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CHAPTER I

The benefits of the new: Short- and long-lasting effects of novelty on the brain and cognition

Abstract

Novelty can have a wide range of beneficial effects on cognition. New stimuli can improve perception and action, increase motivation, elicit exploratory behavior, and promote learning. Here, we review these benefits and how they arise in the brain. Many of the benefits are the result of a cascade of brain responses elicited by novelty, activating several neuromodulatory systems. These neurophysiological responses play out on different time-scales, which seem to correspond to the time scales of different types of novelty-induced beneficial effects on cognition. First, novelty can transiently enhance perception in a similar way as emotional stimuli. This effect is proposed to be mediated by novel stimuli activating the amygdala, enhancing early sensory processing via the amygdala's connections with the visual cortex. Second, novel stimuli can activate the locus-coeruleus norepinephrine system, eliciting a phasic response of the locus coeruleus that peaks around 200 ms post-stimulus. This system is argued to underlie novelty's short-lived effects on action, speeding responses in the milliseconds after its presentation. Third, exploration of a novel environment can trigger the dopaminergic mesolimbic system, promoting dopamine release in the hippocampus. This response can have longer-lasting effects, up to tens of minutes on motivation, reward processing, and learning and memory.

Introduction

When a mammal encounters something new or a change in the environment, this typically results in an overt behavioral orienting response towards the new event (e.g., a turn of the head to get a better look at it (Pavlov & Anrep, 1927; Sokolov, 1963b, 1990). This so-called orienting response is one of the most important characteristics of mammalian behavior, and is assumed to occur automatically (Chong et al., 2008; Escera, Alho, Schroger, & Winkler, 2000; Schomaker, Roos, & Meeter, 2014; Tarbi, Sun, Holcomb, & Daffner, 2011). Each new stimulus can be an unknown threat or source of reward, and therefore detecting and responding to it is crucial for survival (Panksepp, 1998). It is known that the detection of novelty results in a variety of brain responses, and has an immediate effect on cognition. Recent findings in humans suggest that novelty elicits a wide range of beneficial effects on cognition. For example, novelty can strengthen reward processing (Bunzeck, Doeller, Dolan, & Düzel, 2012; Guitart-Masip, Bunzeck, Stephan, Dolan, & Düzel, 2010), drive exploration (Düzel, Bunzeck, Guitart-Masip, & Düzel, 2010; Krebs, Schott, Schutze, & Düzel, 2009), facilitate encoding of visual working memory (Mayer, Kim, & Park, 2011), enhance perception (Schomaker & Meeter, 2012), and speed up

responses (Schomaker & Meeter, 2014a). Animal studies have shown that exploration of a novel environment promotes long-term potentiation (LTP) in the hippocampus, thereby improving memory encoding (Davis, Jones, & Derrick, 2004; S. Li, Cullen, Anwyl, & Rowan, 2003; Sajikumar & Frey, 2004; Sierra-Mercado, Dieguez, & Barea-Rodriguez, 2008; Straube, Korz, Balschun, & Frey, 2003). Novelty simultaneously enhances many cognitive functions, allowing the brain to be optimally tuned to learn about and respond to novel events. Which neural processes underlie these beneficial effects triggered by novelty is not well understood yet. Here, we review findings of novelty's beneficial effects and discuss how they may arise. Tying together findings from a range of studies, we will argue that these effects are induced by different aspects of novelty and are mediated by at least three different mechanisms in the brain.

Brain responses to novelty

Novel stimuli are processed differently than familiar ones. In nonhuman primates, single cell recordings have shown much stronger neural firing to novel as compared to familiar stimuli in inferior temporal cortex (L. Li, Miller, & Desimone, 1993; Xiang & Brown, 1998). In humans, fMRI studies show stronger activity for novel compared to familiar stimuli across fusiform, lingual and medial temporal cortex (Duan, Dai, Gong, & Chen, 2010; Kaplan, Horner, Bandettini, Doeller, & Burgess, 2014; Stoppel et al., 2009; Yamaguchi, Hale, D'Esposito, & Knight, 2004). The hippocampus has often been associated with novelty detection (Knight, 1996; Lisman & Grace, 2005), especially with exploration of spatial novelty (Bast, Wilson, Witter, & Morris, 2009; Jeewajee, Lever, Burton, O'Keefe, & Burgess, 2008; Kaplan et al., 2012; Lisman & Grace, 2005). More stimulus-specific novelty signals appear to be stronger in the adjacent perirhinal cortex and other areas in of the temporal lobe than in the hippocampus (Staresina, Fell, Do Lam, Axmacher, & Henson, 2012). Moreover, novelty can drive activity in the amygdala – on its own and in interaction with emotional content (Blackford et al., 2010; Kiehl et al., 2005; Schwartz et al., 2003; Wright et al., 2003; Zald, 2003). It thus seems that new stimuli generate stronger neural responses across many higher perceptual and multimodal areas. Several mechanisms can explain such stronger responses to novel compared to familiar stimuli, such as predictive coding, repetition suppression, but also repetition enhancements (Bogacz & Brown, 2003; Meeter, Myers, & Gluck, 2005; Segaert, Weber, de Lange, Petersson, & Hagoort, 2013), but as yet little evidence exists to prefer one over the others.

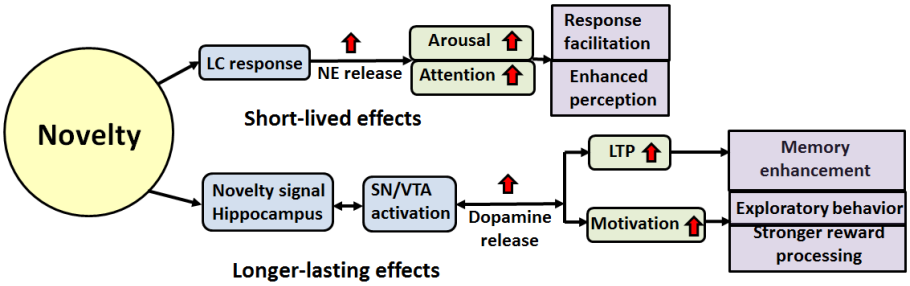

Figure 1. *Short-lived and longer-lasting effects of novelty on cognition. Detection and processing of novelty can affect different cognitive processes. Short-lived effects can be mediated by the locus coeruleus (LC). Stimulus novelty or deviant stimuli activate the LC which results in an increase in norepinephrine (NE) release (Aston-Jones & Cohen, 2005b), and may modulate arousal and attentional processes, by which it can result in response facilitation and possibly enhanced perception. Longer-lasting effects can be regulated by a functional loop between the hippocampus and substantia nigra/ventral tegmental area (SN/VTA; Düzel et al., 2010; Lisman & Grace, 2005). Environmental or contextual novelty activates the hippocampus, increasing dopamine release from the SN/VTA that can project back to the hippocampus, thereby promoting long-term potentiation (LTP), thereby enhancing learning and memory. By increasing mesolimbic*

activation a novelty signal in the brain can increase motivation and stimulate exploratory behavior, which in turn can promote learning. Note, that these effects are bidirectional.

Several psychophysiological indices of novelty processing have been identified using the novelty oddball task while the brain's response is measured using the electroencephalogram (EEG) technique. In the novelty oddball task frequent repeated *standard* stimuli, infrequent *targets* (the 'oddballs'), and infrequent deviant non-repeated *novel* stimuli are presented in random sequence. The stimuli can be presented in any sensory modality, but usually visual or auditory stimuli are used. The novel stimulus typically elicit an event-related potential (ERP) with a large anterior N2 component (also referred to as N2b), and a large novelty P3 component peaking over frontocentral regions.

The anterior N2, peaking over frontal scalp regions around 250-300 ms for visual stimuli, is believed to reflect the automatic detection of novelty (Chong et al., 2008; Tarbi et al., 2011) and is not sensitive to context or expectations (Schomaker et al., 2014). The lingual gyrus, a brain region in the ventral visual stream, has been linked to the perceptual part of novelty detection (Stoppel et al., 2009). This suggests that it could be the electrophysiological reflection of the stronger processing of novel stimuli in higher perceptual areas.

The novelty P3 is believed to be a psychophysiological index of the involuntary orienting response (Escera et al., 2000; Escera, Yago, & Alho, 2001), while others have argued that it reflects the voluntary orienting of attention to deviant or novel information (Berti, 2008; Chong et al., 2008). The P3a has very similar characteristics as the novelty P3; it peaks frontally, in the same time-window. In fact, using a factor analysis the two components could not be distinguished, suggesting they reflect the same process (Simons, Graham, Miles, & Chen, 2001). The novelty P3 can be distinguished, however, from the somewhat later P3b (or P300) component (Spencer, Dien, & Donchin, 1999, 2001). This component peaks over posterior regions and has been associated with memory-related processes (Polich, 2007; Polich & Criado, 2006), although others have argued that it reflects task-related decision-making processes rather than memory (Verleger, 2008). Specifically targets elicit a large amplitude P3b. Novel stimuli also elicit a P3b, but with a smaller amplitude (He, Lian, Spencer, Dien, & Donchin, 2001). Figure 2 shows the characteristics of the novelty-related ERP components.

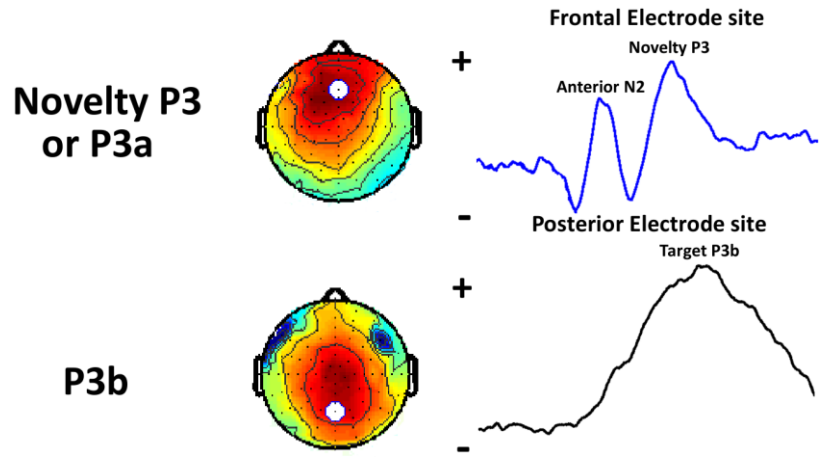

Figure 2. *Anterior N2 and P3 Subcomponents. The anterior N2 and novelty P3 (or P3a) peak over frontal regions, whereas the target P3b peaks somewhat later over posterior regions. Topographic plots reflect data from a principal component analysis parsing the novelty P3 and P3b elicited by novels and targets respectively in a visual novelty oddball paradigm, and the corresponding grand-average ERPs from Schomaker, & Meeter, 2014b.*

Neuromodulatory responses to novelty

In addition, some of the major neurotransmitter systems have been associated with novelty processing. New stimuli can activate the locus coeruleus (LC; Sara et al., 1994; Vankov et al., 1995), which releases norepinephrine, and environmental novelty and pictures of unknown scenes are known to stimulate dopaminergic neurons in the substantia nigra and the ventral tegmental area (VTA; Bunzeck & Düzel, 2006; Li, et al., 2003). Moreover, new environments and exploration are known to increase acetylcholine (ACh) efflux (Giovannini et al., 2001). It is not yet clear, however, how novelty stimulates the release of dopamine, ACh and NE. Novelty could directly activate the noradrenergic, cholinergic, and dopaminergic neurons, or indirectly by a novelty signal traveling from other regions. Several computational models have proposed that the hippocampus generates a novelty signal, which then either drives the medial septum to release ACh (Hasselmo, 2006; Meeter et al., 2005), or the VTA to release dopamine (Lisman & Grace, 2005). The central idea in these models is that the hippocampus, through a functional loop, regulates its own plasticity in response to novelty. Although little evidence has so far been found to support such a conjecture, alternative models have not yet been proposed.

While a hippocampal novelty signal may drive ACh and dopamine release in response to novelty, it almost certainly does not drive NE release. The LC responds very swiftly to stimuli, at about 110 milliseconds in primates (Bouret & Richmond, 2009). A hippocampal response to stimuli is often detected not before 200 milliseconds (Jutras & Buffalo, 2010), which would be after the LC response. A simpler explanation is suggested by findings that the LC is strongly driven by responses that are simply loud or complex: loud noises, bright flashes (Grant, Aston-Jones, & Redmond, 1988; Rasmussen, Morilak, & Jacobs, 1986). As has been discussed above, novel stimuli seem to generate much stronger responses across a wide set of perceptual areas than familiar stimuli. It may be that it is this neural loudness that drives LC activity: LC may simply respond to any surge in cortical input it receives.

These three neuromodulators are released widely through the brain, can stimulate learning, and could plausibly be related to some or all aspects of the brain's novelty response (Hasselmo, 1995; Lisman & Grace, 2005; Meeter, Talamini, & Murre, 2004; Nieuwenhuis et al., 2005). Nevertheless, it has never been established whether they, in isolation or in combination, underlie the orienting response towards novelty and its consequences for cognition and behavior

Attention to Novelty

The central characteristic of the orienting response is that the organism orients towards the stimulus that elicits it. Novel stimuli thus attract attention, even when there is no incentive to pay attention to them or even when performance suffers. Consistent with novel stimuli attracting attention, novel stimuli are encoded better into visual working memory than familiar ones (Mayer et al., 2011; Mayer, Kim, & Park, 2014). Mayer and colleagues suggested that this effect was mediated by more efficient allocation of attentional resources to novel than to familiar items, rather than low-level stimulus characteristics. Another line of research has shown that when participants have to report the location of a probed word in an array responses are faster and performance is better for novel compared to repeated familiar words. This has been called the 'novel popout' phenomenon (Johnston, Hawley, & Farnham, 1993; Johnston & Schwarting, 1997; Reicher, Snyder, & Richards, 1976), and is also believed to rely on attentional processes (Strayer & Johnston, 2000), however, the reliability of these findings has been questioned and the results also be explained by effects of cognitive load (Christie & Klein, 1996), or inter-item associations (Diliberto, Altarriba, & Neill, 1998).

Novelty and perception

Novelty can sharpen perception in a similar way as peripheral exogenous cues (Carrasco, Ling, & Read, 2004), or emotional stimuli. In the typical emotional cueing paradigms images of faces acting as cues are followed by a low contrast stimulus that is difficult to see. Faces with a negative emotional expression have consistently been shown to enhance perception of a target relative to neutral faces (Bocanegra & Zeelenberg, 2011; Phelps et al., 2006; Vuilleumier, 2005). In an adapted version of such a paradigm, the cues were novel versus familiar stimuli. The novel stimuli increased sensitivity to low contrast visual targets compared to familiar stimuli (Schomaker & Meeter, 2012). Novel cues also led to a more conservative response criterion, which is consistent with known effects of attention (Rahnev et al., 2011). The emotional and novel cues may thus elicit an attentional response, promoting processing of subsequently presented stimuli (Bocanegra & Zeelenberg, 2011; Schomaker & Meeter, 2012).

Although much remains to be clarified, emotional stimuli are believed to enhance perception through activation of the amygdala, then strengthening sensory processing via the amygdala's connections with the visual cortex (Anderson & Phelps, 2001; Morris et al., 1998). The orienting response towards novelty has been associated with fundamental motivational circuits linked to the same attentional processes related to emotionally significant information (Bradley, 2009; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010; Zald, 2003). Furthermore, both novel and emotional stimuli are known to activate the amygdala (Blackford et al., 2010; Kiehl et al., 2005; Schwartz et al., 2003; Wright et al., 2003; Zald, 2003). Novelty could thus enhance perception via the same mechanisms as by which emotional stimuli are thought to enhance perception.

Facilitating task performance

The fact that novel stimuli capture attention has consequences for task performance. The orienting response to novel stimuli can pull attention away from task-related processes, resulting in distraction (Näätänen, 1992). However, the orienting response can also have exactly the opposite consequence. The orienting responses has been suggested to include a call for processing resources (Filion, Dawson, Schell, & Hazlett, 1991; SanMiguel, Morgan, et al., 2010; Zimmer, 1992), eliciting a general increase in arousal and of attentional resources. This increase could spill over to other stimuli presented in the temporal and/or spatial vicinity, enhancing their processing (Aston-Jones & Cohen, 2005b).

Novelty's distracting effects on behavior are well established. Distraction by task-irrelevant novel sounds can prolong reaction times and reduce accuracy on a visual categorization (animal/clothes) task (Wetzel, Schroger, & Widmann, 2013). Such effects occur across as well as within sensory modalities, and have been reported for the visual modality (Bendixen et al., 2010; Berti & Schroger, 2006), auditory modality (Berti & Schroger, 2004; Escera et al., 2000; Mager et al., 2005; Parmentier & Andres, 2010; Parmentier, Elsley, Andres, & Barcelo, 2011; Parmentier, Turner, & Elsley, 2011; Rinne, Sarkka, Degerman, Schroger, & Alho, 2006; Schroger & Wolff, 1998b; Wetzel et al., 2013; Wetzel, Widmann, Berti, & Schroger, 2006), and tactile modality (Ljungberg & Parmentier, 2012; Parmentier, Ljungberg, Elsley, & Lindkvist, 2011). A variety of studies have suggested that the transient increase in arousal and/or attention due to novelty can also have a range of positive effects on task performance (DiGirolamo, 1998; SanMiguel, Linden, & Escera, 2010; SanMiguel, Morgan, et al., 2010; Wetzel, Widmann, & Schroger, 2012).

When distraction becomes facilitation: Requirements for novelty's short-lived beneficial effects on behavior

Whether new information results in distraction or facilitation of performance depends on several factors. First, behavioral distraction typically occurs when the novel stimuli are informative about target occurrence and time of appearance, but not when they are uninformative (Parmentier, Elsley, & Ljungberg, 2010; Wetzel et al., 2013; Wetzel et al., 2012). For example, when a deviant novel sound (i.e. a burst of white noise) provides information about the onset of a visual target digit, further processing of the novel sound is required, resulting in behavioral distraction (Parmentier et al., 2010). In contrast, when the same sound is entirely task-irrelevant such further processing is not required – and distraction does not occur.

Second, whether distraction or facilitation occurs depends on the attentional demands of the task at hand: When demands are low novelty results in facilitation, while when demands are novelty results in distraction (Lv et al., 2010; SanMiguel, Linden, et al., 2010; Schomaker & Meeter, 2014a, 2014b). In one study, novel sounds resulted in faster classification (face/scrambled face) and better recognition memory when working memory load was low (no load classification task/remember one face; SanMiguel, Linden, et al., 2010). When working memory load was high (remember three faces), novel sounds decreased performance. A reason for this could be that in a task with low attentional demands, attention may wander (Forster & Lavie, 2009; Lavie, 1995). Novel stimuli may improve performance by refocusing attentional resources or by eliciting a general alerting response. In this case any distracting effect of novelty, the 'orienting cost', is outweighed by an 'alerting benefit' (SanMiguel, Linden, et al., 2010). In contrast, when demands are high, all attentional resources are already used to perform the task (Kahneman, 1973), leaving no room for a novelty-induced alerting benefit. Furthermore, the depletion of attentional resources may result in a failure to suppress task-irrelevant (novel) stimuli (Lv et al., 2010; Schomaker & Meeter, 2014b), resulting in increased distraction by the novel stimuli.

A third variable of importance is the complexity of both the novel stimulus and its context. Schomaker and Meeter (2014a) had participants respond to an auditory target while viewing a stream of novel and standard visual stimuli. Novel visual stimuli facilitated responses to the auditory targets, but only when they were both infrequent as a category (deviant) and visually more complex than other stimuli in the stream (the *stimulus context*). When the stimulus context was as complex as the novel stimuli or more so, no such facilitation was found. Note, complexity can be defined in many ways, but all definitions have in common that more complex stimuli have a large variety of features that cannot be easily compressed (see for example Rigau, Feixas, & Sbert, 2005).

Interestingly, the conditions in which response facilitation is found are strikingly similar to the conditions in which the novelty P3 is elicited: Only stimuli that are deviant and complex elicit a frontal novelty P3 (Barkaszi, Czigler, & Balazs, 2013; Schomaker et al., 2014).

Indeed, although in the literature the novelty P3 has often been associated with behavioral distraction (Berti, Roeber, & Schroger, 2004; Berti & Schroger, 2001, 2004; Escera et al., 2001; Munka & Berti, 2006; SanMiguel, Corral, & Escera, 2008; SanMiguel, Morgan, et al., 2010; Schroger, Giard, & Wolff, 2000; Schroger & Wolff, 1998a), some studies have instead hinted to a dissociation between the two. Wetzel, et al. (2013) found that the novelty P3 is automatically elicited by environmental novel sounds and deviant white noise, but that consequences for behavior depend on whether target-related information is conveyed (i.e. regarding the time and probability of target occurrence in a visual classification task). Moreover, the novelty P3 has been associated with improved task performance. SanMiguel, Morgan, et al. (2010) found that responses to visual targets on a simple classification task (face/scrambled face) were facilitated during the presentation of novel sounds that also elicited a novelty P3. In other words, the novelty P3 does not always reflect distraction (an 'orienting cost'), but can also reflect alerting effects that underlie the facilitation of target processing (SanMiguel, Morgan, et al., 2010). One other study directly linked the novelty P3 to beneficial effects. In a visual two-choice task, the novelty P3 was enhanced in children with attention deficit hyperactivity disorder (ADHD) compared to the normal control group, while at the same time omission errors were reduced for the children with ADHD (van Mourik et al., 2007).

The authors argued that "distraction can have beneficial effects". Wetzel, et al. (2013) found that a frontal novelty P3 for novel stimuli resulted in facilitation, while no facilitation was found for deviants that elicited a more central P3 component. Here, we propose that the same mechanism underlies both the frontal novelty P3 ERP component and novelty's beneficial effects on behavior.

Facilitation: The novelty P3 and the role of the LC-NE system

Interestingly, both novelty's facilitating effects and the P3 have been associated with the LC-NE system (Donchin, 1981; Nieuwenhuis et al., 2005; Nieuwenhuis et al., 2010; Wetzel et al., 2012). The P3 has been shown to depend on NE in several ways. For example, a P3-like response in monkeys was fully attenuated when the LC was lesioned (Pineda, Foote, & Neville, 1989), and by a psychopharmacological intervention that depletes NE (Swick, Pineda, & Foote, 1994; Swick, Pineda, Schacher, & Foote, 1994). In turn, novelty can drive LC phasic activity. For example, strong bursts of activity were seen in a large population of noradrenergic neurons of the LC in rats that were placed in a novel environment (Sara, Vankov, & Herve, 1994; Vankov, Herve-Minvielle, & Sara, 1995). Also for humans the P3 has been related to pupil diameter (Murphy et al., 2011), believed to be a measure of LC activity (Murphy et al., 2014; Jepma, & Nieuwenhuis, 2011). Prestimulus pupil size and P3 exhibited an inverted U-shape relation, with large P3 amplitudes being associated with intermediate pupil diameter *and* optimal task performance on a visual oddball task (Murphy et al., 2011). Similarly, a gene that affects noradrenergic activity has been related to P3 amplitude (Liu et al., 2009).

As noted above, there are different P3 subcomponents that have different neural generators, associated with different processes. Polich (2007) suggested that the dopaminergic system plays a role in the generation of the frontal novelty P3/P3a, whereas a parietal noradrenergic system was suggested to underlie the P3b. However, there are also reasons to believe the novelty P3 is related to the noradrenergic LC-NE system. The LC is connected to the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC; Aston-Jones & Cohen, 2005a; Aston-Jones & Cohen, 2005b), and prefrontal cortex (Sara, 2009), which are all suggested to be sources of the novelty P3 (ACC: Dien, Spencer, & Donchin, 2003; prefrontal cortex: Knight, 1984; OFC and ACC: Lovstad et al., 2012) – supporting a role of the noradrenergic system in eliciting the novelty P3.

It is thus possible that the LC-NE response to novelty is both related to the novelty P3 and novelty's subsequent facilitatory effects on behavior. The strongest arguments in favor of such a link are that the conditions for facilitation are similar to those for elicitation of a novelty P3, and the timing of the effects. The adaptive gain theory predicts that the potentiating effect of NE are transient and show peak efficacy 100-200 ms post-stimulus (Aston-Jones & Cohen, 2005a, 2005b; Nieuwenhuis et al., 2005). In line with this prediction, novelty has been reported to facilitate responses between 0-200 ms after presentation (Schomaker & Meeter, 2014a). However, direct evidence for the putative relations between LC-NE, the novelty P3 and facilitatory effects of novelty is lacking. Ideally, the novelty P3 and LC activity (for example as indexed by pupil dilation) should be measured at the same time in humans while novelty-induced facilitatory effects are observed.

Effects on learning and exploration

In addition to short-term effects on attention and arousal, there are also longer-term effects of novelty on learning. Since a novel stimulus or novel environment by definition provides opportunities for learning, many theories have suggested that novelty is a signal that triggers exploration and learning (Hasselmo, Bradley, Wyble, & Wallenstein, 1996; Meeter et al., 2005; Recce & Harris, 1996; Tulving & Kroll, 1995).

Novelty's exploration bonus: The lure of the unknown

Exploring new opportunities and environments is a crucial aspect of mammalian behavior. In fact, foraging species must have a drive to explore new environments, in order to survive (Panksepp, 1998). Also in present day lifestyles curiosity may help survival: Elderly with higher curiosity were found to have better chances of being healthy and alive five years later (Swan & Carmelli, 1996), and openness to actions has been associated with longevity (Jonassaint et al., 2007). An interest in the new can thus be beneficial, but to optimally adapt behavior to the current situation the brain has to make a trade-off between paying attention to well-known rewarding information and unknown information that might result in more profitable outcomes. It has been suggested by computational theories of reinforcement learning that novelty may promote exploratory behavior novelty by eliciting an 'exploration bonus' (or novelty bonus), motivating exploratory behavior in search for reward (Düzel et al., 2010; Kakade & Dayan, 2002; Knutson & Cooper, 2006). Reward anticipation is suggested to be enhanced and exploratory behavior is promoted as an effect (for a review and a model of novelty-related motivation of anticipation and exploration by dopamine (NOMAD) see Düzel et al., 2010). Empirical evidence for this theory has shown that novel stimuli and anticipation of novel stimuli can indeed activate the dopaminergic reward system, enhancing reward prediction responses (Bunzeck, Doeller, Dolan, & Düzel, 2012; Wittmann et al., 2007), ensuring that novel opportunities are evaluated until the potentially rewarding outcome is known (Krebs, Schott, Schutze, & Düzel, 2009). A novelty signal from the hippocampus increases substantia nigra/ventral tegmental area (SN/VTA) activation in response to reward through a functional hippocampal-VTA loop, increasing phasic dopamine release in the striatum (Bunzeck et al., 2007; Guitart-Masip et al., 2010; Krebs, Heipertz, Schuetze, & Düzel, 2011; Lisman & Grace, 2005). As such novelty can trigger dopamine release, energizing motivation and boosting memory (Düzel et al., 2010; Wittmann et al., 2007). In the other direction, reward can accelerate novelty processing (Bunzeck, Doeller, Fuentemilla, Dolan, & Düzel, 2009), a process believed to be controlled by dopamine that also modulates memory retrieval performance (Apitz & Bunzeck, 2013; Eckart & Bunzeck, 2013).

Novelty's long-lasting beneficial effects: Promoting memory

Animal studies have repeatedly shown that exploration of a novel compared to a familiar environment can promote learning. Neurophysiologically, it can increase long-term potentiation (LTP) in the hippocampus, thereby improving memory encoding (Davis, Jones, & Derrick, 2004; McGaugh, 2005; Uzakov, Frey, & Korz, 2005). After exploring new environments early LTP in rats was turned into long-LTP in the hippocampus, specifically in the dentate gyrus, whereas it was not in a familiar environment (Straube, Korz, & Frey, 2003). Behaviorally, an effect of novelty on learning has been show for example for taste memory: A strong novel taste can facilitate memory formation for a different weak taste in rats (Merhav & Rosenblum, 2008).

In humans the idea that novelty can enhance memory for unrelated information is less extensively researched, but several studies hint towards such an enhancing effect as well. Wittman, et al. (2007) found that anticipation of novelty activated both the hippocampus and SN/VTA, while enhancing memory encoding of subsequently presented novel items. One functional magnetic resonance imaging (fMRI) study provides evidence for the idea that experiencing (in addition to anticipating) novelty can enhance memory in humans. Participants were first exposed to a series of either novel or familiar scenes, and then had to study a list of words. When participants were exposed to the novel scenes, they had better recollection and free recall of the words than when they were exposed to familiar scenes (Fenker et al., 2008). Novelty co-activated both the SN/VTA and hippocampus; however, this did not correlate with its memory enhancements. Recently, we investigated whether active exploration of a novel environment enhances learning on an unrelated task in humans as well. In a within-subjects design participants explored a novel and a previously familiarized virtual environment *after* which they

performed a word learning task. Exploration of a novel environment enhanced recall, believed to be hippocampus-dependent, but not recognition memory, believed to be relatively hippocampus-independent (Schomaker, van Bronkhorst, & Meeter, 2014).

Several studies have also looked at novelty effects on encoding at the level of single items. One such study, using pupillometry, found that pupil constriction during encoding was stronger for complex natural visual scenes that were later remembered, and for novel compared to familiar scenes at retrieval (Naber, Frassle, Rutishauser, & Einhauser, 2013). Remarkably, pupil constriction was also strong for familiar items that were misjudged as novel. Therefore authors argued that pupil constriction reflects subjective novelty, which is associated with the strength of memory formation (Kishiyama, Yonelinas, & Lazzara, 2004; R.T. Knight, 1996; Lisman & Grace, 2005).

In another type of studies, recognition memory is typically better for new items than for items that were previously familiarized in a preceding phase (Kormi-Nouri, Nilsson, & Ohta, 2005; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Tulving & Kroll, 1995). This effect is known as the 'novelty effect'. Similarly, in the Von Restorff or isolation effect, memory is better for words presented in a deviant novel font than for words presented in a standard font (Hunt, 1995; Rangel-Gomez & Meeter, 2012; Bruce & Gaines, 1976; Dunlosky, Hunt, & Clark, 2000; Geraci & Manzano, 2010; Geraci & Rajaram, 2004; Von Restorff, 1933; Rangel-Gomez, Hickey, & Meeter, 2013; Schmidt, 1985), and for objects presented in novel rather than standard colors (Kishiyama, Yonelinas, & Knight, 2009; Kishiyama et al., 2004). Interestingly, this type of novelty-induced facilitation is further enhanced by the D1/D2 receptor agonist apomorphine in humans (Rangel-Gomez et al., 2013).

Several neuromodulatory systems have been suggested to underlie the effects of novelty on learning, such as dopaminergic inputs (Lemon & Manahan-Vaughan, 2006; Li et al., 2003; Lisman & Grace, 2005; Roggenhofer et al., 2010; Sajikumar & Frey, 2004), noradrenergic inputs (Kitchigina, Vankov, Harley, & Sara, 1997; Straube, Korz, Balschun, et al., 2003; Uzakov et al., 2005; Vankov et al., 1995) through beta-adrenoreceptors (Kemp & Manahan-Vaughan, 2008), and cholinergic inputs (Barry, Heys, & Hasselmo, 2012; Bergado, Frey, Lopez, Almaguer-Melian, & Frey, 2007; Hasselmo, 1999; Meeter et al., 2004).

Involvement of norepinephrine in novelty benefits seems inconsistent with the results of Naber et al. (2013). Typically, pupil dilation has been linked to norepinephrine release (de Gee, Knapen, & Donner, 2014; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Jepma & Nieuwenhuis, 2011; Murphy et al., 2014; Murphy et al., 2011). The data of Naber et al. (2013) suggest that subjective novelty correlates with low NE release, and low NE release with better encoding. The authors argued that the pupil response they detected was likely to reflect acetylcholine release. However, norepinephrine has been strongly implicated in exploration benefits in nonhuman animals, (Harley, 1987; Harley, 2007; Madison & Nicoll, 1986). The dopaminergic and noradrenergic systems have also been suggested to mediate these effects in concert, working through their reciprocal connections (Briand, Gritton, Howe, Young, & Sarter, 2007; Harley, 2004; Sara, 2009). All three neuromodulatory systems are thus viable candidates for a role in the process of increased plasticity in response to novelty.

What differentiates these three systems is the time scale on which the effects occur. Effects of ACh release have been argued to peak some two seconds after release (Hasselmo & Fehlau, 2001), while effects of NE release may act on even shorter time scales (Mongeau et al., 1997). On the other hand, activation of dopaminergic D1/D5 receptors has been found to lower the threshold for LTP and learning in the hippocampus up to tens of minutes later (Kentros et al., 2004; Li et al., 2003; Straube, Korz, Balschun, et al., 2003). If novelty would affect memory on a trial-by-trial basis it would support a role for norepinephrine or acetylcholine, while effects that last an entire experiment would favor involvement of the dopamine system.

Effects on memory have been reported for both time scales. The novelty effect and the Von Restorff effect play out at the time scale of individual word presentations (i.e., seconds), consistent with fast short-lived responses of ACh or NE, but both effects can be explained by mechanisms that have little to do with novelty itself. The Von Restorff effect has been argued to be an effect of distinctiveness at test, rather than novelty during study (Dunlosky et al., 2000; Rangel-Gomez & Meeter, 2013). The novelty effect may simply be proactive interference: Items that are studied repeatedly for separate lists may lead to source discrimination problems, with memories from different lists then interfering with one another at test (Aberg & Nilsson, 2001; Dobbins, Kroll, Yonelinas, & Liu, 1998). Proactive interference procedures are equivalent to what occurs for the familiar items that are presented on different occasions in novelty effect studies.

Effects that are more clearly linked to encoding all play out at a longer time scale. Novelty-induced memory enhancements seen in nonhuman animals depend on a long-lasting state that may last up till 30 minutes after exposure to a novel environment (Li, et al., 2003; Straube, Korz, Balschun, et al., 2003). Seeing novel scenes affected learning ten minutes after the viewing (Fenker et al., 2008), but a recent attempt to find a similar effect on an item-by-item basis failed (Rangel-Gomez & Meeter, submitted). Such longer-term effects of novelty are most consistent with the idea that dopamine modulates the novelty-induced benefits for memory via a functional loop between the midbrain SN/VTA and the hippocampus, as proposed by Lisman & Grace (2005). Also other evidence has accumulated for an important role of dopamine in increasing plasticity in the hippocampus (Jay, 2003; Lemon & Manahan-Vaughan, 2006; Li et al., 2003; Lisman & Grace, 2005; Roggenhofer et al., 2010; Sajikumar & Frey, 2004). This suggests that the same mechanism underlies both the benefits of novelty for learning, and the exploration bonus (Blumenfeld, Preminger, Sagi, & Tsodyks, 2006; Lisman & Grace, 2005).

Conclusion

Novelty elicits strong responses across a wide variety of brain areas, and stimulates several neuromodulatory systems. Unsurprisingly, novelty has many effects on cognition. Novel stimuli can attract attention to themselves, leading to distraction from concurrent tasks, but also to facilitation. Furthermore, environmental novelty can induce exploration and boost memory formation. The neurophysiological responses to novelty play out on different time-scales, which can explain the differences in the timing of novelty's effects on different aspects of cognition. Although much remains uncertain, we argued that the orienting of attention towards novel stimuli may result from amygdalar activation affecting early sensory processing regions in the brain. Both the dopaminergic and noradrenergic system play a crucial role in mediating novelty's other effects on cognition. Since both systems are activated by different types of novelty, innervate different forebrain areas, and have different neurophysiological properties, they differentially affect cognitive processes. Novelty's beneficial effects on behavior are typically short-lived, showing peak efficacy around 200 ms poststimulus, which is in line with the timing of the LC-NE (phasic) response. A range of empirical findings suggest that this LC-NE system underlies the novelty P3 and novelty's beneficial effects on behavior. In contrast, novelty's boosting effects on memory are typically longer-lasting. Evidence from neuroimaging studies and psychopharmacological interventions support the idea that the functional SN/VTA loop with the hippocampus and the dopaminergic system underlie these effects.