Novelty and Memory: Electrophysiological and Pharmacological Studies

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Chapter 1. Introduction

In the early 1900's, while researching conditioned responses, Pavlov found that his dogs did not show the conditioned responses when in the presence of new persons in the room. Instead they oriented their attention towards the new element in the environment. This behavior was identified as the 'what is it' response (Pavlov, 1927); later it was called the orienting reflex (Sokolov, 1963). Humans also typically attend to novel objects and events. For example, babies fixate their gaze longer on novel than on familiar pictures (Welch, 1974). In fact, novel objects elicit a whole range of brain responses; one of them may be a novelty learning advantage. Novel items have been suggested to be encoded in a different, stronger way than familiar items, leading to that they are subsequently better remembered (Hasselmo & Stern, 2006; Meeter, Talamini, & Murre, 2004). This dissertation investigates whether such a memory benefit of novelty exists, as part of a broader investigation of how the human brain deals with novelty.

Neurological markers of novelty detection and processing

Neurons in the temporal cortex are known to fire strongly in presence of novel stimuli, a response that is reduced after repeated presentations (Xiang & Brown, 1998). The enhanced neural responses to novelty have also been studied using event related potentials (ERPs). These studies have suggested that there are two distinguishable stages occurring when the individual is faced with a novel element/environment. The first is the detection of the novel stimulus, which is postulated to be indexed by the Novelty N2 component, and that is supposed to be independent of the allocation of attention (Rangel-Gomez, Hickey, van Amelsvoort, Bet, & Meeter, 2013; Tarbi, Sun, Holcomb, & Daffner, 2010). The second stage is the processing of the novel stimulus for being used in the task in hand and/or to be encoded into long term memory. This stage has been postulated to be indexed by the novelty P3 component (Polich & Criado, 2006).

The novelty N2 is related to perceptual novelty and is highly sensitive to learning, being strongly reduced with even a single repetition of the novel stimulus (Ferrari, Bradley, Codispoti, & Lang, 2010). Although many describe the novelty N2 as a marker of perceptual novelty exclusively, Daffner and colleagues (2000) propose that the novelty N2 component is actually a complex that depends not only on perceptual novelty, but also on the probability and significance of the stimulus. Moreover, in an influential review article Pritchard and colleagues (1991) proposed a division of the N2 into three subcomponents, the N2a, N2b, and N2c. These have been reformulated by Folstein and Van Petten (2008)

as mismatch negativity (equivalent to the N2a), the anterior N2 (equivalent to the N2b), and the posterior N2 (equivalent to the N2c). The N2a/mismatch negativity has a fronto-central maximum distribution and is conceptualized as an automatic response to an auditory or visual outlier (Alho, Woods, & Algazi, 1994). The N2b (also known as novelty N2) is a frontal component usually observed in the visual oddball task (Crottaz-Herbette & Menon, 2006), and is more or less automatic: It is elicited by a consciously perceived outlier that may be task irrelevant (Daffner et al., 2000; Tarbi et al., 2010). The N2c (centrally expressed) is not associated to novelty, but to tasks that require the resolution of certain degree of conflict in choice reaction task (Kopp & Wessel, 2010).

The P3 has similarly been divided into two subcomponents, the P3a – or novelty P3 (fronto-central), and the P3b – or classic P3 (centro-parietal) (He, Lian, Spencer, Dien, & Donchin, 2001; Polich & Criado, 2006). In 1975, two groups, using auditory (Squires, Squires, & Hillyard, 1975) and visual (Courchesne, Hillyard, & Galambos, 1975) oddball paradigms, found a P3 component elicited by task-irrelevant novel stimuli, which was more centro-frontally localized than the traditional parietal P3. Squires and colleagues (1975) called this fronto-central P3 the P3a, Courchesne et al. (1975) called it the novelty P3. It has been associated with the evaluation of novel stimuli for subsequent behavioral action, and postulated to be a marker of a conscious attentional switching mechanism (Friedman, Cycowicz, & Gaeta, 2001), or distractibility (SanMiguel, Morgan, Klein, Linden, & Escera, 2010). The P3b component may index stimulus meaning and significance, more than novelty detection, and is maximal at centro-parietal as opposed to fronto-central locations (Ferrari et al., 2010; Squires et al., 1975). The P3b is enhanced for stimuli that are relevant for later decisions or responses (Courchesne et al., 1975).

Neuromodulation of Novelty and Memory for novel elements

The first stage in the processing of novel stimuli, novelty detection, has been suggested to be important for long-term memory formation (Tulving, Markowitsch, Craik, Habib, & Houle, 1996). Recognizing something as new would set off a cascade of events that results in the formation of a new memory (Hasselmo & Stern, 2006; Lisman & Grace, 2005; Meeter, Murre, & Talamini, 2004) – either through activation of the dopaminergic or cholinergic circuitry. With regard to dopamine, Lisman and Grace (2005) proposed that a hippocampal-VTA loop is involved in the detection and further processing of novelty. Novel stimuli would be detected by the hippocampus (apparently by a comparison with contents stored in long-term memory), which would then transmit a novelty signal via the subiculum, the nucleus accumbens, and the ventral pallidum to the VTA. The VTA would then release DA in the hippocampus, which in turn would enhance hippocampal LTP (long term potentiation, which is a form of synaptic plasticity that may be the molecular mechanism of long-term storage of information in the brain, Ryan, Joilin, & Williams, 2015). In the case of acetylcholine, Hasselmo (1999), Hasselmo, Bradley, Wyble and Wallenstein (1996), and

Meeter, Talamini and Murre (2004), among others, proposed that a novelty signal increases ACh release, which in turn shifts the brain to a learning mode.

One of the first studies that illustrates that there is a memory benefit for novel stimuli is one by Hedwig von Restorff in 1933 (Von Restorff, 1933). Although von Restorff was not aiming to identify a novelty benefit per se, her paradigm has been extensively used to study potential advantages due to novelty for memory (e.g. Fabiani & Donchin, 1995; Rangel-Gomez & Meeter, 2013; Wiswede, Russeler, Hasselbach, & Munte, 2006). In her paradigm, participants studied novel stimuli (also referred to as salient or isolated stimuli) among a series of familiar stimuli. The novel stimuli were remembered better than their familiar counterparts. What causes the von Restorff effect remains unclear. Some accounts have emphasized processing operating at retrieval (e.g. McDaniel, Dornburg, & Guynn, 2005), but others focus on processing at encoding (e.g., Fabiani & Donchin, 1995). As early as the 1970s it has been proposed that the von Restorff effect is influenced by the extra attention paid to the isolated stimuli, which can vary as a function of presentation time and position in a sequence of stimuli (Johansson, 1970). Others have emphasized the importance of the novelty of the isolates (Kishiyama, Yonelinas, & Lazzara, 2004), consistent with theories that give novelty a key role in learning (Hasselmo, Wyble, & Wallenstein, 1996).

Animal studies have indicated that the exploration of novel environments can be beneficial for memory formation. Salvetti, Morris and Wang (2014) found that exposing rats to a novel environment just before the encoding phase of a delayed matching-to-place task, improves memory for the location of food 24 hours later (also see, S. Li, Cullen, Anwyl, & Rowan, 2003). Dong and colleagues (2012) explained this phenomenon at the molecular/structural level. These authors found that novelty exploration facilitates long-term depression in hippocampal field CA1, which has been proposed to be involved in spatial learning. This animal evidence supports the novelty encoding benefit hypothesis by Endel Tulving and colleagues (1996), which states that novelty assessment represents an early stage of long-term memory encoding, and that encoding of the incoming information is dependent of its novelty. Therefore the probability of long-term storage varies directly with the novelty of the information.

Overall, it is still to be proven whether there is a real benefit due to novelty for memory, and if that is the case, how it arises. In the present thesis I present multiple studies into novelty's influences on memory.

Overview of the dissertation

As described above, several computational theories of memory have hypothesized that different neurotransmitters are involved in the responses of the brain to novelty. There have been attempts to explain the role of those neurotransmitter systems in the elicitation of novelty responses; however, the existing models have been mostly based on non-human

animal evidence that is suggestive but not yet conclusive. In **Chapter 2**, we present a systematic review of the literature since 2000, focusing on human studies that manipulated the different neurotransmitter systems, and how these results compare to the existing models. This review shows that studies involving humans present a more complex picture than that postulated by the models. We found evidence that the responses to novelty are modulated by several neurotransmitters; dopamine, acetylcholine, norepinephrine and serotonin. However, the effects of neuromodulation depend on the stage of the response to novels, the specific molecular characteristics of the neurotransmitter and the brain structure investigated. Additionally, gaps were found in the literature, such as the lack of current studies in the noradrenergic modulation of novelty responses.

As mentioned before, novelty is thought to be important for learning, with for example the notion that novelty results in the release of dopamine, which then strengthens long term potentiation (LTP) (Lisman & Grace, 2005). In line with such theories, the Von Restorff effect has often been proposed to reside at encoding: novelty aids encoding of the novel stimuli, which then causes the Von Restorff effect (Fabiani & Donchin, 1995). On the other hand there is the idea that the advantage for novel words in a Von Restorff paradigm happens at retrieval (Hunt & Lamb, 2001). In the remaining chapters we will study these two hypotheses.

To test the idea of dopamine being important for the benefits for memory due to novelty, conducted a pharmacological challenge using a von Restorff paradigm, **Chapter 3** reports the results of this study. Here we presented participants with a modified version of the Von Restorff paradigm, while we administered either a placebo or the drug apomorphine (a D1/D2 dopamine receptor agonist that is supposed to enhance dopaminergic activity). This study showed that the modulation of dopamine only has an effect on the detection of the novel stimuli (as indexed by the N2 ERP component), and none on later processing (as indexed by the P3a ERP component). Additionally, we found that the von Restorff effect was modulated by the dopaminergic manipulation, in such a way that only when apomorphine was administered novel words were remembered better than standard ones.

In **Chapter 4** we tested the idea of a novelty benefit for memory by analyzing electrophysiological indexes of novelty (N2 and P3 ERP components) at encoding while participants were performing a von Restorff task. If novelty is beneficial at encoding there should be an enhanced amplitude of the novelty ERP components for words that were correctly remembered. Our results showed no differences between correctly and erroneously recalled trials, indicating that the advantage of novelty (as manipulated in the von Restorff task) did not occur at encoding.

Another way to clarify how the novelty-related advantage for memory occurs is by manipulating the encoding of the familiar and novel stimuli. It has been previously established that the von Restorff effect depends on the strategy used at encoding (Fabiani, Karis, & Donchin, 1985, 1990). In **Chapter 5** we manipulated the amount of attention given

to the familiar and novel stimuli at encoding. In this way we also tested the question whether attention is implicated in the detection of novels. Participants had to preferentially attend to novel stimuli in half of the blocks and to familiar stimuli in the other half. Our manipulation added to the existing body of literature that postulates that attention is not required for the detection of novelty.

Since our results indicated that the novelty-related advantage for memory formation may be less straightforward than previously thought, we performed an extensive study about memory formation and novelty, which included a novelty manipulation closer to the commonly used 3-stimulus oddball task in which the novel stimuli are task-irrelevant. By including task-irrelevant background pictures that were either novel or familiar, together with the lists of words that had to be remembered, we made the novel stimuli task-irrelevant as in the oddball task. Additionally, we included different types of novelty, so we could test if the memory effects on the ERP components are dependent on the type of novelty used in a specific task. **Chapter 6** presents the results of this manipulation. Participants were asked to learn a set of words, which were presented in the foreground while task-irrelevant pictures were presented in the background. Those pictures could be either fractals (stimulus novels, which were computer generated, unique for this study) or landscapes (contextual novels, which were common pictures that were only presented once during the experiment). The results indicated that contiguously presented novel pictures do not affect memory for target words.

Finally, in **Chapter 7** we analyze and discuss all these results in light of the remaining challenges, the unanswered questions and the contribution of our work