Maastricht Student Journal of Psychology and Neuroscience

Maastricht Student Journal of Psychology and Neuroscience
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Editorial

Dear reader of our Maastricht Student Journal of Psychology and Neuroscience,

We present to you: volume 8 of our Maastricht Student Journal of Psychology and Neuroscience.

The journal's main aim is to provide students with the valuable experience of both publishing and reviewing scientific articles. Therefore, the current objective is to increase the number of students that obtain these experiences and, consequently, increase the number of papers that we publish in our beloved journal.

With the previous volume, we started putting our journal on the FPN-map by raising awareness among students and staff. Since then, many changes have occurred. We have been able to attract new section editors that handle the papers that are submitted and guide authors through the entire process. Xanthate Duggirala, Alexandra Emmendorfer, Lilian Kloft, Noralie Krepel, Natasha Mason, Vaishnavi Narayanan, and Boukje Nass are all PhD students that enthusiastically joined our team with the aim to be able to handle larger amount of input in the future. Moreover, we strengthened bonds with both the 'research Practical' and the 'MaRBLe' programme. By connecting this journal to these programmes in the FPN curriculum we envision special research Practical' and 'MaRBLe' editions to be published in the future.

Finally, the FPN board has granted us teaching hours that are dedicated to doing this work. We highly appreciate this gesture. Not just for the time we put into making this possible, but more so for the acknowledgement and appreciation we hereby receive. We all strongly feel that our journal has something to offer to the students and receiving the time to dedicate to this journal makes us feel supported in our quest.

With the described changes, we set the path for expanding our journal and make it flourish. However, there is one thing that seems to lack behind: the input from the authors. I realise that this needs time; the word needs to be spread, examples of published work need to be provided to make students enthusiastic about publishing their work. Hence, this edition is distributed at the final symposium of the research practical with the aim to inspire students to submit their papers. Additionally, I would like to call for reviewers who are willing to add being a reviewer to their curriculum vitae. In the meantime, we eagerly work on our growth and welcome your contributions.

The current edition holds four papers. Lukas Leube has given his critical and prospective view on the role of the medial temporal lobe in memory and spatial processing. Monika Toth has reviewed various sources of evidence for the role of amphetamine in memory consolidation processes. Maja Völker evaluated the potential for manipulating memory processes to be used in treating addiction. Finally, Ioana Staicu carefully considered if oxytocin administration may play a role in the

treatment of symptoms in autism spectrum disorder. On behalf of the editorial board: thank you for your work.

As the papers in the present edition all explore new avenues and exploring novel hypotheses I wish for you, the reader of our journal, to feel inspired by the papers to think outside the box. Moreover, I hope the inspiration to explore extends to concrete aims and objectives to also submit your work to our journal.

Peter van Ruitenbeek

On behalf of the editorial board,

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LUKAS ALEXANDER LEUBE

Imaginary systems? Perspectives on hippocampal function beyond memory

Opinion

Viewing the hippocampus as a structure specifically dedicated to memory is no longer viable. However, functional characterization of this structure and its involvement in learning and memory is still necessary. This perspective article argues that the hippocampus principally processes spatial contexts or scenes. It highlights findings on hippocampal involvement in episodic prospection, navigational planning and online perception. Finally, it discusses how the hippocampus may analogically process non-spatial information via representation in a conceptual cognitive space. The relevance of spatial mnemonic techniques for further research is emphasized.

Keywords: Hippocampus, memory, spatial cognition, episodic prospection

"[Simonides] inferred that persons desiring to train this faculty [of memory] must select places and form mental images of the things they wish to remember and store those images in the places, so that the order of the places will preserve the order of the things, and the images of the things will denote the things themselves, and we shall employ the places and images respectively as a wax writing-tablet and the letters written on it." - Cicero (undated)

INTRODUCTION

Historically, the hippocampus and, by extension, the whole medial temporal lobe (MTL) has been conceptualized as containing or representing a system dedicated to long term memory (LTM). This MTL - LTM hypothesis was originally formulated in response to observations of (anterograde) amnesia in patients that suffered bilateral hippocampal lesions (Scoville & Millner, 1957). More recent investigations using functional neuroimaging have shown that metabolic activity in the

hippocampus is associated with the acquisition of novel information as well as its subsequent retrieval (Lepage, Habib & Tulving, 1998; Zeineh, Engel, Thompson & Bookheimer, 2003). Models of long term potentiation (LTP) have demonstrated that the hippocampus is capable of inducing long lasting changes to the strength of synaptic connections. This process is a prerequisite for hebbian learning, which likely enables the formation of new memories (Bliss & Collingridge, 1993). Considering these findings, it stands without question that the hippocampus participates in the encoding and retrieval of mnemonic representations.

However, the conceptualisation of the hippocampus and MTL as a system that is specifically dedicated to memory should be called into question. Gaffan (2002), for instance, maintained that the MTL - LTM system hypothesis is harmful because it may impede scientific progress. He argued that it is emblematic of an approach that localizes cognitive functions "intuitively and in a haphazard and piecemeal fashion" (Gaffan, 2002). He contrasted it to viewing the brain as a hierarchical processing system, which he considered more appropriate. Following this

line of reasoning, the hippocampus may participate as a crucial component in a multilevel process that results in the phenomenological experience of remembering, but it ultimately cannot be the sole locus of memory.

Gaffan (2002) raised several convincing arguments in favor of this hierarchical view. He presented evidence that (1) memories are not stored in the MTL, that (2) the prefrontal cortex and its connections with the MTL are likewise essential for normal memory functioning and that (3) the hippocampus is involved in perceptual processes (Gaffan, 2002). Since then, more evidence in favor of these arguments has emerged. Memory engrams have been found in the posterior parietal cortex, rather than the hippocampus (Brodt, Gais, Beck, Erb, Scheffler & Schönauer, 2018). The medial prefrontal cortex seems to play an important role in memory consolidation and retrieval for recent as well as distant memories (Leon, Bruno, Allard, Nader & Cuello, 2010). Furthermore, the hippocampal involvement in online perception (meaning the instantaneous automatic processing of one's current sensory input) has been repeatedly demonstrated (Aly, Ranganath & Yonelinas, 2013;

Chadwick, Mullally & Maguire, 2013). Collectively, these findings demonstrate that the hippocampus and (long-term) memory cannot be linked to each other in a one-to-one fashion. This raises the following question: What then precisely is the function of the hippocampus and how does it play into learning and memory?

Past, Future and Presence: Modelling of spatial contexts

Similar to the deliberations presented by Gaffan (2002), Nadel and Hardt (2011) likewise argue against the MTL - LTM system hypothesis. In their comprehensive review on "memory systems" they conceptualize episodic (and thus hippocampus-dependent) memory as entailing a specific spatial context (Nadel & Hardt, 2011). This is in line with how Tulving originally defined episodic memory as entailing "temporo-spatial relations" (Tulving, 1972). However, Nadel and Hardt (2011) note that the hippocampus is also involved in the initial acquisition of non-episodic

information. Such knowledge may then be "semantisized" in a brain wide consolidation process and become independent from the hippocampus (Nadel & Hardt, 2011). Importantly, the gain of hippocampal independence entails a loss of contextual specificity. One might infer from this that the hippocampus principally processes spatial contexts or scenes. The presence of a spatial context can be considered the defining feature of episodic memory that distinguishes it from semantic information.

Evidence for the hippocampus' role in processing spatial information is not restricted to memory research. The following will perhaps highlight some key findings regarding hippocampal involvement in episodic prospection, navigational planning and online perception in order to elaborate on its function beyond memory.

Episodic prospection or "future simulation" is the mental construction of possible future scenarios. It engages a similar network of brain regions as episodic remembering, which includes the hippocampus (Schacter, Addis & Szpunar, 2017). A popular method for researching episodic prospection using fMRI

is the experimental recombination paradigm. Here, participants have to generate lists of familiar *objects*, *persons* and *places* prior to testing. During imaging, they are then asked to imagine novel future scenes in which these three aspects are combined. Crucially, this experimental approach allows for both manipulation of the novelty of these scenarios as well as controlling for the amount of specific detail that is generated. As it turns out, the hippocampus is more engaged during imagination of novel combinations and its activity correlates with the amount of specific detail contained within them (Schacter, Addis & Szpunar, 2017). Furthermore, populations that usually perform worse on measures of delayed recall, such as depressive patients or older adults, also show peculiarities in episodic prospection: Their scenes seem to lack detail and appear to be less specific and more stereotypical (Schacter, Addis & Szpunar, 2017). Importantly, cognitive deficits have been associated with hippocampal volume loss in both depression (Sheline, Sanghavi, Mintun & Gado, 1999) as well as aging (Reichel, Bedenk, Czisch & Wotjak, 2017). The hippocampus might thus model the spatially coherent scene

that underlies the respective imagination. Naturally, the creation of a novel and detailed scene would place more demands on the hippocampus than generating a stereotypical and thus quasi-semantic context.

The ubiquitous involvement of the hippocampus in spatial navigation is well documented, primarily in rodents. Evidence shows that the hippocampus contains "place cells" that are tuned to specific locations within a given environment. Furthermore, distinct neural populations seem to "preplay" movement trajectories during route planning (Bendor & Spiers, 2016). An investigation by Brown and colleagues (2016) demonstrated that this mechanism is also present in humans. They were able to relate hippocampal activation to prospective navigational goals, as well as intervening locations along the planned route.

Critically inclined people might object that these future oriented mental activities (episodic prospection and route planning) still essentially constitute memory processes, as they require retrieval of previous knowledge. However, there is also experimental evidence showing that the hippocampus is

involved in online perception. In particular, it seems to contribute to the perception of an environment as a continuous whole. Simply stated, the hippocampus is involved in extrapolating visual information beyond the actual stimulus. In an experimental setting, this phenomenon can be demonstrated with the boundary extension effect (Intraub & Richardson, 1989). This effect describes the phenomenon of people judging a visual stimulus (such as a picture) to be smaller during repeated viewings compared to the initial presentation. As it can be detected less than 50 ms after viewing a stimulus, boundary extension is undoubtedly part of online perception (Intraub & Dickinson, 2008). Chadwick and colleagues showed that the boundary extension effect correlates with functional connectivity between the hippocampus and the visual cortices (Chadwick, Mullally & Maguire, 2013). Boundary extension is a form of elaborative processing, which would be a necessary step in modelling spatial contexts as part of online perception

Accounting for the described findings, Zeidman and Maguire (2016) recently proposed an anatomical model, which differentiates functional roles within the hippocampus in

relation to the processing of spatial scenes. Principally, they make a distinction between the anterior and the posterior hippocampus. In this model, the anterior part is explicitly involved in the construction of spatial scenes during episodic simulation, while the posterior part has a more perceptual function. Taken together, there is substantial evidence that the hippocampus principally processes spatial contexts or scenes, both during perception of current spatial environments as well as during episodic imagery.

Pseudo-spatial properties of abstract information

Thus far, the present article has argued that the hippocampus principally models spatial contexts or scenes. However not all types of information, whose acquisition depends on the hippocampus, seem to have spatial properties. Eichenbaum and Cohen (2014) reasoned that the hippocampus also processes non-spatial bits of information in terms of their trajectories in conceptual "memory space". This implies that the same principles governing the processing of spatial relations apply to

other types of information, e.g. conceptual similarity or temporal distance.

This idea is very appealing, because it makes sense from an evolutionary perspective. The hippocampus might have been a purely spatial structure originally, which is in line with the close neural link between olfactory identification and spatial navigation (Dahmani, Patel, Yang, Chakravarty, Fellows & Bohbot, 2018). However, over time its function might have become generalized and transferred upon other dimensions that can be described in spatial terms. One has to consider and appreciate the fact that we as humans resort to spatial schemata for representation of all types of information. On an intuitive level, one can realize that by considering how our language deals with abstract concepts. To give a few examples: We characterize personality traits, such as self-esteem, as being *high* or *low*. Time is moving *forward.* Political views are organized on a spectrum from *right* to *left.* This of course is very anecdotal. However, there is more far reaching evidence for mental representation of higher order knowledge in spatial terms. The spatial numerical associations of response codes (SNARC) effect for instance

shows that mental representations of number magnitudes have spatial properties (Wood, Willmes, Nuerk & Fischer, 2008).

These pseudo-spatial attributes of human knowledge become most apparent when one considers the effectiveness of spatial mnemonic strategies. A particularly popular one in educational settings is "mind-mapping". It means arranging information that is to be encoded on a two dimensional plane (i.e. a blackboard or a piece of paper). Here different conceptual dimensions can be displayed in spatial terms: Distance can express similarity, size can indicate importance, connections can imply belonging to a category, etc. Several investigations have shown that encoding information with mind-maps leads to superior recall when compared to simply studying said information in a text (Hallen & Sangeetha, 2015; Lalyanasundaram, Abraham, Ramachandran, Jayaseelan, Bazroy, Singh & Purty, 2017). One possible explanation of this effect is that spatially arranging information facilitates hippocampal processing.

A similar case can be made for the mnemonic techniques employed by participants in "memory championships". These

people compete on tasks like remembering extraordinary long digit spans. Maguire and colleagues have shown that their brains do not show any structural differences compared to controls (Maguire, Valentine, Wilding & Kapur, 2002). Rather, their superior memory performance stems from proficient use of spatial mnemonics, such as the "method of places" (Maguire et al., 2002). In the quote, which prefaces this article, Cicero describes this technique. It associates each bit of information with a location in an imaginary scene. Despite necessitating the encoding of *additional* information, this method is very effective (Maguire et al., 2002). It could very well serve as a metaphor for hippocampal function at large: The spatial scene in which the "images" are placed represents the pseudo-Euclidean cognitive space that is processed by the hippocampus, whereas the "images" themselves represent the bits of information that are encoded.

In recent years evidence for this view has been emerging: The hippocampal circuit has been shown to process auditory spectral (Constantinescu, O'Reilly & Behrens, 2016), and other types of stimulus feature information (Theves, Fernandez &

Doeller, 2019) in a manner that is analogous to spatial information.

CONCLUSION

The present article has argued that the hippocampus principally processes spatial contexts or scenes. This function is a critical component of visuospatial perception and any form of episodic imagery, meaning both episodic recall and prospection, as well as counterfactual imagery. Furthermore, it is crucial for any activity requiring spatial reasoning, such as navigational planning. Analogous to spatial scenes containing objects, the hippocampus may process constellations of abstract information via representation in a conceptual cognitive space. In order to reach a better understanding of how the hippocampus processes non-spatial information, future research could investigate the working mechanisms of spatial mnemonic aids. Techniques such as “mind-mapping” and the “method of places” might ultimately be effective because they organize information in a form, which

is more readily processed by the hippocampus, e.g. by adding spatial and/or associative components. This kind of hippocampal "spatialization" could ultimately be a domain-general aspect of human cognition.

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MONIKA TOTH

The effects of amphetamine on the neurobiology of memory consolidation from a pharmacodynamic and toxicological perspective

Executive Summary

The psychostimulant drug amphetamine improves animal and human short-term and long-term memory via its direct and indirect impact on several neurotransmitters. One possible account suggests that amphetamine aids the process of memory formation, referred to as consolidation. This idea is supported by independent findings on the drug-induced neurobiological and –chemical effects, and memory consolidation. Despite a substantial overlap, the link between these findings has not yet been extensively

investigated. Additionally, both acute and chronic amphetamine use can cause neurotoxicity, which affects consolidation. Therefore, the aim of this executive summary was to examine the effects of amphetamine on the neurobiology of consolidation taking the drug's pharmacodynamic and toxic properties into account. The presented evidence shows that amphetamine facilitates consolidation, since it engages receptors, neurotransmitters and neuromodulators that are essential for memory formation. One example is dopamine, which is the main mediator of the amphetamine-induced memory effect. However, chronic amphetamine treatment has to be regarded with caution due to receptor down-regulation and toxicity.

Keywords: amphetamine, consolidation, memory, toxicity, neuroplasticity

INTRODUCTION

The psychostimulant drug amphetamine (AMPH) has recently gained increased interest in research, since it was found to aid memory via its impact on neurotransmission and neuroplasticity (Giorgetti, Hotsenpiller, Ward, Teppen, & Wolf, 2001; Myhrer, 2003). For instance, AMPH improved short-term and long-term memory (STM and LTM) of multiple sclerosis (MS) patients with baseline memory deficits as measured by an auditory/verbal-learning task (Sumowski et al., 2011). Moreover, 0.25 mg/kg acutely administered AMPH improved working memory of patients with schizophrenia (Barch & Carter, 2005). The STM drug effects can be explained by AMPH's capacity to improve attention as evidenced in both rat (Meneses et al., 2011; Turner & Burne, 2016) and human studies (Servan-Schreiber, Carter, Bruno, & Cohen, 1998; Silber, Croft, Papafotiou, & Stough, 2006). Thus, AMPH via its direct enhancing effect on attention may contribute to better STM, and thus, may facilitate encoding (i.e., maintaining information in memory for short term).

However, the above mechanism might not fully account for improved LTM. The reason is that creation of new LTM traces is known to involve a process by which a particular memory is transformed from an unstable short-term state into a stable long-term state. This is referred to as consolidation (Debiec, LeDoux, & Nader, 2002). Thus, one possibility is that AMPH affects consolidation (Leri et al., 2013). This process is rather complicated and fragile involving several neurotransmitters and cascades of molecular processes (Cooke, 2006; Debiec et al., 2002; Nicoll & Malenka, 1995) which can be influenced by AMPH (Carvalho et al., 2012; Nicoll & Malenka, 1995; Stahl, 2013). Despite this link between AMPH and consolidation the drug's neurochemical and neurobiological effects on memory formation specifically have not yet been investigated extensively. There are only a few studies exploring this connection. Therefore, the aim of this executive summary was to examine how AMPH might influence the neurobiology of consolidation. Several animal and human studies investigating the process of consolidation and AMPH either in connection or independently are reviewed in this paper. Furthermore, links

and overlaps between the drug-induced CNS effects and the process of memory consolidation are established. In addition, this drug is known to cause oxidative stress, toxicity and inflammation in the central nervous system (CNS) (Carvalho et al., 2012; Patrick & Markowitz, 1997). For this reason the drug's pharmacodynamic and toxic properties were taken into account, as well in order to able to weigh the evidence for AMPH to be used as a memory enhancing drug.

Memory consolidation

Formation of memory relies on synaptic changes and modified gene expression initiated by several neurotransmitter systems in the brain involving brain structures such as the cortex, the hippocampus and the striatum (Squire, 2004; Porras & Mora, 1992). Long-term potentiation (LTP) has been suggested as a likely candidate for the neurophysiological substrate of memory formation (Cooke, 2006). LTP implies a long-term change in post-synaptic potentials upon brief stimulation triggered and

maintained by robust calcium (Ca2+) influx. This on the one hand leads to functional changes; that is strengthening of existing synapses. On the other hand it results in structural changes whereby new neuronal connections are established (Cooke & Bliss, 2006). Finally, as a result of persistent modifications of the synaptic architecture new ribonucleinic acid (RNA) is produced, and new proteins are synthesized with temporary alterations in synaptic transmission (Debiec et al., 2002).

LTP mechanisms are primarily dependent on glutamatergic receptors, such as the N-methyl-D-aspartate (NMDA) and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes. The crucial role of NMDA receptors in the cascade of chemical events related to memory consolidation has been demonstrated in several animal (Rodrigues, Schafe, & LeDoux, 2001; Rubin, 2004) and human studies of fear conditioning (Kalisch et al., 2009; Parwani et al., 2005). In particular, Kalisch et al. (2009) showed using a fear conditioning and extinction paradigm that the NMDA partial agonist D-cycloserine (500mg) improved fear

memory consolidation relative to placebo in healthy human subjects.

Induction of LTP relies on large synaptic depolarisation caused by increased glutamate (Glu) influx via the NMDA receptors. Moreover, the coagonist glycine (Gly) is essential for the removal of the magnesium block in the NMDA receptors, since it enables Ca2+ influx (Stahl, 2013). This is vital as LTP strongly depends on Ca2+ availability (Nicoll & Malenka, 1995; Stahl, 2013). Ca2+ does not only trigger, but also maintains LTP for both short-term (< 1hour) and long-term (1hour < LTP > 3hours). Additionally, it activates an enzyme called calcium-calmodulin-dependent kinase II (CaMKII). This enzyme on the one hand makes AMPA receptors more permeable to sodium ions, which increases the sensitivity of the cell to incoming information. On the other hand, it promotes the synthesis of new AMPA receptors (Cooke & Bliss, 2006).

Furthermore, several second messengers such as nitric oxide (NO), cyclic guanosine monophosphate (cGMP) and cAMP response element-binding protein (CREB) are required for LTP (Cooke, 2006). Interestingly, Ca2+ has been suggested to

stimulate the diffusion of NO from the post-synaptic membrane into the pre-synaptic terminal (Cooke, 2006) where NO can encourage Glu production (Raju et al., 2015). Additionally, CREB is known to be involved in synthesis of brain-derived neurotropic factor (BDNF), which is necessary for successful memory consolidation (Cooke, 2006). For instance, Lee & colleagues (2004) found that when the BNDF synthesis inhibitor oligodeoxynucleotides was infused into the dorsal hippocampus of the rat 90 min prior to contextual fear conditioning LTM was impaired. In contrast, the protein synthesis independent STM was intact. Thus, encoding was successful, but the protein dependent memory consolidation and subsequent retrieval was dysfunctional without BDNF.

BDNF was reported to rapidly and reversibly potentiate postsynaptic gamma-amino butyric acid (GABA) subtype a (GABAa) receptors in the rat hippocampus leading to increased intracellular Ca2+ influx, which promotes LTP (Mizoguchi, Ishibashi, & Nabekura, 2003). In addition, activation of the inhibitory presynaptic GABAa receptors was found to enhance LTP in the rat hippocampus (Ruiz, Campanac, Scott, Rusakov, &

Kullmann, 2010). In particular, Ruiz et al. (2010) presented evidence that muscimol, a selective endogenous neurosteroid with high-affinity for GABAa receptors led to increased depolarization in the rat hippocampus while it enhanced action potential dependent Ca2+ transients and facilitated glutamatergic transmission. In contrast, the GABAa antagonist gabazine led to hyperpolarization and attenuation of action potential dependent Ca2+ transients. Proper functioning of these receptors requires the neurotransmitter GABA (Stahl, 2013). Thus, both pre- and postsynaptic GABAa receptors are necessary for successful LTP. The presented evidence collectively suggests that successful consolidation relies on cascades molecular processes that necessitate the availability of Ca2+, Glu, GABA, NO, CREB and BDNF.

AMPHETAMINE

Pharmacodynamics

This section presents evidence how AMPH can affect processes underlying consolidation based on the drug's pharmacodynamic properties, whereby it is ultimately suggested to affect consolidation.

The core structure of AMPH is made up of β-phenylethylamine and a α- methylgroup. The latter prevents the oxidation of the amine group by monoamine oxidase enzymes (MAO) and potentiates the ability of AMPH to easily cross membranes (Carvalho et. al, 2012), including the blood-brain barrier (BBB) (Kousik, Napier, & Carvey, 2012). In the brain AMPH interacts with monoamine transporters of dopamine (DA), norepinephrine (NE) and serotonin (5-HT). As such, it blocks the reuptake of these monoamines (Carvalho et al., 2012; Stahl, 2013). Additionally, AMPH promotes DA, NE, 5-HT, acetylcholine (ACh), Glu, Gly and GABA release from nerve

terminals (Carvalho et al., 2012; Porras & Mora, 1993). Most of these neurotransmitters are also involved in consolidation. For this reason, AMPH's impact on Glu, GABA, Gly and their neuromodulator DA will be further investigated.

Dopamine

AMPH most prominently affects brain DA levels via interactions with several subtypes of DA (1-5) receptors, which are found in brain structures crucial for memory such as the hippocampus, striatum and the prefrontal cortex (Stahl, 2013). Acutely, AMPH enhances extracellular DA levels via the above outlined mechanisms and inhibition of MAO, the enzyme that normally breaks down monoamines (Hutson, Tarazi, Madhoo, Slawecki, & Patkar, 2014). According to evidence AMPH-induced DA discharge enhanced the level of occupancy of the inhibitory DA2 receptors. This was confirmed by decreased binding of the specific DA2 receptor radio tracer IBZM [(I)(S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-(1-ethyl-2-pyrrolidinyl)methyl benzamide] in human subjects (Laruelle et al., 1996).

Furthermore, it was found using immunochemistry of hippocampal slices of DA1 knock-out mice that DA1 receptors are critical for LTP induction (Granado et al., 2007). In sum, as AMPH increases DA levels and the engagement of several subtypes of DA receptors in the hippocampus it is reasonable to assume that it affects LTP, and thus, memory consolidation.

Furthermore, AMPH is postulated to a mediate interactions between 5-HT and DA (Pehek & Bi, 1997; Porras & Mora, 1993). For instance, Pehek and Bi (1997) examined the effects of pre-treatment of rats with the DA2 antagonist haloperidol (1.0 mg/kg/ml, ip), the 5-HT type 2 antagonist ritasterin (1.0 mg/kg/ml, ip and 5.0 mg/kg/ml, ip), and vehicle on AMPH-stimulated (5.0 mg/kg/ml, ip) cortical DA-efflux using *in vivo* microdialysis. According to the findings ritaserin on the one hand reduced the AMPH induced DA increase in the nucleus accumbens (NAc) and the striatum. On the other hand it enhanced the AMPH-induced DA release in the cortex. These findings show dependency of AMPH induced DA release on 5-HT and DA receptors.

Glutamate

AMPH has been found to induce excessive Glu efflux and availability, and increased expression of AMPA and NMDA receptors in the NAc and striatum (Hutson et al., 2014; Stahl, 2013). For example, it was found that AMPH-induced (0.5 or 2.0 mg/kg, sc) Glu efflux in the NAc of the rat was hindered by the NMDA receptor antagonist MK-801 (0.25 mg/kg, ip) (Rahman & Bardo, 2008). Moreover, in the same experiment reduced surface expression of AMPA receptors was reported. Taken together this evidence suggests that AMPH acts on Glu receptors via downstream mechanisms by changing their expression. Another study found similar results concerning AMPA expression in the NAc of rat upon chronic AMPH treatment (Nelson, Milovanovic, Wetter, Ford, & Wolf, 2009). Thus, it seems that these effects on the glutamatergic receptors can contribute to elevated excitatory transmission and improved consolidation. Additionally, a recent study presented evidence that AMPH influx into the ventraltegmental brain neurons *in vitro* caused endocytosis of

the excitatory amino acid transporter type 3, which is known to be a Glu transporter subtype in DA neurons. Therefore, the authors suggested that AMPH modulates Glu transmission via its impact on the DA transporter (DAT) system (Underhill et al., 2014). Taken together, these findings further support AMPH's ability to enhance LTP, and as such, consolidation due to direct and indirect effects on Glu transmission via DA.

GABA and Glycine

GABA has an important inhibitory role in the CNS (Stahl, 2013) that can be attenuated by AMPH (Jiao, Liu, Li, Liu, & Zhao, 2015). A recent review suggested a possible account according to which the activation of GABAa receptors by AMPH decreases DA transmission (Jiao et al., 2015). This is plausible as neuronal excitability is assumed to be a result of a synergy between excitatory and inhibitory activities. Since, GABAergic neurons often have Glu receptors and GABA is known to modulate Glu release compensatory changes in any or both of these systems may reflect an interaction between them (Stahl, 2013). In other

words, if AMPH increases Glu excitation directly and indirectly via DA, a compensatory inhibitory mechanism is required to increase the inhibition in order to produce homeostasis. Indeed, systematic injections of 5 mg/kg AMPH into the neostriatum of living rats resulted in increase in Gly and GABA levels (Porras & Mora, 1993). This effect could be blocked by intraperitoneally injected DA2 antagonist haloperidol (3mg/kg) suggesting indirect mediating effects of DA via a possible interplay between excitatory (i.e., Glu, Gly) and inhibitory (i.e., Gly, GABA) pathways. In explanation, Gly is known to sub-serve both inhibitory and excitatory functions within the CNS. Furthermore, it promotes the action of Glu via its role as a coagonist at NMDA receptors (Stahl, 2013). Thus, neuroplasticity can be affected by AMPH-induced changes directly and indirectly with DA being the crucial mediator of the excitatory and inhibitory actions.

Neurotoxicity

Psychostimulant drugs are assumed to alter the function of the BBB, which likely contributes to their neurotoxicity (Kousik et al., 2012). AMPH produces excessive monoamine levels, since it is a weak MAO inhibitor, and as a potent releaser and regulator of monoamine transporter function (Patrick & Markowitz, 1997). Surplus availability of these monoamines and the Glu-induced intracellular Ca2+ influx leads to severe oxidative stress and production of reactive oxygen species (ROS) via two mechanisms: auto-oxidation and monoamine metabolism via MAO (Carvalho et al., 2012).

Furthermore, excitotoxic consequences of extensive Glu discharge caused by AMPH have been linked to neuronal cell death and NO-mediated nitration of proteins in DA terminals resulting in reactive nitrogen species (RNS) and apoptosis (Carvalho et al., 2012). Hence, AMPH-induced ROS and RNS may activate apoptotic pathways. Indeed, in support of this toxic route it has been proposed that chronic administration of 4mg/day AMPH into the rat brain via an implanted osmotic

pump led to significant striatal DA depletion, nerve terminal swelling and fiber degeneration (Ricaurte, Bryan, Strauss, Seiden, & Schuster, 1985). Additionally, hyperthermia is another mechanism whereby AMPH causes severe oxidative stress. Since, AMPH is a stimulant it can cause dysfunctional thermoregulation in the CNS via monoamine modulation, and changes in blood flow and tissue thermoregulation (Carvalho et al., 2012).

CONCLUSION

Based on the presented evidence AMPH influences the cellular and nuclear events required for synaptic plasticity and consolidation via its direct and indirect neurochemical impact on neurotransmission and gene expression. It has indirect effects on the glutamatergic system mostly mediated via DA, triggered by increased intracellular Ca2+ and co-agonized by elevated extracellular Gly availability (Cooke & Bliss, 2006; Porras & Mora, 1992). The elevated availability of Ca2+ further induces

and maintains plasticity (Cooke & Bliss, 2006); hence, improves consolidation. Indeed, it has been shown that AMPH-induced plasticity is dependent on DA receptor activity with DA1 increasing and DA2 decreasing AMPA expression in the rat prefrontal cortex (Hutson et al., 2014).

Furthermore, AMPH can facilitate BDNF production as evidenced by rat studies in which both acute and chronic AMPH administration increased BDNF micro RNA expression in the cortex and amygdala respectively (Hutson et al., 2014). Moreover, co-transmitter Gly is needed for removing the magnesium block of the NMDA receptors during LTP induction (Stahl, 2013). Hence, as AMPH increases Gly levels it can foster LTP induction.

In support of the idea that AMPH aids memory as a result of enhanced consolidation Leri et al. (2013) conducted an experiment in which rats were infused subcutaneously with AMPH (0.03, 0.5, 1 or 2 mg/kg) or vehicle immediately or 4h post-training for 13 consecutive days. According to their findings based on the win-stay and fear conditioning tasks only lower

AMPH doses (0.03 and 0.05) improved performance significantly. Moreover, this was only apparent when AMPH was injected immediately after training, but not later. This led the authors to conclude that lower AMPH doses increase memory consolidation.

Despite the outlined enhancing effects on consolidation chronic AMPH use may deplete endogenous antioxidants leading to down-regulation of the enzyme tyrosine hydroxylase, which is involved in the endogenous biosynthesis of DA from tyrosine. Moreover, it can lead to down-regulation of these receptors (Angelucci, Gruber, El Khoury, Tonali, & Mathe, 2007). This could negatively affect consolidation in the long-term. Nevertheless, current investigations suggest that mixed AMPH salts at therapeutic doses are unlikely to directly kill DA neurons (Angelucci et al., 2007).

Furthermore, NO acts as a second messenger during LTP and is involved in RNS caused by AMPH (Cooke, 2006). In addition, AMPH induced Glu influx has severe excitotoxic properties resulting in apoptosis (Carvalho et al., 2012). These

toxic effects indicate caution in regards to therapeutic application. However, for the time being there is no evidence specifically investigating AMPH's neurotoxic effects on memory formation. Therefore, further research is needed in order to explore this field.

In conclusion, AMPH has a facilitating impact on consolidation both acutely and chronically. However, more animal and human studies are needed to define appropriate dosing required for improving memory consolidation. Additionally, AMPH both directly and indirectly influences neuroplasticity in a positive manner. In this process DA is the critical mediator of the excitatory and inhibitory actions that promote memory formation. However, due to the drug's neuro- and excitotoxic properties caution is required when it comes to chronic treatment, as long-term application can result in down-regulation of receptors involved in consolidation. This can lead to memory depletion rather than improvement. Future research should investigate the specific impact of both acute and chronic AMPH treatment on memory consolidation especially in humans.

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MAJA PALOMA VÖLKER

Can Drug Addiction be Treated by Manipulating Memory?: A Literature Review of Memory-Based Treatments and a Qualitative Comparison with Conventional Treatments

Perspective

Drug addiction constitutes a major health problem in modern society. Most of the current treatments have demonstrated limited effectiveness in long-lasting treatment results because they focus on acute symptoms of the illness while neglecting important factors that maintain addiction. Memory manipulation therapies appear to be promising alternatives that act on mechanisms that maintain addiction. The aim of this review is to summarize the existing research about memory manipulation for drug addiction and to evaluate the potential as an

addition to currently used treatments. In this paper, memory-related processes that are associated with addiction etiology are explained. Additionally, several findings suggest the potential of memory manipulation to reduce the impact of drug-related memories and associated stimuli on behaviour. The reviewed studies provide support that targeting maladaptive drug memories might be a valuable therapeutic approach that seems to prevent relapse. Three types of memory manipulation treatment are reviewed; namely extinction training, reconsolidation therapy, and eye movement desensitization and reprocessing. Finally, the paper concludes with implications for treatment of addiction using the described approaches to adapt drug-related memories.

Keywords*:* memory, drug addiction, reconsolidation, retrieval, EMDR

INTRODUCTION

In recent years, several instances have contributed to the discussion about the use of recreational drugs. For example, the display of drug abuse has increased tremendously in mass media, with TV shows such as “Narcos” and “Breaking Bad” rising in popularity. Moreover, several countries have eased their regulations regarding the possession and consumption of cannabis to increase the control over drug-related problems. For example, in Canada, a law that legalizes recreational use of marihuana was passed in July 2018 with the purpose to improve control over consumption (Cox, 2018).

Another drug-related topic that is currently discussed is the problematic development with the opioid epidemic in the United States. Many doctors have become progressively liberal in prescribing opioids to chronic pain patients (Maxwell, 2011). Although these drugs are very effective in relieving pain, they also have a very high addictive potential (Ballantyne & Shin, 2008). The increase of opioid prescriptions in the US has been

associated with more cases of opioid addiction and death from overdose (Wilkerson, Kim, Windsor & Mareiniss, 2016).

The example of the opioid epidemic in the US illustrates that it is important to shed light on potential risks associated with excessive drug consumption. At first, the choice to consume drugs might have great appeal, as they promise pleasurable experiences and relieve negative affect. However, with repeated consumption the ability to control one's own behavior decreases (Volkow & Morales, 2015). Eventually, drugs may begin to interfere with daily life because activities other than drug consumption lose their pleasurable properties. The individual might neglect other activities for obtaining more drugs regardless of any sacrifice (National Institute on Drug Addiction, 2018).

Drug addiction is characterized by the uncontrollable craving for and intake of a substance despite the harmful effects. The drug interferes with the quality of life by impairing the drug user physically and mentally (American Psychiatric Association, 2013). Grant and colleagues (2016) report an estimated prevalence of 9.9% for a lifetime diagnosis of substance abuse

disorder (SUD) in the US, showing that it constitutes a common health issue. Extensive research on neural mechanisms has revealed that drug addiction can be partly explained by associative learning, including Pavlovian and Instrumental conditioning, meaning that situational or environmental cues present during the consumption of the substance will be stored and can elicit drug-seeking behaviors (Everitt, 2009). Pavlovian conditioning in addiction is a process that links drug effects to cues that are present in the environment. After repeated exposure within the context of drug use, these originally neutral cues become conditioned stimuli (CS) that are associated with the predicted drug effects. The CS will elicit anticipatory bodily responses that oppose these predicted effects (Siegel, 2005). Within this context, instrumental conditioning operates in conjunction with Pavlovian conditioning. By means of this process, an association between drug effects and drug-seeking behaviours is established. The pleasurable effects of the drug act as positive reinforcers, meaning that they increase the likelihood of drug-seeking behaviours (Everitt & Robbins, 2005). Given

sufficient repetition, the cue-induced drug seeking becomes habitual and behavioural control is lost (Milton & Everitt, 2012).

The treatment of drug addiction is a complicated and exhausting process for the drug addict due to the associated withdrawal effects, as the body must adapt to the absence of the drug. Additionally, current treatment forms for drug addiction leave the patient vulnerable to relapse as soon as being exposed to conditioned drug cues in an everyday context (Milton & Everitt, 2013). The National Institute on Drug Abuse (2018) reports relapse rates that range from 40-60% following treatment. These figures necessitate the development of treatment forms that prevent relapse in the long term.

Multiple research lines have identified a promising treatment approach to target the issue of relapse after the patient leaves medical care. Memory manipulation can be used to disrupt the ability of different environmental stimuli to elicit craving and drug-seeking behaviors. The intervention might result in effective long-term treatment for addiction by using the mechanisms of instrumental learning and classical Pavlovian conditioning. To counteract some of the underlying memory

mechanisms, potentially effective approaches that have been suggested include disruption of addiction memory reconsolidation, extinction treatments, and eye movement desensitization and reprocessing. This paper briefly describes established addiction treatments and their limitations before reviewing current findings to answer the question of whether memory manipulation is a suitable and perhaps better therapeutic approach to treat drug addiction.

Definition of Drug Addiction

The DSM-V (American Psychiatric Association, 2013) provides four main symptom categories to define addiction, clinically termed as substance use disorder (SUD). Firstly, there are several symptoms which can be classified as impairments in regulating drug consumption, for example taking increasingly larger amounts of the drug. Moreover, impaired functioning in social aspects, for example, the inability to cope with responsibilities, is given as diagnostic criterion. An additional

category covers the irresponsible usage of substances regarding situational factors, for example driving under the influence, and the harmful effects of the drug. Lastly, the DSM-V points out the pharmacological effects caused by the drug as an indicator for SUD, namely higher tolerance for the drug and withdrawal effects during abstinence. For a diagnosis of SUD, at least two criteria across a period of 12 months must be met.

Drug Addiction and Memory Mechanisms

Fundamental mechanisms of SUD can be explained in terms of an interplay between instrumental learning and classical conditioning. By means of instrumental learning, drugs are reinforcing the behaviours that are required to obtain them. This means that the individual learns what actions are required to receive the positive effects that the drug produces. By this process of instrumental learning, the drug behaviours that are required to experience the effects of the drug are reinforced (Everitt & Robbins, 2005). Over time, the ability to wilfully

modulate the behaviour in presence of stimuli decreases drastically (Everitt & Robbins, 2016). In the long run, drug-seeking behaviours may become habitual and compulsive. This means that the individual is unable to refrain from performing drug seeking behaviours despite the awareness that the consumption might entail negative consequences (Milton & Everitt, 2012).

The instrumental learning in drug addiction is mediated by classical conditioning. By means of classical conditioning, stimuli that are present in the environment during drug consumption gain incentive value and motivational salience (Everitt & Robbins, 2016). Initially, the drug effects constitute the unconditioned stimulus that triggers a biological response aimed at returning homeostasis. Cues that are repeatedly present during drug use become conditioned stimuli (CS) that are associated with the predicted drug effects (Siegel, 2005). The body will attempt to prepare for the drug effects by establishing opposite effects to the drug that are experienced as withdrawal symptoms and cravings (Milton, 2013). The CS imposes an uncontrollable motivational state upon the individual to engage

in reward-seeking behaviors that were reinforced by instrumental learning (Cartoni, Balleine & Baldassarre, 2016; Everitt & Milton, 2005; Milton & Everitt, 2012).

In a physiological context, one of the most important neural correlates of drug addiction is the limbic corticostriatal system. To delve deeper into the brain mechanisms, the basolateral and central parts of the amygdala are responsible for encoding the association between CS and the drug effects as an unconditioned stimulus (Everitt, 2009; Volkow & Morales, 2015). In addition, the repeated pairing of the stimulus with drugs leads to increased activation of the ventral striatum, most importantly the nucleus accumbens, by increasing the concentration of dopamine (DA) (Everitt & Robbins, 2005; Milton & Everitt, 2012). The concentration will also increase for subsequent encounters with CS and signal reward prediction (Volkow & Morales, 2015). This process is normally implicated in adaptive learning mediated by natural reinforcers such as food (Robbins, Ersche & Everitt, 2008; Milton & Everitt, 2012). The activation of the nucleus accumbens by the release of DA, therefore, increases behavioural motivation (Everitt, 2009). The

orbitofrontal cortex plays an important role in the acquisition of goal-directed behaviour as it links actions that are necessary to obtain a certain outcome with the representation of the predicted outcome value (Everitt & Robbins, 2005; Schoenbaum & Shaham, 2008). With sufficient repetition the drug seeking behaviour becomes habitual, which is represented by dorsal striatal activation. This mechanism accounts for the fact that the intake of drugs shifts from being a conscious decision to an automatic process in which the individual engages in drug seeking behaviour (Everitt & Robbins, 2016). Conjointly, the changes in activation patterns of these structures contribute strongly to addictive behaviour.

Current Treatments for Drug Addiction

Currently, various treatment approaches are used by therapists to treat SUD. In the following section, the most widely employed approaches, medication-based and behavioural therapies, will be

discussed to conclude how memory manipulation treatments might help to improve upon their effectiveness.

To begin with medication-based treatment, the clinician provides the patient with an alternative, relatively safe substance to replace the drug of abuse. By replacing the drug with a legal substitute, the withdrawal effects are reduced which usually interfere with the treatment and drug craving (Douaihy, Kelly & Sullivan, 2013). For an effective treatment, the alternative substance must be tailored to the mechanisms of the abused drug. For example, the therapist might prescribe buprenorphine or methadone to treat opioid addiction because they maintain the effects of illicit drugs. Both medications act as opioid agonists, meaning that they activate opioid receptors in the brain (Whelan & Remski, 2012). Compared to commonly misused drugs like heroin, these medications constitute a much safer alternative, mainly because of lower risk of overdosing (Soyka, 2017).

Nevertheless, the medications may have severe and sometimes even lethal side effects (Douaihy et al., 2013). Despite having a lower risk of overdose than their illicit counterparts, the

replacement medications can still cause respiratory depression if they are administered in wrong doses (Douaihy et al., 2013; Whelan & Remski, 2012). Additionally, buprenorphine may induce hepatitis while methadone may cause heart problems (Whelan & Remski, 2012). Moreover, there is no guarantee that patients comply with the medication schedule outside of treatment facilities.

Besides medication-based treatments, many psychosocial therapies have been used in a clinical context within the past few years. One form is contingency management (CM), during which the patient receives rewards for remaining abstinent. These rewards can take multiple forms depending on the individual patient (Jhanjee, 2014). For example, inpatients could be granted some time outside of the treatment facility in exchange for cooperative behaviour. To increase the effectiveness of CM, it might be useful to combine it with other therapeutic interventions. Recently, van den Brand and colleagues (2018) conducted a study to test whether financial incentives as an add-on to smoking cessation groups improve treatment outcomes. Both the control and the experimental

groups, consisting of smokers, received smoking cessation training in a group setting. The experimental group was additionally rewarded with vouchers during a period of 12 months following the training sessions if they remained abstinent. The results indicate that in the experimental group more participants remained abstinent with a proportion of 41% while in the control group only 26% of the participants remained abstinent.

On the one hand, CM has been found to improve compliance with treatment programs (Jhanjee, 2014). However, despite positive effects on abstinence outcomes during treatment (d=0.58, 95% CI=0.25 to 0.90), there is not much support for effectiveness on relapse prevention (Dutra et al., 2008; Blonigen, Finney, Wilbourne & Moos, 2015). Additionally, providing materialistic rewards for the patient is expensive. For that reason, CM is not employed often in the clinical context (Jhanjee, 2014).

As a final example of psychosocial treatments, the patient can engage in cognitive behavioural therapy (CBT) with a focus on identifying maladaptive beliefs and behaviours; and teaching

the patient appropriate coping strategies (Milton & Everitt, 2012). CBT seems to be effective for a broad range of drugs of abuse (Jhanjee, 2014). There are multiple interventions that have been put forward within the umbrella term CBT. Several studies have identified social skills training as the most effective intervention. The patient learns how to initiate social interaction and to cope with peer pressure regarding drug consumption (Blonigen et al., 2015). CBT was found to have a small, but significant effect for the treatment of SUD (g = 0.154, p < .005); with the largest effect for cannabis dependence (Hofmann, Asnaani, Vonk, Sawyer & Fang, 2012, Magill & Ray, 2009).

Even though CBT is a widely accepted therapeutic approach, it might not be suited for every patient. For successful treatment, cooperation by the patient is crucial as it requires recognition of and willingness to change dysfunctional beliefs. Therefore, it might not be effective for patients that have been obliged to complete treatment. Moreover, CBT requires sufficient cognitive capacities to identify maladaptive beliefs and behaviours and adapt them. Some patients might lack insight

into the underlying beliefs as contributing factors to their disorder.

In sum, it has to be noted that neither type of therapy described above sufficiently targets the conditioned responses that are a crucial component in maintaining addiction. Medication-based treatments are only suitable to temporarily replace drugs rather than treating causes and preserving aspects of SUD. CM provides an incentive to remain abstinent, but no attempt is made to identify the causes of SUD and triggers of relapse in form of CS. CBT approaches the causes and stimuli of abuse and relapse more, but it requires the patient to consciously adjust dysfunctional beliefs and behaviours. However, conditioning is a subconscious process. Even if the patient successfully identifies CS, this is not sufficient to prevent their impact on behaviour. A cognitive approach might not be suitable to reverse the influence of drug-associated stimuli on behaviour. Neglecting these maintaining factors leaves the individual more vulnerable to relapse in critical situations (Milton & Everitt, 2012). To treat SUD effectively in the long run, an alternative treatment approach that specifically targets

associations between CS and drug-seeking behaviours should be proposed. As the following part of the review argues, this might be accomplished with memory manipulation treatments. Rather than a single intervention, these treatments may be combined with the previously mentioned therapy forms to increase their effectiveness.

Memory Manipulation as Addiction Treatment

A memory manipulation treatment approach might be an effective way to reduce the risk of relapse after patients have left medical care (Milton & Everitt, 2012). It has been well-established that CS can elicit strong drug cravings and motivate drug-seeking behaviours, which in turn might result in relapse (Everitt & Robbins, 2005). The following approaches attempt to disrupt the impact of CS on behaviour.

Research in the field of neurobiology has identified two possible mechanisms of memory manipulation, extinction and reconsolidation (Torregrossa & Taylor, 2012). Firstly,

reconsolidation refers to the process by which reactivated memories are stabilized and updated before they are stored in long-term memory. One underlying molecular mechanism of reconsolidation has been identified as the synthesis of a neuronal protein which is regulated by the expression of the early immediate gene Zif268. The disruption of the synthesis of this protein may strongly interfere with reconsolidation (Milton, 2013). Addiction treatments can make use of this property by specifically manipulating maladaptive drug memories before they are updated and stored in long-term memory (Merlo, Milton & Everitt, 2015). As was discussed previously, some maladaptive memories can be identified as stored associations between a conditioned stimulus and drug seeking. Targeting those associations during retrieval by means of disrupting protein synthesis might decrease stimulus effects on behaviour. Reconsolidation can be disrupted by administering a pharmacological agent that interferes with protein synthesis just before drug-related CS exposure (Lee, Milton & Everitt, 2006). Ultimately, this might weaken the association between the

stimulus and the drug (Taylor, Olausson, Quinn & Torregrossa, 2009).

In a study by Lee and colleagues (2006), rats were conditioned to press a lever for a cocaine injection in response to a light cue. In subsequent sessions, at the basolateral amygdala (BLA) the rats were infused with Zif268 antisense oligodeoxynucleotides (Zif268 ASO), which suppress the expression of the early gene Zif286, just before exposing them to the CS again. The BLA has been found to be part of a mechanism by which CS exert control over drug seeking behaviour (Everitt, 2009). The suppression of Zif268 expression during memory retrieval effectively interfered with protein synthesis. Consequentially, the reconsolidation of memories that concerned the association between the conditioned light cue and cocaine administration was disrupted. As a result, the CS did not elicit the previously observed cocaine seeking behavior anymore ($p < .03$). Additionally, the rats did not show signs of relapse following reconsolidation training.

To disrupt reconsolidation in humans, propranolol has been put forward as a safe medication. The β-blocker disrupts

protein synthesis that is important for restabilising memory traces by binding to β-adrenoceptors in the brain. It is thought to be more effective in altering emotionally relevant memories because it reduces amygdala activity (Thomas, Saurnier, Pitman, Tremblay & Brunet, 2017). This property might be used to alter emotional drug memories of patients. So far, propranolol is the only medication to alter reconsolidation that has been approved to be used on humans (Lonergan et al., 2016).

In a pilot study, the effects of propranolol during retrieval periods were tested in patients with SUD (Lonergan et al., 2016). The subjects were randomly allocated to either a control (n=8) or experimental condition (n=9). In a total number of 6 sessions, the participants were given either propranolol or a placebo. An hour after ingestion, they were asked to read a text that described a personalized drug experience, meant to trigger drug cues and induce cravings. An analysis of the data showed that only the experimental group displayed a significant decrease in craving scores after completion of the last session (d= 1.40). These results suggest that propranolol can be used to reduce craving by preventing reconsolidation.

However, correct timing of propranolol administration has been found to be crucial to reproduce the desired effects. Thomas and colleagues (2017) found that only receiving the medication 60-75 min prior to retrieval effectively interfered with memory reconsolidation (*n*=50). Post-retrieval administration has failed to replicate the positive effects of reconsolidation interventions (*n*=36). A likely explanation for this phenomenon is that propranolol takes 1-2 hours to exert its full effects.

Treatment of SUD with propranolol has been found to have many advantages over conventional pharmacological manipulations. The intervention requires fewer treatment sessions and therefore significantly reduces treatment costs and effort. Additionally, patients do not have to take the medication daily. It is sufficient to administer propranolol prior to a therapy session. Moreover, the intervention could be translated into clinical settings easily and is accepted very well by patients (Lonergan et al., 2016). Additionally, propranolol has no addictive potential which is a big advantage for treating patients with SUD (Noyes, 1982).

Alternatively, extinction refers to the disruption of the association between the drug seeking and conditioned cues by preventing reinforcement (Torregrossa & Taylor, 2013). Consequentially, drug seeking behaviours should gradually decrease. The therapist exposes the patient to different stimuli that elicited drug-related behaviours in the patient's history of drug abuse. During the exposure periods, the patient is not allowed to consume any drugs. After multiple sessions, the procedure will eventually create a new association between the cues and the absence of reinforcement (Milton & Everitt, 2012).

Rather than eliminating the original association, maladaptive behaviours are inhibited by extinction (Taylor et al., 2009). Bouton (2004) proposes that the response to CS will depend on the context, which allows conditioned responses to be reinstated in critical environments. To improve treatment success, it might be useful to apply extinction procedures in real-life environments rather than treatment facilities (Taylor et al., 2009).

The extinction paradigm was tested in rats by Xue and colleagues (2012) using conditioned place preference (CPP),

meaning that a certain environment was used as the CS. The rats received injections of morphine in the same environment across multiple sessions. Due to the reinforcing effects of the drug, they developed a preference for that specific place compared to another environment where they merely received saline injections. In the following phase of the experiment, the rats were exposed to the conditioned place to retrieve the associated drug memories. Afterwards, they were withdrawn from the drug-associated environment and returned to it after varying delay periods. During this second exposure, the extinction training took place, meaning that there was no reinforcement by injecting morphine to the rats. If the delay between retrieval and extinction was of short duration, more precisely between 10 min to 1 hour, the association between the drug and the environment was weakened ($p < .05$, n= 9-11 per condition). These findings indicate that there is a limited time window in which extinction manipulation is effective.

The research group elaborated on this experiment by testing extinction procedures in abstinent heroin addicts. The subjects were tested for their reactivity towards neutral or

heroin cues following manipulation of memory retrieval and extinction training during which they were exposed to drug-related cues without drug reinforcement. The participants were assigned to one of three different conditions. A control group was exposed to a videotape that contained neutral cues whereas the two other groups saw clips that contained heroin cues. The manipulation with heroin cues was intended to elicit retrieval of drug-related associations. Afterwards, each group received extinction training during which they were exposed to different drug cues after varying delay periods. The subjects that were assigned to the neutral condition received the extinction 10 minutes after watching the video. The groups that were subjected to heroin cues experienced a delay period of either 10 minutes or 6 hours before the extinction training. Similar to the results from their previous experiment, the researchers found that only the group who had a short delay between memory retrieval and the training exhibited significantly lower levels of heroin craving and lower blood pressure following drug cue exposure compared to the control group ($p < .05$, n=16-18 per condition). Neither group showed reactivity in response to

neutral cues. These data add evidence to the notion that the delay between retrieving drug-related memories and extinction procedures should be short. More importantly, these results suggest that extinction could be a potential intervention for treating SUD.

Another alternative treatment approach that might be useful in SUD therapy is eye movement desensitization and reprocessing (EMDR). This approach makes use of the vulnerability of memories during reconsolidation. Originally, EMDR was developed to decrease the magnitude of traumatic memories (Qurishi, Markus, Habra, Bressers & Jong, 2017). More recently, attempts have been made to use EMDR for disrupting memories that are associated with drug consumption (Hase, Schallmayer & Sack, 2008). During therapy sessions, the patient is instructed to make horizontal eye movements (EM) during recall of drug memories to exhaust the capacity of working memory (WM). These drug memories can take multiple forms; patients may envision situations in which they felt an intensive craving, positive feelings that are associated with the drug or mental representations of CS (Wise & Marich, 2016). The limited

resources of the WM are allocated in favor of EM and do not suffice for maintaining a vivid representation of the drug memories (van den Hout & Engelhard, 2012). In this way, EMDR is supposed to desensitize the patient to these memories and reduce their impact on drug-related behaviour (Qurishi et al., 2017).

Hase and colleagues (2008) investigated the therapeutic effects of EMDR in 30 subjects with alcohol addiction. The experimental group received EMDR sessions in addition to treatment as usual (TAU). To retrieve drug-related memories, participants were asked to recall specific situations of craving or relapsing. Following the EMDR sessions, the patients reported more reductions in alcohol craving in comparison with a control group which only received TAU ($p < .001$). Moreover, it was found that EMDR might have the potential to prevent relapse in the long-term as the reduction in craving was maintained in most participants in assessments after 1 and 6 months. However, the success in relapse prevention has to be investigated further in real life situations in which patients encounter craving-

eliciting stimuli. Currently, this study constitutes the only randomized trial for EMDR therapy with addiction patients.

Some additional support for EDMR in addiction treatment is provided by a case study of a woman with treatment-resistant gamma-hydroxybutyric acid (GHB) addiction (Qurishi et al., 2017). EMDR sessions were added to her regular therapy. At the beginning of each session, patient and therapist identified a memory representation which triggered high levels of craving, mainly positive experiences with GHB consumption. The patient was instructed to maintain the identified representation actively while making horizontal EM. Following this intervention, the patient reported less craving when recalling the previously identified experiences. Additionally, she maintained abstinence during the treatment and 6 months later at the follow-up assessment.

In another study, the effects of EM on the vividness of substance-related memories and craving was tested in a sample of smokers (Littel, Hout, & Engelhard, 2016). Participants were instructed to recall a situation or emotional state in which they gave in to the craving to smoke a cigarette. During the main

task, the experimental group was asked to think of the previously identified memory while performing EM while the control group was asked to keep the eyes fixated. Results showed a significant increase in memory vividness (d = 0.71) and craving scores (d = 0.89) following recall of craving-related memory in the control, but not in the experimental group following recall combined with EM.

DISCUSSION

The use of memory manipulation appears to have potential for the treatment of drug addiction in the future, given that it has been supported by multiple research lines. The reviewed treatments target conditioned responses and stimulus associations that play an important role in the maintenance of SUD and relapse. Furthermore, memory manipulation stands out from most of the established treatments since it seems more effective in preventing relapse (Hase et al., 2008; Lee et al., 2006; Milton & Everitt, 2012; Xue et al., 2012) Nevertheless, one should

be cautious to translate those findings into a clinical context. Studies regarding the use of reconsolidation interference and EMDR to specifically treat SUD have been scarce. The experiments that have been mentioned need to be replicated to establish the robustness of results and to discern any potential side effects.

Especially regarding reconsolidation as a treatment tool, little is known about the impact on drug memories in human subjects. So far, successful treatment with pharmacological reconsolidation disruption in humans has been limited to propranolol (Lonergan et al., 2016). The manipulation of memories of an individual with pharmacological interventions is a rather intrusive approach. Further careful testing in humans should be conducted to investigate the impact of reconsolidation treatments and to rule out that non-related memories are affected. The effects of other pharmacological agents such as Zif268 ASO should be carefully examined for addiction treatments in humans before it can be fully utilized in a clinical context. As pharmacological agents may have various

side effects, extinction and EDMR therapies have an advantage over reconsolidation strategies.

One problem of extinction in comparison to reconsolidation is that drug seeking behavior might reappear after some time following the intervention, a phenomenon known as spontaneous recovery; after relapses from abstinence; or if a CS is encountered in a new context (Torregrossa & Taylor, 2013). An effort should be made to address this issue, as it is crucial for transferring extinction into treatment in real life. Improvement in outcomes of extinction might be accomplished by alternating the context of CS exposure in sessions. EMDR has to be studied more to draw conclusions whether it prevents the reinstatement of drug seeking behaviors.

Additionally, the studies by Xue and colleagues (2012) on extinction showed that there is a limited time window in which the intervention is effective. The associations between drug effects and CS in addicts have been established a long time before treatment in repeated fashion though. Future research may attempt to improve the outcomes of extinction for SUD,

possibly by combining it with other memory manipulation treatments or TAU.

In general, the long-term effects of memory manipulation should receive more attention in addiction research. In the study by Hase and colleagues (2008), the impact of EDMR was investigated across a span of 6 months, but it would be crucial to research whether the treatment success lasted for extended periods. It is of utmost importance to conduct careful testing trials across a few years to be able to make more general assumptions about treatment success and to dissect possible side effects with certainty.

Another limitation of memory manipulation treatments is that addiction is maintained by a complex pattern of associations between various cues and drug seeking behaviours. This imposes a major challenge for manipulation treatments, as it might not be feasible to target every single association. Taylor and colleagues propose that extinction training should be conducted in drug-related contexts, but they acknowledge that this might not be practical for clinicians. Regarding this, EMDR may have an advantage in comparison to the other treatments

since it covers complete memories of situations with multiple drug cues. However, the therapist must rely on the patient's ability to identify memories that are relevant to the maintenance of addiction. This might be difficult for some patients.

Future research should attempt to increase the number of subjects and investigate the effects of memory manipulation interventions across extended time periods. Moreover, it would be an interesting direction to explore how the described treatments can be combined with other therapy forms. There are multiple well-established therapies as for example CBT that have been found to be effective in the treatment of SUD. Memory manipulation treatments might be a valuable addition to TAU. Furthermore, additional studies should try to identify factors that constitute a suitable environment for memory manipulation therapies. If the manipulation-based treatments are found to have long-lasting positive treatment outcomes and to have few side effects, then it would be reasonable to include these interventions into regular SUD therapy.

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IOANA STAICU

Oxytocin in autism spectrum disorders:
role and potential application

Perspective

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting a significant percentage of the population. Affected individuals present with limited interests and impaired communication and social interactions. Despite researchers' attempts, no specific pharmacotherapy has been developed, with behavioural interventions rendering the best results so far, yet their ability to alleviate social impairments remains rather limited. However, evidence suggests that oxytocin intake could improve social functioning in some of these individuals.

The aim of this paper is to evaluate the proposed mechanisms underlying dysregulation in the oxytocinergic system and to assess the results and discuss the limitations of several clinical studies involving oxytocin administration in ASD patients.

Keywords: autism; ASD; intranasal oxytocin; amygdala

INTRODUCTION

Autism spectrum disorder (ASD) is an umbrella term for a collection of neurodevelopmental disorders, characterized by a triad of the following symptomatology: persistent impairments in social interaction, impaired social communication and a narrow range of interests and repetitive behaviour (American Psychological Association, 2013), with symptoms starting typically in early childhood (World Health Organisation, 2018). What makes ASD particularly difficult to study is its incredible complexity, both in respect to the heterogeneity of symptoms and the underlying biological mechanisms, with each autistic individual offering a unique perspective on this pathology. In addition to the wide range of phenomena that describe it, ASD is often accompanied by comorbidities such as epilepsy, intellectual disability (Atladóttir et al., 2015) or macrocephaly (Campbell et al., 2014).

ASD is part of a cluster of disorders, namely the pervasive developmental disorders (PDD). It can be classified

according to severity of the symptoms and extent of support required (World Health Organisation, 2018). High-functioning individuals (formerly diagnosed as having Asperger's syndrome) have a higher chance of living an independent life, while for the low-functioning ones, the prognosis is usually poor, due to their impaired social functioning, stressing the need for effective treatments.

Available treatments for ASD are still limited, despite the number of years since its formal description by Leo Kanner and Hans Asperger in the 1940s, and the relatively high prevalence in the general population (approximately 1%, according to Elsabbagh et al., 2012). Early behavioural interventions seem to render the best results, with Applied Behavioural Analysis (ABA) and Early Intensive Behavioural Intervention (EIBI) as some of the most successful therapies, targeted specifically at improving social behaviours (Granpeesheh, Tarbox, & Dixon, 2009; Tonge, Bull, Brereton, & Wilson, 2014); however, these are particularly costly, time-consuming and require early intervention by highly skilled professionals. To this date, there is no pharmacological

therapy designed specifically for autism. Antipsychotic medication such as risperidone and aripiprazole are the most frequently prescribed to reduce aggresive behaviours, but are associated with serious side-effects and do not promote social functioning (McPheeters et al., 2011). However, a growing body of evidence points to a dysregulation in the oxytocinergic system of ASD patients, with studies showing mixed results in terms of intranasally administered oxytocin (OXT) improving some of the social impairments. This paper discusses oxytocine levels and its role in social behaviour, the genetic variation in OXT receptor in autism, as well as key brain regions affected in this pathology. Moreover, the results and limitations of several clinical studies testing OXT administration in ASD individuals will be examined.

OXT levels in autism

The neuropeptide OXT plays a pivotal role in social behaviours, promoting nurturing, bonding and parent-infant attachment, as

shown by human and other mammalian studies alike (Rilling & Young, 2014). The hypothesis of an OXT deficit in autism is rather prevalent, yet still a subject of debate. One of the very first studies examining this matter found that peripheral OXT levels in autistic individuals are significantly lower than those found in healthy populations (Modahl et al., 1998). Moreover, Alabdali et al (2014) showed OXT plasma concentrations negatively correlated with severity of autistic symptoms, as evaluated by either the Social Responsiveness Scale (SRS) or the Childhood Autism Rating Scale (CARS). Interestingly, Parker et al (2014) found that low OXT concentrations in plasma were predictive of impaired social interaction and a poorer theory of mind (the skill of discerning between one's state of mind and the others') in autistic individuals as well as in healthy controls. Their results also contradicted the OXT deficit hypothesis, as its levels did not significantly vary between groups (Parker et al., 2014). While there is no general consensus with regards to peripheral concentrations of OXT as a valid biomarker for ASD, it seems that it is a fair indicator of social impairment.

The OXT receptor gene in autism

The role of OXT in social behaviour is also supported by genetic findings. It appears that OXT receptor knock-out mice display aberrant characteristics in this respect, showing impaired social memory and recognition (Lee, Caldwell, Macbeth, Tolu, & Young, 2008) and deterioration of mother-offspring bonding (Nishimori et al., 2008). This motivated researchers to explore whether there are genetic differences in the OXT receptor gene (OXTR) in the autistic population. As such, a 2015 meta-analysis found four single-nucleotide polymorphisms (SNPs) in the OXTR significantly associated with ASD (rs7632287, rs237887, rs2268491, rs2254298) (LoParo & Waldman, 2015). One of them (rs237887) was particularly linked to face recognition memory in a sample of 198 families with a single autistic child, as reported by Skuse et al. (2014). The researchers found that the SNP was associated with poor recognition memory, which is characteristic of ASD, in patients as well as their immediate relatives (parents and siblings) (Skuse et al., 2014).

In addition to alterations in the DNA sequence, epigenetic mechanisms were also found to be involved with the expression of OXTR. Gregory et al. (2009) analyzed the methylation levels at the promoter region of the OXTR gene, which are predictive of a gene's expression. Using post-mortem brain tissue from autistic individuals, they found this region was heavily methylated in the autistic group, which subsequently correlated with a decreased expression of the gene when compared to controls (Gregory et al., 2009). A limitation of this study, though, is the small sample size, which consisted of only 8 patient-control pairs, yet there seems to be evidence for epigenetic mechanisms accounting for different expression of OXTR in ASD patients.

OXT and the amygdala

The amygdala, a key region with regards to social functioning and emotion processing, seems to also be affected in the ASD population, in terms of both structure and functional

connectivity with other brain areas. While there is evidence that children with ASD aged 2-4 years show amygdala enlargement correlated with social impairments (Nordahl et al., 2012), scans from older patients (8 years onwards), point to a gradual reduction in its volume, with the enlargement disappearing completely during adolescence (Barnea-Goraly et al., 2014). Preckel & Kanske (2018) hypothesized that early amygdala overgrowth could be a potential compensatory mechanism for social deficits, especially in the context of low OXT levels. Hennessey et al (2018) prompted for longitudinal neuroimaging studies, as the available data are either a one-time measurement, or only show how this brain structure evolves over the span of 1-4 years.

There also appears to be a decreased functional connectivity between the amygdala and several cortical regions (occipital, parietal and prefrontal cortices) in ASD adolescents when compared to controls (mean age = 16 years), as shown by a resting state fMRI study (Rausch et al., 2016). In addition to this, clinical studies point to exogenous OXT as an effective molecule

in both restoring activity in the amygdala and its connectivity to other regions (Watanabe et al., 2014), and promote pro-social behaviours (Anagnostou et al., 2014; Tachibana et al., 2013).

Intra-nasal administration of OXT - a potential treatment

As discussed so far, OXT shows a clear involvement in ASD, with its low peripheral levels linked to disrupted social functioning (Alabdali et al., 2014; Modahl et al., 1998; Parker et al., 2014); alterations in both gene sequence and expression of OXTR could serve as biological bases (Gregory et al., 2009; LoParo & Waldman, 2015; Skuse et al., 2014). Moreover, a link between the amygdala and social behaviours has been hypothesized to exist in the context of ASD (Nordahl et al., 2012; Preckel & Kanske, 2018; Rausch et al., 2016). As such, several researchers aimed to test whether intranasally administered OXT would benefit this population in terms of social functioning.

Promising results following acute or long-term OXT administration come from studies with various age groups. Anagnostou et al. (2014) reported on a case series of 15 ASD youths (aged 10-17) who received doses up to 0.4 IU/kg intra-nasal OXT for 12 weeks, twice a day. The patients showed improvements with regards to social cognition/function, theory of mind and face recognition when assessed at week 12, with some of the changes persisting up to another 12 weeks after treatment discontinuation (Anagnostou et al., 2014). Another study reported similar findings after 8 ASD males (aged 10-14) were exposed to increasing doses of intra-nasal OXT (8/16/24 IU), with each dose being administered daily for two months. Authors noted significant improvements in 6 of the children in terms of social and communication scores, but only in one of the three assessment tools used, namely the Autism Diagnostic Observation Schedule – Generic (ADOS-G) (Tachibana et al., 2013). In spite of the encouraging outcomes and lack of serious adverse effects, a major limitation of both of the studies is the sample size and the absence of a placebo group.

Watanabe et al. (2014) proposed a more robust design, with 40 ASD adult males (aged >20) randomized in a double-blind, placebo-controlled trial. After receiving a single dose of either 24 IU intra-nasal OXT or a placebo, the participants were assessed by their ability to make decisions about social cues that had incongruent verbal and non-verbal content. It was previously observed that autistic patients have difficulty when asked to make non-verbal information-based judgements (NVJs). The authors noted that the group receiving OXT scored significantly better in terms of the number of NVJs and reaction time to these stimuli. Moreover, fMRI scans taken during the task showed a normalization in amygdalar activity, an increased activity in the medial prefrontal cortex and anterior cingulate cortex, as well as an enhanced connectivity between the two, which correlated with the OXT-induced behavioural effects (Watanabe et al., 2014).

Nevertheless, two randomized, double-blind, placebo-controlled trials failed to observe any benefits of administering OXT in ASD patients over placebo. Dadds et al (2014) compared

the effects of intra-nasally administering either 12 or 24 IU of OXT versus placebo in 38 ASD males (aged 7-16), once a day, for four consecutive days. The group receiving OXT did not significantly differ from the placebo group with regards to emotion recognition, social interaction skills and general behavioural adjustment. The authors noted, however, that their assessment of outcome measures differed from other studies with respect to time: while other trials evaluated patients while under OXT influence, theirs analysed the pre-post changes in the aforementioned outcome measures (Dadds et al., 2014). Guastella et al (2015) reported similar findings, with their study of 50 male ASD patients (aged 12-18) receiving either 18 or 24 IU of OXT or placebo intra-nasally, twice a day, over the course of 8 weeks. Patients were assessed using the Social Responsiveness Scale, as completed by their caregiver, and the Clinical Global Impression-Improvement Scale, as reported by a clinician. Other outcome measures consisted of assessment of presence, severity and frequency of repetitive behaviours, as recorded by a caregiver. Said outcomes were registered at baseline, at weeks 4 and 8 after commencing treatment, and at a 3 month follow-up.

The authors concluded that patients receiving OXT did not significantly improve on any of the outcome measures, yet caregivers' assessments seemed to be positively influenced by the belief that their patients were in the treatment group (Guastella et al., 2015).

DISCUSSION

In summary, OXT shows questionable potential in terms of improving social impairments in ASD. Evidence supporting its use comes from genetic studies showing polymorphisms in the OXT receptor gene (LoParo & Waldman, 2015; Skuse et al., 2014) and its decreased expression (Gregory et al., 2009), but also from altered activity in key brain areas associated with social behaviour (Nordahl et al., 2012; Preckel & Kanske, 2018; Rausch et al., 2016; Watanabe et al., 2014) and overall low levels of peripheric OXT (Alabdali et al., 2014; Modahl et al., 1998; Parker et al., 2014). Nevertheless, in spite of encouraging results from Anagnostou et al. (2014), Tachibana et al. (2013) and Watanabe

et al. (2014), studies with larger sample sizes and more robust designs failed to replicate their findings (Dadds et al., 2014; Guastella et al., 2015). A clear limitation of the studies with positive findings is the small number of subjects and lack of a control group (Anagnostou et al., 2014; Tachibana et al., 2013). Furthermore, an evident drawback of all discussed studies is the fact that the majority of the participants recruited was male. This could potentially introduce a gender bias and consequently lead to results that may not be relevant for females.

Possible explanations regarding the conflicting results could be the heterogeneity in the doses of OXT administered, as well as the different age groups studied. The latter aspect is particularly important, as age could influence the maturation of the amygdala and its functional connectivity with other brain regions, thus potentially determining the response of an ASD individual to OXT treatment. This calls for a more unified approach in terms of studying the effects of intra-nasal administration of OXT in this population. Another point to consider would be the necessity of follow-up studies to assess

the impact of OXT intake on brain development and potential side-effects that were not detectable at the time of the administration. Only two of the studies described conducted a follow-up assessment after discontinuation of treatment, around a similar time point (12 weeks): while they showed conflicting results, with Anagnostou et al. (2014) reporting positive findings and Guastella et al. (2015) noting no significant improvement, neither of them found any serious adverse reactions. However, it is important to know if there are any long-lasting changes of OXT administration on brain development, therefore patients should be monitored for a longer period of time after termination of treatment.

It can be concluded that more research needs to be conducted in order to establish whether or not OXT is an efficient pharmacological treatment for ASD patients.

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