunktion könnte ausschließlich bei sehr starkem MDMA-Konsum nachweisbar werden.

Hinsichtlich der psychopathologischen Daten erschwert die Inkonsistenz bisheriger Studien die Einordnung der generierten Daten. Einige Studien konnten einen Zusammenhang zwischen der Menge der konsumierten MDMA-Tabletten und psychopathologischen Auffälligkeiten feststellen (68, 69), während andere Studien diesen Zusammenhang nur bei Konsumenten feststellten, die ihren Konsum als problematisch bewerteten (70). Zudem werden in Querschnittstudien bereits zuvor existierende psychopathologische Auffälligkeiten nicht in Betracht gezogen. Unglücklicherweise existiert nur eine begrenzte Anzahl an longitudinalen Untersuchungen. Eine prospektive Studie bestätigt die Ergebnisse der vorliegenden Studie. Soar und Kollegen (71) konnten über einen Zeitraum von 10 Jahren belegen, dass 24% der MDMA-Konsumenten bereits vor der Aufnahme des Konsums psychopathologische Auffälligkeiten zeigten. Eine longitudinale Studie (72) konnte zudem, unter Verwendung einer verhältnismäßig großen Stichprobe, feststellen, dass Personen bereits vor der Aufnahme des MDMA-Konsums mit höherer Wahrscheinlichkeit an einer psychiatrischen Störung erkranken.

In der vorliegenden Studie konnte kein Zusammenhang zwischen bereits bestehenden psychopathologischen Auffälligkeiten und zukünftigem MDMA-Konsum gefunden werden. De Win und Mitarbeiter (73) untersuchten inwieweit Depression, Impulsivität und „sensation seeking“ ein prädiktives Maß für den zukünftigen MDMA-Konsum darstellen. Bemerkenswerterweise hatten diese Parameter keinen Einfluss auf den zukünftigen Konsum

von MDMA. Eine weitere longitudinale Studie von Thomasius und Mitarbeitern (74) konnte zeigen, dass sich psychopathologische Auffälligkeiten bei ehemaligen und auch aktiven MDMA-Konsumenten über eine längere Periode nicht verändern. Allerdings wiesen die ehemaligen MDMA-Konsumenten eine erhöhte Psychopathologie auf. Möglicherweise sind die Effekte von MDMA hinsichtlich psychopathologischer Auffälligkeiten erst bei zunehmendem Konsum evident. So haben Falck und Mitarbeiter (75) Konsumenten mit einer Lebenszeitdosis von mindestens 50 Tabletten MDMA untersucht, welche deutlich mehr depressive Symptome aufwiesen als eine zweite Probandengruppe mit einer geringeren Lebenszeitdosis. Über den gesamten Untersuchungszeitraum von zwei Jahren war hingegen eine Abnahme der depressiven Symptomatik in beiden Gruppen zu verzeichnen. In diesem Zusammenhang ist eine Studie von Verheyden und Mitarbeitern hervorzuheben (76), die untersuchte, warum MDMA-Konsumenten ihren Konsum beendeten. Hierbei konnten zwei Gruppen unterschieden werden. Eine Gruppe der Konsumenten gab ihren Konsum wegen einer oder mehr von 19 verschiedenen psychologischen Problemen auf, während die andere Gruppe ihren Konsum wegen Veränderungen ihrer persönlichen Lebensumstände aufgab. Die Hälfte der Konsumenten aus ersterer Gruppe wies dabei eine mit der Lebenszeitdosis assoziierte klinische Depression auf. Verheyden und Mitarbeiter konkludierten, dass Personen mit bereits existierenden psychologischen Auffälligkeiten besonders prädestiniert für den Konsum von MDMA sind, oder, dass spezifische Konsumenten besonders vulnerabel für die Folgewirkungen von MDMA sind. Befunde von Soar und Mitarbeitern (77) stimmen mit diesen Ergebnissen überein. In dieser Studie berichteten Konsumenten, welche ihren Konsum als problematisch empfanden, auch über einen persönlichen oder familiären psychiatrischen Hintergrund.

Weiterhin besteht Unklarheit darüber, ob die berichteten psychopathologische Auffälligkeiten ausschließlich mit dem Konsum von MDMA in Verbindung gebracht werden können. Die Mehrheit der Konsumenten berichtet über weiteren Substanzkonsum von Cannabis, Amphetamin, Alkohol und Kokain (78, 79). Es besteht immerhin die Möglichkeit eines den

neurotoxischen Einfluss von MDMA potenzierenden Ineraktionseffekts durch den Mischkonsum anderer Drogen (80). Einige Studien zeigen, im Vergleich zu singulärem MDMA-Konsum, einen schädlicheren Effekt von Polydrogenkonsum hinsichtlich psychopathologischer Auffälligkeiten (69, 81-85).

Die bestehende Literatur bezüglich Amphetaminkonsum und psychopathologischen Auffälligkeiten ist spärlich. In einigen Studien wird über eine Assoziation von Langzeitkonsum und psychopathologischen Auffälligkeiten berichtet. Wang und Mitarbeiter (86) kommen in ihrer Langzeitstudie zu dem Ergebnis, dass über einen längeren Zeitraum abstinente Amphetaminkonsumenten einen verminderten, persistierenden striatalen Glukose-metabolismus aufweisen. Die Autoren vermuten einen Zusammenhang mit psychopathologischen Auffälligkeiten dieser Konsumenten. Eine Metastudie von Marshall und Werb (87) bietet eine kritische Übersicht der aktuellen Studien mit Bezug auf Amphetaminkonsum und psychopathologischen Auffälligkeiten. Marshall und Werb kritisieren die mangelnde Kausalitätsbestimmung hinsichtlich der Assoziation von Amphetaminkonsum und psychopathologischen Auffälligkeiten, welche mit den bisherigen Querschnittstudien nicht hinreichend gelang. Eine prospektive Studie von Degenhardt und Mitarbeitern (88) konnte einen Zusammenhang zwischen frühem Amphetaminkonsum und der Entwicklung einer Depression nachweisen. Eine prospektive Studie aus Thailand (89) kam zu ähnlichen Resultaten, wobei die depressiven Symptome bei denjenigen, die ihren Amphetaminkonsum beendeten, weniger stark ausgeprägt waren. Die hier durchgeführte vorliegende Studie legt jedoch einen kausalen Zusammenhang zwischen einer global erhöhten Psychopathologie und nachfolgendem Amphetaminkonsum nahe, welcher bislang noch nicht beschrieben wurde. Eine Ergänzung der wissenschaftlichen Literatur mit prospektiven Studien bezüglich beginnender Konsumenten scheint somit fruchtvoll.

5.2. Limitationen

Die in der vorliegenden Arbeit vorgestellten Studien beinhalten einige Einschränkungen. Allgemein ist zu beachten, dass die Reihe der durchgeführten prospektiven Studien einen Zeitraum zwischen 12 und 24 Monaten des Konsums von MDMA und Amphetamin betrachten. Eine Unterscheidung zwischen subakuten und längerfristigen Folgen des Konsums wird damit erschwert. Es können somit nur bedingt Aussagen über persistierende Folgewirkungen des Konsums von MDMA und Amphetamin getroffen werden. Zudem verfügen die vorgelegten prospektiven Studien über kein experimentelles Design, die Konsumentengruppenzugehörigkeit der Probanden wurde nicht experimentell manipuliert. Direkte, experimentelle Studien zum Konsum von MDMA und Amphetamin zur definitiven Bestimmung der Kausalität sind aufgrund der ethischen Tragweite zumeist ausgeschlossen. Eine definitive Bewertung der Kausalität bezüglich der durchgeführten Studien ist somit erschwert. Die Klassifizierung der Probanden als starke Konsumenten durch eine Einnahme von 10 oder 15 MDMA-Tabletten kann zudem als willkürliches Kriterium betrachtet werden. Um Probanden mit einer hohen Wahrscheinlichkeit hinsichtlich zukünftigen MDMA-Konsums zu gewinnen und gleichzeitig die Effizienz der vorliegenden Studien zu garantieren, wurden Probanden rekrutiert, welche bereits über eine minimale Erfahrung mit MDMA und Amphetamin verfügten. Neuere Untersuchungen (90-92) legen jedoch nahe, dass bereits minimale MDMA-Exposition zu messbaren Veränderungen des serotonergen Systems führen könnten. Andere Studien konnten dies jedoch nicht bestätigen (60, 93). Eine weitere Einschränkung betrifft die Validität des von den Probanden berichteten Substanzkonsums innerhalb der 12 und 24 monatigen Testintervalle. Stichprobenartige Haaranalysen einiger zufällig ausgewählter Probanden bestätigten zwar, mit Ausnahme eines Probanden, grundsätzlich die Aussagen der Probanden zum Substanzkonsum. Mögliche fehlerhafte Aussagen zum Substanzkonsum aller Probanden sind damit aber nicht vollständig auszuräumen. Außerdem besteht Unklarheit hinsichtlich der Konzentration und Reinheit der

konsumierten Substanzen. Ergebnisse aus polizeilichen Untersuchungen zeigen allerdings, dass 99,65% der konfiszierten Ecstasy Tabletten eine einzige psychoaktive Substanz enthielten. Von diesen Tabletten enthielten schließlich 96,8% ausschließlich MDMA als psychoaktive Substanz (3). Zudem bringt der unter MDMA- und Amphetaminkonsumenten übliche Begleitkonsum von Cannabis weitere Einschränkungen mit sich. Cannabis ist ein biologisches Produkt, dessen Wirkstoffkomposition und Reinheitsgrad somit starken Schwankungen unterliegt. Die durch Probanden berichtete kumulative Lebenszeitdosis ist damit lediglich eine ungefähre Schätzung des Expositionswerts

5.3. Konklusion / Thesen

Zusammenfassend zeigt sich ein signifikanter Effekt des Konsums von MDMA auf das visuelle Paar-Assoziations-Lernen, welcher eine spezifische Vulnerabilität hippocampaler Hirnareale für schädigende Einflüsse des MDMA-Konsums nahelegt. Angesichts der Berücksichtigung einer Vielzahl potentieller störender Variablen könnte selbst moderater Freizeitkonsum von MDMA über einen relativ kurzen Zeitraum bedenklich sein. In Übereinstimmung damit zeigt sich eine mit moderatem MDMA-Konsum einhergehende Veränderung hippocampaler Aktivität, auch wenn ein möglicher moderierender Effekt von begleitendem Cannabiskonsum nicht ausgeschlossen werden kann. Darüber hinaus scheinen Personen mit global erhöhten psychopathologischen Parametern besonders vulnerabel für zukünftigen Amphetaminkonsum zu sein.

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7. Publikationen

Im Nachfolgenden sind die dieser Dissertationsschrift zu Grunde liegenden Veröffentlichungen aufgeführt und nachstehend angehängt. Die ersten beiden Arbeiten haben das Peer-Review-Verfahren erfolgreich durchlaufen und sind bereits akzeptiert und in den Zeitschriften *Addiction* (Impact-Factor: 4,313) und *Psychopharmacology* (Impact-Factor: 4,077) publiziert. Zum Zeitpunkt der Abgabe dieser Dissertationsschrift ist die dritte Arbeit bei der Zeitschrift *Addiction* eingereicht und befindet sich im Peer-Review-Verfahren.

Wagner D, Becker B. Koester P, Gouzoulis-Mayfrank E, Daumann J (2012) *A prospective study of learning, memory, and executive function in new MDMA users.* Addiction. 2012 Jul 26 [Epub ahead of print].

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7.1 Anteil des Kandidaten an den eingereichten Arbeiten

Die diesen Arbeiten zugrunde liegenden Prozessschritte von der Probandenrekrutierung, über die Planung und Durchführung der neurokognitiven, bildgebenden und psychopathologischen Testung, bis hin zur Dateneingabe und –pflege sind nach Rücksprache mit Herrn Prof. Dr. rer. nat. J. Daumann und Frau Prof. Dr. med. E. Gouzoulis-Mayfrank von mir mit Unterstützung durch Herrn Dr. rer. nat. B. Becker und Herrn M.Sc.-Psych. P. Köster durchgeführt worden. Die statistische Auswertung und Interpretation der neurokognitiven und bildgebenden Daten habe ich unter Einbeziehung fruchtbarer Diskussionen mit den oben genannten Koautoren eigenständig durchgeführt. Die vorliegenden wissenschaftlichen Publikationen zu Neurokognition und Psychopathologie habe ich, wiederum unter Einbeziehung konstruktiver Beratschlagungen mit den Koautoren, selbstständig verfasst. Hinsichtlich der bildgebenden Daten habe ich Herrn Dr. Dipl.-Psych. Benjamin Becker bei der statistischen Auswertung und der Interpretation, sowie bei der Erstellung des Manuskriptes maßgeblich unterstützt.

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A prospective study of learning, memory, and executive function in new MDMA users

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ABSTRACT

Aims It is still unclear if cognitive abnormalities in human 3,4-methylenedioxymeth-amphetamine (MDMA) users existed before the beginning of use or if other confounders could explain the deficits. The present study was conducted in order to assess the relationship between beginning MDMA use and subsequent cognitive performance and to overcome previous methodological shortcomings. **Design** A prospective cohort study in new MDMA users between 2006 and 2009 with a follow-up duration of 12 months. **Setting and Participants** Of the 149 almost MDMA-naive subjects examined at the initial assessment, 109 subjects participated again after 1 year. During this period, 43 subjects did not use any other illicit substance apart from cannabis; 23 subjects used more than 10 pills MDMA (mean = 33.6). These groups then were compared by means of multivariate analyses of variance. **Measurements** Change scores between the initial examination and follow-up on a neuropsychological test battery including measures of learning, memory, and frontal executive functions [Auditiv-Verbaler Lerntest (AVLT), Lern- und Gedächtnistest (LGT) 3, digit span test, digit symbol test, Stroop task, Trail-making test]. In addition, a comprehensive number of possibly relevant confounders including age, general intelligence, cannabis use, alcohol use, cigarette use, medical treatment, participation in sports, nutrition, sleep patterns and subjective wellbeing was assessed. **Findings** Groups did not differ in any of the potential confounders. However, significant effects of immediate and delayed recall of a visual paired associates learning task between MDMA users and controls were found (respectively, $F_{(1,64)} = 11.43$, $P = 0.001$, $\eta^2 = 0.136$ and $F_{(1,64)} = 11.08$, $P = 0.002$, $\eta^2 = 0.144$). No significant differences on the other neuropsychological tests were found. **Conclusions** MDMA appears to impair visual paired associates learning in new users, suggesting serotonergic dysfunction in hippocampal regions as a consequence of MDMA use.

Keywords 3,4-Methylenedioxymethamphetamine, cognition, MDMA, memory, neuropsychology, paired-associates learning.

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INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA), commonly referred to as 'ecstasy', is a psychostimulant drug which is popular among young adults. In Europe, the life-time prevalence of MDMA use is 5.6% in the 15–34-year-old population, with highest prevalence estimates in the United Kingdom (12.7%) [1]. For North America the life-time prevalence rates are generally estimated higher than in Europe [2]. MDMA is used illegally as a recreational drug, in particular by visitors of techno clubs and rave parties [3].

MDMA and related substances act primarily upon indirect serotonergic and dopaminergic mechanisms in the central nervous systems (CNS). Since the mid-1980s, repeated administrations of MDMA to experimental animals have suggested neurotoxic degeneration of serotonergic axon terminals followed by a decrease of 5-HT (5-hydroxytryptamine; serotonin) concentration in brain tissue [3]. This effect persists even after several years [4,5]. Studies investigating different markers of 5-HT [main metabolite in cerebral spinal fluid (5-hydroxyindoleacetic acid), 5-HT transporter density, postsynaptic 5-HT receptors] in human users, support

the hypothesis that the suggested neurotoxic potential of MDMA which was reported in laboratory animal research could be relevant to humans [5–10]. With this it is to be considered that, in contrast to the neurodegeneration hypotheses, neuroregulatory mechanisms are suggested to underlie MDMA-induced serotonergic dysfunction [11]. 5-HT is involved in many functional systems, including psychopathology, neuroendocrine and sleep regulation as well as regulation of vegetative functions. Additionally, a number of impairments in cognition and stimulus processing are conceivable as a consequence of MDMA-induced serotonergic dysfunction.

With regard to cognitive performance, a large number of cross-sectional studies and a handful of longitudinal investigations indicate that the most consistent findings have been decrements in memory and learning performance [12]. However, deficits in working memory, planning ability and central executive control, as well as high cognitive impulsivity, have also been reported [3,13,14].

In general, most studies on the cognitive effects of MDMA suffer from several methodological problems (e.g. pre-existing differences, polydrug use, differences in lifestyle). Therefore, a prospective methodological approach was applied in order to assess cognitive performance. In the present study, a comprehensive neuropsychological test battery was applied to assess cognitive performance over the course of 1 year in new MDMA users. In addition, a comprehensive number of possibly confounding variables including age, general intelligence, cannabis use, alcohol use, cigarette use, medical treatment, participation in sports, nutrition, sleep patterns and subjective wellbeing were explored and controlled for with regard to the statistical analyses. The goal was to address the following questions.

- Does the use of MDMA over a period of 1 year lead to a cognitive performance decrease?
- Which cognitive domains are most vulnerable to be affected by initial/incipient use of MDMA over a period of 1 year?
- Are the potential effects of initial/incipient MDMA use on cognitive impairments confounded by age, general intelligence, cannabis use, alcohol use, cigarette use, medical treatment, participation in sports, nutrition, sleep patterns and/or subjective wellbeing?

METHOD

Participants

One hundred and forty-nine new MDMA users with no current physical disorder and no current or previous history of neurological or psychiatric disorder (Axes I and II according to DSM-IV criteria; APA, 1994) were included in the study. Further exclusion criteria were the following: ingestion of any other illicit psychotropic substances besides cannabis on more than five occasions before the day of the first examination; a history of alcohol misuse (according to DSM-IV criteria, APA 1994); and regular medication (except for contraceptives). Main inclusion criterion at baseline was a high probability of future ecstasy use, operationalized as having first but very limited experience with MDMA (maximum five pills). After 12 months participants were invited back. Of the initial 149 subjects, 109 subjects [72 males, 37 females; age range at baseline: 18–35 years, mean: 23.42 years, standard deviation (SD) 4.76] participated in the second assessment. Cognitive assessment was carried out when participants were abstinent from cannabis on both study days in order to rule out acute intoxication effects. Given the fact that most MDMA users also use cannabis it would have been implausible to recruit MDMA users with a longer period of abstinence [15]. Furthermore, participants had to be abstinent from any other illicit substance for at least 7 days in order to rule out acute intoxication effects. Subjects were recruited via advertisements in magazines and newspapers and via notifications posted on campus. The study was part of a larger investigation including psychopathological and neuroimaging measures that will be submitted elsewhere. The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne.

Procedure

Preceding the cognitive assessment, written informed consent was given by all participants. This was followed by a structured interview developed in order to assess the use of illicit psychotropic substances. For all prevalent psychotropic substances, the interview included questions concerning the age of first use, the number of days since the last use, the average and maximal frequency of use measured in days per month, the estimated cumulative life-time dose, the average daily dose, the highest daily dose ever used and the duration of regular use measured in months [for the second assessment, the interview included questions concerning the following criteria: the age of first use (only assessed if the relevant substance had not been used before), the number of days since the last use, the average and maximal frequency of use measured in days per month last year, the estimated cumulative dose last year, the average daily dose last year, the highest daily dose last year and the duration of regular use measured in months last year]. Qualitative drug screens were performed on the day of the examination by means of urine samples for amphetamines, benzodiazepines, cocaine, methadone, MDMA and cannabis (enzyme-multiplied immunoassay; von Minden GmbH

Regensburg, Germany). Furthermore, hair samples were taken randomly in one-third (for economic reasons) of the participants and analysed for the substances MDMA, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxy-N-ethylamphetamine (MDEA), amphetamine, methamphetamine and cannabinoids by the Institute of Legal Medicine of the University of Cologne in order to verify the self-reported substance use. In addition, a questionnaire regarding health behaviour was used in order to control for confounding variables such as alcohol and cigarette use, sleep patterns, nutrition, participation in sports and subjective wellbeing (Fragebogen zur Erfassung des Gesundheitsverhaltens; FEG) [16].

Neuropsychological test battery

The selection of tests in the present study is based on the results of previous cross-sectional and longitudinal studies of MDMA users, which identified alterations in the areas of working memory, learning, memory and frontal executive functions.

Auditiv-Verbaler Lerntest AVLT

Verbal declarative memory performance was examined by the Auditiv-Verbaler Lerntest (AVLT) [17], which is a German version of the Rey Auditory Verbal Learning Test (RAVLT) [18]. This instrument assesses verbal declarative memory performance by means of immediate recall, total acquisition performance across five trials, recall after interference, loss after interference and recognition after 30 minutes.

Lern- und Gedächtnistest LGT 3

Figural visual recognition was assessed by a subtest of the Lern- und Gedächtnistest (LGT) [19], which is a classical paired associates learning task. The test contains 20 logos, each composed of a central figure and a surrounding frame. These logos were presented to the subjects on a sheet of paper for 60 seconds. Immediately thereafter (immediate recall) and after a delay of 1 hour (without a further learning trial—delayed recall), the central figures of the logos were presented combined with four options of frames. Subjects had to find the correct frame. This test has proved to be sensitive in identifying performance deficits in ecstasy users [9].

Digit-Span-Test

This classical working memory task is part of the Hamburg-Wechsler-Intelligenztest für Erwachsene (HAWIE-R) [20], a German version of the Wechsler Intelligence Test (WAIS) [21]. The experimenter reads out a sequence of digits to the participant, who has to recall the words immediately in reverse order.

Digit symbol test

This speed of information processing test consists of nine digit-symbol pairs (e.g. 1/-,2/⊥ . . . 7/Λ,8/X,9/=) followed by a list of 93 digits. Under each digit the subject is instructed to write down the corresponding symbol as quickly as possible. The number of correct symbols within 90 seconds is measured. The test is also part of the HAWIE-R [20], a German version of the WAIS [21].

Stroop task

In order to measure cognitive interference/inhibition, we used a German paper-and-pencil version of the classical Stroop task (Farbe-Wort-Interferenztest) [22,23]. This speed performance test consists of three different kinds of stimuli. In the first run, participants read out names of colours appearing in black ink. In the second run, they are instructed to name the given colour of rectangles. In the third run, names of colours appear in a different ink to the colour named, and the task is to name the colour of the ink. For each run participants are instructed to perform the task as quickly and accurately as possible. The experimenter records the times as well as the corrected and uncorrected errors.

Trail-making test

This test measures mental flexibility [24], and consists of two parts. In part A the participant is instructed to connect 25 circles on a sheet of paper using a ballpoint pen. These circles are numbered from 1 to 25, and participants are required to connect the circles in the correct order as quickly as possible. Part B presents both numbers (1–13) and letters (A–L), and requires the participant to connect numbers and letters alternately in the correct order (i.e. 1-A-2-B-3-C). For both parts the response time is recorded.

Raven Standard Progressive Matrices

In order to control for non-verbal general intelligence, the Raven Standard Progressive Matrices [25] were applied. This instrument comprises a series of diagrams or designs, each with a part missing. Subjects were instructed to select the correct part to complete the designs from a number of options printed beneath.

Statistical analyses

Two groups of subjects were defined: those who did not use any other illicit substance apart from cannabis over the course of the 1-year period (non-users) and those who used at least 10 ecstasy pills (MDMA users). This cut-off has also been used by other authors [26–28].

Subjects who used MDMA one or more times but less than the aforementioned amounts were not entered into the statistical analyses to ensure correctly separated groups. MDMA users and non-users were compared with regard to the following possible confounding variables by means of independent samples *t*-tests: age, general intelligence (Raven score), number of days since last cannabis use, duration of regular cannabis use before the initial assessment and duration of regular cannabis use between the first and the second assessment. Cannabis use was defined as duration of regular use because this measure, compared to age of first use, the average frequency of use, the cumulative life-time dose and the average dose per occasion, has been suggested to have the greatest impact on cognitive performance [29]. In order to operationalize health behaviour we performed a factor analysis (extraction method: principal component analysis; rotation method: varimax with Kaiser normalization) with all scores of the health behaviour questionnaire. The computed factor scores were also considered as potential confounders. Analogously, MDMA users and non-users were compared with regard to these variables by means of independent-samples *t*-tests.

Change scores of all cognitive variables were computed by subtracting the scores of the follow-up assessment from the baseline scores. Thereupon, we conducted three multivariate analyses of variance (MANOVA) with MDMA use (0 versus ≥10 pills) as fixed factor. The first MANOVA addressed attention and information processing speed (Trail making test part A, Stroop task parts A and B, digit symbol test). The second MANOVA addressed episodic memory (AVLT indices, LGT 3 indices). The third MANOVA addressed frontal/executive functioning indices (Trail making test part B, Stroop task part C, digit span test backwards). Moreover, we computed the effect size for each significant difference, operationally defined as η^2. All analyses were performed with IBM SPSS statistical software program version 19 (Chicago, IL, USA).

RESULTS

Health behaviour

Concerning the health behaviour questionnaire, the factor analysis (extraction method: principal component analysis; rotation method: varimax with Kaiser normalization) revealed six factors with an eigenvalue greater than 4. The explained percentage of variance, the numbers of items of each factor and the corresponding eigenvalue, as well as their thematic attribution, are given in Table 1. For each factor the corresponding score per subject was output as a new variable. MDMA users and non-users did not differ with regard to any of these variables. Therefore, it was not reasonable to include these variables in the following MANOVAs as covariate. Corresponding means, SDs and significance levels are also given in Table 1. For example, the variables that belong to the factor associated with subjective wellbeing consist of items such as 'On the following scale, please indicate how you rate your temporary wellbeing' ('. . . how satisfied you are with your . . .' life/job/partnership/leisure time, etc.).

Group characteristics

Of the initial 149 subjects who participated in the first assessment, 109 subjects participated in the second assessment after 1 year. Forty-three subjects did not use any other illicit substance apart from cannabis over the course of the 1-year period (non-users). Twenty-three subjects used more than 10 pills MDMA (MDMA users; mean = 33.6; SD = 7.2; range: 10–62; mean occasions: 13.5; SD = 10.1; range: 4–36). The remaining subjects used MDMA once or more but less than the aforementioned amount and were not included in the further analyses (see the paragraph on statistical analyses). For each group, gender distribution, mean age, mean years of education, mean duration of cannabis use before the first assessment, mean duration of cannabis use between the

Table 1 Factor analysis of the health behaviour questionnaire.

	Factor 1 (sleep)	*Factor 2 (alcohol use)*	*Factor 3 (sport/nutrition)*	*Factor 4 (subjective wellbeing)*	*Factor 5 (medical treatment)*	*Factor 6 (cigarette use)*
Variance explained	7.36%	5.52%	5.21%	5.12%	4.67%	4.45%
Number of items	13	14	10	10	9	8
Eigenvalue	9.13	6.94	6.46	6.35	5.80	5.39
Non-users	–0.18 (±0.92)	0.08 (±0.93)	–0.06 (±1.07)	–0.14 (±0.87)	–0.03 (±0.97)	0.05 (±0.90)
MDMA users	0.14 (±1.20)	–0.09 (±1.18)	0.25 (±0.73)	–0.14 (±1.19)	0.02 (±0.79)	–0.06 (±0.95)
T-/*P*-value[a]	–1.20/0.234	0.64/0.526	–1.26/0.165	0.02/0.983	–0.19/0.849	0.03/0.978

Explained percentage of variance, number of items, eigenvalues, and mean factor values for each users group relating to the factor analysis of the health behaviour questionnaire. Standard deviations are given in parenthesis (extraction method: principal component analysis; rotation method: varimax with Kaiser normalization). [a]Computed by means of independent-samples *t*-tests between mean factor values of non-users and MDMA users (d.f. = 64).

Table 2 Group characteristics.

	Female/male	*Age*	*Cannabis use at baseline*[a]	*Cannabis use within follow-up*[a]	*Days since last cannabis use*[b]	*Raven score*[c]
Non-users	15/28	23.45 (±4.30)	41.52 (±5.24)	5.39 (±0.87)	267.81 (±101.47)	6.59 (±1.07)
MDMA users	09/14	25.52 (±6.51)	44.96 (±12.66)	4.74 (±1.17)	311.26 (±131.51)	9.09 (±1.43)
T-/*P*-value[d]	0.117/733[e]	–1.44/0.155	–0.29/0.770	0.45/0.654	–0.26/0.798	–0.94/0.351

Frequency of gender, mean age, mean duration of cannabis use, mean days since last cannabis use and mean Raven score for each users group. Standard deviations are given in parenthesis. [a]Regular use measured in months. [b]Measured at second assessment. [c]Measure of general intelligence (lower scores indicate better performance). [d]Computed by means of independent-samples *t*-tests between non-users and 3,4-methylenedioxymethamphetamine-users (MDMA) users (d.f. = 64). [e]Computed by means of χ^2 test.

Table 3 Concomitant illicit substance use.

	Cocaine[a]	*Hallucinogens*[b]	*Sedatives*[b]	*Solvents/inhalants*[b]	*Amphetamine*[a]	*Opioids*[b]
Non-users	0.52 (±1.55)	0.06 (±0.25)	0.06 (±0.25)	0.13 (±0.34)	2.9 (±5.40)	0 (±0)
MDMA users	1.04 (±2.42)	0.22 (±1.04)	0 (±0)	0.04 (±0.21)	26.55 (±33.91)	0.13 (±0.34)
T-/*P*-value[c]	–0.43/0.671	–0.55/0.586	1.06/0.295	0.75/0.941	–3.46/0.002	–1.82/0.083

Mean cocaine, hallucinogens, sedatives, solvents/inhalants, amphetamine and opioids use for each users group between the first and the second assessment. Standard deviations are given in parenthesis. [a]Cumulative use between both assessments measured in grams. [b]Cumulative use between both assessments measured in occasions. [c]Computed by means of independent-samples *t*-tests between non-users and 3,4-methylenedioxymethamphetamine-users (MDMA) users (d.f. = 64).

first and the second assessments, mean days since last cannabis use at the second assessment, RAVEN score and corresponding SDs are given in Table 2. The groups did not differ significantly with respect to any of the variables. Therefore, it was not reasonable to include any of the aforementioned covariates in the following analyses. Corresponding significance levels are also given in Table 2. Moreover, there was no considerable use of cocaine, hallucinogens, sedatives, solvents/inhalants or opioids in the sample. In addition, the groups (user, non-user) did not differ with regard to their use of these substances. Therefore, it was not reasonable to enter these variables as covariates in the multivariate analysis. As usual in MDMA users' samples, there was a high concomitant use of amphetamine (correlation MDMA and amphetamine use: $r = 0.571$, $P = 0.004$). Corresponding means and standard deviations of concomitant substance use are given in Table 3. Urine screens of all participants that were included in the analyses were free of amphetamines, benzodiazepines, cocaine, methadone and MDMA. Additionally, hair samples taken randomly by the Institute of Legal Medicine of the University of Cologne confirmed the self-reported substance use in all cases but one (which was excluded from the analyses).

Performance effects

The MANOVA addressing attention and information processing speed revealed no significant main effect of group (non-users versus MDMA users) ($F_{(4,61)} = 2.06$, $P = 0.097$). Mean test scores for both groups as well as significance levels of the corresponding tests of between-subjects effects are given in Table 4. The MANOVA addressing episodic memory revealed a significant main effect of group ($F_{(8,57)} = 2.23$, $P = 0.043$). The corresponding tests of between-subjects effects revealed significant effects of immediate recall ($F_{(1,64)} = 11.43$, $P = 0.001$, $\eta^2 = 0.136$) and delayed recall ($F_{(1,64)} = 11.08$, $P = 0.002$, $\eta^2 = 0.144$) of the LGT 3, but not for any AVLT variable. Mean test scores for MDMA users and non-users as well as significance levels of the corresponding tests of between-subjects effects are given in Table 5. Additionally, for each group, means and standard deviations of both LGT 3 variables are given in Fig. 1. The MANOVA addressing frontal/executive functioning indices revealed no significant main effect of group ($F_{(3,62)} = 2.69$, $P = 0.054$). Mean neuropsychological test scores for MDMA users and non-users as well as significance levels of the corresponding tests of between-subjects effects are given in Table 6. When entering amphetamine use as a covariate into the multivariate analysis, the corresponding effects did not remain significant. However, an analogous multivariate analysis with amphetamine use as grouping variable (0 versus 5 g) revealed no significant effects.

DISCUSSION

The aim of the present investigation was to examine the nature of cognitive deficits in new ecstasy users over the course of a 1-year-period. A neuropsychological test

Table 4 Mean neuropsychological test scores for 3,4-methylenedioxymethamphetamine (MDMA) users and non-users related to attention and information processing speed.

	MDMA users			*Non-users*				
	Mean (SD) (n = 23)			*Mean (SD) (n = 43)*				
Test	*Baseline*	*Follow-up*	*Change score*	*Baseline*	*Follow-up*	*Change score*	*Sig.**	*Hedge's G*
Trail making test A	26.8 (7.2)	24.0 (10.4)	−2.87 (9.5)	25.4 (7.5)	22.3 (6.3)	−3.06 (8.6)	0.935	0.021
Stroop task A[a]	28.1 (4.2)	27.6 (8.8)	−0.56 (7.2)	29.3 (6.6)	27.2 (4.1)	−2.11 (6.9)	0.398	0.221
Stroop task B[b]	46.4 (9.5)	43.5 (7.98)	−2.90 (5.5)	44.5 (7.5)	42.4 (6.6)	−2.00 (4.2)	0.465	−0.192
Digit symbol test	60.8 (9.9)	63.8 (10.2)	3.00 (4.6)	64.3 (10.4)	69.0 (10.3)	4.67 (5.0)	0.189	−0.343

**P*-values refer to tests of between-subjects effects of the corresponding multivariate analyses of variance (MANOVA). [a]Stroop task A: reading condition. [b]Stroop task B: colour naming condition. SD: standard deviation.

Table 5 Mean neuropsychological test scores for 3,4-methylenedioxymethamphetamine (MDMA) users and non-users related to episodic memory.

	MDMA users			*Non-users*				
	Mean (SD) (n = 23)			*Mean (SD) (n = 43)*				
Test	*Baseline*	*Follow-up*	*Change score*	*Baseline*	*Follow-up*	*Change score*	*Sig.**	*Hedge's G*
RAVLT A[a]	7.17 (2.3)	6.91 (1.7)	−0.26 (2.9)	7.49 (1.9)	7.40 (2.2)	−0.09 (2.4)	0.919	−0.066
RAVLT B[b]	52.9 (9.8)	53.3 (8.4)	0.35 (9.6)	56.0 (8.0)	56.6 (8.2)	0.61 (6.5)	0.553	−0.034
RAVLT C[c]	11.4 (2.1)	11.1 (2.1)	−0.31 (2.1)	12.0 (2.5)	12.3 (2.9)	0.30 (2.7)	0.438	−0.243
RAVLT D[d]	1.48 (1.7)	1.57 (2.4)	0.09 (2.1)	1.65 (1.7)	1.51 (1.8)	−0.14 (2.6)	0.789	−0.094
RAVLT E[e]	13.9 (1.5)	13.7 (1.2)	−0.17 (1.3)	14.0 (1.8)	14.1 (1.5)	0.05 (2.0)	0.378	−0.123
RAVLT F[f]	4.65 (0.7)	4.26 (1.2)	−0.39 (1.1)	4.21 (1.1)	4.14 (1.1)	−0.07 (1.2)	0.280	−0.274
LGT 3 logos A[g]	12.4 (3.9)	10.7 (2.9)	−1.78 (3.5)	12.3 (3.6)	12.6 (2.9)	0.26 (2.8)	**0.001**	**−0.667**
LGT 3 logos B[h]	11.8 (4.0)	10.4 (3.3)	−1.35 (3.4)	11.2 (3.9)	12.3 (3.2)	1.09 (3.2)	**0.002**	**−0.746**

**P*-values refer to tests of between-subjects effects of the corresponding multivariate analyses of variance (MANOVA). Significant *P*-values are given in bold. [a] Rey Auditory Verbal Learning Test (RAVLT) A: immediate recall. [b]RAVLT B: total acquisition. [c]RAVLT C: recall after interference. [d]RAVLT D: loss after interference. [e]RAVLT E: recognition performance. [f]RAVLT F: repetitions required for learning. [g] Lern- und Gedächtnistest (LGT) 3 A: immediate recall. [h]LGT 3 B: delayed recall. SD: standard deviation.

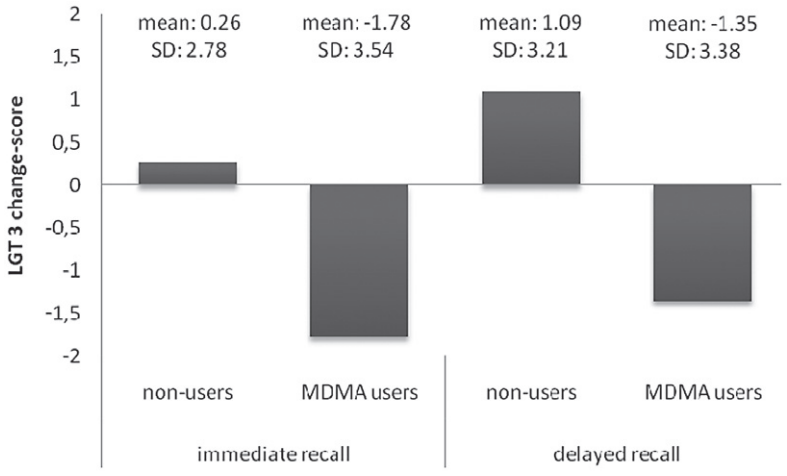

Figure 1 Means and standard deviations of both immediate and delayed recall Lern- und Gedächtnistest (LGT) 3 change scores for non-users and 3,4-methylenedioxymethamphetamine (MDMA)users

Table 6 Mean neuropsychological test scores for 3,4-methylenedioxymethamphetamine (MDMA) users and non-users related to frontal/executive functioning indices.

	MDMA users			*Non-users*				
	Mean (SD) (n = 23)			*Mean (SD) (n = 43)*				
Test	*Baseline*	*Follow-up*	*Change score*	*Baseline*	*Follow-up*	*Change score*	*Sig.**	*Hedge's G*
Trail making test B	69.4 (22.2)	57.8 (25.9)	−11.6 (19.5)	63.1 (21.0)	50.8 (18.3)	−12.3 (18.4)	0.881	0.037
Stroop task C[a]	78.3 (16.1)	67.8 (18.6)	−10.5 (14.2)	72.1 (13.0)	67.7 (11.7)	−4.46 (10.0)	0.051	−0.520
Digit-span backwards	7.65 (2.3)	8.57 (2.6)	0.91 (1.93)	8.02 (1.9)	8.02 (2.3)	0.00 (2.3)	0.107	0.417

**P*-values refer to tests of between-subjects effects of the corresponding multivariate analyses of variance (MANOVA). [a]Stroop task C: interference condition. SD: standard deviation.

battery including tests of learning, memory, working memory and executive functions was administered to 149 subjects, of whom 109 participated in the second assessment after 1 year. In addition, there were no statistically significant differences on a comprehensive number of possibly relevant confounders including age, general intelligence, cannabis use, alcohol use, cigarette use, medical treatment, participation in sports, nutrition, sleep patterns and subjective wellbeing. Significant effects of immediate and delayed recall of a paired associates learning task between subjects who used 10 or more ecstasy pills and subjects who did not use any illicit substance apart from cannabis during the course of the year (non-users) were found. No significant differences were found on any of the other neuropsychological tests.

Deficits in visual and associative learning among ecstasy users have been described previously [9,30–33]. Due to the cross-sectional design of available studies, it was not possible to determine whether the found alterations existed before initiation of use or whether concomitant health behaviour variables were responsible for a percentage of the deficits. In addition, the role of concomitant use of cannabis in this context was not fully understood. In the present study, these methodological concerns were dispelled and a comparably large sample was investigated. Most intriguingly, although pre-existing group differences were ruled out and a comprehensive number of possible confounders were controlled for, the effects of ecstasy on paired associates learning remained significant despite the relatively short time-period (1 year) and the amounts of MDMA used (10–60 pills MDMA, mean: 32.44). Keeping in mind that no significant effect of MDMA on any other cognitive variable was found in the present study, the results indicate a specific effect of relative small amounts of MDMA on paired associates learning. This finding is consistent with the findings of Brown and colleagues [34], who also found significant deficits on an associate learning task in the absence of deficits on other memory tasks. Whether or not the influence of MDMA on other cognitive variables becomes significant with increasing time-periods and amount of use remains unclear, and is a promising hypothesis for future longitudinal investigations. In this respect, our results are inconsistent with the conclusions made by Halpern and colleagues [35]. They suggested that their findings 'might instead reflect correctly that illicit ecstasy use, by itself, does not generally produce lasting residual neurotoxicity'. Potential reasons for the discrepant results could be found in the nature of the samples and the choice of measures that were administered. Because these issues have been already discussed extensively, we refer to the corresponding publications [36–38].

With regard to the intercorrelation between MDMA and amphetamine use in our MDMA users sample, it is unclear if the decrements in visual relational memory can be ascribed to the use of MDMA alone or to the polydrug use of MDMA and amphetamine. However, Gouzoulis-Mayfrank and colleagues [9] reported a significant influence of MDMA use on the immediate and delayed recall score in the same test that was used in the present study. Interestingly, in their sample it was possible to ascribe the effects to MDMA use by means of linear stepwise regression analysis. Therefore, it seems most likely that the decrements in visual relational memory can be ascribed to the use of MDMA rather than to the polydrug use of MDMA and amphetamine. Furthermore, after taking into account the potential effect of the use of other illicit drugs by means of multiple regression analyses, Schilt and colleagues [27] reported that ecstasy use was dose-related to verbal memory impairments, and there was still a significant association thereof.

Given that the hippocampus plays a fundamental role in relational memory [39], the findings of the present study support the hypothesis that the neural basis for the detrimental effects of MDMA on neurocognition appears to be a hippocampal dysfunction. Studies using animal models have shown that MDMA causes selective and persistent lesions of central serotonergic nerve terminals [4,5,40–42]. In addition, Kish and colleagues reported serotonin transporter changes in human MDMA users

[43]. In particular, the hippocampus and parahippocampus display relatively high rates of serotonergic denervation after MDMA exposure [4]. Moreover, serotonin plays a central role in hippocampal neurogenesis inherent to learning and memory processes [44]. As a result, Gouzoulis-Mayfrank and colleagues [9] proposed that this may explain why hippocampal systems might be more sensitive to serotonin depletion than neocortical brain regions. Furthermore, it possibly accounts for the pattern of cognitive performance in ecstasy users with more consistent decrements in memory and learning performance compared to other cognitive domains that are dependent only on neocortical function. As mentioned previously, Brown and colleagues [34] also found significant deficits on an associate learning task in the absence of deficits on other memory tasks. However, they also found no deficits in ecstasy users on tests which have been shown to be more specific to the hippocampus and therefore interpreted their findings to complex interactions between multiple brain regions including the prefrontal cortex rather than to the hippocampus alone. The contributory role of other brain areas has also been illustrated by Burgess and colleagues who found reduced left parietal lobe activity during word recognition in abstinent MDMA users [45].

The underlying molecular mechanisms of these long-term effects have yet to be elucidated. Studies in laboratory animals have supported the involvement of oxidative stress in MDMA neurotoxicity by decreasing the levels of antioxidants in serotonergic terminals [46,47]. Additionally, mitochondrial dysfunction and hyperthermia have been associated with administration of MDMA and subsequent toxicity to serotonergic terminals. Moreover, inflammatory cytokines, the ubiquitin proteasome system, environmental stress, neurotrophic factors and apoptotic proteins have been reported recently as potential mediators of MDMA toxicity that may also explain the terminal as the somatic degeneration [47]. In addition, by affecting basal synaptic transmission and long-term potentiation (LTP; an activity-induced increase in synaptic efficacy) via activation of serotonin receptors systems in the hippocampus, decreases in memory performance seem likely. Deciphering these molecular mechanisms is a promising task for further research. Moreover, neuroregulatory mechanisms are suggested to underlie MDMA-induced serotonergic dysfunction rather than neurodegeneration [11]. Similarly, this issue is an important target for future studies.

There are some methodological limitations which are inherent to open-trial studies and are outlined below. First of all, although we chose a prospective approach, the design was not experimental and therefore a causal relationship between MDMA use and decline in paired associates learning may not be presumed as a matter of course. Additionally, for reasons of practicability the minimal abstinence period from cannabis in the present study was 12 hours. Therefore, we cannot rule out an impure distinction between subacute and long-term effects of cannabis use. However, the mean time since last cannabis use did not differ between MDMA users and controls. Furthermore, the quantity of use was reported by the participants themselves. Nevertheless, studies validating self-reported voluntary substance use found a high reliability of the reported drug quantity [48–50]. Additionally, hair samples taken randomly by the Institute of Legal Medicine of the University of Cologne confirmed the self-reported substance use in all cases but one (which was excluded from the analyses). Another limitation concerns the concentration and purity of illicit drugs and their mode of consumption. However, evidence from German police seizures suggest that 99.65% of the confiscated ecstasy pills in 2008 contained only one psychoactive ingredient. MDMA was found in 96.8% of the confiscated ecstasy pills. The remaining share of 3.2% of the confiscated ecstasy pills consisted of 1-(3-chlorphenyl)-piperazine (m-CPP), amphetamines, methamphetamine or MDA [51]. Cannabis is a natural product, inherently variable in its strength and composition. Therefore, estimates of the life-time cumulative exposure of illicit drugs represent only crude approximations of actual exposure [3,52]. Furthermore, subjects were aware that their drug use was critical to the research design, and this awareness may have caused selection bias or created expectation effects, and subjects who took ecstasy may have experienced anxiety about confirming [53]. However, the significant differences were found specifically in paired associates learning, and not in other domains of cognitive functioning.

In conclusion, a significant effect of MDMA use on visual paired associates learning was found, suggesting specific deterioration of hippocampal functioning. Given the fact that memory impairments remained significant after controlling for a large variety of confounders, our findings may raise concerns with regard to MDMA use, even in recreational amounts over a relatively short time-period.

Declarations of interest

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constituting a potential conflict of interest. This pertains to all the authors of the study, their spouses or partners and their children (aged under 18).

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ORIGINAL INVESTIGATION

Memory-related hippocampal functioning in ecstasy and amphetamine users

A prospective fMRI study

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Abstract
Rationale Recreational use of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) has been associated with memory impairments. Functional neuroimaging studies with cross-sectional designs reported altered memory-related hippocampal functioning in ecstasy-polydrug users. However, differences might be pre-existing or related to the concomitant use of amphetamine.
Objective To prospectively investigate the specific effects of ecstasy on memory-related hippocampal functioning.
Methods We used an associative memory task and functional magnetic resonance imaging (fMRI) in 40 ecstasy and/or amphetamine users at baseline (t1) and after 12 months (t2). At t1, all subjects had very limited amphetamine and/or ecstasy experience (less than 5 units lifetime dose). Based on the reported drug use at t2, subjects with continued ecstasy and/or amphetamine use (n=17) were compared to subjects who stopped use after t1 (n=12).
Results Analysis of repeated measures revealed that encoding-related activity in the left parahippocampal gyrus changed differentially between the groups. Activity in this region increased in abstinent subjects from t1 to t2, however, decreased in subjects with continued use. Decreases within the left parahippocampal gyrus were associated with the use of ecstasy, but not amphetamine, during the follow-up period. However, there were no significant differences in memory performance.
Conclusions The current findings suggest specific effects of ecstasy use on memory-related hippocampal functioning. However, alternative explanations such as (sub-)acute cannabis effects are conceivable.

Keywords Amphetamine · Cognition · Ecstasy · fMRI · Hippocampus · Longitudinal design

Introduction

The popular recreational drug "ecstasy" (3,4-methylenedioxymethamphetamine [MDMA]) causes selective and persistent lesions to central serotonergic nerve terminals in laboratory animals (Fischer et al. 1995; Green et al. 2003; Hatzidimitriou et al. 1999). Although these data cannot be extrapolated directly to human recreational users, a growing number of studies suggest that MDMA might be harmful to the serotonergic system in humans. Several studies reported subtle abnormalities in psychological and neurocognitive functioning in MDMA users that might reflect functional sequelae of long-lasting alterations in serotonergic systems (Gouzoulis-Mayfrank and Daumann 2006a; Green et al. 2003; Parrott 2000; Reneman et al. 2006; Schilt et al. 2007). Recent reviews and well-controlled studies suggest ecstasy-specific impairments in learning and memory (Fox et al. 2002; Gouzoulis-Mayfrank and Daumann 2009;

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Gouzoulis-Mayfrank et al. 2003; Kalechstein et al. 2007; Schilt et al. 2007, 2008; Zakzanis et al. 2007; but see Halpern et al. 2011). Given this selective pattern of mnemonic impairments, the authors consistently suggested that dysfunctions in the hippocampal formation might represent the neuroanatomical basis of memory deficits in ecstasy users. However, in some studies ecstasy users demonstrated impairments in memory functions primarily associated with the frontal cortex (Brown et al. 2010; Quednow et al. 2006). These findings might suggest that memory deficits in ecstasy users are not only the result of hippocampal dysfunction, but also of dysfunction of frontal regions.

In recent years, functional magnetic resonance imaging (fMRI) has increasingly been used to investigate the neural correlates of ecstasy-associated memory impairments. Ecstasy users displayed abnormal neural activity in the associative memory-related network, including (para-)hippocampal regions (Daumann et al. 2005; Roberts et al. 2009). However, findings from a recent study addressing the specific effects of ecstasy and other drugs of abuse on cognitive brain function could not confirm specific effects of ecstasy on hippocampal functioning (Jager et al. 2008). In this study memory impairments and hippocampal dysfunctions were associated with the use of amphetamine, a drug commonly co-used by ecstasy users.

Moreover, methodological problems hamper the interpretation of previous fMRI studies. In particular the lack of pre-use data, poorly matched controls and the widespread co-use of cannabis and amphetamine in ecstasy users represent important confounding factors (Gouzoulis-Mayfrank and Daumann 2006b; Lyvers 2006; Pedersen and Skrondal 1999). In addition, the generalizability of findings remains limited because most studies focused on heavy users. Summarizing, results regarding the effects of ecstasy use on functional brain activity and the neuroanatomical basis of ecstasy-associated memory impairments remain inconclusive.

The aim of the present study therefore was to investigate the specific effects of moderate ecstasy use on memory-related brain function. Based on previous studies in this field of research, effects in hippocampal regions were of particular interest. To control for known confounders in this field of research, a prospective longitudinal design with moderate users of ecstasy and amphetamine was incorporated. Specific effects of ecstasy and commonly co-used amphetamine were disentangled estimating dose–response relationship.

Materials and methods

Participants

Subjects in the present study were part of a larger prospective study on the effects of recreational drug use. A subsample of 50 participants was examined at baseline (t1) and after an interval of 12 months (t2) using fMRI. Main inclusion criterion at baseline was a high probability of future ecstasy and/or amphetamine use, operationalized as having "first but very limited experience with ecstasy and/or amphetamine." Exclusion criteria at baseline were: (1) having used more than five ecstasy tablets and/or 5 g amphetamine, (2) use of all other illicit substances except for cannabis, (3) childhood diagnosis of attention-deficit hyperactivity disorder (ADHD) and (4) any current or previous axis I psychiatric diagnosis (exceptions: nicotine dependence, cannabis abuse and dependence). Further exclusion criteria on both study days were: (1) history of alcohol abuse and/or dependence (according to DSM IV, APA 1994), (2) regular intake of any medication (regular use was defined as using the medication at least once a week), (3) intake of any psychotropic substances except for cannabis 7 days prior to testing, (4) use of cannabis on the day of the examination. Additional exclusion criteria for the fMRI investigation were (1) left-handedness, (2) pregnancy and (3) other known contraindications for MRI scanning.

Procedure

Following a detailed study description, written informed consent was obtained from all participants. All subjects subsequently underwent a structured interview according to the DSM IV. To exclude participants with childhood ADHD, all participants completed the German version of the Wender Utah Rating Scale (WURS) (Ward et al. 1993) and were excluded if they exceeded the recommended cut-off score (Ward et al. 1993). On both study days, subjects underwent a detailed structured interview assessing the use of amphetamine and ecstasy, including the following parameters of use: (1) age of first use, (2) time since the last use in days, (3) average frequency of use measured by average days of use per month, (4) maximum days of use per month ever, (5) estimated cumulative lifetime dose, as well as (6) average and (7) highest daily or one night dose ever used. Studies validating self-reported voluntary substance use found a high reliability of the reported drug quantity (Martin et al. 1988; Rothe et al. 1997). Randomly taken hair samples from approximately 50 % of study participants were analyzed for amphetamines (amphetamine, methamphetamine, MDMA, 3,4-methylenedioxyamphetamine [MDA], 3,4-methylenedioxy-*N*-ethylamphetamine [MDEA]) and cannabinoids (tetrahydrocannabinol [THC], cannabidiol [CBD], cannabinol [CBN]) by the Institute of Legal Medicine of the University of Cologne (detailed information on the analysis protocols are given in the Supplementary information). Results from this quantitative analysis confirmed the self-reported substance use patterns. Qualitative drug screens were performed on the day of the

examination with urine samples for amphetamines, benzodiazepines, cocaine, methadone, MDMA and cannabis (enzyme-multiplied immunoassay; von Minden GmbH). In order to control for confounding variables, concomitant substance use and health behaviour were assessed on both study days. Current intellectual functioning was assessed by the Raven Standard Progressive Matrices (Raven 2000). Cannabis use was assessed by a cannabis-specific version of the drug interview. Additionally, the following aspects were assessed: (1) use of alcohol and tobacco (frequency of alcoholic drinks per week, cigarettes per week, years of tobacco use), (2) use of medication (number of uses: hypnotic, analgesic, stimulating and sedative medications per week) and (3) sleep (hours of sleep per night, frequency of sleep problems).

The study was in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee of the Medical Faculty of the University of Cologne.

Associative memory task

On both study days, participants performed an associative memory task. In a previous study, this task was used to assess differences in hippocampal functioning between ecstasy users and controls (for details, see Daumann et al. 2005). Briefly, the associative memory fMRI-paradigm consisted of two encoding and one retrieval fMRI time-series. A blocked periodic design was used with alternating active and control conditions. Participants learned 16 visually presented face–profession combinations in the active condition of the encoding runs. During the active condition of the retrieval run the 16 faces were displayed without the profession. Participants then had to indicate to which of two given categories (academic or artistic) they belonged. In the control condition, facial contours were displayed. During the retrieval condition, participants had to indicate whether the left or right ear of the contour was larger. Total scanning time was 8:15 min.

Imaging parameters

fMRI data was acquired on a clinical 1.5-T Philips ACS NT Gyroscan (Philips, The Netherlands) using a single-shot multislice T2* weighted gradient echo EPI sequence (imaging parameters: TR, 3,000 ms; TE, 50 ms; flip angle, 90°; matrix, 64×64; field of view, 192×192 mm, 30 contiguous slices parallel to the AC–PC line covering the whole brain; voxel size, 4×4×7 mm, no interslice gap). A total of 56 dynamic scans for each of the two encoding runs and the retrieval run were recorded. Each time-series was preceded by five dummy scans to allow for equilibration of the MRI signal. For anatomic reference and to exclude subjects with apparent brain pathologies, a T1-weighted Fast Field Echo sequence (imaging parameters: TR, 25 ms; TE, 4.6 ms; TI, 400 ms; flip angle, 30°; matrix, 256×256; slice thickness, 2 mm) was obtained. Images were acquired using a standard head coil.

Data analysis

To obtain information about the impact of continued ecstasy and amphetamine use on cognitive performance and associated neural activity, the sample was divided into two groups: (1) users who completely stopped ecstasy and/or amphetamine use after t1 (controls), and (2) users who continued use after t1 (at least five ecstasy tablets and/or 5 g amphetamine in the 12-month follow-up period) (users). In line with previous research strategies in ecstasy users (Bedi and Redman 2008; Parrott et al. 1998; Daumann et al. 2004), subjects with only sporadic use after t1 were excluded from further analysis. Between-group differences for age, education, substance use, potential confounders (use of alcohol (frequency of alcoholic drinks per week), nicotine (years of tobacco use, cigarettes per week), and medication (frequency of hypnotic, analgesic, stimulating and sedative medications per week), as well as the quality of sleep (hours of sleep per night, frequency of sleep problems) and performance were analyzed by means of unpaired Student *t*-tests; in case the normality assumption was violated by means of Mann–Whitney *U*-test. Gender distribution was analyzed by means of Pearson χ^2 test. Differences in performance between both study days were analyzed by means of repeated measures analyses of variance (ANOVA) with the between-subject factor GROUP (controls vs. users) and the within-subject factor TIME (t1 vs. t2). In addition, change scores between t1 and t2 were computed. Analyses were computed using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL).

Functional magnetic resonance imaging data were preprocessed and analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Images were initially realigned to the first image of each scan. Mean images were subsequently normalized with the SPM5 MNI template (resampled to 2×2×2 mm^3 voxels), and smoothed with a Gaussian kernel (triple voxel size). Raw time-series were detrended by the application of a high-pass filter (cutoff period: 128 s). The preprocessed data were analyzed using a two stage procedure for repeated measures ANOVA (Henson and Penny 2003). Separate analyses of the two identical encoding runs revealed similar activation patterns. Consequently, the encoding runs were summarized on the first level analysis. In an initial step, subject-specific changes in BOLD response were assessed using linear contrasts of the GLM parameters. To explore between-group differences at baseline, contrasts of task were entered into separate two-sample *t*-tests. Separate contrasts for the main

effects of task and time (t1, t2) were computed for each subject. Main effects of the factors GROUP and TIME and interaction effects of the factors GROUP × TIME were computed entering the appropriate first level contrasts in two-sample *t*-tests.

Because of our a priori hypothesis, analyses were restricted to anatomically defined task-specific regions of interest (ROI) (WFU pickatlas (Maldjian et al. 2003, 2004; Tzourio-Mazoyer et al. 2002). Based on findings from previous studies analyses were restricted to the hippocampus and parahippocampus. All analyses were computed with the standard threshold of $p<0.05$ and corrected for multiple comparisons (family-wise error [FWE]). For the ROI analyses the FWE correction was implemented in a small volume correction, based on the size of the ROIs. Minimum cluster size was set to ten voxels.

Results

Participants and group-assignment

Of the 50 users who participated in the fMRI investigation at baseline, 40 users (30 males, ten females; age range at baseline: 18–30 years, mean: 22.30 years, SD: 3.48) could be re-examined at follow-up (86 %). Ten participants dropped out because they either moved without giving notice of their new address ($n=7$), simply lost interest in the study ($n=2$), or developed a manifest psychiatric disorder ($n=1$). From the 40 users who could be re-examined, 12 had stopped to use ecstasy and amphetamine after t1 and served as a control group (CG). Seventeen participants fulfilled the criteria for continued use of ecstasy and/or amphetamine during the follow-up period (at least five ecstasy tablets and/or 5 g amphetamine between baseline and follow-up) (UG). Eleven participants reported only sporadic use of ecstasy and/or amphetamine during the follow-up period and therefore, were excluded from the analyses (for completeness demographic data and drug use patterns of the sporadic user group [SG] are presented in Tables 1, 2 and 3).

Demographics, drug use and confounders at baseline

The experimental groups were of comparable age ($t(27)=0.54$, $p=0.60$), education ($t(27)=0.34$, $p=0.74$) and gender distribution (Pearson $\chi^2(1, n=29)=0.513$, $p=0.474$) and reported similar patterns of previous ecstasy and amphetamine use at baseline. At baseline UG had used more amphetamine ($t(27)=-2.19$, $p=0.04$) and reported a shorter time since the last use of ecstasy ($t(27)=2.81$, $p=0.01$) and amphetamine ($t(24)=2.16$, $p=0.04$). Analysis of potential confounding variables at baseline yielded no significant between-group differences in current intellectual functioning ($t(27)=0.17$, $p=0.86$), quality of sleep (average hours of sleep: $t(27)=-0.14$, $p=0.89$, frequency of sleep problems: $t(27)=0.23$, $p=0.82$). Moreover, the groups reported comparable use of cannabis (all $p>0.13$), alcohol ($t(27)=0.82$, $p=0.42$), nicotine (cigarettes per week: $t(27)=-0.57$, $p=0.57$; years of use: $t(27)=0.20$, $p=0.84$) and medication (mean number of uses per week: hypnotic medication — UG, 0.20, SD 0.07; CG, 0.00, SD 0.00, $t(27)=1.16$, $p=0.26$; analgesic medication — UG, 0.13, SD 0.38; CG, 0.08, SD 0.03, $t(27)=0.90$, $p=0.38$; stimulating medication — UG, 0.02, SD 0.07; CG, 0.47, SD 0.10, $t(27)=-0.76$, $p=0.45$; sedative medication — UG, 0.05, SD 0.11; CG, 0.03, SD 0.02, $t(27)=0.40$, $p=0.69$) (for details on demographics and drug use patterns at baseline, see Tables 1 and 3).

Patterns of interim drug use

Interim abstinent users reported complete abstinence from ecstasy and amphetamine at follow-up, but continued to use cannabis. Although, a direct between-group comparison revealed no significant differences in any parameter of interim cannabis use (all $p>0.192$), the UG reported a higher interim cumulative cannabis dose (mean interim dose in grams: UG, 146.65, SD 194.06; CG, 71.56, SD 100.98). In addition, the CG reported a substantial shorter time since last cannabis use (mean time since last use in days: UG, 25.40, SD 76.44; CG, 13, SD 100.98). Analysis of further potential confounding variables at follow-up yielded no significant between-group differences regarding the use of alcohol ($t(27)=-0.11$, $p=0.92$), nicotine ($t(27)=0.27$, $p=0.79$), and medication (mean number of uses per week: hypnotic medication: UG, 0.10, SD 0.17; CG, 0.06, SD 0.14, $t(27)=0.77$, $p=0.45$; analgesic medication: UG, 0.20, SD 0.19; CG, 0.16, SD 0.18, $t(27)=0.56$, $p=0.58$; stimulating medication: UG, 0.04, SD 0.09; CG, 0.47, SD 0.10, $t(27)=-0.14$, $p=0.89$; sedative medication: UG, 0.06, SD 0.09; CG, 0.03, SD 0.08, $t(27)=0.68$, $p=0.50$) (for details on interim drug use patterns, see Tables 2 and 3).

Performance

Repeated-measures ANOVA with group (users vs. controls) as between-subject factor and time point (t1 vs. t2) revealed neither a significant main effect of group and time point and no significant interaction on associative memory performance (all $p>0.102$) (Fig. 1). Additional analysis of change scores (t2−t1) revealed that both groups showed improved performance at t2 and that improvements were larger in the controls (UG, mean, 1.12, SD, 3.67; CG, mean, 2.00, SD, 2.95; estimated effect size using Cohen's $d=0.27$, $r=0.13$). However, within- and between-group differences failed to reach statistical significance (all $p>0.48$).

Table 1 Baseline demographic features and drug use patterns of interim abstinent users (controls, $n=12$), users who continued using ecstasy and/or amphetamine (user, $n=17$) and sporadic users (sporadic, $n=11$)

	Controls ($n=12$)	User ($n=17$)	Sporadic ($n=11$)
Demographics			
Age	23.42±3.97	22.71±3.18	21.91±3.17
	(18–30)	(18–28)	(18–27)
Gender m:f[a]	11:1	14:3	6:5
Education (years)	15.17±3.03	14.80±2.65	14.81±2.36
	(11–20)	(10–19)	(12–18)
Cannabis use patterns			
Age of first use	15.58±1.83	15.59±2.37	14.64±1.50
	(13–19)	(12–21)	(12–17)
Lifetime dose (g)	814.33±891.34	762.74±893.32	476.81±4898.55
	(2.5–2,880)	(0–3,640)	(3–1,250)
Duration of regular use (months)	53.90±32.16	56.40±39.79	42.90±31.11
	(0–96)	(0–122)	(3–108)
Days of use per month (average)	11.95±11.65	13.09±11.61	14.68±11.56
	(0–30)	(0–30)	(0–30)
Days of use per month (maximum) [2]	19.92±12.59	22.10±11.39	21.91±9.79
	(0–30)	(0–30)	(3–30)
Average daily dose (joints)	2.70±1.29	2.53±2.04	2.11±1.86
	(0.5–4.5)	(0.5–6.0)	(0.5–6.0)
Highest daily dose ever used (joints)	9.25±8.99	10.35±6.67	7.36±6.35
	(1–30)	(0.5–20)	(0.5–20)
Time since last use (days)[b]	175±281.20	111.62±214.49	126.55±383.25
	(1–730)	(1–545)	(1–1,280)
Number of positive THC screenings at baseline t1	4	9	6
Ecstasy use patterns			
Age of first use	19.78±2.53	20.56±3.15	19.60±3.71
	(15–22)	(16–26)	(15–27)
Lifetime dose (pills)	2.66±1.77	3.26±1.59	3.15±1.75
	(0–5)	(0–5)	(0–5)
Average one night dose (pills)	1.01±0.30	1.40±0.93	1.37±1.31
	(0.5–1.5)	(0.5–3)	(0.5–3)
Highest one night dose (pills)	1.61±0.65	2.07±1.19	1.67±1.26
	(1–3)	(1–4)	(0.5–4)
Time since last use (days)**	828.33±769.06	194.40±331.87	350.35±314.20
	(180–2,373)	(9–1,277)	(24–1,095)
Amphetamine use patterns			
Age of first use	19.67±2.45	19.88±3.16	18.90±3.34
	(15–22)	(16–25)	(15–27)
Lifetime dose (g)*	2.29±1.63	3.52±1.38	2.41±1.71
	(0–5)	(0–5)	(0–5)
Average one night dose (g)	0.39±0.23	0.53±0.33	0.47±0.32
	(0.20–0.90)	(0.15–1.10)	(0.15–1.00)
Highest one night dose (g)	0.85±0.68	1.23±0.80	615.00±272.89
	(0.30–2.50)	(0.20–3.00)	(0.25–1.00)
Time since last use (days)[2]*	470.67±759.15	208.31±481.90	123.30±216.25
	(14–2,373)	(14–570)	(7–720)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The t-values were calculated using unpaired t-test; two-tailed ($df=27$)

[a]Comparison tested with Pearson χ^2 test ($df=1$); exact significance (two-sided) are reported

[b]Comparison tested with Mann–Whitney U-test; asymptotic significance (two-sided) reported

*Significant difference, $p<0.05$

**Significant difference, $p<0.01$

Table 2 Patterns of interim drug use of interim abstinent users (controls, $n=12$), users who began using ecstasy and/or amphetamine on a regular basis (user, $n=17$) and sporadic users (sporadic, $n=11$)

	Controls ($n=12$)	User ($n=17$)	Sporadic ($n=11$)
Interim cannabis use patterns			
Interim cumulative dose (g)	71.56±100.98 (0–285)	146.65±194.06 (0–650)	40.27±79.26 (0–260)
Duration of regular use (months)[a]	5.92±1.79 (0–12.5)	8.64±5.39 (0–72.0)	5.90±5.82 (0–13.0)
Days of use per month (average)	11.83±10.85 (0–30)	18.67±9.62 (0–30)	15.16±13.87 (0–30)
Days of use per month (maximum)	19.29±10.99 (0–30)	23.62±8.29 (0–30)	20.70±11.14 (0–30)
Average daily dose (joints)	2.00±1.04 (1.00–4.20)	2.26±2.06 (0.30–6.90)	1.92±0.88 (1.00–3.00)
Highest interim daily dose (joints)	5.87±6.42 (1.00–20)	5.58±4.37 (1.00–16)	7.07±5.34 (1.00–15)
Time since last use (days)[a]	13.57±24.46 (1–68)	25.40±76.44 (1–300)	44.57±99.76 (1–270)
Number of positive THC screenings at follow-up t2	3	10	5
Interim ecstasy use patterns		$n=15$	$n=7$
Interim cumulative dose (pills)	×	9.50 ±7.89 (0–30)	2.95±4.22 (0–12)
Days of use per month (average)	×	0.96±1.48 (0.5–4.5)	0.02±0.32 (0.2–1.5)
Days of use per month (maximum)	×	2.71±2.36 (1.0–10.0)	2.00±3.10 (0.2–2.0)
Average 1-night dose (pills)	×	1.36±0.66 (0.5–2.5)	1.17±0.96 (0.25–2.00)
Highest interim 1-night dose (pills)	×	2.02±1.06 (0.75–4.0)	2.64±3.45 (0.25–3.00)
Time since last use (days)	×	86.33±80.12 (14–27)	75.43±55.32 (20–180)
Interim amphetamine use patterns		$n=16$	$n=6$
Interim cumulative dose (g)	×	10.61±7.52 (0.20–30.00)	0.75±0.89 (0.10–2.50)
Days of use per month (average)	×	2.11±2.18 (0.8–6.5)	0.30±0.63 (0.1–0.5)
Days of use per month (maximum)	×	4.21±4.88 (2.0–15.0)	2.00±1.86 (0.1–2.0)
Average 1-night dose (g)	×	0.77±0.65 (0.25–2.50)	0.45±0.24 (0.10–0.75)
Highest interim 1-night dose (g)	×	1.14±0.67 (0.25–3.00)	0.59±0.32 (0.10–1.00)
Time since last use (days)	×	47.44±73.03 (10–300)	89.00±62.72 (14–180)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The *t*-values were calculated using unpaired *t*-test; two-tailed ($df=27$)

[1]Comparison tested with Mann–Whitney *U*-test; asymptotic significance (two-sided) reported

*Significant difference, $p<0.05$

**Significant difference, $p<0.01$

Functional MRI

All subjects had a normal structural MRI scan without focal brain lesions or anatomical abnormalities.

Associative memory

Separate analyses for effect of the factor TASK at baseline revealed no significant between group differences. Whole-

Table 3 Patterns of alcohol and tobacco use at baseline (t1) and during the 12-months follow-up period (t1–t2) for interim abstinent users (controls, n=12), users who began using ecstasy and/or amphetamine on a regular basis (user, n=17) and sporadic users (sporadic, n=11)

	Controls (n=12)	User (n=17)	Sporadic (n=11)
Alcohol and tobacco use at baseline (t1)			
Alcoholic drinks per week**	6.37±0.59 (2.0–7.5)	6.08±1.08 (3.0–8.5)	4.00±2.04 (2.0–8.0)
Cigarettes per week	26.48±11.46 (7.1–47.8)	28.74±10.79 (11.9–50.3)	24.36±23.37 (4.2–60.0)
Years of tobacco use	5.25±4.03 (1.5–12.0)	4.95±3.70 (0.5–12.0)	3.90±3.64 (3.0–12.0)
Interim alcohol and tobacco use (t1–t2)			
Alcoholic drinks per week	6.20±1.17 (4.5–9.0)	6.26±1.63 (3.0–9.0)	4.72±2.53 (1.5–8.0)
Cigarettes per week	25.50±18.6 (15.5–54.0)	23.29±23.87 (9.0–60.0)	29.81±25.63 (8.0–72)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The t-values were calculated using unpaired t-test; two-tailed (df=27)

*Significant difference, p<0.05

**Significant difference, p<0.01

brain analysis of the encoding tasks revealed a significant BOLD effect for the main effect of the factor TASK (encoding > control) in the associative memory network. ROI analysis indicated bilateral activity within the hippocampal formation, most pronounced in the right parahippocampal gyrus (Fig. 2; maximum t-value located at Talairach space, x=31, y=−9, z=−13; t=9.66). Whole-brain and ROI analysis revealed no significant main effect of the factor TIME. Whole-brain analysis of the interaction effects of the factors GROUP × TIME revealed no significant results; however, ROI analysis of the hippocampal formation indicated a significant interaction effect of the factors GROUP × TIME in the left parahippocampal gyrus (Fig. 3; maximum at x=−19, y=−40, z=−4; cluster size 14 voxels; t=6.33, p< 0.05, FWE corrected). Analysis of the individual BOLD response differences between baseline and follow-up (t2> t1) at the maximum of the parahippocampal cluster indicated increased activity in the CGs between t1 and t2; but decreased activity in the UGs. Because the groups showed a large variation in the amount of cannabis used between t1 and t2 (see Table 2) an additional ANCOVA with the estimated cumulative interim dose of cannabis as covariate was performed. After controlling for the amount of cannabis used between t1 and t2 the interaction effect of the factors GROUP × TIME in the left parahippocampal cluster remained significant (maximum at x=−19, y=−40, z=−4; cluster size 21 voxels; t=7.04; FWE corrected).

Analyses of the retrieval task revealed a significant main effect of the factor TASK in the associative memory network (for detailed description, see Becker et al. 2010). However, ROI analysis revealed that during retrieval no significant activity passed the threshold for significance within the hippocampal formation (minimum voxel size: 10, p<0.05, FWE and small volume corrected). Whole-brain and ROI analyses revealed no significant main or interaction effect. Analysis of between-group differences for the effect of the factor TASK (retrieval > control) at both time points revealed no significant results.

To further explore the group × time interaction effect during encoding, individual parameter estimates for the pooled encoding conditions were extracted from a spherical ROI (radius=6 mm) centered at the maximum t-value of the parahippocampal cluster. Repeated-measures ANOVAs for the encoding condition with group (controls vs. users) as between-subject factor and time point (t1 vs. t2) as within subject factor revealed a significant interaction (F(1,26)= 20.27, p<0.001) in the absence of a main effect of group (F (1,26)=0.49, p=0.49) or time point (F(1,26)=0.83, p= 0.37). Post hoc multiple comparisons using Bonferroni-corrected paired t-tests revealed increased encoding-related

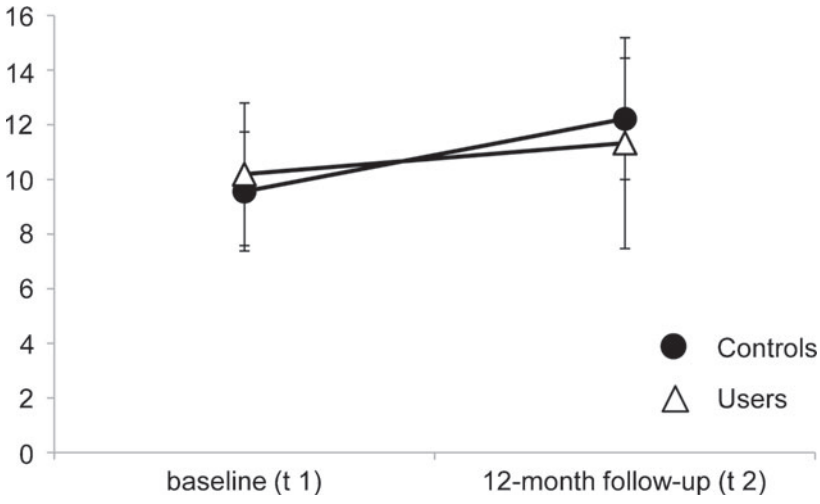

Fig. 1 Mean (±standard deviation) correct retrieved profession categories during the retrieval run of the associative memory task (maximum correct responses=16) of interim abstinent users (controls, n=12) and users who began using ecstasy and/or amphetamine on a regular basis (user, n=17) at baseline (t 1) and 12-month follow-up (t 2)

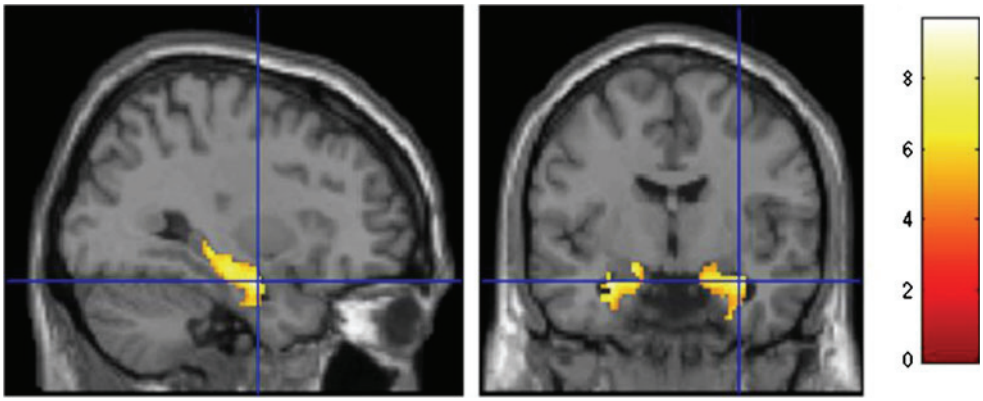

Fig. 2 Main effect of task for the pooled encoding conditions of the associative memory task (active>control; $p<0.05$, FWE and small volume corrected) in the ROI comprising the hippocampus and parahippocampal gyrus (bilateral). Maximum *t*-value located at $x=31$, $y=-9$, $z=-13$ (Talairach space)

activity from t1 to t2 in the control group ($t(11)=-2.95$, $p=0.013$), whereas users displayed a significant decrease from t1 to t2 ($t(16)=3.38$, $p=0.004$) (Fig. 4). In addition post hoc test using Bonferroni-corrected unpaired *t*-tests were used to test for between-group differences at both time points. Compared to controls, users displayed significantly higher encoding-related activity at t1 ($t(27)=-3.57$, $p=0.001$), but not at t2 ($t(27)=1.65$, $p=0.11$).

Correlation analyses

To disentangle specific contributions of ecstasy and amphetamine use to interim changes in left parahippocampal BOLD response in the UGs, individual contrast images for the main effect of the factor TIME and different parameters of interim amphetamine ecstasy use (interim cumulative dose, highest reported interim 1-night dose, time since last use at t2) were entered in an SPM simple regression. Statistical power of this exploratory analysis was increased restricting the analysis to the left parahippocampus (structurally defined using WFU pickatlas; Maldjian et al. 2003, 2004; Tzourio-Mazoyer et al. 2002). A higher cumulative interim ecstasy dosage was related to lower activity at t2 relative to t1 (maximum at $x=-28$, $y=-42$, $z=0$; cluster size 12 voxels; $t=5.76$, $p<0.001$, uncorrected). An additional analysis of correlations between interim changes and parameters of cannabis use revealed no significant results.

Discussion

The present prospective study investigated the effects of moderate recreational ecstasy use on hippocampal functioning. fMRI was used to examine memory-related hippocampal functioning in 40 subjects with very low amphetamine and/or ecstasy experience (less than five units lifetime dose). After a 12-month follow-up subjects were re-examined. At the 12-month follow-up subjects were classified according to their interim ecstasy and/or amphetamine use: (1) subjects with continued use during follow-up (>5 ecstasy tablets and/or > grams of amphetamine) ($n=17$) and (2) subjects with complete abstinence after the initial examination. To clearly separate the groups 11 subjects with only sporadic use during the follow-up period were excluded from further analysis. Analysis of behavioral data revealed no significant differences between abstinent and continuing users in associative memory performance as measured by retrieval accuracy. However, encoding-related activity in the left parahippocampal gyrus changed differentially between the groups. Repeated-measures analysis revealed a significant GROUP × TIME interaction effect in this region such that encoding-related activity decreased in continuing ecstasy and/or amphetamine user but increased in abstinent subjects from baseline to follow-up. In subjects with continued use, decreases within the parahippocampal gyrus showed a dose–response relationship with the extent of interim

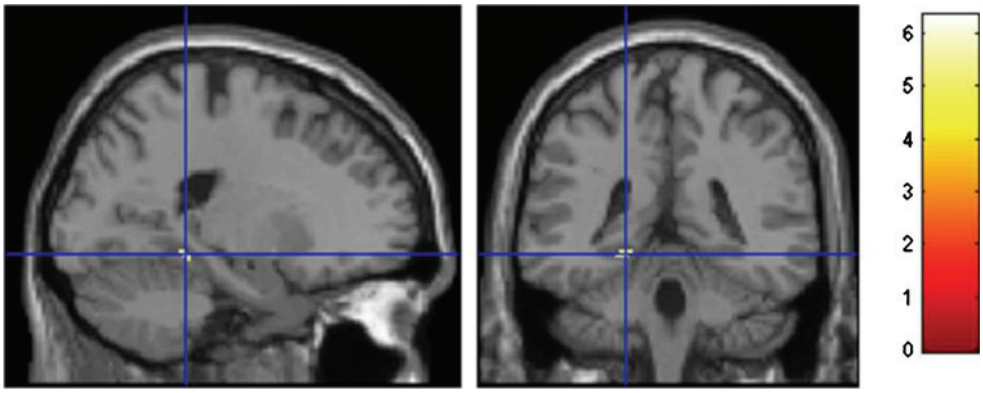

Fig. 3 Group × time interaction effect in left parahippocampal gyrus during encoding. Crosshairs at maximum *t*-value ($t=6.33$; $p<0.05$, FWE and small volume corrected) located in Talairach space at $x=-19$, $y=-40$, $z=-4$

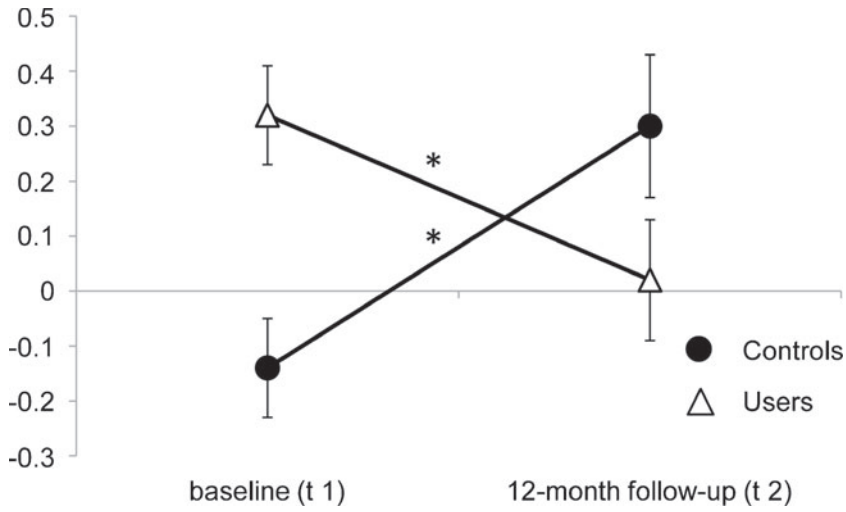

Fig. 4 Extracted parameter values for the encoding condition at baseline (t1) and 12-month follow-up (t2). Post hoc Bonferroni-corrected paired *t*-tests revealed increased encoding-related activity from t1 to t2 in the control group ($t(11)=-2.95$, $p=0.013$), whereas users displayed a significant decrease from t1 to t2 ($t(16)=3.38$, $p=0.004$)

ecstasy use, but not interim amphetamine or cannabis use, suggesting ecstasy-specific effects.

Besides the effects of ecstasy alternative explanations of the observed effects are conceivable. First, regular use of cannabis has been associated with altered hippocampal functioning up to 7 days after last use (Eldreth et al. 2004; Jager et al. 2007; Nestor et al. 2008; Becker et al. 2010). Continuing users in the present study had more THC-positive urine samples at follow-up and had used more cannabis during the follow-up period; therefore, confounding (sub-acute) effects of cannabis on hippocampal functioning cannot be excluded. However, between-group effects remained stable after controlling for interim cannabis use and decreases within the continuing users did not show significant associations with the time since last cannabis use. Second, already at the initial examination future abstinent and future regular users demonstrated differences in hippocampal activity. Differences in the abstinence periods at baseline might have confounded the initial data acquisition. However, interim regular users reported similar abstinence periods prior to both examinations suggesting that the lengths of abstinence might not fully account for the observed hippocampal decreases in this group. Moreover, baseline differences might represent pre-existing differences in hippocampal functioning that might lead to continued ecstasy and/or amphetamine use.

In line with previous cross-sectional studies in moderate users of ecstasy (Halpern et al. 2004; Gouzoulis-Mayfrank et al. 2003; Reneman et al. 2006), the present study did not detect significant deficits in memory performance. However, a prospective study found that a low cumulative dose of ecstasy (mean cumulative dose, 3.2 tablets) was associated with a subtle decline in verbal memory (Schilt et al. 2007). In this study neuropsychological performance in incident ecstasy users before and after a period of first ecstasy use was compared to baseline and follow-up performance of matched controls, who did not start to use ecstasy. Using change scores (follow-up minus baseline) the authors found that verbal memory performance changed differentially between the groups. Ecstasy naïve controls showed improved performance at follow-up, whereas incident users failed to improve. Notably, analysis of change scores in the present study revealed a similar, yet non-significant pattern of attenuated re-test effects in the continuing users. Given that estimated effect sizes in both studies were rather small the sample size in the present study was not sufficient to detect possible effects on the behavioral level.

Despite this lack of effects on the behavioral level we found significantly decreased parahippocampal activity after continued use. This is in line with previous cross-sectional reports on decreased parahippocampal activity in heavy poly-drug ecstasy users (Daumann et al. 2005) and adolescents with moderate ecstasy use (Jacobsen et al. 2004). Decreases within the left parahippocampal gyrus showed a dose–response relationship with the extent of interim ecstasy use, but not with parameters of interim amphetamine or cannabis use, suggesting ecstasy-specific effects. Previous findings on specific effects of amphetamine on hippocampal functioning in the context of ecstasy use (Jager et al. 2008) could not be confirmed in the present sample. Diverging results might be explained in terms of differences in study design and sample characteristics. Whereas the previous study used a multiple regression approach to disentangle ecstasy- and amphetamine-specific effects, the present study used a prospective longitudinal design. Moreover, heavy ecstasy users participating in the previous study had used substantially larger cumulative doses of ecstasy and amphetamine, than the moderate users in the present study. It is conceivable that ecstasy-specific effect might become apparent even with low cumulative ecstasy doses, whereas amphetamine-specific effects become only apparent with higher cumulative doses. Admittedly, associations between interim ecstasy use and changes in neural activity were rather weak in the present sample. Due to the relatively low doses

of interim ecstasy use and the short follow-up period, parameters of ecstasy use showed very limited variation in the present sample. Furthermore, confounders such as variations in the amount of MDMA within the ecstasy tablets used, or inaccuracies in self-reported drug use are likely to have a stronger biasing effect on dose–response relationships in samples with moderate use, compared to samples with heavier use patterns. Findings from the correlational analysis therefore represent preliminary findings that need to be confirmed in future studies.

In contrast to previous investigations from our own research team and other groups (Daumann et al. 2003, 2004; Moeller et al. 2004; Quednow et al. 2006), the present study failed to find evidence of ecstasy-associated dysfunctions in fronto-parietal regions. Again, the comparably low cumulative doses of ecstasy and amphetamine used in the present sample might explain the diverging results. Deficits in fronto-parietal regions might only become apparent after heavy and prolonged use.

The hippocampus and parahippocampus display relatively high rates of serotonergic denervation after MDMA exposure and relatively low recovery after abstinence in animal studies (Fischer et al. 1995; Hatzidimitriou et al. 1999). Human ecstasy users show long-term alterations in biochemical markers of the serotonergic system (Ricaurte et al. 1990; McCann et al. 2008; Kish et al. 2010; Reneman et al. 2001). Serotonin mediates vasoconstriction and in laboratory animals and MDMA has been shown to induce persisting effects on cerebral blood flow (Ferrington et al. 2006; Rosa-Neto et al. 2004) Findings from a recent prospective study in low dose ecstasy users suggest sustained effects of ecstasy on brain microvasculature (de Win et al. 2008). As it has been proposed that changes in vasculature directly affect the BOLD signal underlying functional MRI (Carusone et al. 2002), findings from the present study might suggest ecstasy-related changes in brain microvasculature, possibly mediated by lower serotonergic tone in the continuing users.

However, further analysis of the interaction effect in the parahippocampal region revealed that the interaction was also driven by relatively increased activity in the interim abstinent users. Given that some studies suggest normalization of the serotonergic system after prolonged abstinence (Buchert et al. 2004), we cannot exclude the possibility that recovery processes in the abstinent users might underlie the present findings. To recruit participants with a high probability of future ecstasy use and to avoid large oversampling, we decided to recruit participants who had first but very limited experience with ecstasy and/or amphetamine at baseline. However, recent findings from prospective studies with novice ecstasy users suggest that even first low cumulative doses of ecstasy might lead to measureable alterations in serotonergic functioning (de Win et al. 2007, 2008; Schilt et al. 2007). Given that adolescent ecstasy users with moderate use have shown reduced hippocampal activity (Jacobsen et al. 2004) and serotonergic alterations in ecstasy users might be reversible (Buchert et al. 2004), interaction effects in the present sample might reflect long-term recovery processes in the abstinent users. However, in other studies the moderate use of ecstasy was not associated with measurable alterations (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004) and findings from a follow-up study suggest that altered cerebral activation patterns, at least in former heavy ecstasy users, do not reverse after several months of abstinence (Daumann et al. 2004).

Although the prospective design of this investigation might help to overcome some methodological shortcomings of previous studies, we are well aware of its methodological limitations, inherent to virtually every open-field study. First, although this study incorporated a prospective design, most known confounders were controlled for and a broad range of methods was used to recruit participants (advertisement in magazines and newspapers, notifications posted on campus, radio interviews), we cannot exclude that unknown factors or selective sampling might have contributed to the present findings. Only experimental designs with randomly selected samples could offer evidence of causality; however, direct experimental approaches in humans remain controversial. Second, most participants used amphetamine and ecstasy. During the last years this pattern of poly drug use has become established in recreational ecstasy users (Gouzoulis-Mayfrank and Daumann 2006a; Smart and Ogborne 2000). Even though alterations in the present sample were only related to the extent of interim ecstasy use, and interim doses of amphetamine and ecstasy were not associated (Pearson correlation; $p=0.649$), we cannot completely rule out that complex interaction effects among the drugs might have led to the present findings. Third, drug histories were assessed by self-report. Before participants were included in the baseline examination they were interviewed about their drug histories (without being told of the precise inclusion and exclusion criteria). Furthermore, analysis of randomly taken hair samples was used to confirm self-reported drug use at baseline and follow-up. However, due to short hairstyles and the fact that the adherence of drugs onto hair varies strongly depending on the physical characteristics of the hair and the kind of care applied to it, we cannot completely rule out that inaccuracies in the reported drug histories might have biased our results. Fourth, there was no control on purity or amount of MDMA in the ecstasy tablets used. However, recent data suggest that in the years 2006 and 2007 nearly 99 % of the tablets sold as ecstasy were monopreparations, with approximately 98 % containing MDMA (EMCDDA Annual report: the state of the drugs problem in Europe 2007). Fifth, in the present study we did not control for acute alcohol intoxication. The use of breath analyzers in future studies

might help to overcome this shortcoming. Finally, although detailed information about the pattern of drug use was assessed within the drug use interview, the environment in which the drug was actually used was not assessed. Findings from previous studies suggest that the neurotoxic effects of MDMA may be enhanced under certain conditions, such as hot, overcrowded surroundings and long periods of dancing; possibly mediated by an increase in body temperature (Colado et al. 1998; Green et al. 2003; Parrott 2004). However, there does not seem to be an easy solution for this issue.

In conclusion, findings from the present prospective study suggests that moderate use of ecstasy is associated with altered hippocampal functioning. However, confounding effects of cannabis on hippocampal functioning could not be ruled out. Further research should address the specific effects of cannabis in the context of ecstasy use and incorporate longer follow-up periods to address progression, persistency and reversibility of the alterations.

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Conflicts of interest None of the authors has declared any conflict of interest.

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A prospective study of self-reported psychopathology in new MDMA and d-amphetamine users

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A prospective study of self-reported psychopathology in new MDMA and d-amphetamine users

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Abstract

Aims: It still remains unclear whether psychopathological abnormalities described in human 3,4-methylenedioxymeth-amphetamine users (MDMA users) and d-amphetamine users (AMPH users) existed before the beginning of use or if they develop with ongoing use. The present study was conducted in order to assess this relationship and to overcome previous methodological shortcomings.

Design: A prospective cohort study in 96 new MDMA and d-amphetamine users between 2006 and 2011 with a follow-up duration of 24 months. In order to explore the impact of MDMA and AMPH use on self-reported psychopathology, multivariate analyses of variance were conducted. In order to examine the impact of previous psychopathology on subsequent use, partial correlation analyses were applied.

Setting and Participants: Over the course of the two-year follow-up period, 31 subjects used neither MDMA nor AMPH (non-users); 37 subjects used between 1 - 14 tablets of MDMA (mean: 5.18, SD: 3.86), and 28 subjects used 15 or more tablets of MDMA (mean: 43.73, SD: 45.63). 33 subjects used between 1 - 14 grams of AMPH (mean: 4.46, SD: 3.65), and 32 subjects used 15 grams or more (mean: 64.52, SD: 104.59).

Findings: No group differences concerning self-reported psychopathology were found. However, there was a significant relationship between globally increased self-reported psychopathology at the beginning of the study and subsequent AMPH use.

Conclusions: The data of the present study suggest that a certain psychopathological profile could form a risk factor for later use of amphetamines.

Introduction

Methylenedioxymethamphetamine (MDMA) and d-amphetamines (AMPH) are popular drugs among young adults, with mean lifetime prevalence rates of 3.3% and 8.9% respectively for North America (1) and 5.8% and 5.2% for Europe (2). Both substances are used illegally as recreational drugs, especially by visitors of techno clubs and rave parties (3).

Regular MDMA use is associated with increased psychopathological symptoms such as anxiety, depression and executive dysfunction, impulse control disturbances and psychoses (4-6). However, it still remains unclear whether the long-term use of MDMA causes psychopathological symptoms or whether psychopathological symptoms encourage the onset of MDMA use. A study by Medina and Shear (5) revealed that ecstasy use is often initiated after the development of an Axis I mood or anxiety disorder. Furthermore, it is assumed that people with psychosis have an increased risk of lifetime drug use (7) and that substance abuse is a key risk factor for relapse of psychosis (8). Moreover, it was found that people suffering from a psychosis or ones having received the diagnosis of schizophrenia are at higher risk to develop drug dependence than non-clinical controls; so illicit drug use is common in schizophrenia (9). However, one consistent critique of the current studies is that the observed effects may be due to concomitant cannabis use, which is common among MDMA users (5, 10).

With regard to AMPH, a study by Zweben, Cohen and Christian (11) showed that approximately 25% of amphetamine (particularly methamphetamine) users present with psychiatric symptoms. In that study, AMPH-induced psychosis was found to be a key clinical symptom of heavy AMPH use (12). Besides schizophrenia, depressive symptoms and anxiety disorders are commonly associated with regular use of AMPH (11, 13, 14). A recent study by Glasner-Edwards et al. (15) even assumes that depression is the most widely distributed comorbid psychiatric disorder among substance-dependent

adults. Other psychotic symptoms related to AMPH use include paranoia, visual and auditory hallucinations, impulsivity (16), inappropriate affect and hostile behavior (17).

In general, most studies on the detrimental effects of MDMA and AMPH suffer from methodological problems. For instance, it is unclear whether the detected abnormalities existed before the beginning of use or whether club drug use causes psychopathological impairments. Moreover, the confounding role of cannabis in this context is often neglected (18). In order to overcome these methodological shortcomings, a prospective methodological approach was applied to assess self-reported psychopathology in new MDMA and AMPH users. Additionally, the use of cannabis was assessed. The goal was to address the following questions:

- Does the use of MDMA and/or AMPH lead to an increased self-reported psychopathology?
- Is the intensity of self-reported psychopathology at the first assessment (T_0) associated with the subsequent cumulative use of MDMA and/or AMPH?
- Is the intensity of self-reported psychopathology associated with the concomitant use of cannabis?

Materials and Methods

Participants

148 beginning recreational drug users with no current physical and no current or previous history of neurological or psychiatric disorder (Axis I and II according to DSM-IV criteria; APA, 1994) were included in the study. Further exclusion criteria were the following: ingestion of any other illicit psychotropic substances besides cannabis on more than five occasions before the day of the first examination; a history of alcohol abuse (according to DSM-IV criteria, APA 1994); and the taking of regular medication (except for contraceptives). The main inclusion criterion at baseline was a high

probability of future MDMA or AMPH use, operationalized as having had the first but still very limited experience with MDMA and/or AMPH (a maximum of 5 pills of MDMA or, respectively, 5 grams of AMPH). After a follow-up period of one year, participants were invited again (T_1). Of the initial 148 subjects, 109 subjects participated in the second assessment after the one-year follow-up period. Ninety-six subjects (63 males, 33 females; age range at baseline: 18-35 years, mean: 22.99 years, SD: 4.53) participated in the third and final assessment (T_2). Psychopathological assessment was carried out when participants were abstinent from cannabis on the study day in order to rule out acute intoxication effects. Given the fact that most MDMA users also use cannabis regularly, it would have been implausible to recruit MDMA users with a longer period of abstinence (19). Subjects were recruited via advertisements in magazines and newspapers and via notifications posted on campus. The study was part of a larger investigation including cognitive and neuro-imaging measures which have in part been published (20-23) and will in part be submitted elsewhere. The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne.

Procedure

Preceding each psychopathological assessment (T_0, T_1, T_2), written informed consent was given by all participants, followed by a structured interview that was developed in order to assess the use of illicit psychotropic substances. For all prevalent psychotropic substances, the interview included questions concerning the age of first use, the number of days since the last use, the average and maximal frequency of use measured in days per month, the estimated cumulative lifetime dose, the average daily dose, the highest daily dose ever used and the duration of regular use measured in months. (On the 2nd and 3rd assessments, respectively, the interviews included the following questions: age of first use (assessed only if the relevant substance had not been used before), the number of days since the last use, the average and maximal frequency of use measured in days per month last year, the estimated cumulative dose last year, the average daily dose last year, the highest daily dose last year

and the duration of regular use measured in months last year). Qualitative drug screens for amphetamines, benzodiazepines, cocaine, methadone, MDMA and cannabis (enzyme-multiplied immunoassay, von Minden GmbH) were performed on the day of the examination by means of urine samples. In addition, hair samples were randomly taken in one third (for financial reasons) of the participants and analyzed for the substances, MDMA, MDA, MDEA, amphetamine, methamphetamine and cannabinoids by the Institute of Legal Medicine of the University of Cologne in order to verify the self-reported substance use.

Self-reported psychopathology

Self-reported psychopathology was assessed by a German version of the Symptom Checklist-90-Revised (SCL-90-R) (24). The SCL-90-R is a 90-item multidimensional self-report inventory designed to assess a broad range of psychological distress and emotional status. Each of the 90 items is rated on a 5-point Likert scale of distress caused by psychic symptoms in the previous seven days, ranging from ´not at all´ (= 0) to ´extremely´ (= 4). The SCL-90-R consists of the following nine primary symptom categories: somatization (12 items), obsessive-compulsive (10 items), interpersonal sensitivity (9 items), depression (13 items), anxiety (10 items), hostility (6 items), phobic anxiety (7 items), paranoid ideation (6 items), and psychoticism (10 items). Additionally, the Global Severity Index (GSI) provides a measure of overall distress. Research has reported acceptable levels of internal consistency and sensitivity to psychotropic medication and psychotherapy (25). Moreover, the instrument is normalized for four different populations: psychiatric inpatients and outpatients as well as healthy adult and adolescent non-patients (25-27).

Statistical analyses

In order to explore the impact of MDMA and AMPH use on self-reported psychopathology, two multivariate analyses of variance were conducted (one for MDMA; one for AMPH). The within-

subjects factor was defined as time of assessment (T_0,T_1,T_2); the between-subjects factor was defined as user group, and the dependent variables comprehended the nine primary symptom categories and the GSI, measured using the SCL-90-R. For this purpose the subjects were divided into three different groups. With respect to MDMA use, the three groups were defined as follows: (1) those who did not use any MDMA over the course of the two-year period; (2) those who used between 1 - 14 tablets; and (3) those who used 15 or more tablets. With respect to AMPH, the groups were defined analogously: (1) those who did not use any AMPH over the course of the two-year period; (2) those who used between 1 - 14 grams of AMPH; and (3) those who used 15 grams or more of AMPH.

Furthermore, correlation analyses between all psychopathological variables of the first assessment (T_0) and the subsequent AMPH and MDMA use were performed in order to examine the impact of previous psychopathology on subsequent use. The results were then revised by means of partial correlation with cannabis use as covariate in order to account for an interaction effect of the prevalent concomitant cannabis use. All analyses were performed with SPSS statistical software program version 16 (Chicago, IL).

Results

Group characteristics

Over the course of the two-year follow-up period, 31 subjects used neither MDMA nor AMPH (non-users), 37 subjects used between 1 - 14 tablets of MDMA (mean: 5.18, SD: 3.86) and 28 subjects used 15 or more tablets of MDMA (mean: 43.73, SD: 45.63). 33 subjects used between 1 - 14 grams of AMPH (mean: 4.46, SD: 3.65) and 32 subjects used 15 grams or more (mean: 64.52, SD: 104.59). For each group, gender distribution, mean age, mean cumulative cannabis use between the first and the last assessment as well as corresponding standard deviations are given in Table 1.

As described above, polydrug use is popular. This phenomenon could also be observed in the present sample. Of the subjects who used MDMA over the course of the two years (T_0-T_2), 26 individuals additionally used AMPH and cannabis, 16 used either AMPH or cannabis. Only one subject did not use any other illicit drug apart from MDMA. Of the subjects who used AMPH, 29 additionally used MDMA and cannabis, 23 showed concomitant cannabis use, and only six did not use any other illicit drug apart from AMPH.

Self-reported psychopathology

The MANOVAs addressing the impact of MDMA and AMPH use over the course of this study upon self-reported psychopathology at the last assessment (T_2) revealed—for both the MDMA users and the AMPH users—no significant time x group interaction effect for the general model (MDMA: $F(40,148)= 0.97$, $p= .530$; AMPH: $F(40,148)= 1.08$, $p= .369$). Correspondingly, the corresponding univariate tests did not reveal significant time x group interaction effects for any of the SCL-90-R variables.

The correlation analysis addressing psychopathology at the first assessment (T_0) and subsequent AMPH use revealed significant results. Positive correlations between AMPH use and prior somatization ($r= .267$, $p= .009$), obsessive-compulsive symptoms ($r= .211$, $p= .039$), anxiety ($r= .350$, $p= .000$), hostility ($r= .269$, $p= .008$), phobic anxiety ($r= .262$, $p= .010$), psychoticism ($r= .353$, $p< .001$), and the global index for overall distress (GSI = global severity index; $r= .321$, $p= .001$) were found. The high concomitant cannabis use in AMPH users raises the question concerning the extent to which the significant results are caused by the AMPH use itself or by the concomitant cannabis use. Thus, the results of the correlation analysis were verified by follow-up partial correlation analysis with cannabis

use over the course of this study as covariate. All values remained significant. The results of the corresponding partial correlation analysis are given in Table 2.

Moreover, the results revealed positive correlations between MDMA use (T_0-T_2) and anxiety at T_0 (r= .258, p= .011) as well as MDMA use (T_0-T_2) and psychoticism at T_0 (r= .238, p= .020). Because of the considerable effects regarding self-reported psychopathology and subsequent AMPH use and due to the fact that a large part of the MDMA users additionally use AMPH, we assumed that the positive correlation between MDMA use and prior anxiety and psychoticism could be ascribed to an intercorrelation effect of the MDMA and AMPH use. A corresponding partial correlation analysis between the SCL-90-R variables at T_0 and the subsequent MDMA use (T_0-T_2) as well as AMPH use (T_0-T_2) as covariate revealed no significant effects and thus confirmed our assumption.

Discussion

The aim of the present prospective study was to examine the relationship between MDMA and AMPH use and self-reported psychopathology. 96 new users were examined three times over a follow-up period of two years, thus making it possible to account for premorbid differences. The hypothesis that MDMA and/or AMPH use leads to subsequent increased psychopathology in new users within two years could not be confirmed. No differences between users who took 15 or more tablets/grams, users who took between 1 and 14 tablets/grams and controls with respect to self-reported psychopathology were found. Interestingly, there was a significant relationship between globally increased self-reported psychopathology at the beginning of the study and subsequent AMPH use.

The findings in the recent literature on MDMA and psychopathology are inconsistent. Several studies could not show an association between MDMA and self-reported psychopathology while others could. For example, Parrott and colleagues (28) as well as Sumnall and colleagues (29) report that

psychobiological symptoms were directly associated with the quantity of use, while Verheyden and colleagues (30) report this solely with respect to subjects who perceive their use as problematic. Unfortunately, only a few longitudinal studies exist. In addition, pre-existing psychopathological symptoms frequently are not taken into account in cross-over studies. In an evaluation of the psychiatric case studies of the last 10 years, Soar, Turner and Parrott (31) stated that merely 24% of the subjects had a psychiatric disorder before initiation of MDMA use. The authors interpreted this as evidence for the causal impact of MDMA on psychic well-being. A longitudinal study of a huge sample (N = 2462) of adolescents and young adults (4) revealed that in comparison with non-users, MDMA users show a higher probability of meeting the criteria of a DSM-IV diagnosis, but this was prior to the onset of use rather than as a result of it (21).

In the present study, no convincing indication for self-reported psychopathology and a relationship to later MDMA use was found De Win and colleagues (32) examined the predictive value of depression, impulsivity and sensation seeking for the subsequent first use of MDMA by recruiting 188 MDMA-naïve subjects with a high risk for subsequent MDMA use. Remarkably, none of the three parameters predicted subsequent use or had any impact on it. Another interesting finding comes from a longitudinal study by Thomasius and colleagues (33). Recent and abstinent MDMA users did not change over the course of this investigation concerning psychopathological symptoms, whereas ex-users showed the highest psychological strain. In a newer study by Falck and colleagues (34), subjects with a lifetime dose of 50 tablets of MDMA indeed showed more symptoms of depression than subjects who had used fewer doses of MDMA; overall, however, a decrease was observed over the course of two years for these psychopathological variables. Especially interesting in this context is an investigation by Verheyden and colleagues (35), in which ex-users were asked about their reasons for having stopped using MDMA. The authors could differentiate two groups. One group had stopped on account of suffering from one or more of 19 different psychological problems, whereas the other

group had stopped because of changes in their life/personal circumstances. In the group with psychological problems, half of the subjects suffered from clinical depression, whereby the actual depressive period was directly associated with the cumulative lifetime doses. The authors concluded that some subjects had had a higher vulnerability to the harmful effects of MDMA or that they had initiated use because of pre-existing psychological problems. The results of Soar and colleagues (36) are In line with these findings. However, in this study subjects who perceived their usage as problematic also reported a personal or family psychiatric background.

Additionally, it is unclear whether the reported relationship between psychopathology and MDMA use could be ascribed to the harmful effects of MDMA. The majority of users show concomitant use of (illicit) substances like cannabis, AMPH, alcohol or cocaine (37, 38). It is possible that the simultaneous use of stimulants and drugs like MDMA acts synergistically, thereby enhancing the harmful effects of MDMA (39). Several studies indicated that concomitant use has an impact on increased psychopathologic values as opposed to MDMA ingestion alone (29, 40, 41). Thomasius and colleagues (40) found that MDMA co-users and co-users without any MDMA use showed an increased global psychopathology in comparison with non-users, but there was no difference between these two user groups. Bedi and colleagues (41) compared MDMA polydrug users and cannabis polydrug users with a group using legal drugs. Whereas the anxiety and depression scores were higher in concomitant users in comparison to users of legal drugs, there was no difference between MDMA users and cannabis users. Other studies emphasize the special role of cannabis (42-44). Daumann and colleagues (45) compared MDMA users who additionally used cannabis with groups of cannabis users and non-users: MDMA users showed increased psychopathological values. However, these values were associated with longer duration and earlier onset of cannabis use. The differences between the two groups disappeared when the impact of the two parameters were statistically controlled for. A longitudinal study by the same researchers confirmed these results.

MDMA users were compared with controls who did not use any illicit substance apart from cannabis (43). Subjects who continuously used MDMA over the course of the 18 months of this investigation did not differ from subjects who stopped using MDMA after the first assessment with regard to psychopathology. However, differences between subjects concerning their cannabis use were found. Subjects who stopped using cannabis had lower psychopathological scores than subjects who continued using cannabis. Further, Morgan and colleagues (44) found increased psychopathological scores in both MDMA user groups in a comparison of recent users, abstinent users and non-users, but this association could be explained by the subjects' cannabis use rather than by their MDMA use. This association could not be confirmed in a longitudinal study by Falck and colleagues (34): In their study, cannabis and MDMA use had no impact on depressive symptoms.

The currently available literature concerning AMPH and psychopathology is sparse. One of the best-known psychic side-effects of AMPH use is drug-induced psychosis, which was already mentioned in the British literature in 1957 (46). Symptoms of this type of psychosis are anxiety, distrust, the feeling of being observed and of being persecuted (47). Furthermore, auditory and visual hallucinations, arousal and agitation were observed (48). The amphetamine psychosis emerges in consumers without any prior predisposition for schizophrenia (49), and can persist for several months (50). Hitherto, it has not been possible to make a clear statement on whether the neurotoxic potential of AMPH has a long-term, persisting influence upon the emergence of psychiatric disorders. However, in several recent studies it was possible to reveal indications for the presence of psychopathological abnormalities in relation to long-term use. For example, Wang and colleagues found in their longitudinal study a persisting decrease of the glucose metabolism in the region of the striatum of five AMPH users even after a considerable time of abstinence. They assumed that this decrement was related to the persisting psychopathological abnormalities of the users (amotivation, anhedonia) (51). Another recent study, from 2010, also addresses the relationship between psychiatric disorders,

the psychosocial functional level and the substance abuse of the subjects (15). 526 methamphetamine users were examined for a second time three years after their participation in a special addiction therapy by means of the Mini-International Neuropsychiatric Interview and the Addiction Severity Index regarding their psychosocial functional level and psychiatric abnormalities. Criteria for a recent or past psychiatric disorder were found in 48.1% of the subjects, whereby affective disorders, anxiety disorders and antisocial personality traits made up the largest part. Furthermore, subjects with psychiatric disorders showed an increased methamphetamine use during the three years after the treatment as well as an increase in psychosocial impairments in comparison to subjects without such psychiatric disorders. A review by Marshall and Werb (52) gives a critical overview of the recent studies which deal with AMPH use and its relationship to psychiatric abnormalities. The authors illustrate the problem that while a variety of studies have indeed found a relationship between AMPH usage and psychopathological symptoms, it has not been possible to make clear statements with regard to causality because of their cross-sectional design. In a prospective cohort study, Degenhardt and colleagues could detect an association between an early onset of AMPH use in adolescence and the development of depression in adulthood (53). A prospective study from Thailand revealed comparable results. The authors found a significant relationship between AMPH use and subsequent depressive symptoms, whereby the symptoms were less marked in adults who had stopped using AMPH over the course of the 12 months of this study than they were in adults who had continued using AMPH (54). However, the results of the present study suggest an inverse causal relationship between a global increased psychopathology and later AMPH use, which, to the authors' knowledge, has not been described before. Therefore, the literature would benefit from more prospective studies with new users.

The prospective design of the present study has several advantages in comparison to investigations in which subjects are examined cross-sectionally or longitudinal studies in which subjects already show

regular use, thus precluding the possibility of taking premorbid differences into account. However, the following limitations have to be taken into account for the interpretation of the present results. First, the subjects themselves reported the quantity of substance use. We cannot rule out that subjects made incorrect indications about the quantity of their drug use, and, in line with that, it is possible that we underestimated the real quantity of their drug use. However, the subjects did not know the criteria for being included or excluded in this study, a fact which makes incorrect indications seem less likely. In addition, studies validating self-reported voluntary substance use have found a high reliability of the reported drug quantity (55, 56). Additionally, hair samples were randomly taken and confirmed the self-reported substance use. Furthermore, the concentration and purity of the Ecstasy tablets could not be controlled: It is unclear whether the tablets used by the subjects contained MDMA or similarly acting analogues like MDE, MDA, MDBD or amphetamine. The tablets vary in potency and range from highly psychically active doses to placebos. The tablets are not distinguishable for the user: Similar looking tablets could contain substances from different classes (57). Furthermore, the classification of users with a quantity of 15 or more tablets over the course of the two years of this study could be regarded as a random criterion. Further research with other classification criteria would be preferable. Further still, a selection bias could have played a role in recruiting the subjects for the present study. It is thus possible that subjects who perceived their use as problematic were less willing to participate in the present investigation, which included a variety of tests and took place in a department of a university hospital. Accordingly, the extent of the psychopathological symptoms could have been underestimated. While 148 subjects could be recruited for the initial assessment, 109 participated again in the second assessment. At the third assessment, then, the number of subjects fell to 96. The reasons for this attrition among subjects of the study could not be fully clarified. Whereas some individuals moved and thereby forestalled the possibility of being contacted again, it is possible that others did not answer the invitations because they perceived themselves as highly stressed. Furthermore, it is possible that subjects who had

developed a severe usage problem did not participate in the study because they could not handle the included self-reflection of this test battery. So, it is possible that in the present investigation psychically healthy subjects with stable life circumstances are over-represented.

In conclusion, the data of the present study suggest that certain psychopathological profiles could form a risk factor for later use of amphetamines. Given the data of the present study, it could not be confirmed that the use of MDMA or amphetamines leads to subsequent increased self-reported psychopathology in new users within two years.

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Tables

Table 1. Group characteristics

	female / male	age	cannabis use *[1]
Non-users	9 / 22	23.77 (± 3.87)	145.9 (± 193.3)
MDMA users			
1-14 tablets	13 / 24	21.14 (± 2.81)	274.2 (± 405.0)
15+ tablets	11 / 17	24.57 (± 6.08)	328.5 (± 590.5)
AMPH users			
1-14 grams	12 / 21	22.43 (± 4.55)	198.5 (± 227.4)
15+ grams	12 / 20	22.85 (± 4.76)	388.4 (± 631.1)

Frequency of gender and mean age. *[1] Cumulative cannabis use between the first and the last assessments per group. Standard deviations are given in parenthesis.

Table 2. Results of a partial correlation analysis between SCL-90-R variables at T_0 and the subsequent AMPH use (T_0-T_2) with cannabis use (T_0-T_2) as covariate.

SCL-90-R variable	Correlation	Significance (2-tailed)
Somatization	**.258**	**.012**
Obsessive-compulsive	**.212**	**.039**
Interpersonal sensitivity	.151	.144
Depression	.113	.276
Anxiety	**.340**	**.001**
Hostility	**.249**	**.015**
Phobic anxiety	**.275**	**.007**
Paranoid ideation	.080	.439
Psychoticism	**.333**	**.001**
Global Severity Index	**.312**	**,002**

Significant correlations are given in bold type.