Novelty and Memory: Electrophysiological and Pharmacological Studies

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Chapter 7. Discussion and Summary

In this dissertation a number of studies were presented that investigated the relationship between novelty and memory. In the coming section we will discuss our findings in light of the current literature, providing new insights and opening the path for future endeavors.

About the molecular mechanisms of novelty responses

In our review of the literature (Chapter 2) we found that four neurotransmitters have been linked to novelty responses in the brain: Dopamine, norepinephrine, acetylcholine and serotonin. Our systematic review compared the existing models (mainly developed from animal data) with the human evidence. Experimental studies into the relationship between those four neurotransmitters and novelty responses were found to be scarce. Only for two experimental studies involving neurotransmitters were found, dopamine and acetylcholine. Very little research has been done regarding acetylcholine, and the one study that we found that performed a pharmacological challenge of the cholinergic system only covered muscarinic receptors. Also, we did not find any studies addressing the serotonergic neuromodulation in an experimental manner, nor were studies found in humans challenging the noradrenergic system.

Among the neurotransmitters, dopamine has been researched the most; multiple studies in humans and animals, using several different techniques were found in the literature. ERP studies using pharmacological challenges for this neurotransmitter have shown that the increase in dopaminergic activity upregulates the initial detection of novelty, but effects of later processing of novelty, indexed by the novelty P3 component, is less clear. For example, dexamphetamine reduced the amplitude of the auditory P3a (Albrecht et al., 2010), and amphetamine produced a novelty-like ERP response to targets (non-novel stimuli), reducing the discriminability of the P3a for novelty (Albrecht et al., 2010; Gabbay et al., 2010). On the other hand, higher densities of the D4 receptor have been found to be associated with an enhanced P3a (Strobel et al., 2004).

The role of dopamine in novelty processing is thus not yet clear. Therefore we decided to perform a pharmacological challenge study using a specific dopaminergic D1/D2 receptor agonist, namely apomorphine (Chapter 3). We used a von Restorff task in which participants studied words that were either presented in a normal font, or in a unique, novel font and color. We found that enhanced dopaminergic activity, through apomorphine, results in better memory specifically for novel font items, and in a larger amplitude of the N2 component (as an index of novelty detection). However, later processing (as indexed by the P3 component) was not affected by our pharmacological challenge (i.e., no difference in the amplitude of the P3 component was found between

drug and placebo conditions). These results confirm what our review of literature indicated, the effects of dopamine may differ for the two traditionally delineated phases of novelty processing, namely novelty detection and later processing. Our evidence suggest that D1/D2 receptors maybe involved in the detection, but not in later processing.

Novelty and Memory. How does this work?

Although von Restorff did not argue that the effect she found was due to novelty, more recently researchers have argued that the memory advantage is a novelty effect (Axmacher et al., 2010; Kishiyama et al., 2004; Parker et al., 1998). However, almost 100 years after von Restorff's seminal paper, and after several studies linking novelty with memory advantages, we still do not fully understand how this advantage works. Computational models aiming to explain memory formation and novelty, argue that novel elements facilitate long term potentiation (LPT), thus aiding and providing advantage for memory formation (Duzel et al., 2010; Lisman & Grace, 2005; Meeter, Murre, et al., 2004). We conducted three studies trying to understand this memory novelty relationship.

In our first study (chapter 4) we tested the ERP components related to correctly recalled and forgotten words in a von Restorff paradigm (as previously described). We did find the typical Von Restorff effect, namely a memory advantage for the novel font words. We then investigated whether any effect of novelty could be found at encoding (expected if novelty was giving an advantage during learning).Based on previous work, we expected the amplitude of the P3a component of the ERPs to be predictive of subsequent recall particularly for novel font words. However, we did not find a significant difference here. Additionally our results raise an important question. If novelty processing at encoding (as indexed by the N2 and P3 ERP components) is not related to the von Restorff effect, what process is responsible for it? A possible explanation is that the advantage occurs at recall, meaning that novels and standards in the von Restorff paradigm would be encoded in the same way, but during retrieval certain cues can be used to identify novel stimuli more easily.

In a follow-up study (chapter 5), we manipulated the allocation of attention to the different elements of a Von Restorff task (novel or familiar), since it has been established that the strategy at encoding affects the size of the Von Restorff effect (Fabiani et al., 1985, 1990). Previous studies tried to manipulate attention by presenting a concomitant distracting task or element. We attempted a different approach. In our study participants had to consciously pay attention only to either the novel or standard font words. We found that novels were remembered better than standards, when only asked for one kind of words at a time; however, when both types were asked together the effect was not present. This results confirm that encoding strategy modulates the von Restorff effect (see Fabiani & Donchin, 1995); when attention during encoding was manipulated, novel elements lost their advantage for memory.

Our final study (Chapter 6) tried a different approach, to look at the effects of novelty of task-irrelevant items on learning. In short, the task consisted of the presentation of to-be-learned words together with pictures in the background, which were irrelevant to the task. The pictures were either novel or standard. We tested two forms of novelty. Stimulus novelty refers to stimuli that have never been experienced, and contextual novelty refers to stimuli that may have been experienced before, but are presented only once in the current context. The novel pictures that possessed stimulus novelty were fractals newly created for this experiment; or contextual novels were landscapes that could be familiar to the participants, but were presented only once in the experiment. Both categories of novels were intermingled with either fractals or landscapes that were presented repeatedly. With this paradigm, we found that novel images did not provide any benefit for the learning of words presented in conjunction with them – if anything, there was a small memory disadvantage for these words. These results, in conjunction with those in the literature, show that the effect of novel pictures in memory formation depends on the timing of the presentation. Novels presented minutes before the items to be learned will aid memory (Fenker et al., 2008; Schomaker & Meeter, 2014a), whereas novel items presented simultaneously will have no effect (as we found in this study). Interestingly, animal studies suggest that exploration of novel environments affect plasticity in the hippocampus through dopamine release, an effect that also seems to play out over the time scale of minutes (Li et al., 2003).

Summing up the previous results, we showed in three different studies that the von Restorff effect (assumed by many to be a novelty effect) may be related to other characteristics of the stimuli, like salience during retrieval, not to novelty as indexed by the N2 and P3 novelty ERP components. Second, we have presented a new way to measure a novelty advantage for memory. With this task, we did not find any strong benefit of novelty for memory. This may be due to *timing:* comparison with studies in the literature shows that novelty may affect learning on the time scale of minutes, just not the time scale of seconds that would yield the item-by-item effects that have been investigated in this dissertation.

In conclusion

Novelty has often been tied to memory – with novelty being theorized to be a signal that results in better learning. This presumed relationship between novelty and memory can be studied at the neurotransmitter system level, as indicated in several animal models. Not many studies have looked at acetylcholine, serotonin or norepinephrine, but there is extensive evidence linking dopamine with the novelty-memory connection. Here, we showed that dopamine may indeed be linked to novelty detection. However, a comprehensive model of these effects is still to be constructed.

For many years, the novelty advantage for memory was measured primarily through the Von Restorff effect. The work presented here opens a new perspective by providing evidence that separates the Von Restorff effect from the effect of novelty for memory. Electrophysiology has provided ERP markers of novelty detection and processing, N2 and P3a. The processes underlying these ERP components cannot explain the Von Restorff effect, since there is no difference in the amplitude elicited at the moment of encoding between elements remembered or forgotten later. This may indicate that the Von Restorff effect does not happen at encoding. Our studies of the Von Restorff effect may indicate that there is no novelty-encoding relationship, but they may also be taken to indicate that the von Restorff paradigm is not suitable to investigate the novelty benefits for memory. A more fruitful approach may be to make novelty independent of the material that is being studied, as we attempted in chapter 6. With the new paradigm presented there, no benefit of novelty for learning was evident, at least on a time scale of individual items. However, other work has suggested that effects of novelty do exist on a time scale of minutes, and interestingly dopamine has been linked to these effects.

In summary, novelty is probably fundamental for cognition. The processing of new elements elicits a consistently strong neural response, which can be indexed by specific ERP components. These components may also be the expression of the workings of several neurotransmitter systems, which facilitate the detection, processing and storage of the novel information. This dissertation has provided some information to delineate the connections between novelty and the formation of memories, but much remains to be investigated.