Novelty and Memory: Electrophysiological and Pharmacological Studies

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Chapter 2. Neurotransmitters and Novelty: A Systematic Review

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Abstract

Our brains are highly responsive to novelty. However, how novelty is processed in the brain, and what neurotransmitter systems play a role therein, remains elusive. Here, we systematically review studies on human participants that have looked at the neuromodulatory basis of novelty detection and processing. While theoretical models and studies on nonhuman animals have pointed to a role of the dopaminergic, cholinergic, noradrenergic and serotonergic systems, the human literature has focused almost exclusively on the first two. Dopamine was found to affect electrophysiological responses to novelty early in time after stimulus presentation, but evidence on its effects on later processing was found to be contradictory: While neuropharmacological studies mostly yielded null effects, gene studies did point to an important role for dopamine. Acetylcholine seems to dampen novelty signals in the medial temporal lobe, but boost them in frontal cortex. Findings on 5HT (serotonin) were found to be mostly contradictory. Two large gaps were identified in the literature. First, few studies have looked at neuromodulatory influences on behavioral effects of novelty. Second, no study has looked at the involvement of the noradrenergic system in novelty processing.

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Introduction

Ever since the work of the russian physiologists in the 1800s and early 1900s (Pavlov, 1927; Sechenov, 1866), it has been known that novel stimuli and events elicit unique responses in brain and behavior. In his seminal experiments on the conditioned salivation response, for example, Pavlov found that his dogs stopped reacting to a conditioned stimulus when outsiders entered the experimental room. He called this disruption the "what is it" response, a reaction to novelty (Pavlov, 1927). This response is also referred as the 'orienting reflex', and found both in animals and humans (Berlyne, 1958; Sokolov, 1963).

Although the orienting response has been extensively studied, it is still unclear how responses to novelty come about at the neural level. Several theorists have suggested that novel stimuli affect behavior through eliciting a powerful neuromodulatory response, activating either the cholinergic (Hasselmo, Bradley, et al., 1996; Meeter, Murre, et al., 2004; Ranganath & Rainer, 2003; Wilson & Rolls, 1990), noradrenergic (Schomaker & Meeter, 2014a; Vankov, Herve-Minvielle, & Sara, 1995), dopaminergic (Duzel, Bunzeck, Guitart-Masip, & Duzel, 2010; Lisman & Grace, 2005), or serotonergic system (Bell, Shokrian, Potenzieri, & Whitaker-Azmitia, 2003). Although there is evidence that all of these systems are indeed activated by novelty, it is much less clear what role they play in mediating neural and behavioral responses to it. Here, we will review the role of neuromodulatory systems in the generation of novelty responses as measured by BOLD signals in fMRI, or evoked related potentials (ERP)s in ERP research, or behavior. We will start with a short overview of theories that have postulated such a role, and the evidence from the nonhuman animal literature that has been used to support these theories. Then, we will present a systematic review of studies in human participants, to assess the extent to which these studies point to a role involving neuromodulatory systems in mediating novelty responses.

Acetylcholine.

Neurons in the nucleus basalis of Meynert (an area that provides cholinergic output to several cortical regions) were found in nonhuman primates to have enhanced firing rates to novel pictures; when those pictures were presented repeatedly, firing decreased (Wilson & Rolls, 1990). These and other data have inspired several models and theories that give a central role to acetylcholine (ACh) in a cascade set off by novelty. Hasselmo (1999), Hasselmo, 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. This novelty signal would be generated in the hippocampus; it was hypothesized to consist of a brief period of depressed firing, caused by the fact that the novel pattern did not elicit any recall in the hippocampus.

Norepinephrine.

Also the noradrenergic system has been found to respond to novelty. In rats, neurons in the locus coeruleus – which is the main source of norepinephrine (NE) for most brain areas – present a clear phasic response to sensory stimuli, which is enhanced when those stimuli are novel. This enhancement is reduced after repetition (Vankov et al., 1995). In a comprehensive theory of the functioning of the locus coeruleus/NE, Aston-Jones and Cohen (2005) presented a hypothesis on how NE is involved in novelty responses. Novelty would be among a group of highly salient events that elicit a locus coeruleus response in a non-conditioned manner. The resulting release of NE would then increase the gain in cortical processing, resulting in a stronger cortical response to the stimulus that would be reflected in the P3 ERP component (Nieuwenhuis, Aston-Jones, & Cohen, 2005). Indeed, novel stimuli typically elicit a Novelty P3 (Courchesne et al., 1975; Squires et al., 1975), which has been related to the evaluation of novel stimuli for further behavioral action (Friedman et al., 2001) and to the orienting response (Cycowicz & Friedman, 1998).

Dopamine.

Most attention has been paid to dopaminergic involvement in novelty responses. Neurons in dopaminergic projection areas, primarily the VTA (Ventral Tegmental Area), have been found to respond to novel stimuli (Schultz, 1998). 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 (Dopamine) in the hippocampus, which in turn would enhance LTP (Long Term Potentiation) in the structure. Indeed, several models have focused on how DA stimulates learning and exploration, and promotes planning (Suri, Bargas, & Arbib, 2001).

Dopaminergic transmission has been addressed in recent years with the comprehensive 'NOvelty-related Motivation of Anticipation and exploration by Dopamine (NOMAD)' model (Duzel et al., 2010). This model gives a role to both tonic and phasic firing of the dopaminergic neurons, having to do with the anticipation and actual exposure to novelty. Anticipation of novelty produces tonic firing of DA neurons, and motivates exploration. Actual exposure to novel stimuli triggers phasic DA firing, which would, through cascades linked to the D1 and D5 receptors, help transform transient synaptic plasticity into long-lasting plasticity (S. Li et al., 2003). The combination of tonic and phasic DA responses enhances learning and consolidation of the new stimuli. The relationship between expectation and presentation of novel stimuli and novelty has been explored further. Novel stimuli are found to activate the VTA (ventral tegmental area) and the substantia Nigra (another dopamine-projecting area) only when they were unexpected

(Wittmann, Bunzeck, Dolan, & Duzel, 2007). However, the enhancement of DA activity due to novelty may be structure-specific. In the putamen and striatum, DA activity was reported to be reduced in the presence of novel stimuli (Hakyemez, Dagher, Smith, & Zald, 2008).

Serotonin (5HT).

The serotonergic system is rarely mentioned in the context of novelty responses. It may, in fact, inhibit them (Azmitia, Dolan, & Whitaker-Azmitia, 1990). The S-100β gene has been proposed to be important for the growth of the serotonergic neural system. Transgenic S-100β mice, which have lower levels of 5HT as compared with non-transgenic mice, showed enhanced novelty seeking and exploration, and decreased harm avoidance, as compared with controls (Bell et al., 2003).

Summary

The models and theories discussed above all, stipulate that there is a novelty signal, presumably generated by the hippocampus, that triggers a phasic release in a neurotransmitter system – either that of ACh, NE or DA. This release then changes dynamics in many brain areas at once, which could underlie the behavioral responses to novelty. Most models have concentrated on the consequences of novelty for learning, with only NOMAD going beyond this and linking dopamine to exploration.

Evidence from nonhuman animal studies have already provided evidence for an increase of release of ACh, NE and DA in response to novelty. Here, we will catalogue what evidence is available for the second hypothesized step – from neurotransmitter release to behavioral responses to novelty. To increase comparability, we will concentrate on experimental studies done on human volunteers.

Methods

For the present study we searched in the PubMed database PubMed for journal articles from 1993 to 2013 (search performed in December 2013). The original keywords introduced were: Dopamine or norepinephrine or serotonin or ACh – and Novelty (in title/abstract). We reviewed studies done with: human participants, using experimental manipulations and tasks. This latter criterion meant that we excluded any study looking solely at the 'novelty seeking' personality trait. Novelty seeking was defined by Cloninger (1987) in his tridimensional personality questionnaire (TPQ) as a tendency to be exhilarated in the presence of novel stimuli, which leads to frequent exploration in pursuit of novelty. Virtually all studies looking into this trait was targeted at explaining individual differences, which is why they were excluded in our search criteria. In our original search 50% of the

studies were associated with this personality trait. In figure 1 a flow diagram of our literature search is show, resulting in the final sample of studies to be reviewed.

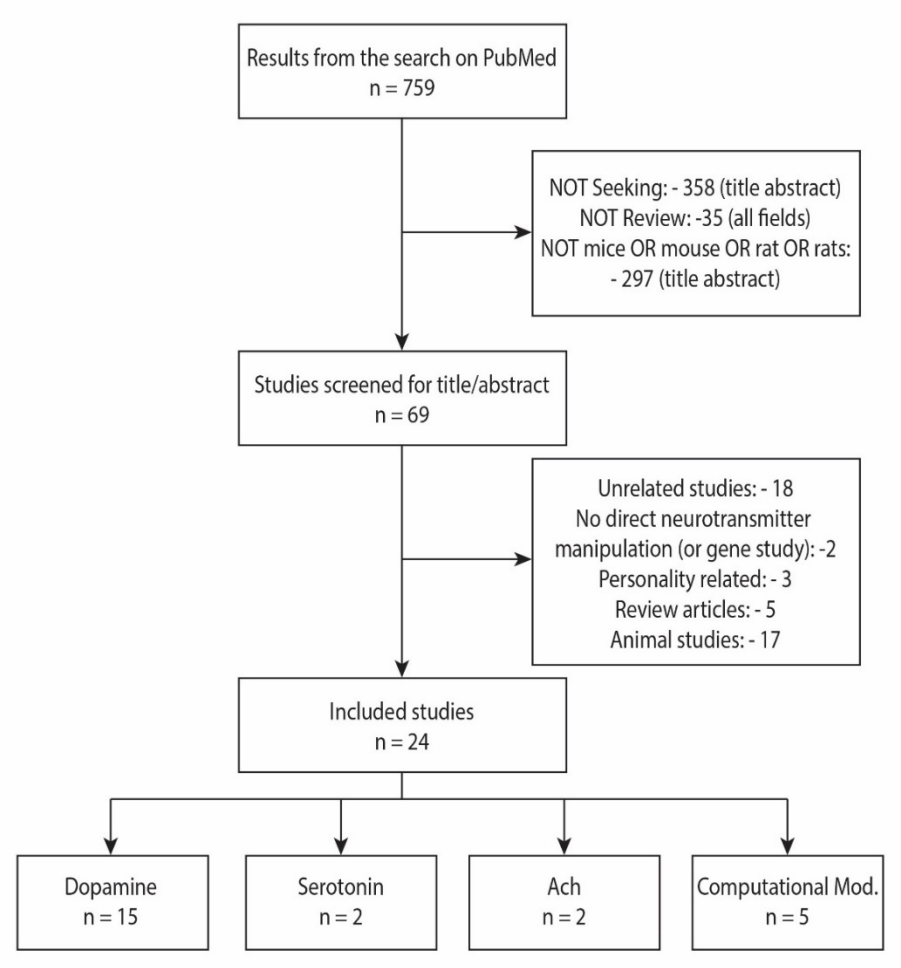

Figure 1. Flow chart presenting the process of selection of the studies to be included in the study. Exclusion criteria were meant to exclude both studies using nonhuman animals, and studies into the personality trait of novelty seeking.

Results

The results of the search and review of the literature on neurotransmitters and novelty are presented in Tables 1 and 2. Given that most studies investigated dopaminergic transmission, we listed these separately in Table 1. Table 2 is devoted to the other neurotransmitter systems.

Dopaminergic transmission and Novelty.

The studies listed in Table 1 suggest that DA is involved in several steps of novelty processing, but also that different ways to affect the dopaminergic system may have different consequences.

Several studies show that an increment in dopaminergic activity results in faster and enhanced novelty detection. The D1/D2 receptor agonist apomorphine was found to increase the N2b, an early Evoked Response Potential (ERP) component to novel stimuli (Rangel-Gomez et al., 2013). Moreover, L-Dopa (a DA precursor whose administration increases dopamine release) was found to lead to an earlier discrimination between novel and just studied scenes in the medial temporal lobe, relative to placebo (Eckart & Bunzeck, 2012) – to incredibly fast responses at intervals below 100 ms after stimulus onset. In a follow-up study, however, the same group found that when reward was offered to participants, L-Dopa delayed the onset of novel / familiar differences seen in the Event Related Fields (ERFs) (Apitz & Bunzeck, 2013). The authors suggested that reward anticipation already results in dopamine release, which would then combine with L-Dopa to a higher-than-optimal level of dopamine transmission.

Concerning later processing the picture is complex. Most studies have looked at the novelty P3 component elicited by novel stimuli mentioned above (Courchesne et al., 1975; Squires et al., 1975). This component is probably equivalent to a response to deviant stimuli known as the P3a (Schomaker & Meeter, 2014a; Simons, Graham, Miles, & Chen, 2001; Squires et al., 1975), to distinguish it from the somewhat later and more posterior P3b component elicited by target stimuli (Polich & Criado, 2006).

Pharmacological challenges of the dopamine system have found inconsistent results on the amplitude of the novelty P3, but the preponderance of evidence suggests that the novelty P3 is not affected by dopaminergic manipulations. Dextroamphetamine, a DA/NE reuptake inhibitor (increasing DA availability), was found to diminish the auditory novelty P3 component to novel auditory stimuli (as well as the P3b to target stimuli) in an auditory oddball task, but had no effect on the visual novelty P3 elicited in a visual oddball task (Albrecht, Martin-Iverson, Price, Lee, & Iyyalol, 2010). In a different study, the same substance showed no effect on the P3a to novel auditory stimuli in a 3-stimulus oddball task (Gabbay, Duncan, & McDonald, 2010). The D1/D2 agonist apomorphine did not alter the novelty P3 either, both when this component is elicited by infrequent targets in a

standard auditory oddball task (Luthringer et al., 1999), or when it is elicited by novel font words in a Von Restorff paradigm (Rangel-Gomez et al., 2013). Behaviorally, apomorphine administration was found to increased memory performance specifically for novel font words (Rangel-Gomez et al., 2013), while L-Dopa administration was found to either have no effect on memory (Eckart & Bunzeck, 2012) or a detrimental one (Apitz & Bunzeck, 2013). The same substances that enhance novelty detection thus seem to have limited or no effect on the later processing of novel events and stimuli.

Gene studies, on the other hand, tended to show that greater DA availability/activity is related to a larger amplitude of the novelty P3 component. Some have investigated the COMT gene, of which some alleles are related to higher DA availability in the brain than other alleles. In one study, it was found that elevated DA availability is related to an enhanced novelty P3 component (Heitland, Kenemans, Oosting, Baas, & Bocker, 2013). A similarly enhanced novelty P3 pattern was found for alleles of the DAT1 gene that are related to smaller densities of DA transporters, which in turn imply increased extracellular DA availability (Garcia-Garcia, Barcelo, Clemente, & Escera, 2010b; M. Garcia-Garcia, I. C. Clemente, J. Dominguez-Borras, & C. Escera, 2010b). Although results with COMT and DAT genotypes are thus consistent, those two are related to different activity configurations of the DA system. COMT has been related to changes in the tonic level of DA, while DAT has been connected to changes in phasic responses (Bilder, Volavka, Lachman, & Grace, 2004). It is thus possible that COMT and DAT variations affect the novelty P3 through different pathways.

Additional studies have looked specifically at the D4 receptor. The DRD4/7R+ allele, linked to reduced D4 receptor functioning, was found to be related to reduced reactivity to strangers (Lakatos et al., 2003), and to less novelty preference in behavioral observations of toddlers (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001). However, no effect of this gene was found on the novelty P3 to novel sounds (Birkas et al., 2006). In another study, the effect of the 7R+ allele was found to depend on overall dopamine status, as reflected in blinking rate (Karson, 1983). In individuals with a high blinking rate (reflecting a more active dopamine system) the 7R+ allele was associated with an enhanced novelty P3, while it was associated with a decreased novelty P3 in low-rate blinkers (Strobel et al., 2004).

Another way to assess novelty responses is to look at repetition suppression, the difference between the response elicited by a stimulus the first time it is presented (i.e., when it is novel), and the same stimulus when it has been presented repeatedly (i.e., has become familiar). A stronger repetition effect indicates that novel stimuli are processed differently than familiar ones. The administration of L-Dopa diminished repetition suppression effects in hippocampus, parahippocampal cortex and substantia nigra/ventral tegmental area (Bunzeck, Guitart-Masip, Dolan, & Duzel, 2013).

Overall, there is strong evidence that dopamine positively influences early responses to novelty that have been traditionally been associated with novelty detection, such as the N2b component and early old/new effects found with MEG. Findings on later novelty

processing, most notably the novelty P3, are more ambiguous. Whereas gene studies have yielded evidence for an effect of DA on the P3, pharmacological challenges have generally supported the opposite conclusion that there is no relation between the dopaminergic system and the novelty P3. One possible reason is suggested by findings that the effect of DA on various cognitive processes (e.g., working memory, cognitive control) may follow an 'inverted U' curve (Cools & D'Esposito, 2011). This may be the case for novelty as well (Apitz & Bunzeck, 2013) with pharmacological challenges being more likely to reflect the downward as well as the upward sloping part of the curve. However, evidence for such a curve is sparse, so this remains a suggestion that has to be further investigated.

Alternatively, contradicting findings may be due to differential effects on tonic and phasic levels of DA transmission, a distinction that is central in for example the NOMAD model (Duzel et al., 2010). It is phasic responses that are mostly hypothesized to underlie novelty responses. Some genetic variations, notably of the DAT1 gene, may mostly affect phasic DA release (Bilder et al., 2004), whereas dopaminergic receptor agonists such as apomorphine would tonically stimulate dopaminergic receptors. However, other pharmacological challenges, notably L-dopa and dextroamphetamine, may affect tonic and phasic dopamine transmission equally (Breitenstein et al., 2006), and COMT gene variation, which may affect the novelty P3 in the same way as DAT1 gene variations do, seems to mostly affect tonic release (Bilder et al., 2004). Since these challenges were found to affect novelty responses in the same way as receptor agonists do, it is not very likely that a difference between tonic and phasic transmission underlies the contrasting findings from pharmacological and genetic studies.

Table 1. Summary of the experimental studies related to Dopamine

Authors	Year	Technique	Type	Sample	Design	Task	Results
Albrecht, Martin-Iverson, Price, Lee, & Iyyalol	(2010)	EEG/ERPs	E/Ph	T – 18 F – 7 A – 25	2 Sessions Dexamphetamine (DA/NE Agonist) / Placebo Counterbalanced	Auditory-visual 3-stimulus oddball paradigm	Dexamphetamine – ↓ auditory P3, No effect on visual P3
Apitz & Bunzeck	(2013)	MEG/ERFs	E/Ph	T – 38, F – 18 D/20 – 10/F Drug: A – 26 Plac: A – 24	1 Session / 2 Groups Drug – L-Dopa Placebo	Novel/familiar recognition task + Reward	L-Dopa: ↑ time for old-new effect (amplitude differences in the ERFs) ↓ retrieval (d')
Auerbach, Benjamin, Faroy, Geller, and Ebstein	(2001)	B	G	T – 64 A – 1 Gender not provided	Genotyping for DRD4 (7-/7+)	The Laboratory Temperament Assessment Battery – Task Orientation Episode	7+ showed less sustained attention and novelty preference than 7-
Birkas, Horvath, Lakatos, Nemoda, Sasvari-Szekely, Winkler & Gervai	(2006)	EEG/ERPs	G	T – 57 F – 32 A – 6	Genotyping for DRD4 (7-/7+)	During cartoon presentation, task irrelevant sequence of sounds. 3-types: Standard, deviant, and novel (environmental sounds)	No effect of 7+ on early ERP responses 7+ carriers ↓ late negative components
Bunzeck, Guitart-Masip, Dolan, & Duzel	(2013)	fMRI	E/Ph	T – 48 F – 29 A – 22	3 Groups (16 part x 3) 1. L-Dopa (DA Precursor), 2. Galantamine (Cholinesterase Inhibitor), 3. Placebo.	Modified RS paradigm. Indoor/outdoor. 2nd session, incidental recognition memory test.	L-Dopa: Attenuated RS in HP, PHC and SN/VTA Galantamine: Reversed RS in Mesolimbic regions.
Eckart & Bunzeck	(2012)	MEG/ERFs	E/Ph	T – 47 F – 24 A – 26	3 Groups: L-Dopa (n=16), Galantamine (n=16), Placebo (n=15)	Familiarization with indoor/outdoor pict, intermixed with novel pictures. Subjective rating scale and 'd2-test of attention' on 3 time points.(Before, 30 min/after, and 2 hrs after intake) On day 2 – Incidental recognition test.	↑ DA but not ↑ Ach accelerated the onset of novelty signals in MTL. ↑ Ach shifts neural substrates of novelty from MTL to PFC No effect on recognition memory
Gabbay, Duncan, & McDonald	(2010)	EEG/ERPs	E/Ph	T – 62 Choosers: 37 / F – 21 Nonchoos: 25 / F – 9 Age not reported	Pre-screening 4 sessions with d-amp Division in Choosers/Non-Choosers 3 sessions: 15 mg, 10 mg, Placebo	3-Stimulus auditory oddball task.	Choosers: Targets elicited P3a after d-amp, but not after placebo Non-choosers: No effect of d-amp on P3a N100 and RON, ↑ for Non-choosers
Garcia-Garcia, Barcelo, Clemente, & Escera	(2010b)	EEG/ERPs	G	T – 40 F – 32 A – 22	Genotyping for DAT1 polymorphisms 9R+/9R-	Task-cueing protocol inspired by the WCST, with auditory cue indicating change to a novel task (proven to elicit nP3)	9R+ Larger reaction times costs than 9R- ↑ nP3 for 9R+
Garcia-Garcia, Barcelo, Clemente, & Escera.	(2011)	EEG/ERPs	G	T – 40 F – 34 A – 22	Genotyping for: COMT and ANKK1Taq1A	Task-cueing protocol inspired by the WCST, with auditory cue indicating change to a novel task (proven to elicit nP3)	Interaction between COMT and ANKK1 accounts for ↓ nP3. Only for genotyping with a balance between DA concentration and receptor densities

Garcia-Garcia, Clemente, Dominguez-Borras, & Escera	(2010b)	EEG/ERPs	G	T – 40 F – 32 A – 22	Genotyping for DAT1 polymorphisms 9R+/9R-	Auditory-visual distraction in negative and neutral contexts. Sounds were task irrelevant and either novel or standard	9R- : No distraction by – emotion 9R+ : Distraction by – emotion, ↑ nP3 regardless of condition
Heitland, Kenemans, Oosting, Baas, & Böckerd	(2013)	EEG/ERPs	G	T – 60 F – 60 A – 21	Genotyping of: DAT1, COMT and 5HTTLPR	Auditory Novelty Oddball Paradigm	COMT Met/Met – Enhanced DA: ↑ nP3a DAT 1 – Striatal DA: No diff in P3a between 9R+ and 9R- COMT Met/Met ↑ P3b than Val/Val and for DAT 1 9R+ than 9R- 5HTTLPR – Short Allele - ↑ 5HT(Tonic) – ↑ nP3a and ↑ P3b than long allele
Lakatos, Nemoda, Birkas, Ronai, Kovacs, Ney, Toth, Sasvari-Szekely, & Gervai	(2003)	B	G	T – 90 Families with healthy, full term, first-born infants	Genotyping for DRD4 (7-/7+) and 5HTTLPR (long/short allele)	Ainsworth Strange Situation, on videotapes of interactions between mothers and infants	In present of a stranger. ↓ anxiety for infants with 7+ (DRD4) and long allele (5HTTLPR)
Luthringer, Rinaudo, Toussaint, Bailey, Muller, Muzet, & Macher	(1999)	EEG/ERPs	E/Ph	T – 8 F – 0 A – 28	Participants intern 12 hours before apomorphine administration. Drug/placebo - 2 sessions	Auditory Novelty Oddball Paradigm	P300 and CNV not significantly altered, tendency towards increased P300 latency
Rangel-Gomez, Hickey, van Amelsvoort, Bet, & Meeter	(2013)	EEG/ERPs	E/Ph	T – 26 F – 17 A – 22	2 Sessions Apomorphine/Placebo Counterbalanced	Von Restorff Paradigm: studying normal-font and novel-font words	Apomorphine: ↑ Encoding of novels ↑ Amplitude of N2b
Strobel. Debener, Anacker, Muller, Lesch, & Brocke	(2004)	EEG/ERPs	G	T – 72 F – 46 A – 23	Genotyping for DRD4 (7-/7+)	Auditory novelty oddball	Sample was divided in Low and High blinkers, high blinkers, 7+ ↑ nP3 than 7- low blinkers, 7- ↑ nP3 than 7+

Abbreviations:

Technique: EEG – Electroencephalograms, ERPs – Event Related Potentials, MEG – Magnetoencephalograms, ERFs – Event Related Fields, fMRI – Functional Magnetic Resonance Imaging, PET – [11C]raclopride Positron Emission Tomography, B – Behavioral. **Type:** E – Experimental, Ph – Pharmacological Challenge, G – Gene study. **Sample:** T – Total Sample, F – Females, A – Average age. **Task:** WCST – Wisconsin Card Sorting Test. RS – Repetition Suppression

Results RON – Reorienting Negativity, nP3 – Novelty P3 component, CNV – Contingent Negative Variation, FN400 – Mid-frontal negativity to the old/new effect. DA – Dopamine, Ach – Acetylcholine, NE – Norepinephrine, GABA – Gamma-Aminobutyric acid, d-amp – d-amphetamine. HP – Hippocampus, PHC – Parahippocampal cortex, SN/VTA – Substantia Nigra/Ventral Tegmental Area, MTL – Medial Temporal Lobe, PFC – Prefrontal Cortex, LPF – Left Prefrontal cortex, PR – Perirhinal cortex.

Other neurotransmitters associated with novelty processing.

Compared to DA, few studies have addressed the role of other neurotransmitter systems in novelty processing. We could identify four studies involving the serotonergic system, four addressing the cholinergic system, and none addressing the noradrenergic system.

5HT has been addressed solely in gene studies. The long allele of the 5HTTLPR gene is associated with increased 5HT transporter expression and, potentially, less 5HT availability, relative to the short allele (Heils et al., 1996). Long allele carriers showed an enhanced P3a component elicited by novel stimuli relative to short allele carriers (Heitland et al., 2013). On the other hand, short allele-carrier toddlers showed stronger responses to novel individuals in a behavioral observation task (Lakatos et al., 2003). Additionally, Tyr, a genotype resulting in a decreased postsynaptic effectiveness of the 5HT 2a receptor (Ozaki et al., 1997), may be related to diminished novelty responses in the hippocampus. During a novelty detection task, which included previously-familiarized, standard (always the same) and novel (only presented once during the task) items, Tyr carriers made significantly more false alarms than controls. Additionally, when presented with novel stimuli Tyr carriers showed reduced right anterior hippocampal activation as compared to non-carriers (Schott et al., 2011). These contradictory results are difficult to reconcile. It may be that 5HT affects novelty responses differently through its 2a receptor than through other receptors, but it is equally plausible that 5HT does not affect novelty responses in any consistent fashion, and instead affects each task differently.

Surprisingly, given that Ach has been long identified as central for novelty detection, this neurotransmitter has scarcely featured in experimental studies in humans. The cholinesterase inhibitor galantamine, an allosteric potentiating the ligand of human nicotinic acetylcholine receptors, which could be assumed to increase ACh concentrations when administered once, seems to decrease neural responses to novelty in the medial temporal lobe (Eckart & Bunzeck, 2012). It also blunts repetition suppression in temporal and medial temporal areas (Bunzeck et al., 2013), suggesting that ACh decreases responses to novel stimuli in those areas. Moreover, the muscarinic antagonist scopolamine enhanced BOLD signal, during encoding, for words not recently studied relative to familiar words (Bozzali, MacPherson, Dolan, & Shallice, 2006). On the other hand, galantamine was also found to increase novelty signals in the prefrontal cortex (Eckart & Bunzeck, 2012), and another cholinesterase inhibitor, rivastigmine, was found to increase the novelty P3 to novel sounds (Klinkenberg, Blokland, Riedel, & Sambeth, 2013). This increase was reversed when the cholinergic M1 receptor blocker Biperiden was administered concurrently. These finding all suggest that ACh acts to diminish differences in processing between novel and familiar stimuli in the medial temporal lobe, but does the reverse in other parts of the cortex. Since both of these results were obtained both through administration of cholinesterase blockers and through muscarinic receptor blockers, it seems that the effects of ACh on novelty processing are mainly mediated by muscarinic receptors.

Table 2. Summary of the experimental studies related to Serotonin, Acetylcholine, GABA, grouped by neurotransmitter. Abbreviations are as in Table 1

Authors	Year	Technique	Type	Sample	Design	Task	Results
Serotonin							
Enge, Fleischhauer, Lesch, & Strobel	(2011)	EEG/ERPs	G	T – 72, F – 46 A – 24	Genotyping for 5HTTLPR	Auditory Novelty Oddball Paradigm	↑ N1 for targets in short allele carriers that were more engaged in effortful processing.
Heitland, Kenemans, Oosting, Baas, & Böckerd	(2013)	EEG/ERPs	G	T – 60 F – 60 A – 21	Genotyping of: DAT1, COMT and 5HTTLPR	Auditory Novelty Oddball Paradigm	COMT Met/Met – Enhanced DA: ↑ nP3a DAT 1 – Striatal DA: No diff in P3a between 9R+ and 9R- COMT Met/Met ↑ P3b than Val/Val and for DAT 1 9R+ than 9R- 5HTTLPR – Short Allele - ↑ 5HT(Tonic) – ↑ P3a and ↑ P3b than long allele
Lakatos, Nemoda, Birkas, Ronai, Kovacs, Ney, Toth, Sasvari-Szekely, & Gervai	(2003)	B	G	T – 90 Families with healthy, full term, first-born infants	Genotyping for DRD4 (7-/7+) and 5HTTLPR (long/short allele)	Ainsworth Strange Situation, on videotapes of interactions between mothers and infants	In present of a stranger. ↓ anxiety for infants with 7+ (DRD4) and long allele (5HTTLPR)
Schott, et al.	(2011)	fMRI	G	T – 41 F – 19 A – 17	Genotyping for 5-HTR2a His452Tyr	Novel/familiar recognition task + Delayed recognition task	Tyr Carriers – Diminished HP novelty response, ↑ tendency to judge stimuli as familiar during delayed recognition
Acetylcholine							
Bozzali, MacPherson, Dolan, & Shallice	(2006)	fMRI	E/Ph	T – 18 F – 11 A – 26	2 Sessions Scopolamine/Placebo Counterbalanced Drug after study phase	Encoding + recognition Recognition – Inclusion (simple recog. decision), Exclusion (judgment based on context)	Scopolamine produces enhanced activity in LPF and PR, as compared with placebo, in the exclusion condition for novel pictures that were correctly identified Correlation between drug-related signal change in LPF and PR cortices.
Bunzeck, Guitart-Masip, Dolan, & Duzel	(2013)	fMRI	E/Ph	T – 48 F – 29 A – 22	3 Groups (16 part x 3) 1. L-Dopa (DA Precursor), 2. Galantamine (Cholinesterase Inhibitor), 3. Placebo.	Modified RS paradigm. Indoor/outdoor. 2nd session, incidental recognition memory test.	L-Dopa: Attenuated RS in HP, PHC and SN/VTA Galantamine: Reversed RS in Mesolimbic regions.
Eckart & Bunzeck	(2012)	MEG/ERFs	E/Ph	T – 47 F – 24 A – 26	3 Groups: L-Dopa (n=16), Galantamine (n=16), Placebo (n=15)	Familiarization with indoor/outdoor pict, intermixed with novel pictures. Subjective rating scale and 'd2-test of attention' on 3 time points.(Before, 30 min/after, and 2 hrs after intake) On day 2 – Incidental recognition test.	↑ DA but not ↑ Ach accelerated the onset of novelty signals in MTL. ↑ Ach shifts neural substrates of novelty from MTL to PFC
Klinkenberg, Blokland, Riedel & Sambeth	(2013)	EEG/ERPs	E/Ph	T – 19 F – 12 A – 22	4 Sessions: 1. Placebo 2. Biperiden 3. Rivastigmine 4. Biperiden + rivastagmine	Auditory Novelty Oddball Paradigm	↑ Ach (due to Rivastigmine – Cholinesterase inhibitor) produces enhanced amplitude of nP3a, and shorter latency for N100.

Discussion.

Animal studies have provided clear evidence that novel stimuli activate many neuromodulatory systems at once. However, how these systems relate to the processing of novelty and the behavioral reactions to it is unclear. Here, we reviewed studies performed on human volunteers that shed light on this question. The studies reviewed above clearly point to an involvement of the dopaminergic and cholinergic systems in novelty processing. No study could be identified that investigates the role of the noradrenergic system, while findings on the serotonergic system were highly contradictory.

The influence of DA on novelty processing seems to differ according to the stage of processing. Early differential responses to novel stimuli, traditionally linked to novelty detection, seem to be enhanced by DA. Evidence for effects of DA on later stages is more ambiguous. Some studies, notably those looking at gene polymorphisms, suggest that DA enhances the processing underlying the novelty P3, while pharmacological studies have generally suggested that there is no role for DA in these later stages. These inconsistencies may be due to an inverted U-relationship between dopamine transmission and novelty processing (Apitz & Bunzeck, 2013); however, this remains to be investigated. An alternative explanation in terms of differential effects on tonic and phasic transmission was found to be untenable, as pharmacological challenges that affect tonic and phasic transmission equally affect novelty processing in a similar way as challenges that only affect tonic transmission.

Concerning the cholinergic system, increased ACh transmission was found to diminish differences in processing between novel and familiar stimuli in the medial temporal lobe. This confirms a prediction of one computational model (Meeter, Murre, et al., 2004, cf. Figure 9A), which has suggested that this area only generates a novelty signal when ACh release is low. However, the reverse was found for the frontal cortex. Frontal old/new differences and the auditory novelty P3 (often sourced to the frontal cortex; Wronka, Kaiser, & Coenen, 2012), were found to be increased in size when ACh transmission was boosted, and decreased when it was blocked. This is consistent with a role for ACh in generating cortical novelty responses. However, no data was available that confirms or disconfirms any role of ACh in generating behavioral responses to novelty.

For both DA and ACh, the reviewed studies thus clarify part of the role of the neurotransmitter system, while leaving other parts open. For 5HT, the available studies yield contradictory findings, while for NE no study was found that directly investigated the role of this neurotransmitter system. However, the largest gap in the literature is that very few studies have tried to link neurotransmitter systems to behavioral effects of novelty. A few studies have looked at memory performance, and only one (Lakatos et al., 2003) has looked at behavior towards novel stimuli. This is the case even though orienting and exploration are the most notable responses to novelty, as already noted long ago (Pavlov, 1927; Sechenov, 1866).

In summary, the evidence reviewed here points to a role of the dopamine system in determining the initial neural response to novelty, most notably that in the medial temporal lobe, while this response is dampened by cholinergic transmission. Later responses to novelty emanating from the frontal cortex seem to be under influence of the cholinergic system. Whether or not they are also affected by the dopaminergic system is currently unclear. Meanwhile, the role of the noradrenergic system in novelty processing remains to be investigated.