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Review

MDMA and brain activity during neurocognitive performance: An overview of neuroimaging studies with abstinent 'Ecstasy' users

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ABSTRACT

MDMA/Ecstasy has had a resurgence in popularity, with recent supplies comprising higher strength MDMA, potentially leading to increased drug-related harm. Neurocognitive problems have been widely reported in ecstasy users, equally some studies report null findings, and it remains unclear which factors underlie the development of neurocognitive impairments. This review covers the empirical research into brain activity during neurocognitive performance, using fMRI, fNIRS, and EEG. Our main conclusion is that chronic repeated use of recreational ecstasy can result in haemodynamic and electrophysiological changes that reflect recruitment of additional resources to perform cognitive tasks.

Findings are consistent with serotonergic system changes, although whether this reflects neurotoxicity or neuroadaptation, cannot be answered from these data. There is a degree of heterogeneity in the methodologies and findings, limiting the strengths of current conclusions. Future research with functional neuroimaging paired with molecular imaging, genetics or pharmacological challenges of the serotonin system may help to decipher the link between serotonergic and cognitive changes in ecstasy users.

1. MDMA: general introduction and effects on serotonin

3,4-methylenedioxymethamphetamine or MDMA has recently undergone a resurgence in popularity. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) European drug report 2016, around 2.1 million young adults (15–34) used ecstasy/MDMA recreationally in the European Union last year (1.7% of total population for this age group). In the UK there has been a statistically significant increase in prevalence of use in 15–34 year olds from a low point of 2.5% in 2012, to 3.5% in 2014. This followed a gradual decline in use since 2000 where prevalence was 4.5% in this population (European drug report, 2016). This return in popularity follows innovations by drug producers to improve negative perceptions about low quality ecstasy in the drug market. This has led to increases in tablet/powder/crystal strength, so that many MDMA pills now often contain around 150 mg of MDMA (Drugs Information and Monitoring System, Annual Report 2015). Thus recreational ecstasy use poses a serious public health concern and highlights new challenges that the modern drug market poses (EMCDDA European Drug Report, 2016). Harm reduction strategies are thus urged to target novice users who are consuming high strength MDMA without being aware of the related psychological and psychobiological harm.

MDMA is a stimulant and empathogen drug, which can generate powerful feelings of euphoria and closeness to others, and which is used recreationally as 'Ecstasy' (Degenhardt and Hall, 2009; McCann and Ricaurte, 2007; Parrott, 2001, 2004, 2013). It has a particular affinity for the serotonin transporter (SERT), but it also affects other monoamine reuptake mechanisms such as the norepinephrine transporter (Hysek et al., 2011), therefore it has more wide ranging actions than many 'classic' stimulants (McDowell and Kleber, 1994). Nevertheless, its primary mode of action is to reverse the normal actions of the serotonin transporter, and this can release 80% of available serotonin into the synapse (Green et al., 1995). Pre-clinical research has established that repeated dosing with high doses of MDMA causes 'serotonergic neurotoxicity' in rats, monkeys, and other animal species, with reduced serotonin activity specifically in cortical brain regions. With humans,

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the first neuroimaging studies found a reduced density of serotonin transporters specifically in thalamic and striatal regions in abstinent Ecstasy/MDMA users (McCann et al., 1998; Semple et al., 1999). Lower indices of serotonin activity have been confirmed in many subsequent human studies, using an array of neuroimaging procedures (Benningfield and Cowan, 2013; Cowan 2007; Di Iorio et al., 2012; Erritzoe et al., 2011; Kish et al., 2010; Reneman et al., 2006).

The working hypothesis for these serotonergic changes is that they reflect distal axotomy – the loss of synaptic terminals from the long-fine serotonin axons terminating in the higher brain regions. There is an ongoing debate over whether such serotonergic changes reflect neurodegeneration, or other changes such as neuroplasticity (Biezonski and Meyer, 2011). Whatever the underlying mechanism is, serotonin activity is clearly reduced after chronic MDMA exposure. After reviewing the alternative explanatory models, Biezonski and Meyer (2011) concluded: "*Given the plethora of evidence showing the 5-HT and SERT-depleting effects of MDMA, this substance can certainly be considered 'neurotoxic' in terms of causing serotonergic dysfunction*" (p. 86). In another review which included further empirical findings, Benningfield and Cowan (2013), similarly concluded: "*The current evidence strongly suggests that human recreational MDMA use leads to chronic reductions in neocortical serotonin signalling*" (p. 255).

In the following sections, imaging studies are reviewed that investigated the link between brain functions and cognitive performance in human MDMA users employing molecular imaging (e.g., positron emission tomography [PET] and single-photon emission computed tomography [SPECT]), functional neuroimaging (e.g., functional magnetic resonance imaging [fMRI]), electroencephalography (EEG), and near-infrared spectroscopy (fNIRS). Given the focus of this review on neurocognition, is important to note that most studies in this area attempt to control for IQ differences, and in the majority of cases there is little difference in IQ between ecstasy using populations and controls (e.g. Roberts et al., 2013a; Roberts and Montgomery, 2015a,b).

2. Molecular imaging studies with cognitive performance measures

Reneman et al. (2000) investigated whether MDMA use produced alterations to post-synaptic 5-HT2A receptors and memory function, by administering the – radioligand [123I]R91150, as well as a verbal memory test (Rey Auditory Verbal Learning Test – RAVLT) to 5 MDMA users and 9 controls. Binding ratios were significantly higher in the MDMA user group, in the occipital cortex. It is suggested that the higher density of 5-HT2A receptors, reflects upregulation of postsynaptic 5-HT2A receptors as a result of 5-HT depletion. Performance on the memory task was significantly reduced in MDMA users relative to controls and this was correlated with mean 5-HT2A receptor binding in the MDMA group. The authors suggest that these results reflect memory deficits that are attributable to MDMA induced 5-HT deficits. However, it was also conceded that this should be treated as pilot data, due to the small sample size.

Serotonin transporter densities were examined in 22 current MDMA users, 13 former users and 13 controls by Reneman et al. (2001). SERT and memory function (using the RAVLT) were assessed to observe if there were correlations between the two and whether prolonged abstinence could lead to recovery. Current MDMA users displayed lower cortical [^{123}I]ßCIT binding than controls, however, no significant differences in binding were observed between former users and controls. Immediate and delayed recall performance on the RAVLT was poorer for both ecstasy user groups relative to controls. However, this was not correlated with [^{123}I]ßCIT binding. It was concluded that the lower SERT densities in current MDMA users reflects neurotoxic effects, which may be reversible.

McCann et al. (2008) conducted PET using [^{11}C]DASB to investigate SERT binding, alongside [^{11}C]WIN 35,428 to investigate dopamine transporter (DAT) binding. The MDMA users in this study had all reported having sequential doses of MDMA (2 or more doses over a 3–12 h period). Subjects also underwent formal neuropsychiatric testing (tests of memory, attention and executive function). The results indicated that SERT binding was significantly reduced in multiple brain regions for MDMA users relative to controls (occipital cortex, parietal cortex, temporal cortex, anterior cingulate cortex, posterior cingulate cortex, dorsolateral prefrontal cortex [DLPFC], and hippocampus). The reductions were greatest in cortical regions (especially the occipital cortex) and there were no significant differences in SERT binding in subcortical regions. No differences were observed between users and controls in DAT binding in the caudate or putamen, and no relationship was found between measures of MDMA use and DAT binding, suggesting normal dopamine function. There was, however, a significant negative correlation between SERT availability in the hippocampus and duration of MDMA use. These results reflect the specificity of MDMA as a selective serotonin neurotoxin and suggest that sequential dosing is associated with lasting decreases in SERT. Memory performance was also correlated with SERT binding in the DLPFC, orbitofrontal cortex and parietal cortex, across groups. However, curiously the strength of this relationship was greater in controls than in MDMA users suggesting that MDMA use potentially disrupts this relationship, or that compensatory recruitment of other resources are being used.

Kish et al. (2010) undertook a comprehensive neuroimaging and cognitive performance study of 49 moderate Ecstasy users, and 50 non-user controls. They found significant SERT binding reductions in every region of the cerebral cortex, and the hippocampus. A particular strength of this study was the wide range of potential confounds being controlled: recent MDMA use was confirmed through biochemical analysis of hair samples, the influence of other psychoactive drugs was systematically covered, while gender, gene polymorphism, and chronic tolerance, were also monitored. For these reasons, it was concluded that SERT binding reductions were not related to structural brain changes, polydrug use, blood testosterone or estrodial levels, gender, psyvholoical health or SERT gene polymorphism. The study included a neurocognitive test battery, and whereas performance on simpler tasks such as Trail Making Test-A were normal, more complex tasks such as Trail Making Test-B and California Word Learning were significantly impaired. Furthermore, lower performance on short-term-memory tasks was correlated with lower SERT within the insular cortex and hippocampus.

An imaging study employing 2-deoxy-2-(^{18}F)fluoro-D-glucose Positron Emission Tomography (in rest) in 19 male MDMA users and 19 male drug-naïve controls revealed that MDMA users show significantly decreased regional cerebral brain glucose metabolism (rMRGlu) in the bilateral dorsolateral prefrontal and inferior parietal cortex, bilateral thalamus, right hippocampus, right precuneus, right cerebellum, and pons (at the level of raphe nuclei) (Bosch et al., 2013). Within the MDMA user group, worse verbal learning and delayed recall performance were correlated with lower rMRGlu in bilateral frontal and parietal brain regions, while reduced recognition performance was additionally associated with less rMRGlu in the right mediotemporal and bihemispheric lateral temporal cortex. Moreover, a higher cumulative lifetime dose of MDMA was related to lower rMRGlu in the left dorsolateral and bilateral orbital and medial prefrontal cortex, left inferior parietal and right lateral temporal cortex. The authors therefore concluded that memory deficits related to MDMA use arise from a combined fronto-parieto-mediotemporal dysfunction.

Thus, there are several molecular imaging studies that report neurocognitive performance changes that are in parallel with serotonergic and metabolic adaptations following repeated use of MDMA. One strength of using PET and SPECT imaging is that radioligands can be used that show specificity for SERT or 5-HT2A receptors, this can reduce the potential for polydrug use to confound results as the most commonly co-used drugs are not known for their serotonergic effects. MDMA use is regularly associated with SERT reductions (for a meta-analysis and review see Roberts et al., 2016b), whereas the association

Table 1
fMRI studies with ecstasy users.

Authors	Methodology	Findings
Becker et al. (2013)	Prospective fMRI study on 40 ecstasy/amphetamine users <5 doses at t1 and >5 doses at t2) during associative memory. At follow up split into: 17 'users' (14 male, mean age = 22.71 ± 3.18, MLD = 3.26 ± 1.59, interim dose = 9.50 ± 7.89 tablets) 11 'sporadic users' (6 male, mean age = 21.91 ± 3.17, MLD = 3.15 ± 1.75, interim dose = 2.95 ± 4.22) and 12 abstinent interim controls (mean age = 23.42 ± 3.97, MLD = 2.66 ± 1.77).	No task differences. Ecstasy related decreased activation in left parahippocampal gyrus
Daumann et al. (2003b)	Functional analysis during n-back task: 11 heavy ecstasy users (8 male, mean age = 27.00 ± 3.92 MLD = 258.18 ± 220.25 tablets), 11 moderate ecstasy users (8 male, mean age = 23.27 ± 2.49, MLD = 27.36 ± 5.61), 11 non-user controls (mean age = 25.64 ± 2.34).	No task performance differences. Heavy users showed weaker BOLD responses in left frontal and temporal regions on the most difficult level of the task (2-back) relative to the other two groups (at liberal significance level $p < 0.01$, and $p < 0.001$ uncorrected). Both user groups showed increased activation in the right parietal cortex with 1 and 2 back tasks. Extent of previous drug use did not correlate with BOLD signal changes.
Daumann et al. (2003b)	Functional analysis during n-back task: 8 pure ecstasy users (no regular use of any other drugs, mean age = 25.30 ± 3.62, MLD = 74.50 ± 70.53 tablets), 8 polyvalent ecstasy users (concomitant use of ecstasy and amphetamines and cannabis, mean age = 26.41 ± 3.70, MLD = 56.25 ± 28.38 tablets), 8 non-user controls (mean age = 25.55 ± 3.22)	No task performance differences. Pure MDMA users showed reduced BOLD activation in the temporal gyrus and angular gyrus in the 1-back task compared to controls. Pure MDMA users had lower signal changes compared to polyvalent users in the striate cortex and higher BOLD response in the premotor cortex. Pure MDMA users showed lower activation than both other groups in the angular gyrus during 2-back (more difficult) level of the task.
Daumann et al. (2004)	Functional analysis during n-back task, in an 18 month longitudinal study: 30 ecstasy users (at time 1, reducing to 21 users by time two) a group that were abstinent during the interval period (n = 8, 6 male, mean age = 24.50 ± 1.60 MLD = 243.75 ± 271.87 tablets) and a group that continued to use ecstasy during the interval period (n = 9, 5 male, mean age = 25.67 ± 3.97, MLD = 149.44 ± 179.38 tablets, interim dose = 35.56 ± 22.83 tablets)	No group differences in task performance at time 1 or 2.Continuing users showed increased activation from baseline in two clusters in the parietal cortex during the most difficult level of the task (2-back) at time 2 compared to time 1. Increase in haemodynamic activation between time 1 and time 2 associated with higher one night dose of MDMA.
Daumann et al. (2005)	fMRI during episodic memory in 12 ecstasy users (7 male, mean age = 26.27 ± 3.66, MLD = 201.73 ± 224.18 tablets, mean time since last dose = 51.64 ± 56. 37 days) and 12 matched controls (7 male, mean age = 26.25 ± 2.56)	Ecstasy related reductions in left anterior hippocampus. Equivalent task performance
Jacobsen et al. (2004)	Functional analysis during selective and divided attention and verbal working memory: 6 adolescent ecstasy users (average of 10 episodes of MDMA use, mean age at first use = 15.8, little use of other drugs other than cannabis and alcohol, mean age = 17.3), 6 adolescent ecstasy naïve controls (matched for age and gender)	No task performance differences. Ecstasy users showed reduction in left hippocampal deactivation at the most difficult level of an n-back working memory task. Time since last use negatively correlated with left hippocampal activity.
Jager et al.	Prospective study on 25 participants pre and post first ecstasy use. i.e. minimal exposure (9 male, at follow up: mean age = 22.8 ± 2.7 MLD = 2.0 ± 1.4, mean time since last	No observed behavioural or

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Table 1 *(continued)*

Authors	Methodology	Findings
(2007).	dose = 11.1 ± 12.9 weeks). fMRI during WM, attention and associative memory	neurophysiological effects.
Jager et al. (2008)	Functional analysis during working memory, attention and associative memory tasks: 33 ecstasy users (MLD = 322 ± 357 tablets), 38 non-user controls	No significant effects of ecstasy or any other drugs on performance or brain activity relating to working memory (modified Sternberg task) and attention (SAT task). However in the associative learning task ecstasy use predicted lower activity in the left DLPFC and higher activation in the right middle occipital gyrus, reflecting compensatory mechanisms.
Moeller et al. (2004)	Functional analysis during immediate and delayed memory task: 15 ecstasy users (12 male, mean age = 24.7 ± 3.4, mean lifetime uses = 193.5 ± 239.7), 19 non-user controls (11 male, mean age = 25.4 ± 6.0)	Equivalent task performance. Ecstasy users displayed significantly greater BOLD activation compared to controls in three clusters: 1-the left medial and superior frontal gyri with extending activation to the right medial superior frontal gyri, bilateral anterior cingulate gyri, and right middle frontal gyrus. 2- left thalamus extending to left caudate and putamen, left parahippocampal gyrus, left hippocampus and left insula. 3- right hippocampal gyrus extending to the right hippocampus, right thalamus, right lentiform nucleus, right putamen, right insula, and right temporal cortex. Effects remained after controlling for other drugs except in the prefrontal cortex after controlling for cannabis use.
Raj et al. (2010)	Functional analysis during a semantic recognition task in 16 ecstasy polydrug users (10 male, mean age = 23.6 ± 2.7, 12 with a history of MDMA use, mean episodes of use = 43.33 ± 40.73)	During semantic recognition, but not encoding- lifetime episodes of MDMA use and lifetime dose were both inversely correlated with% BOLD signal change at BA 9. Lifetime episodes of use was inversely correlated with BOLD signal change in BA 18 and 21/22. After controlling for other drugs the correlation at BA 9 remained significant.
Roberts et al., 2009	fMRI during face learning task. Twenty ecstasy users (mean age = 22.4 (18.1–28.4), MLD = 406.5 (50–1500)) 20 drug naïve controls (10 male, mean age = 22.5 (18–29)), 14 cannabis users (12 male, mean age = 22.4 (18.3-32))	Ecstasy users worse at task than controls. Ecstasy users display reduced anterior cingulate and parietal cingulate cortex activity, and increased frontal cortex, left temporal and right parietal lobe activity.
Roberts et al., 2009	Functional analysis during Go/NoGo task in 20 ecstasy users (10 male, mean age = 22.4 ± 0.7, MLD = 406.5 ± 88.1 tablets) and 20 drug naïve controls (10 male, mean age = 22.5 ± 0.6).	Ecstasy users displayed greater activity in right middle and inferior frontal gyri, right middle frontal

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Table 1 *(continued)*

Authors	Methodology	Findings
		gyrus and right inferior parietal lobule, during successful response inhibitions, compared to controls. Ecstasy users also displayed greater error activation in the right middle and inferior temporal gyri. It is suggested that increased activation despite equivalent performance, shows increased neuronal recruitment to inhibit in ecstasy users.
Watkins et al. (2013)	Two part fMRI semantic encoding and retrieval task: 23 ecstasy users (17 male, mean age = 24.57, median LD = 1250 (300–12500) tablets, 11 controls (5 male, mean age = 22.36)	No performance differences. However ecstasy users show greater activation in BA7, 39 and 40 during encoding. Lifetime dose associated with right superior parietal lobe activation

MLD = mean lifetime dose (ecstasy), fMRI = functional Magnetic Resonance Imaging, BOLD = Blood Oxygen Level Dependent, WM = working memory, SAT = sustained attention task, DLPFC = dorsolateral prefrontal cortex, BA = Brodmann's area, BIS = Barratt's Impulsivity Scale.

between SERT and cognitive performance is less clear. Kish et al. (2010) use a large sample as well as controlling for many confounders and suggest SERT reductions are associated with poorer cognitive performance. McCann et al. (2008) also note this association but suggest this is not MDMA specific. Overall the data are in line with neuroimaging measures being able to detect neuronal adaptation prior to functional deficits manifesting themselves.

3. *fMRI* studies and neurocognitive performance (Table 1)

In the first functional imaging experiment with ecstasy users, Daumann et al. (2003a) administered an *n*-back task to 11 moderate ecstasy users, 11 heavy users and 11 healthy controls, during fMRI. Task performance was equivalent between groups and there were no differences in activation at any level of the task at $p < 0.05$ level (corrected). Whereas using a more liberal significance level ($p < 0.01$, and $p < 0.001$ uncorrected) heavy users showed weaker BOLD responses in left frontal and temporal regions on the most difficult level of the task (2-back) relative to the other two groups. Also, both user groups showed increased activation in the right parietal cortex with 1 and 2 back tasks. However, extent of previous drug use did not correlate with BOLD signal changes. It is suggested that these results may reflect subtle brain functioning alterations associated with MDMA use. Given that at the most appropriate corrected significance level, ecstasy users showed cortical activations that are equivalent to controls, and that there were no performance differences between groups, as well as small sample size it seems pertinent to treat this study as an exploratory analysis for future research to build on.

In a similar fMRI/n-back study, Daumann et al. (2003b) studied BOLD activation in 8 pure ecstasy users (no regular use of any other drugs), 8 ecstasy polydrug users, and 8 healthy controls. Performance on the n-back was equivalent between the three groups and all groups showed typical cortical activation patterns during the task. At the more difficult 2-back level of the task, pure MDMA users showed lower activation than both other groups in the angular gyrus. It is concluded from these results that MDMA is associated with neuronal alterations that may reflect MDMA-induced neurotoxicity and that altered fMRI patterns are not associated with concomitant use of other drugs. The strength of this study is the inclusion of what the authors term a 'pure' ecstasy user group, as an attempt to reduce findings from polydrug use. At the most difficult level of the task MDMA users showed reduced BOLD compared to both other groups in the inferior temporal gyrus, the angular gyrus and the striate cortex, suggesting an ecstasy-specific effect in these brain regions that is more pronounced as task difficulty increases. However, as with many studies in this area the sample size is potentially problematic when interpreting the effects.

Furthermore, a longitudinal study from the same research group (Daumann et al., 2004) conducted an 18-month follow-up fMRI study, using the n-back in ecstasy polydrug users. The ecstasy users were categorised according to whether they chose to continue (n = 5) or cease (n = 8) use during the 18-month period. Task performance was equivalent between groups at time 1 and 2. fMRI results at time 1 suggested no differences in cortical activation between the two groups. At time 2 cortical activation patterns did not alter significantly for any level of the n-back task from baseline in the interim abstention group, whereas the continuing users showed increased activation from baseline in two clusters in the parietal cortex during the most difficult level of the task (2-back). Correlational analysis revealed that in the continuing users, increase in haemodynamic activation between time 1 and time 2 in the two clusters in the parietal cortex was associated with higher one-night dose of MDMA. Consequently, the results suggest a role for higher nightly doses in neuronal damage. The authors also suggest that neuronal damage in ecstasy users is long lasting, as the interim abstinent group did not differ (or improve) in their activation at time 2 compared to time 1, assuming that activation at time 1 was atypical. The use of a longitudinal design obviates the problems

associated with between groups designs and can assess effects of continued use over time. However, the attrition rate has a tendency to increase over longer periods of time, which explains the small sample size for follow up analysis despite recruiting 30 participants into the study initially. Nevertheless, this study provides some interesting evidence that continued use can lead to further neuronal changes (despite equivalent task performance between time 1 and time 2). Unfortunately these results are complicated somewhat by continuing users, also using amphetamines, whereas the abstinent group had abstained from amphetamine use also.

Moeller et al. (2004) studied activation in 15 MDMA users and 19 controls, whilst completing an immediate and delayed memory task. Ecstasy users displayed significantly greater BOLD activation in the left medial and superior frontal gyri, the left thalamus and right hippocampal gyrus. Most of these effects remained after controlling for use of other drugs. However, after controlling for cannabis, the effect was no longer significant in the prefrontal cortex. The authors suggest that the observed increase in activation of the BOLD signal could be due to MDMA users being less "efficient" at the working memory task, resulting in an increase in neuronal activity to perform at a similar level as controls. They also argue that increased BOLD fMRI activation in the hippocampus may be MDMA specific. Similarly Jacobsen et al. (2004) observed a reduction in left hippocampal deactivation (i.e. greater activation) in a group of 6 adolescent MDMA users relative 6 controls (matched for age and gender) at the most difficult level of an n-back working memory task, despite equivalent task performance. Correlational analysis revealed that time since last use was negatively correlated with left hippocampal activity, whereby more recent users had greater activation as measured by percent signal change, than those with the greatest duration of abstinence, potentially reflecting recovery of hippocampal neuro-circuitry after long periods of abstinence. However this study is described as a pilot study due to its small sample and lack of pre-MDMA exposure data. Conversely, hippocampal activity was restricted in ecstasy users relative to controls (analysis was confined to the hippocampus) whilst performing at an equivalent level in an episodic memory retrieval task (Daumann et al., 2005), again the authors concluded that fMRI results provide an index of abnormal cognitive function in the absence of memory deficits. A more recent prospective study (Becker et al., 2013) assessed hippocampal function during an associative memory task in 40 ecstasy users who had minimal exposure to ecstasy ($<$ 5 tablets, as well as $<$5 g of amphetamine) at time 1, and 17 participants who had continued ecstasy but had limited amphetamine use 12 months later at time 2 (interim dose of 9.5 tablets). There were no significant differences on task performance between Times 1 and 2. However, encoding related activity in the left parahippocampal gyrus decreased in the continuing ecstasy/amphetamine user group at time 2. This decrease in activation inversely correlated significantly with interim ecstasy use, but not amphetamine use, leading the authors to conclude that moderate use of ecstasy is related to changes in hippocampal functioning.

Jager et al. (2008) assessed the concomitant use of other drugs in 71 participants recruited on the basis of variations in the amount and type of drugs that they used. Thirty-three heavy MDMA users (322 tablets) and 38 non users (both groups showing considerable variation in the type and amounts of drugs they were using) completed tasks of working memory, attention and associative memory tasks in association with fMRI procedures. This study employed multiple regression analyses to parse drug effects on cognitive performance. Ecstasy use indices did not predict cognitive performance in any of the 3 domains being investigated. Moreover, there were no significant effects of ecstasy or any other drugs on brain activity relating to working memory (modified Sternberg task) and attention (Selective Attention Task). However, in the associative learning task ecstasy use predicted lower activity in the left DLPFC and higher activation in the right middle occipital gyrus. The authors suggest these results reflect long term adaptation or compensatory reorganisation of a fronto-visual network. Conversely the same research group (Jager et al., 2007) observed no behavioural or neurophysiological effects of a 'low dose' of ecstasy during working memory, associative memory and attention tasks, in a prospective study on 25 participants pre and post their first ecstasy using episode. Taken together, these results suggest that a single episode of a low dose of ecstasy (such as those given in MDMA assisted psychotherapy) may have limited neuroadaptation impact compared to higher doses (such as that associated with recreational ecstasy use).

BOLD signal change during a semantic recognition task (in which, performance was not associated with MDMA use) in 12 ecstasy polydrug users was assessed by Raj et al. (2010) in a region of interest fMRI analysis (left BA 9, 18, 21/22 and 45). Lifetime episodes of MDMA use and lifetime dose were both inversely correlated with%BOLD signal change at BA 9. Lifetime episodes of use was inversely correlated with BOLD signal change in BA 18 and 21/22, though no such correlations were observed for the encoding phase of the task, suggesting that MDMA affects verbal recognition but not encoding. These results were complicated by inverse correlations between lifetime cocaine use and BOLD signal activation in left BA 9 and 18 as well as a statistically significant inverse correlation between cannabis use and activation in left BA 9. Nonetheless, after controlling for lifetime cocaine and cannabis use, the association between MDMA use and BA 9 activation remained statistically significant. Correlational analyses such as these can give us an indication of cumulative effects of ecstasy on neural activation; however using lifetime episodes as an indicator of intensity of use is problematic as this does not give an indication of nightly doses. Furthermore this study had a small sample size and all participants were polydrug users (with a fairly high amount of LSD and methamphetamine use).

Semantic memory was also investigated by Watkins et al. (2013) with a two-part fMRI encoding and recognition task. Twenty-three ecstasy users were compared to 11 controls, and whilst their task performance did not differ, activation was greater during the encoding phase of the task for ecstasy users in BA7, 39 and 40. Furthermore peak activation in the right superior parietal lobe was correlated with lifetime dose of ecstasy. Once again this study demonstrates an ecstasy-related decrease in cortical efficiency for semantic memory.

Neurophysiological correlates of impulse inhibition were explored in 20 ecstasy users and 20 drug naïve controls by Roberts et al., 2009. fMRI data showed that ecstasy users displayed greater activity in right middle and inferior frontal gyri, right middle frontal gyrus and right inferior parietal lobule, during successful response inhibitions (STOPS) on a Go/NoGo task, compared to controls. Ecstasy users also displayed greater error activation in the right middle and inferior temporal gyri. Deactivation in the left medial frontal gyrus and left posterior cingulate was significantly greater for controls on error trials. It is suggested that the increased activation displayed by ecstasy users despite no significant behavioural differences, shows increased neuronal recruitment required to inhibit in this group. Recruitment of additional resources to maintain performance, suggests a subtle functional impairment that would have not been exposed with behavioural measures alone. Roberts et al., 2009 recorded fMRI during another cognitive measure − facial recognition/learning. The abstinent Ecstasy/MDMA user group were significantly worse at face learning than the illicit drug control group of abstinent cannabis users, and the legal drug control group of non-users. The functional neuroimaging revealed *hyper*activity in various brain regions, including the frontal cortex, left temporal lobe, and right parietal lobe. It also revealed *hypo*activity in the anterior cingulate, and parietal cingulate cortex.

Overall these data suggest that fMRI can be used as a sensitive measure of neuronal changes prior to the appearance of performance indicators of cognitive deficits. However, gaining concrete conclusions from the literature is problematic due to several of these studies having small sample sizes − a problem that is common in fMRI research. Moreover to make sense of whether an increase or a decrease in BOLD reflects a subtle neuronal deficit, it is necessary to understand the

direction of task performance, for example, the strongest indication of MDMA related neuroadaptation comes from studies such as Moeller et al. (2004), Watkins et al. (2013), Roberts et al., 2009; Roberts and Garavan (2010) that suggest significant increases in BOLD, despite equivalent performance, in studies with adequate sample sizes. Prospective studies are a useful tool in this area and can provide information about neuroadaptation in relation to initiating/continuing use. Becker et al. (2013) suggest reliable changes in hippocampal functioning following intake of under 10 tablets. However the hippocampal activity in this study is in a different direction to that in Moeller et al. (2004), perhaps reflecting divergent hippocampal activity based on task type (immediate and delayed recall vs associative memory).

4. fNIRS studies and neurocognitive performance (Table 2)

A novel functional imaging technique to assess neurocognition in ecstasy user populations is functional NIRS. Similar to fMRI, it is an indirect measure of neuronal activation, based on the principle that neuronal firing and haemodynamic response are closely linked. This technique uses near-infrared light to calculate amounts of circulating oxy and deoxy-Hb in the PFC. There are currently only 3 published articles in the ecstasy-neurocognition literature, the first of which (Roberts et al., 2014) assesses performance of ecstasy polydrug users, polydrug controls and drug naïve controls during a multitasking stressor. Multitasking performance was similar between groups in this instance; however, fNIRS suggested ecstasy users displayed lower oxygenated Hb response relative to drug naïve controls in the left DLPFC and the right DLPFC, which the authors conclude could be related to cerebral vasoconstriction. Roberts and Montgomery (2015a) observed increases in oxy-hb in ecstasy users relative to controls during equal performance on an inhibitory control task in several voxels indicating increased activation in the inferior right medial prefrontal cortex, and the right and left dorsolateral prefrontal cortex. Interestingly, a regression analysis suggested that after controlling for alcohol and cannabis use indices, recency of ecstasy use was a significant predictor of oxy-Hb at 2 voxels pertaining to the right PFC. Similarly, during a word fluency task completed by 20 ecstasy users and 20 non-user controls (Roberts and Montgomery, 2015b), ecstasy users displayed increased oxy-Hb compared to controls over several voxels located over the left DLPFC and the right medial PFC. Performance was equivalent between groups. Further to this, ecstasy use indices – lifetime dose, last 30-day use and frequency of use were significant predictors of oxy-Hb increase in several voxels, after controlling for alcohol and cannabis indices. The interpretation of these two studies is that ecstasy users are showing heightened responses (increased effort) in 5-HT rich areas of the PFC to achieve similar performance to controls during executive tasks. This is understood to be a compensatory mechanism necessitated by neurocognitive decline (Table 2).

5. Electroencephalograpy and sensory evoked potential stuides

In two highly similar studies, Tuchtenhagen et al. (2011) and Croft et al. (2001) investigated the intensity dependence of auditory evoked potentials with EEG, which has been suggested as an electrophysiological index of serotonergic functioning (Hegerl and Juckel 1993; Juckel et al., 1997). In both studies, currently abstinent, long-term MDMA users showed a significantly stronger gradient of their EEG response to increasing loudness of auditory stimuli compared to regular cannabis users as well as drug-naive controls. Only in the study of Croft et al. (2001), the degree of electrophysiological stimulus intensity dependence was positively correlated with cumulative lifetime use of Ecstasy tablets. The authors from both studies concluded that the electrophysiological pattern was theoretically consistent with the notion of an MDMA-induced serotonergic impairment. In a subsequent longitudinal study, Daumann et al. (2006) assessed the loudness dependence of auditory evoked potentials (LDAEP) at baseline and at an 18-months follow-up in an independent sample of 18 MDMA users without ascertaining a control group. Because of problems with the group assignment and due to a lack of power, abstinent/occasional users did not differ from continuing users regarding baseline LDAEP or its change during the interval. However, frequency of MDMA use, cumulative lifetime dose and period of abstinence were associated with the LDAEP in these users confirming the previous correlation reported by Croft et al. (2001). Although the LDAEP seem to be stable over time this result was interpreted again as consistent with a serotonergic change/neurotoxicity of MDMA. In a subsequent study, Wan et al. (2009) compared the LDAEP of 16 polydrug users with and 23 polydrug users without MDMA use. Again MDMA-experienced polydrug users showed a stronger tangential dipole source activity with increasing loudness of the acoustic stimuli compared to non-MDMA drug users. However, the authors reported an unusually high response to the lowest 60 dB stimulus intensity in both groups, so that they excluded this condition from their final analyses. Interestingly, MDMA users showed a history of more aggressive behaviour and higher aggression scores were correlated with pronounced intensity stimulus dependence of the source activity. Moreover, in a classification analyses intensity dependence as well as aggression scores correctly identified 73.3% of those who have used MDMA regularly and 78.3% of those who had not. Consequently, also these authors concluded that "*chronic ecstasy exposure results in serotonin deficiency condition*" (Wan et al., 2009, p. 1489). Up to now it is, however, still controversial if the intensity dependence of auditory evoked potentials in fact reflects central serotonin activity (for discussion please see: Juckel, 2015; O'Neill et al., 2008).

Casco et al. (2005) investigated amplitude and latency of visual evoked potentials (VEP) employing EEG in small groups of 8 heavy MDMA users (mean 1054 exposures lifetime), 8 moderate MDMA users (52 exposures lifetime), and 18 drug-free control participants. With the exception of one individual, all users reported to be abstinent for at least 6 months. In a simple psychophysical discrimination task the heavy users committed more errors than both other groups. In comparison with the controls, heavy users showed strongly decreased amplitudes of the intermediate (P200) and late (P300) components at the Oz electrode and of the P250 and P300 components at the *Fz* electrode in response to the visual stimulation. However, also moderate users showed significantly lower amplitudes of the P300 component at both investigated electrodes (*Oz*, *Fz*) compared to controls. In contrast, the three groups did not differ in their amplitude of early components (P100 and N150), reflecting intact early processing of visual input. The authors concluded, "*that cortical activity associated with low levels of cognitive processing is altered after prolonged exposure to ecstasy*" (Casco et al., 2005, p. 193).

6. Electroencephalography and event-related potential studies (Table 3)

Gamma et al. (2005) employed EEG during a continuous performance task and assessed event-related potentials (ERPs) to Go and NoGo trials in 16 current polydrug MDMA users and 17 MDMA-naïve controls. Both groups did not differ in task performance and showed robust and normal patterns of P300 anteriorization and delay in the inhibition (NoGo) compared to the execution (Go) condition. However, MDMA users displayed diminished amplitudes of the P300 component above central midline structures across both conditions, higher P300 NoGo amplitudes over the right posterior cortex, and a less anterior location of P300 peaks in the NoGo condition. The authors discussed that lowered midline P300 amplitudes during NoGo trials might reflect reduced cortical inhibition, which would be in line with the observation of behavioural disinhibition of MDMA users (Morgan, 1998; Quednow et al., 2007). However, given that the neuroelectric pattern associated with the switch between execution and inhibition was intact, and that a less pronounced anteriorization of the P300 wave during NoGo trials is usually related to less impulsivity, the authors concluded that their

Table 2
fNIRS studies with ecstasy users.

Authors	Methodology	Findings
Roberts et al. (2014)	Oxy and deoxy-Hb response in the PFC (16 voxels) during multitasking stressor in 20 ecstasy users (12 male, mean age = 21.61 ± 0.52, MLD = 253.86 ± 376.20), 17 polydrug users (12 male, MLD = 21.23 ± 0.79) and 19 drug naïve controls (6 male, mean age = 21.60 ± 0.84).	No task performance differences. Lower oxy-Hb response for ecstasy users compared to drug naïve controls in LDLPFC and RDLPFC.
Roberts and Montgomery (2015a)	Oxy and deoxy-Hb response in PFC (16 voxels) during inhibitory control (RLG) in 20 ecstasy users (13 male, mean age = 21.85 ± 2.76, MLD = 431.75 ± 885.08 tablets) and 20 non-users (7 male, mean age = 20.89 ± 2.05).	No task performance differences. Users display increased activation in the inferior right medial prefrontal cortex, and the RDLPFC and LDLPFC.
Roberts and Montgomery (2015b)	Oxy and deoxy-Hb response in PFC (16 voxels) during semantic access in 20 ecstasy users and 20 controls (same as Roberts et al., 2015a)	Equivalent task performance, with ecstasy users displaying greater oxy-Hb increase than controls in LDLPFC and right MPFC. Lifetime dose, last 30 day use and frequency of use significant predictors at several voxels in a regression model after controlling for alcohol and cannabis.

MLD = mean lifetime dose (ecstasy), Oxy-Hb = oxygenated haemoglobin, deoxy-Hb = deoxygenated haemoglobin, LDLPFC = left dorsolateral prefrontal cortex, RDLPFC = right dorsolateral prefrontal cortex, PFC = prefrontal cortex, RLG = Random Letter Generation, MPFC = medial prefrontal cortex.

Table 3
EEG studies with ecstasy users.

Authors	Methodology	Findings
Tuchtenhagen et al. (2011)	Auditory evoked potentials: 28 ecstasy users (16 male, mean age = 23.25 (18–29), MLD = 93.4 ± 119.9 tablets), 28 cannabis users (15 male, mean age = 22.9 (18–31)), 28 controls (17 male, mean age = 23.5 (18–30)).	MDMA users show a significantly stronger gradient of EEG response to increasing loudness of auditory stimuli compared to regular cannabis users and drug-naive controls
Croft et al. (2001)	Auditory evoked potentials: 22 MDMA users (13 male, mean age = 27.1 ± 5.9, MLD = 225.9 tablets ± 8.2), 19 cannabis users (13 male, mean age = 34.2 ± 9.7), 20 drug naïve controls (10 male, mean age = 29.1 ± 8.4).	Lifetime dose positively correlated with increased EEG response
Daumann et al. (2006)	LDAEP: 18 ecstasy polydrug users at baseline and 18 months follow up (15 male, mean age = 24.72 ± 3.75, MLD = 23.78 ± 35.42 tablets, mean time since last use = 386.39 ± 614.27 days)	No difference in LDAEP from baseline to follow up. However, frequency of MDMA use, cumulative lifetime dose and period of abstinence were associated with LDAEP response.
Wan et al. (2009)	LDAEP: 16 MDMA polydrug users (13 male, mean age = 35.56 ± 11.38, 23 polydrug users without MDMA use (18 male, mean age = 41 ± 10.26)	MDMA polydrug users show stronger tangential dipole source activity with increasing loudness of acoustic stimuli.
Casco et al. (2005)	ERP components of VEPs assessed during a simple discrimination task: 8 heavy ecstasy users (7 male, mean age = 28 ± 2.6, MLD = 1054.1 exposures), 8 moderate users (7 male, mean age = 25 ± 2.0, MLD = 52.4 exposures), and 18 drug free controls (limited drug use, split into 2 sub-groups of 19–23 years n = 9, 3 male and 24–32 years n = 9, 5 male)	Heavy users showed significantly reduced P2 and P3 amplitudes at Oz compared to controls. Moderate users showed significantly reduced P3 amplitude relative to controls. P3 was significantly reduced in both heavy and moderate users compared to controls at Fz. N250 significantly reduced in heavy users relative to controls.
Gamma et al. (2005)	ERP P3 assessed during Go/NoGo preformance in 16 ecstasy users (8 male, mean age = 22.6 (19–27), MLD = 270.2 tablets (43–1500)) and 17 controls (10 males, mean age = 26.0 (22–30), less extensive drug use)	No task performance differences. Ecstasy users show significantly reduced P3 in relation to NoGo trials at midline electrodes Fz and Cz. After controlling for age, education and cannabis use, Fz became non-significant. No between group differences in P3 latencies. No correlation between P3 amplitude or latency and lifetime MDMA use.
Mejias et al. (2005)	ERP components assessed while conducting visual oddball task: 14 ecstasy users (mean age = 24.64 ± 3.13, MLD = 143.07 ± 109.12 tablets), 14 controls (mean age = 25.57 ± 1.74, matched for scores for depression and anxiety and cannabis use)	Ecstasy users slower to respond to fearful stimuli than controls. Ecstasy users showed a greater latency of the P3b component compared to controls for rare stimuli.
de Sola et al. (2008)	ERP components assessed in relation to an auditory oddball paradigm in 14 ecstasy users (6 male, mean age = 25.2 ± 3.3, mean total lifetime use = 207.4 ± 151.0 at baseline), 13 cannabis users (5 male, mean age = 25.1 ± 2.9, daily cannabis use or at least 25 times in lifetime) and 22 drug naïve controls (7 male, mean age = 24.3 ± 3.0). Longitudinal study.	No significant between group differences for P3 amplitude or latency at time 1 or time 2. Correlations between MDMA use and P3 response not significant at time 1 or time 2. However, lifetime cannabis use and P3 latency significantly correlated at time 1, with greater cannabis use

(continued on next page)

Table 3 *(continued)*

Authors	Methodology	Findings
		associated with increased neuronal processing speed.
Burgess et al. (2011)	ERPs analysed during two recognition memory tasks in 15 ecstasy users (7 male, mean age = 24.1 ± 3.6, mean lifetime MDMA uses = 138 ± 119), 14 cannabis users (7 male, mean age = 21.9 ± 3.1) and 13 non-drug users (6 male, mean age = 22.3 ± 3.7)	No between group performance differences. Significantly reduced late positive ERP over left parietal sites in ecstasy users compared to both other groups for the recollection component of the task.
Nulsen et al. (2011)	ERPs analysed during forward and backwards digit span task: 11 ecstasy users (4 male, mean age = 22.9 ± 2.6, MLD = 32.5 ± 27.2 tablets), 13 polydrug controls (4 male, mean age = 23.2 ± 3.3), 13 non-drug controls (4 male, mean age = 23.2 ± 4.5)	Both control groups show significantly reduced P3 in the digit backwards task than the digit forwards task. This difference is not evident in ecstasy users, despite showing greatest discrepancy in performance between the two tasks.
Roberts et al. (2013a)	ERPs analysed during Go/NoGo performance: 20 ecstasy users (10 male, mean age = 23.95 ± 0.57, MLD = 177.65 ± 301.73 tablets) 20 polydrug controls (9 male, mean age = 22.58 ± 0.79), 20 non-drug controls (7 male, mean age = 23.1 ± 0.66).	No between group performance differences. MDMA polydrug users showed a significantly higher mean amplitude of P200 at the frontal midline electrodes Fz and FCz compared to both control groups.
Roberts et al. (2013b)	ERPs analysed during semantic association task performance: 20 ecstasy users, 20 polydrug controls, 20 non-drug controls (same as Roberts et al., 2013a).	No between group performance differences. Marginally significant between-group differences in N2, with greater negativity at occipito-parietal electrodes in ecstasy users compared to drug-naïve controls.
Roberts et al. (2013c)	ERPs analysed during number/letter switching performance: 20 ecstasy users, 20 polydrug controls, 20 non-drug controls (same as Roberts et al., 2013a).	No between group performance differences. MDMA users and polydrug controls displayed a reduction in positivity of the P300 at parieto-occipital electrodes in comparison to the drug-naïve controls. MDMA polydrug significantly increased negativity of N2 at several occipito-parietal electrodes relative to non-MDMA polydrug users and non-drug using controls

MLD = mean lifetime dose (ecstasy), EEG = electroencephalography, LDAEP = loudness dependence of auditory evoked potentials, ERP = event related potentials, VEP = visually evoked potentials

results do not support disturbed inhibitory brain mechanisms in MDMA users (Gamma et al., 2005). Of note, some of the healthy controls in this study reported cannabis, cocaine, LSD, or "magic mushroom" use so that this non-finding has to be interpreted with caution.

Meijas et al. (2005) found a complex pattern of behavioural and ERP differences between 14 MDMA users and 14 matched normal controls using a 'visual oddball' EEG task in which the participants had to detect rare faces with fearful expressions among common happy faces. The authors reported that MDMA users showed slower responses to rare (fearful) stimuli than the controls. Moreover, MDMA users show generally decreased N170 amplitudes during face presentation in general. While controls showed the expected lowered latency of the N200 component to rare fearful stimuli in contrast to common happy stimuli (reflecting attention orientation to novel stimuli) this effect was absent in MDMA users. Finally, MDMA users showed delayed P3b latencies for the detection of rare stimuli. The authors debated their findings in relation to possible changes in attentional processing, particularly to emotional stimuli, in MDMA users, which again would be theoretically consistent with a general serotonergic impairment.

De Sola et al. (2008) compared 14 abstinent ecstasy users, 13 cannabis users, and 22 non-using controls regarding neurocognitive performance and P300 ERPs at baseline and a one-year follow-up. ERPs were evoked using an auditory oddball paradigm involving sustained attention, in which a frequent standard tone and an infrequent "target" tone has to be detected. At the follow-up but not at baseline, abstinent MDMA users were significantly impaired in neurocognitive tests of semantic word fluency, processing speed, and verbal memory recognition. Higher lifetime MDMA use was significantly associated with poorer recognition of verbal memory. However, no group differences in P300 latency and amplitude were found. P300 latency was correlated with cannabis but not with MDMA use. The authors concluded that long-term MDMA use is associated with mild cognitive deficits but not with changes of the attention-related P300 wave. Because the here investigated MDMA users did also not show changes in attentional performance (which is in line with recent meta-analyses: Kalechstein et al., 2007; Rogers et al., 2009), this finding is consistent with the assumption that memory and executive functions rather than attention processes might be affected by chronic MDMA use.

Burgess et al. (2011) studied recognition memory for verbal and non-verbal content using ERPs in 15 MDMA polydrug users, 14 cannabis users, and 13 illicit-drug-naïve healthy controls. In this small sample, the authors did not find significant differences between the three groups regarding word and face recognition performance. However, MDMA polydrug users showed lower ERP amplitudes during word recognition (but not during face recognition) compared to cannabis users and drug-naive controls. This attenuation of the ERP was restricted to the late positive component over left parietal scalp sites, which has been linked with memory recollection processes previously, while the familiarity-related component was unaffected. Because of the specificity of their results the authors resumed that the disturbances in word recollection "*are consistent with the known serotonergic neurotoxicity of MDMA*" but that "*it would be premature to attribute this effect to Ecstasy use alone*" (Burgess et al., 2011, p. 555).

In a further memory ERP investigation, Nulsen et al. (2011) applied forward and backward serial recognition tasks to 11 MDMA users, 13 polydrug users, and 13 non-drug users in order to engage verbal working memory during EEG. The three small groups did not differ in their verbal working memory performance. In controls and polydrug users, the P3b component over the parietal scalp electrodes (*Pz*) was significantly larger in the digits forward task than in the digits backward task. In contrast, MDMA users did not display the increased P3b component in the forward compared to the backward condition. Although MDMA users performed equally well as the other groups, the authors concluded from their ERP findings, that putative working memory deficits of MDMA users might be explained by ineffective allocation of cognitive resources.

In a series of three experiments, Roberts et al. (2013a, b, c), investigated a sample of 20 MDMA polydrug users, 20 non-MDMA polydrug users, and 20 drug naïve controls employing a semantic retrieval task, a Go/NoGo response inhibition task, and a mental set switching task in the course of EEG recording. The groups did not significantly differ in their performance in any of these tasks. However, higher MDMA use intensity predicted a worse performance in the set switching tasks (switching costs) when recent cannabis use was considered in the regression model (Roberts et al., 2013c). During the response inhibition task, MDMA polydrug users showed a significantly higher mean amplitude of the P200 component at the frontal midline electrodes *Fz* and *FCz* when compared to both polydrug controls and drug-naïve controls, respectively (Roberts et al., 2013a). In the semantic retrieval task there was a trend for an overall group effect on the N2 component and further exploration revealed a significant difference between the MDMA-polydrug users and the drug-naïve controls, which was explained by a larger negativity of the N2 wave at occipito-parietal electrodes in the MDMA-experienced polydrug group (Roberts et al., 2013b). Finally, while performing the mental set switching task (the number-letter task) both drug groups displayed a reduction in positivity of the P300 component at parieto-occipital electrodes in comparison to the drug-naïve controls (Roberts et al., 2013c). Additionally, in MDMA polydrug users a significant increase in negativity of the N2 at several occipito-parietal electrodes was detected in comparison to non-MDMA polydrug users and non-drug using controls. The authors concluded from all three experiments that MDMA users have deficits in the processing of executive functions (including response inhibition, set switching, and semantic memory access) although no performance deficits have been revealed. This dissociation was explained by "*compensatory mechanisms or re-allocation of cognitive resources that are deployed to attenuate any observable behavioural differences caused by ecstasy-related disturbances*" (Roberts et al., 2013b, p. 387).

In summary of the ERP data, most researchers suggest that ecstasy related atypicalties reflect serotonergic changes. However, as seen with the fMRI research, in EEG research there are many experimental problems which limit consistent interpretation of the data. These again include small sample sizes, heterogeneous drug user groups and heterogeneity of activity (for example increased or decreased P300) that is open to author interpretation.

7. Conclusions

The evidence from molecular imaging studies is consistent in demonstrating alterations of the serotonin system following ecstasy use (see Roberts et al., 2016b for meta-analysis). Moreover, neurocognitive performance deficits (immediate and delayed recall, working memory) are often associated with reduced SERT binding in frontal, parietal and temporal regions (Kish et al., 2010; McCann et al., 2008). Such areas of the neocortex have long axon projections from the raphe nuclei and are understood to be more vulnerable to MDMA neuroadaptation in preclinical studies (Molliver et al., 1990). Similarly, functional imaging studies assessing haemodynamic responses to neurocognitive tasks show parallel ecstasy related changes in activity to frontal and temporal areas perhaps reflecting similar neuroadaptation or other putative changes to the serotonergic system.

fNIRS studies, for example consistently note increases in oxy-Hb in areas of the PFC associated with executive performance that reflects increased cognitive effort to maintain performance levels. These studies highlight the importance of measuring the haemodynamic response in tasks where performance is similar between groups, it also highlights the dissociation between mental effort and task performance. Ayaz et al. (2012) noted that in human operators, performance can be maintained by adopting alternative strategies or increasing mental effort, however increases in oxy-Hb predict future cognitive failure with increased demands or task changes. Similar increased activity and recruitment of additional resources is suggested in fMRI experiments that

observe ecstasy related increases in BOLD activity in prefrontal areas during cognitive inhibition (Roberts and Garavan, 2010), face recognition Roberts et al., 2009 and immediate and delayed recall (Moeller et al., 2004). Elevated hippocampal activity is also associated with ecstasy use, despite equivalent performance during working memory performance (Jacobsen, 2004; Moeller et al., 2004). Conversely MDMA related reductions in hippocampal activity have been observed during episodic memory (Daumann et al., 2005) and associative memory (Becker et al., 2013). Thus the relationship between MDMA exposure and hippocampal function is not clear from neurocognitive fMRI studies.

Reduced BOLD activation in frontal regions, despite equivalent performance on updating tasks has been reported (e.g. Daumann et al., 2003a,b; Jager et al., 2008), however these changes are subtle and in Daumann et al. (2003a) are reportedly not correlated with ecstasy use. Moreover, the same group Daumann et al. (2004) suggest increases in haemodynamic responses in the parietal cortex are associated with higher nightly doses. Whilst generally the reports on haemodynamic activity during neurocognition in ecstasy users are interpreted in terms of increased cognitive effort, or reduced serotonergic signalling, the direction of the BOLD response (increased or decreased) does suggest a reasonable amount of inconsistency in the results. One potential reason for this could be due to differences in drug use between samples. Indeed, Jager et al. (2007) suggest that low doses of ecstasy produce little performance or haemodynamic changes, and thus may not be as detrimental as regular heavy use. Interestingly a recent review of fMRI studies with moderate/light MDMA users suggests that the evidence for structural and functional brain alterations with low MDMA use is limited (Mueller et al., 2016). In line with this, the extent of previous drug use has been reported to be associated with extend of SERT availability (Kish et al., 2010) and neurocognitive function (Fox et al., 2001). Taken together, perhaps lifetime dosage is one possible explanatory factor for some of the inconsistency of the results, with low doses reflecting markedly less pronounced effects.

The ERP data with ecstasy polydrug users, is often interpreted in terms of atypical/aberrant processing that reflects changes to the serotonin system. Many studies report MDMA related alterations of neuronal activation, despite equivalent task performance. This suggests a greater sensitivity of neuroimaging techniques to detect perhaps subtle cognitive changes. However, again there are several inconsistencies with the methodology and results that make drawing firm conclusions difficult. For example, the investigated samples across all imaging types were generally small and investigated heterogeneous groups of polydrug users with and sometimes without MDMA use. Several ERP studies have investigated changes of the P300 wave showing sometimes higher, lower, or normal amplitudes of this late component (or subcomponents such as the P3b), or increased/decreased haemodynamic responses during cognitive processes, which is a good example for the heterogeneity of the previous results. While most of the authors interpret their finding in the context of the serotonergic neurotoxicity of MDMA, none of the studies have employed reliable biological markers of the central serotonin system so far. Moreover, previous studies investigated cognitive functions, such as attention, working memory, and executive functions, which have been shown to have small to moderate effect sizes in MDMA users (Kalechstein et al., 2007), while verbal memory (specifically delayed recall of words), the domain in which MDMA users are most impaired, has rarely been investigated in functional imaging studies – perhaps due to artefact problems which occur from vocalisations (with the exception of fNIRS).

It is perhaps not surprising that there are inconsistencies in the neuroimaging data, if using these techniques is not utilizing function specific tasks that more reliably yield performance deficits in ecstasy users. For example, much of the literature on executive function in ecstasy users relative to controls has shown to be very inconsistent due to many executive tasks, or working memory tasks relying on multiple cognitive abilities. It has been suggested previously (Montgomery et al., 2005) that, in terms of executive function, there may be a differential pattern of performance deficits based on function type and drug use. Thus working memory tasks, often refer to information processing, which is understood to be relatively unaffected by ecstasy use. In a meta-analysis by Roberts et al. (2016a) it was observed that using function specific tasks, ecstasy users showed performance deficits relative to controls in updating, switching and access to long term memory. Perhaps using function specific tasks would improve the consistency in the literature.

In the future, well-powered studies with more homogeneous drug-using groups might focus on cognitive functions that have been shown to be robustly impaired in MDMA users, such as declarative memory, prospective memory, in order to find the neuronal correlates of these deficits using the neuroimaging techniques. Ideally, these investigations are paired with molecular imaging, genetics or pharmacological challenges of the serotonin system in order to decipher the link between serotonergic and cognitive changes in MDMA users. However, whilst studies investigating brain activity during cognitive performance in ecstasy polydrug users require a degree of caution when interpreting results, many reflect altered neuronal functioning that is in line with neuroadaptation following repeated use. Given the recent increase in MDMA tablet/powder/crystal strength, then the magnitude of potential harm is of greater concern. Harm reduction strategies are thus urged to highlight such concerns to prospective and novice MDMA users.

References

Ayaz, H., Cakir, M.P., Izzetoglu, K., Curtin, A., Shewokis, P.A., Bunce, S.C., Onaral, B., 2012. Monitoring expertise development during simulated UAV piloting tasks using optical brain imaging. In: IEEE Aerospace Conference. USA. pp. 1–11.

Becker, B., Wagner, D., Koester, P., Bender, K., Kabbasch, C., Gouzoulis-Mayfrank, E., Daumann, J., 2013. Memory-related hippocampal functioning in ecstasy and amphetamine users: a prospective fMRI study. Psychopharmacology (Berl.) 225, 923–934.

Benningfield, M.M., Cowan, R.L., 2013. Brain serotonin function in MDMA (ecstasy) users: evidence for persisting neurotoxicity. Neuropsychopharmacology 38 (1), 253.

Biezonski, D.K., Meyer, J.S., 2011. The nature of 3, 4-methylenedioxymethamphetamine (MDMA)-induced serotonergic dysfunction: evidence for and against the neurodegeneration hypothesis. Curr. Neuropharmacol. 9, 84–90.

Bosch, O.G., Wagner, M., Jessen, F., Kuhn, K.U., Joe, A., Seifritz, E., Maier, W., Biersack, H.J., Quednow, B.B., 2013. Verbal memory deficits are correlated with prefrontal hypometabolism in (18)FDG PET of recreational MDMA users. PLoS One 8, e61234.

Burgess, A.P., Venables, L., Jones, H., Edwards, R., Parrott, A.C., 2011. Event related potential (ERP) evidence for selective impairment of verbal recollection in abstinent recreational methylenedioxymethamphetamine (Ecstasy)/polydrug users. Psychopharmacology (Berl.) 216, 545–556.

Casco, C., Forcella, M., Beretta, G., Grieco, A., Campana, G., 2005. Long-term effects of MDMA (Ecstasy) on the human central nervous system revealed by visual evoked potentials. Addict. Biol. 10, 187–195.

Cowan, R.L., 2007. Neuroimaging research in human MDMA users: a review. Psychopharmacology (Berl.) 189, 539–556.

Croft, R.J., Klugman, A., Baldeweg, T., Gruzelier, J.H., 2001. Electrophysiological evidence of serotonergic impairment in long-term MDMA (ecstasy) users. Am. J. Psychiatry 158, 1687–1692.

Daumann, J., Fimm, B., Willmes, K., Thron, A., Gouzoulis-Mayfrank, E., 2003a. Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study. Cognit. Brain Res. 16 (3), 479–487.

Daumann, J., Schnitker, R., Weidemann, J., Schnell, K., Thron, A., Gouzoulis-Mayfrank, E., 2003b. Neural correlates of working memory in pure and polyvalent ecstasy (MDMA) users. Neuroreport 14 (15), 1983–1987.

Daumann, J., Fischermann, T., Heekeren, K., Thron, A., Gouzoulis-Mayfrank, E., 2004. Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. Biol. Psychiatry 56 (5), 349–355.

Daumann, J., Fischermann, T., Heekeren, K., Henke, K., Thron, A., Gouzoulis-Mayfrank, E., 2005. Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. Psychopharmacology (Berl.) 180, 607–611.

Daumann, J., Till, B., Fischermann, T., Rezk, M., Gouzoulis-Mayfrank, E., 2006. Intensity dependence of auditory evoked dipole source activity in polydrug ecstasy users: evidence from an 18 months longitudinal study. J. Psychopharmacol. 20, 236–244.

De Sola, S., Tarancón, T., Peña-Casanova, J., Espadaler, J.M., Langohr, K., Poudevida, S., Farré, M., Verdejo-García, A., de la Torre, R., 2008. Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study. Psychopharmacology (Berl.) 200, 425–437.

Degenhardt, L., Hall, W., 2009. The Health and Psychological Effects of Ecstasy (MDMA) Use. NDARC Monograph No.62. University of New South Wales, Australia.

Di Iorio, C.R., Watkins, T.J., Dietrich, M.S., Cao, A., Blackford, J.U., Rogers, B., Ansari, M.S., Baldwin, R.M., Li, R., Kessler, R.M., Salomon, R.M., Benningfield, M., Cowan, R.L., 2012. Evidence for chronically altered serotonin function in the cerebral cortex of female 3, 4-methylenedioxymethamphetamine polydrug users. Arc. Gen. Psychiat 69, 399–409.

Erritizoe, D., Frokjaer, V.G., Holst, K.K., Christoffersen, M., Johansen, S.S., Svarer, C., Madsen, J., Rasmussen, P.M., Ramsoy, T., Jernigan, T.L., Knudsen, G.M., 2011. In vivo imaging of cerebral serotonin transporter and serotonin (2A) receptor binding in 3, 4-methylenedioxymethamphetamine (MDMA or ecstasy) and hallucinogen users. Arch. Gen. Psychiat 68, 562–576.

European Monitoring Centre for Drugs and Drug Addiction. European Drug Report, Trends and Developments, 2016. Available at http://www.emcdda.europa.eu/system/files/publications/2637/TDAT16001ENN.pdf.

Fox, H., Parrott, A.C., Turner, J.J.D., 2001. Ecstasy/MDMA related cognitive deficits: a function of dosage rather than awareness of problems. J. Psychopharm. 15, 273–281.

Gamma, A., Brandeis, D., Brandeis, R., Vollenweider, F.X., 2005. The P3 in 'ecstasy' polydrug users during response inhibition and execution. J. Psychopharmacol. 19, 504–512.

Green, A.R., Cross, A.J., Goodwin, G.M., 1995. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy). Psychopharmacology (Berl.) 119, 247–260.

Hegerl, U., Juckel, G., 1993. Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol. Psychiatry 33, 173–187.

Hysek, C.M., Simmler, L.D., Ineichen, M., Grouzmann, E., Hoener, M.C., Brenneisen, R., Huwyler, J., Liechti, M.E., 2011. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (ecstasy) in humans. Clin. Pharmacol. Ther. 90 (2), 246–255.

Jacobsen, L.K., Mencl, W.E., Pugh, K.R., Skudlarski, P., Krystal, J.H., 2004. Preliminary evidence of hippocampal dysfunction in adolescent MDMA (ecstasy) users: possible relationship to neurotoxic effects. Psychopharmacology (Berl.) 173, 383–390.

Jager, G., de Win, M.M.L., Vervaeke, H.K., Schilt, T., Kahn, R.S., van den Brink, W., van Ree, J.M., Ramsey, N.F., 2007. Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study. Psychopharmacology (Berl.) 193, 403–414.

Jager, G., de Win, M.M.L., van der Tweel, I., Schilt, T., Kahn, R.S., van den Brink, W., van Ree, J.M., Ramsey, N.F., 2008. Assessment of cognitive brain function in ecstasy users and contributions of other drugs of abuse: results from an fMRI study. Neuropsychopharmacology 33, 247–258.

Juckel, G., Molnar, M., Hegerl, U., Csepe, V., Karmos, G., 1997. Auditory-evoked potentials as indicator of brain serotonergic activity?first evidence in behaving cats. Biol. Psychiatry 41, 1181–1195.

Juckel, G., 2015. Serotonin: from sensory processing to schizophrenia using an electrophysiological method. Behav. Brain Res. 277, 121–124.

Kalechstein, A.D., De La Garza 2nd, R., Mahoney 3rd, J.J., Fantegrossi, W.E., Newton, T.F., 2007. MDMA use and neurocognition: a meta-analytic review. Psychopharmacology (Berl.) 189, 531–537.

Kish, S.J., Lerch, J., Furukawa, Y., Tong, J., McCluskey, T., Wilkins, D., Houle, S., Meyer, J., Mundo, E., Wilson, A.A., Rusjan, P.M., Saint-Cyr, J.A., Guttman, M., Collins, D.L., Shapiro, C., Warsh, J.J., Boileau, I., 2010. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. Brain 133, 1779–1797.

McCann, U.D., Ricaurte, G.A., 2007. Effects of (+/−) 3, 4-methylenedioxymethamphetamine (MDMA) on sleep and circadian rhythms. Sc. World J. 2, 231–238.

McCann, U.D., Szabo, Z., Scheffel, U., Dannals, R.F., Ricaurte, G.A., 1998. Positron emission tomographic evidence of toxic effect of MDMA (Ecstasy) on brain serotonin neurones in human beings. Lancet 352, 1433–1437.

Mc Cann, U.D., Szabo, Z., Vranesic, M., Palermo, M., Mathews, W.B., Ravert, H.T., Dannals, R.F., Ricaurte, G.A., 2008. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/−)3,4-methylenedioxymethamphetamine (ecstasy) users: relationship to cognitive performance. Psychopharmacology (Berl) 200, 439–450.

McDowell, D.M., Kleber, H.D., 1994. MDMA: its history and Pharmacology. Psychiat Ann. 24, 127–130.

Mejias, S., Rossignol, M., Debatisse, D., Streel, E., Servais, L., Guerit, J.M., Philippot, P., Campanella, S., 2005. Event-related potentials in ecstasy (MDMA) users during a visual oddball task. Biol. Psychol. 69, 333–352.

Moeller, F.G., Steinberg, J.L., Dougherty, D.M., Narayana, P.A., Kramer, L.A., Renshaw, P.F., 2004. Functional MRI study of working memory in MDMA users. Psychopharmacology (Berl.) 177, 185–194.

Molliver, M.E., Berger, U.V., Mamounas, L.A., Molliver, D.C., O'Hearn, E., Wilson, M.A., 1990. Neurotoxicity of MDMA and related compunds: anatomic studies. Ann. N. Y. Acad. Sci. 600, 640–661.

Morgan, M.J., 1998. Recreational use of ecstasy (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19, 252–264.

Mueller, F., Lenz, C., Steiner, M., Dolder, P.C., Walter, M., Lang, U.E., Liechti, M.E., Borgwardt, S., 2016. Neuroimaging in moderate MDMA use: a systematic review. Neurosci. Biobehav. Rev. 62, 21–34.

Nulsen, C., Fox, A., Hammond, G., 2011. Electrophysiological indices of altered working memory processes in long-term ecstasy users. Hum. Psychopharmacol. 26, 488–497.

O'Neill, B.V., Croft, R.J., Nathan, P.J., 2008. The loudness dependence of the auditory evoked potential (LDAEP) as an in vivo biomarker of central serotonergic function in humans: rationale, evaluation and review of findings. Hum. Psychopharmacol. 23, 355–370.

Parrott, A.C., 2001. Human psychopharmacology of Ecstasy (MDMA): a review of fifteen years of empirical research. Hum. Psychopharmacol. 16, 557–577.

Parrott, A.C., 2013. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. Hum. Psychopharmacol. 28, 289–307.

Quednow, B.B., Kuhn, K.U., Hoppe, C., Westheide, J., Maier, W., Daum, I., Wagner, M., 2007. Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA (Ecstasy). Psychopharmacology (Berl.) 189, 517–530.

Raj, V., Liang, H.C., Woodward, N.D., Bauernfeind, A.L., Lee, J., Dietrich, M.S., Park, S., Cowan, R.L., 2010. MDMA (ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users: a preliminary fMRI study. J. Psychopharmacol. (Oxf.) 24 (2), 187–201.

Reneman, L., Booij, J., Schmand, B., van den Brink, W., Gunning, B., 2000. Memory disturbances in Ecstasy users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology (Berl.) 148, 322–324.

Reneman, L., Lavalaye, J., Schmand, B., de Wolff, F.A., van den Brink, W., den Heeten, G.J., Booij, J., 2001. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3, 4-Methylenedioxymethamphetamine (MDMA or Ecstasy). Arch. Gen. Psychiatry 58 (10), 901–906.

Reneman, L., de Win, M.M., van den Brink, W., Booij, J., den Heeten, G.J., 2006. Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects. J. Psychopharmacol. 20, 164–175.

Roberts, G.M., Garavan, H., 2010. Evidence of increased activation underlying cognitive control in ecstasy and cannabis users. Neuroimage 52, 429–435.

Roberts, C.A., Montgomery, C.A., 2015a. Cortical oxygenation suggests increased effort during cognitive inhibition in ecstasy polydrug users. J. Psychopharmacol. (Oxf.) 29 (11), 1170–1181.

Roberts, C.A., Montgomery, C.A., 2015b. fNIRS suggests increased effort during executive access in ecstasy polydrug users. Psychopharmacology (Berl) 232 (9), 1571–1582.

Roberts, G.M., Nestor, L., Garavan, H., 2009. Learning and memory deficits in ecstasy users and their neural correlates during a face-learning task. Brain Res. 1292, 71–81.

Roberts, C.A., Fairclough, S., Fisk, J.E., Tames, F.T., Montgomery, C., 2013a. Electrophysiological indices of response inhibition in human polydrug users. J. Psychopharmacol. 27, 779–789.

Roberts, C.A., Fairclough, S.H., Fisk, J.E., Tames, F., Montgomery, C., 2013b. ERP evidence suggests executive dysfunction in ecstasy polydrug users. Psychopharmacology (Berl.) 228, 375–388.

Roberts, C.A., Fairclough, S.H., McGlone, F.P., Fisk, J.E., Montgomery, C., 2013c. Electrophysiological evidence of atypical processing underlying mental set shifting in ecstasy polydrug and polydrug users. Exp. Clin. Psychopharmacol. 21, 507–515.

Roberts, C.A., Wetherell, M.A., Fisk, J.E., Montgomery, C.A., 2015. Differences in prefrontal blood oxygenation during an acute multitasking stressor in ecstasy polydrug users. Psychol. Med. 45 (2), 395–406.

Roberts, C.A., Jones, A., Montgomery, C., 2016a. Meta-analysis of executive functioning in ecstasy/polydrug users. Psychol. Med. 46, 1581–1596.

Roberts, C.A., Jones, A., Montgomery, C., 2016b. Meta-analysis of molecular imaging of serotonin transporters in ecstasy/polydrug users. Neurosci. Biobehav. Rev. 63, 158–167.

Rogers, G., Elston, J., Garside, R., Roome, C., Taylor, R., Younger, P., Zawada, A., Somerville, M., 2009. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. Health Technol. Assess. 13, 1–315.

Semple, D.M., Ebmeier, K.P., Glabus, M.F., O'Carroll, R.E., Johnstone, E.C., 1999. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. Br. J. Psychiatry 175, 63–69.

Tuchtenhagen, F., Daumann, J., Norra, C., Gobbelé, R., Becker, S., Pelz, S., Sass, H., Buchner, H., Gouzoulis-Mayfrank, E., 2011. High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 22, 608–617.

Wan, L., Baldridge, R.M., Colby, A.M., Stanford, M.S., 2009. Enhanced intensity dependence and aggression history indicate previous regular ecstasy use in abstinent polydrug users. Prog. Neuropsychopharmacol. Biol. Psychiatry. 33, 1484–1490.

Watkins, T.J., Raj, V., Lee, J., Dietrich, M.S., Cao, A., Blackford, J.U., Salomon, R.M., Park, S., Benningfield, M.M., Di Iorio, C.R., Cowan, R.L., 2013. Human ecstasy (MDMA) polydrug users have altered brain activation during semantic processing. Psychopharmacology (Berl.) 227, 41–54.

de Sola, S., Tarancon, T., Pena-Casanova, J., Espadaler, J.M., Langohr, K., Poudevida, S., Farre, M., Verdejo-Garcia, A., de la Torre, R., 2008. Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study. Psychopharmacology (Berl.) 200, 425–437.