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Invited review

Unexplored territory: Beneficial effects of novelty on memory

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ABSTRACT

Exploring novel environments enhances learning in animals. Due to differing traditions, research into the effects of spatial novelty on learning in humans is scarce. Recent developments of affordable and fMRI-compatible virtual reality (VR) and mobile EEG systems can help bridge the gap between the two literatures. One promising study showed that spatial novelty also promotes learning in humans. It still remains largely unknown, however, which aspect of novelty underlies the beneficial effect on memory, as novelty, expectations, and volition are often confounded in animal studies. In humans, these factors can be experimentally manipulated, but such studies are currently lacking. Future studies in humans could combine pharmacological interventions, neuroimaging and VR or use mobile EEG to help elucidate whether the plasticity enhancing mechanisms observed in animals, also exist in humans. When the aspects of exploring a novel environment underlying beneficial memory effects have been identified, effective novelty-exposure interventions could be designed to improve learning and counteract age-related memory decline.

1. Introduction

Novelty has been a popular topic of research for decades, making up a rich body of literature. The types of stimuli used in this research vary from very simple to very complex (Schomaker & Meeter, 2015). Due to differing research traditions the types of novel stimuli used in studies in animals and humans are particularly large. In the human literature, new or deviant fonts, sounds, or pictures have been employed as "novel" stimuli (i.e., novelty at the stimulus level), while novelty manipulations in animals often consist of bringing an animal to an entirely novel environment (i.e., spatial/environmental novelty). Novelty research in both animals and humans has been prolific, but unfortunately there is little communication between the two fields. Especially research aimed at investigating spatial novelty in humans is scarce. This short review aims to highlight the gap between the two research traditions and hints toward possible future venues of research to translate interesting findings in animals to research in humans.

2. Effects of novelty on learning and memory

When visiting a new place, you have to navigate through unknown territory, and remember landmarks to find your way back. Quickly learning where to expect danger, and where to find rewards is therefore crucial for survival. Several theories have suggested that to promote learning, novelty elicits a learning signal (Kormi-Nouri, Nilsson, & Ohta, 2005; Lisman & Grace, 2005; Meeter, Myers, & Gluck, 2005; Recce & Harris, 1996; Tulving & Kroll, 1995).

Indeed, exploration of novel environments has consistently been shown to enhance plasticity in the brain to promote learning in animals (Davis, 2004; Lemon & Manahan-Vaughan, 2006; Li, Cullen, Anwyl, & Rowan, 2003; Moser, Moser, & Andersen, 1994; Straube, Korz, Balschun, & Frey, 2003), through a process referred to as behavioral or synaptic tagging (Frey & Morris, 1997, 1998; Sajikumar & Frey, 2004; Wang, Redondo, & Morris, 2010). Especially from rodent studies we have learned that a novelty signal from the hippocampus can travel to the substantia nigra/ventral tegmental area (SN/VTA), causing dopamine release, and promoting plasticity in the hippocampus by lowering the threshold for long-term potentiation (LTP) via a back-projection (Düzel, Bunzeck, Guitart-Masip, & Düzel, 2010; Lisman & Grace, 2005). It was long believed that the VTA was the sole source of novelty-related hippocampal dopamine associated with memory persistence. Recent optogenetics studies, however, have suggested that the locus coeruleus (LC) may be another source of dopaminergic signaling associated with novelty-promoted hippocampal learning (Kempadoo, Mosharov, Choi, Kandel, & Sulzer, 2016; McNamara & Dupret, 2017; Takeuchi et al., 2016).

Also theta activity has been linked to memory encoding during exploratory behavior in both humans and animals (Buzsáki, 2002; Kaplan et al., 2012). A model has suggested that novelty induces an oscillatory theta state in the hippocampus associated with a learning

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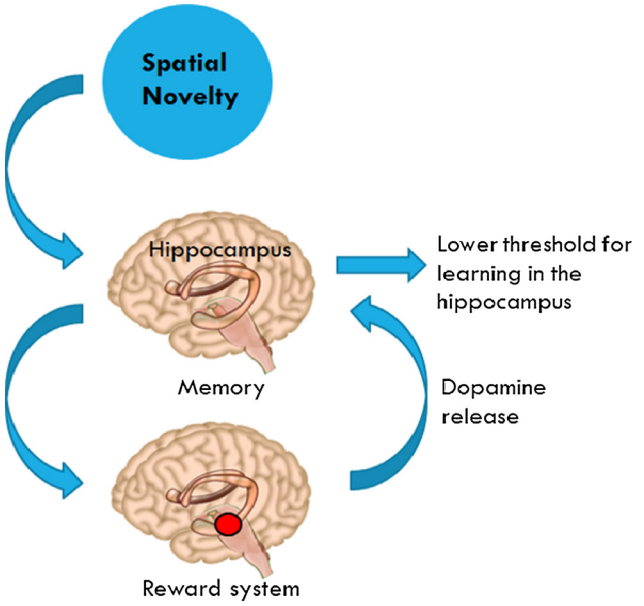

Fig. 1. Schematic showing the putative mechanism by which spatial novelty could promote learning in the human brain. Novelty activates the hippocampus (Knight, 1996), and in turn this novelty signal activates dopaminergic reward circuits. Through a back-projection to the hippocampus, dopamine lowers the threshold for long-term potentiation (Düzel et al., 2010; Lisman & Grace, 2005). Recent studies in rodents have suggested that the locus coeruleus may be an alternative source of novelty-induced hippocampal dopamine (Kempadoo et al., 2016; McNamara & Dupret, 2017; Takeuchi et al., 2016). Simultaneously, novelty may induce a learning rather than recall mode (Lisman & Otmakhova, 2001), and as such, exposure to spatial novelty prepares the brain for learning.

rather than recall mode (Lisman & Otmakhova, 2001).

By triggering plasticity-related protein synthesis, the beneficial effects of novelty on memory can occur *before* and *after* exposure and can linger for several tens of minutes, even after return to a familiar environment (Lemon & Manahan-Vaughan, 2006; Li et al., 2003; Nagai et al., 2007; Roggenhofer et al., 2010; Sajikumar & Frey, 2004; Wang et al., 2010). Importantly, the effects are generalizable, i.e. they are not stimulus-specific. If similar mechanisms exist in humans, these characteristics together could potentially be used in novelty-exposure interventions aimed at improving learning. Some studies have suggested that novelty can promote learning in humans as well (Bunzeck & Düzel, 2006; Düzel et al., 2010; Krebs et al., 2009, 2011; Wittmann, Bunzeck, Dolan, & Düzel, 2007). In animal research, however, typically *spatially* novel environments are used but research exposing human subjects to spatial novelty is very scarce (with one exception, Schomaker, van Bronkhorst, & Meeter, 2014), making it uncertain whether the findings from animal research can be generalized to human research. Fig. 1 presents a schematic of one of the putative mechanisms by which novelty can enhance learning in humans.

Beneficial effects of exploring a novel environment on learning and memory could also be caused by effects of novelty on arousal: Exploration of novel environments results in increases in arousal and locomotor activity (Moser et al., 1994), which in turn can promote LTP and learning as mediated by noradrenergic activity (Cahill & McGaugh, 1998; Sara, Vankov, & Hervé, 1994; Vankov, Hervé-Minvielle, & Sara, 1995).

3. Effects of novelty on learning at the stimulus-level

Due to differences in tradition and practicalities with study design, human studies have used vastly different approaches to investigate effects of novelty on memory than animal studies. Rather than having subjects actively explore new environments, the link between novelty and memory has traditionally been investigated in experimental paradigms where novel and familiar stimuli (e.g., pictures of fractals or landscapes) are presented in an otherwise static context. Such studies found that at the stimulus-level, novelty can also have a beneficial effect on learning. Recognition is typically better for novel compared to previously familiarized items; this is known as the *novelty effect* (Kormi-Nouri et al., 2005; Tulving & Kroll, 1995), however, depending on memory schemas novel events are not always better remembered (Van Kesteren, Ruiter, Fernández, & Henson, 2012)

Also stimuli that differ from other stimuli in a context, e.g., words presented in a different font, are better remembered, an effect known as the *von Restorff* or *isolation* effect (Bruce & Gaines, 1976; Schomaker et al., 2014; von Restorff, 1933). These studies investigated memory for stimuli that are novel themselves and can be distinguished from studies that investigate the effects of novelty on memory for events that are not necessarily novel and that occur close in time. I will refer to the latter as the generalizable effects of novelty on learning.

4. Human research: generalizable effects of novelty on learning

In spite of the robust findings of increased plasticity in animal studies, the effects of environmental **spatial novelty** as opposed to isolated stimulus novelty have rarely been studied in humans (Schomaker & Meeter, 2015). A lack of studies in humans using spatial novelty and its generalizable effect on memory, may be due to differences in research tradition, but is probably also caused by the practical issues involved in exposing participants to new environments (e.g., testing in different locations), while controlling for environmental factors (e.g., familiarity, environmental noise, etc.). Furthermore, neuroscientific methods that could be taken out into the real-world were either non-existent or rather unreliable. Therefore, studies in humans investigating the generalizable effect of novelty on memory typically use pictures of novel scenes instead. Fenker et al. (2008) exposed participants to a series of pictures of novel or previously familiarized scenes before learning a list of words. Exposure to the novel compared to familiar scenes improved word recollection. Novelty co-activated the hippocampus and SN/VTA. Although animal studies suggested that the long-term potentiation in the hippocampus can be enhanced by novelty (e.g., Li et al., 2003; Straube, Korz, & Frey, 2003), no link with memory was observed in this study. A possible reason for this difference is that exposure to novelty in this study consisted of the passive presentation of 2D pictures of novel scenes, rather than active exploration of novel environments, as often used in animal research. This study thus differs from the animal literature in that non-spatial rather than spatial novelty was used, and from the stimulus-based novelty studies described above, in that the to-be-learned events were presented in temporal proximity and were not novel themselves. Differences in designs and the operationalization of novelty therefore make it especially hard to make comparisons between animal and human studies. One proof of principle study tried to bridge the gap between the types of stimuli used in the two literatures by using virtual reality to create spatially novel environments. In this study, participants actively explored 3D novel, and previously familiarized *virtual environments (VEs)*. After exploring a novel VE, hippocampus-dependent recollection on an unrelated word learning task was improved, while hippocampus-independent recognition was not, indicating hippocampal involvement (Schomaker et al., 2014). These behavioral results are in line with the findings of Fenker et al. (2008). Notwithstanding, due to the scarcity of studies in humans, the exact factors resulting in novelty-induced memory enhancements and the neurobiological mechanisms underlying them, are not yet sufficiently understood.

5. Time-course of the beneficial effects of novelty on learning

The novelty effect and the Von Restorff effect play out at the time of individual stimulus presentation (i.e., seconds), while the effects of

spatial novelty have a longer time-scale. In contrast, the generalizable novelty-induced memory enhancements depend on a longer-lasting state; the effects of exposure to a novel environment can linger for up to 30 min (Li et al., 2003), and can even occur in retrospect, i.e., exposure to spatial novelty after memory encoding can improve learning for the material previously presented. In humans, exploration of novel versus familiar VE was shown to improve recall up to 15 min after exposure, indicating that the positive effects of novelty on learning also linger for some time in humans (Schomaker et al., 2014). Similarly, in another study exposure to pictures of novel scenes positively affected learning ten minutes afterwards (Fenker et al., 2008). In an education setting, students were either exposed to novel or familiar course content *before* or *after* reading a story (Ballarini, Martínez, Díaz Perez, Moncada, & Viola, 2013). Memory improvements were observed in students who went to a novel science or music lesson, compared to students who went to a familiar lesson. Improvements were also observed on a visual memory task, further indicating that novelty has a general beneficial effect on learning of unrelated information. Interestingly, the memory benefits were observed when the students experienced the novel lessons 1 h before or after story reading, but not when the events were 4 h apart, suggesting that the effects of novelty on memory are quite long-lasting, but that a critical exposure period exists (Duncan & Schlichting, 2018). The timing of the effects of novelty on memory is thus similar in animals and humans, but optogenetics studies have suggested, that there may be two different mechanisms underlying the time-course of the effects (Kempadoo et al., 2016; Takeuchi et al., 2016). Mirroring the effects of novelty exposure, activation of the LC 30 min *after* a learning event caused memory persistence (Takeuchi et al., 2016), while activation of the VTA at that time point did not produce a memory boost. In contrast, VTA stimulation *during* learning can improve hippocampal memory (McNamara & Dupret, 2017). As novelty can also activate the hippocampus, dopaminergic system, and LC in humans, it is likely that the novelty-induced benefits rely on similar mechanisms (Krebs, Fias, Achten, & Boehler, 2013; Murty, Ballard, MacDuffie, Krebs, & Adcock, 2013). Studying the timeline of the effects may also contribute to the identification of the underlying mechanisms in humans, but studies combining spatial novelty and neuroscientific methods are currently lacking.

6. Identifying the specific factors underlying the effects of novelty on memory

Novelty is multifaceted. A novel environment is not only novel, but also unpredictable by nature: It is impossible to predict something that has never been experienced (Schomaker & Meeter, 2015). In everyday life, however, humans often try to reduce the unexpectedness of visiting a new place, for example by viewing pictures or maps before their visit. Such expectations cannot be easily induced in rodents or primates; therefore, novelty and unexpectedness are often confounded in animal research investigating effects of novelty on memory. Event-related potential studies have shown that it is mostly the unexpectedness of novelty that elicits the psychophysiological responses traditionally associated with novelty processing (Schomaker & Meeter, 2018; Schomaker, Roos, & Meeter, 2014). As a violation of expectations can lead to better memory (Porubanova, Shaw, McKay, & Xygalatas, 2014), any effects of novelty on memory may be caused by the unexpectedness of novel environments, rather than novelty per se. It is therefore crucial that effects of novelty and violated expectations will be teased apart in future studies in humans.

Exploring a new versus a familiar environment could also affect brain and behavior by taxing decision making: In a new environment, active navigational choices are made, whereas navigating through a familiar environment relies strongly on habits. *Active* exploration of, rather than *passive* exposure to environments can promote recollection for landmarks and spatial memory (Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011). It is thus possible that active behavioral choices in a novel compared to familiar environment, rather than the perceptual novelty of the environment itself, underlie beneficial effects of novelty on memory. Future studies investigating effects of spatial novelty compared to familiarity should therefore also take into account the effects of volition. This can be empirically investigated by including both active exploration and passive exposure conditions.

7. Age-related changes in novelty processing

Exploring new opportunities, seeking out new situations and exploring novel environments is a core trait of adaptive mammalian behavior. Foraging species need a drive to explore new environments to survive. Even in modern times curiosity helps humans in survival. Elderly with higher curiosity have better chances of living longer and healthily (Swan & Carmelli, 1996), than elderly with lower curiosity and openness to new experiences is associated with longevity (Jonassaint et al., 2007). In rats, daily three minute exposure to novel environments in the first three weeks of life has been shown to promote LTP, resulting in long-lasting beneficial effects on learning, for at least one year later (Tang & Zou, 2002). Dopaminergic pathways are subject to age-related degeneration (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), and novelty processing is altered in aging populations (Alperin, Mott, Holcomb, & Daffner, 2014; Riis et al., 2009). Assuming the dopaminergic involvement in the effects of novelty on memory, exploration of new environments has been suggested as an intervention to slow age-related memory decline (Düzel et al., 2010), but experimental studies investigating this are lacking.

8. Future directions

Human and animal studies on novelty have very different traditions, but with the advance of neuroscientific methods it has become easier to overcome these differences and build bridges between the two fields. The availability of reliable mobile EEG systems and the successful combination with smartphones (Debener et al., 2012, 2015) would allow to take novelty research to the real-world in humans. EEG could be measured while participants are actively exploring novel versus familiar environments. A linked smartphone could, for example, be used to present an experimental (memory) task. This approach would allow to address a range of interesting questions. For example, does exploration of novel environments indeed induce a theta state, and how does this relate to the beneficial effects of novelty on memory? Although taking research to the real-world may be an ultimate goal of cognitive neuroscience, it also creates new issues. Mobile neuroimaging methods do not (yet) exist and going outside the lab will increase the occurrence of unexpected events, introduce noise, and make it hard to control for relevant factors (such as the degree of novelty/familiarity of the environment).

Pharmacological interventions in humans could further help to elucidate the neurobiological mechanisms underlying the effects of spatial novelty on learning and memory. Building on the animal literature, it would be particularly relevant to address the involvement of dopaminergic, noradrenergic and cholinergic systems as these are all associated with novelty processing and memory (Barry, Heys, & Hasselmo, 2012; Lisman & Grace, 2005; Rangel-Gomez & Meeter, 2016; Sara, 2009).

The advance of affordable immersive realistic 3D VR systems, allows to investigate the effects of spatial novelty while maintaining a high level of experimental control (for example, see Schomaker et al., 2014). fMRI compatible VR systems, such as, the rather expensive VisuaStim Digital goggles by Resonance Technology, already exist and allow to combine neuroimaging methods and VR. Since the effects of novelty can last for several tens of minutes, and can even work in retrospect, cheap VR systems, like Oculus Rift and HTC Vive, can also be combined with neuroimaging techniques, as novelty exposure can take place before or after the learning phase. By using virtual rather than

real environments participants can explore *well-controlled* environments while being in the lab (as has already been successfully done in other fields of research, e.g., Doeller, Barry, & Burgess, 2010; Spiers, 2001). VR also allows to create environments that are similar in size, number of landmarks, and other possible relevant factors. While it may be impractical to have participants explore comparable familiar, and novel environments in the real world, novelty and familiarity can be easily controlled for using VR, as previous exposure is easily checked. The benefits of using virtual rather than real-world environments are even employed in animal studies as well (Aronov & Tank, 2014; Harvey, Collman, Dombeck, & Tank, 2009).

In future research the neurobiological basis of exploring new environments, and the neural mechanism underlying the effects of novelty exploration on learning in humans can be investigated using mobile EEG and smartphones or the combination of VR and neuroimaging techniques. Studies in humans will allow to control for possible confounding factors, which are impossible to control in animals, including the role of explicit expectations and volition. Furthering our understanding of which specific aspect of exploring a novel environment promotes learning, and insight into the neurobiological basis, will be highly valuable when designing novelty-exposure interventions that can potentially counteract and/or slow age-related memory decline.

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