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REVIEW

How Human Electrophysiology Informs Psychopharmacology: from Bottom-up Driven Processing to Top-Down Control

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This review surveys human event-related brain potential (ERP) and event-related magnetic field (ERF) approaches to psychopharmacology and psychopathology, and the way in which they complement behavioral studies and other neuroimaging modalities. The major paradigms involving ERP/ERF are P50 suppression, loudness-dependent auditory evoked potential (LDAEP), mismatch negativity (MMN), P300, mental chronometry, inhibitory control, and conflict processing (eg, error-related negativity (ERN)). Together these paradigms cover a range of more bottom-up driven to more top-down controlled processes. A number of relationships between the major neurotransmitter systems and electrocortical mechanisms are highlighted. These include the role of dopamine in conflict processing, and perceptual processing *vs* motor preparation; the role of serotonin in P50 suppression, LDAEP, and MMN; glutamate/NMDA and MMN; and the role of acetylcholine in P300 generation and memory-related processes. A preliminary taxonomy for these relationships is provided, which should be helpful in attuning possible new treatments or new applications of existing treatments to various disorders.
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INTRODUCTION

Brain activity involves changes in the electric and magnetic fields on which behavior depends. These changing fields can be recorded from the human scalp, resulting in the electroencephalogram (EEG) and the magnetoencephalogram (MEG), respectively. EEG and MEG reflect spontaneous brain activity, but may also contain the response of the brain to specific events: event-related potentials (ERPs) and event-related fields (ERFs), respectively.

The use of ERP/Fs allows us to rephrase questions about putative cognitive functions in terms of brain activity, which provides a more objective basis for identifying mechanisms underlying behavior, behavioral disorders, and the effects of drugs. This review discusses pertinent applications of this strategy in relation to psychopharmacology, or 'electropsychopharmacology'. More generally, inferences of specific drug effects on components of information processing as based on the analysis of behavioral data, must often rely on unproven assumptions. Therefore, any independent additional source of information about stimulus processing and response preparation, including ERPs or ERFs, could be valuable. Furthermore, like functional magnetic resonance imaging (fMRI), ERP/Fs provide a direct window on brain mechanisms that are reflected in performance measures only indirectly. They thus have explicit added value to inform the psychopharmacology of cognition and affective processes. Finally, they are particularly applicable in populations for which many tasks are overly demanding, and for whom measures requiring less active co-operation are preferable.

In the case of the EEG, the recorded signal results from volume conduction of the electrical component of neural activity, more specifically the graded waxing and waning of postsynaptic potentials throughout the cerebral cortex (with very limited exceptions, there are no extracortical contributions to EEG or MEG). With volume conduction there is only a microscopic delay between the brain activity

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and its reflection in the electrode-recorded signal. The amount of this delay is far below the millisecond level that characterizes the time scale of most neurophysiological activity. Thus, relative to the other measures of human brain activity, EEG and MEG have a high temporal resolution: changes in the activity can be followed on a millisecond basis. Figure 1 presents a typical collection of parallel EEG and MEG signals.

In comparison with some other methods, EEG has a poorer spatial resolution: it is less accurate in indicating where in the brain the activity is located. This is mainly because of the weak conductive capacity of the skull, which results in substantial blurring of the electrical signals from the brain as they are recorded from the scalp.

MEG is based on the principle that any change in the electrical activity involves a change in the magnetic field as well. Nerve cells also generate intracellular current flow from dendrites to cell body, resulting in a magnetic field that can be detected at the scalp with SQUID (superconducting quantum interference device) sensors. The unique feature of the MEG technique is the relative transparency of the skull, scalp, and brain tissue to the magnetic fields. Magnetic signals do not suffer from weak volume conduction, and therefore, MEG offers a much higher spatial resolution. In addition, MEG is reference free, whereas EEG is dependent on the location of the reference site. Also MEG is complementary to EEG, in that it is only sensitive to current flow that is parallel to the skull (as in most of the cortical sulci, but not on gyral crests).

The extraction from the relatively tiny ERP/Fs from the ongoing EEG (MEG) uses the fact that ERP/Fs are time locked to discrete events, such as stimuli. This involves a sufficient number of repeated measures and application of the method of signal averaging. This method is based on the idea that the background E/MEG has no fixed temporal relationship with the point in time at which the stimulus was presented; on the other hand the ERP/F has a much more constant time course relative to the stimulus (see Box 1).

Multiple sensors covering most of the head form the basis for constructing time-varying signal distributions (across the head), or topographies for EEG, MEG, ERP, or ERF. In turn, these topographies serve as the basis for inferring the intracranial generators (or 'sources') of the scalp-recorded signals. Especially for EEG/ERP, this a cumbersome enterprise, because of the limited spatial resolution, but also because of the underdeterminacy of the problem. In practice, relative localization is feasible; absolute localization must be added by other techniques such as fMRI (as has been successful in some cases, eg, the 'error-related negativity (ERN)'; see Box 2).

This review surveys pertinent applications of ERP/Fs to psychopharmacology: we discuss how ERP/Fs shed light on a comprehensive range of information processing components in terms of their cortical substrates, and the effects of neurotransmitter system manipulation on them. Specifically, we address regulating inhibitory mechanisms intrinsic to sensory cortex; context-dependent cortical responses to novel or otherwise potentially relevant events; electrocortical reflections of attention allocation to salient events that are instrumental in memory updating; and a range of cortical mechanisms that are involved in translating perceptual information into action tendencies, and in regulating and monitoring the selection of adequate responses to relatively complex environmental demands (see Table 1; Box 3 and 4). As should be clear from the above discussion, the number of brain mechanisms potentially reflected in ERP/Fs is limited. On the other hand, it has been suggested that the essence of brain function can be captured in a limited set of principles. These principles map quite well on the set of ERP/F phenomena to be discussed, as will be detailed in the sections to follow. This in turn suggests that ERP/Fs as discussed presently are actually quite representative for brain function as a whole.

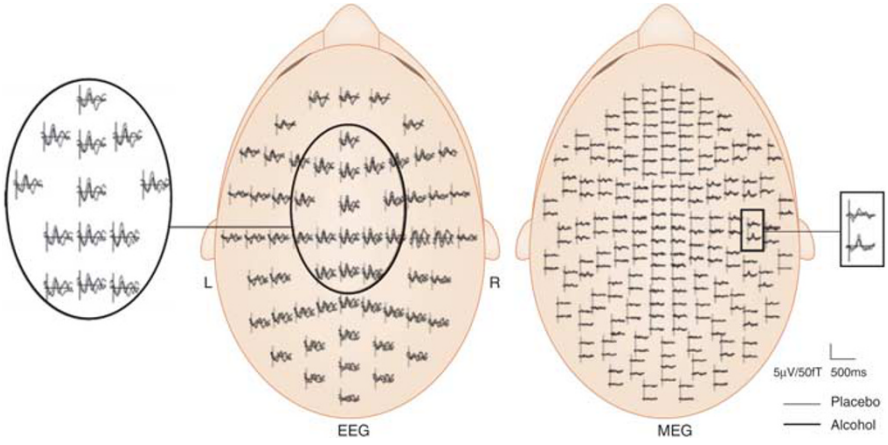
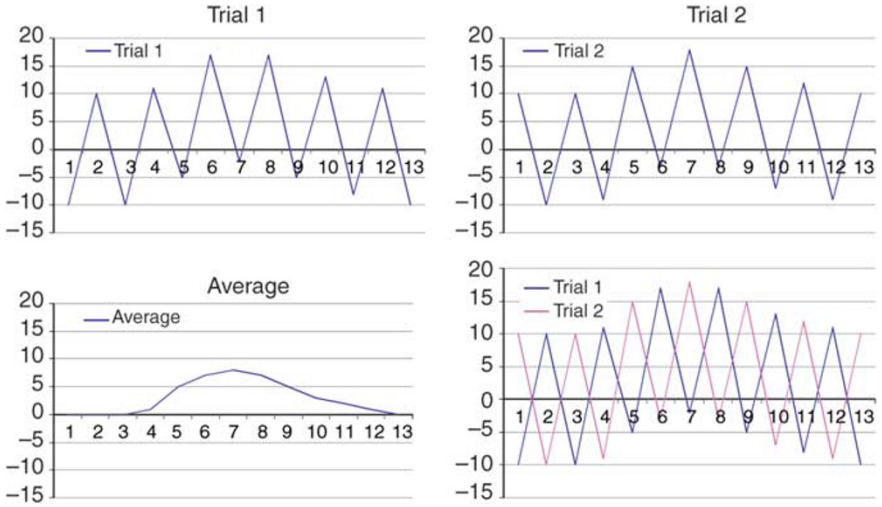


Figure 1. ERPs en ERFs elicited by unexpectedly changing sounds ('mismatch negativity') recorded with EEG and MEG from the same subject after alcohol and placebo administrations. This figure also demonstrates that MEG signals are more localized over temporal cortex than EEG signals. Adapted from (Kähkönen *et al*, 2005a, b).

Box 1 Signal averaging

The electroencephalograms (EEGs) or magnetoencephalogram (MEGs) recorded during and after each stimulus presentation are subsequently subjected to (signal) averaging. For example, the same stimulus is presented on a number of trials. On one trial the background signal might be in an ascending phase at the moment of stimulus presentation, going from negative to positive; on a second trial it might be in a descending phase. If sufficient trials are collected and EEG (MEG) amplitudes at the moment of stimulus presentation are averaged across trials, the result will approximate zero. The same principle would hold for all points in time after stimulus onset. On the other hand, that part of the E/MEG that is specifically related to the presentation of the stimulus, is supposed to have a fixed temporal relation with it. If on each trial the stimulus causes an increase in negativity, which peaks at about 100 ms after its presentation, averaging across trials of the amplitudes at 100 ms after the stimulus would still result in this same negative peak.

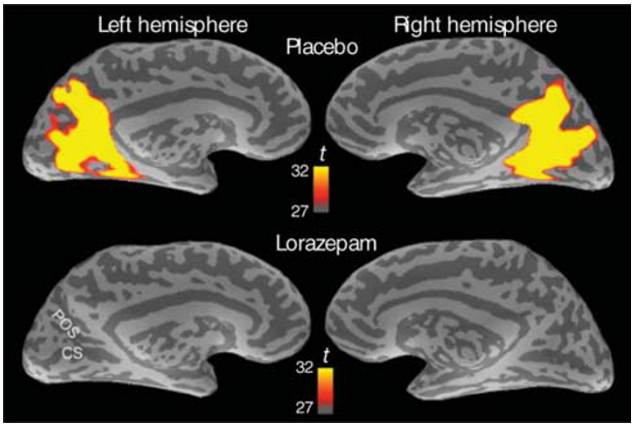
The figure presents an idealized example of exact counter-phase between the background activity on trial 1 and that on trial 2. In that case only two trials are needed to average out the background activity completely. In practice the phase relations vary much more randomly from trial tot trial, and many more trials are needed for sufficient reduction of the background activity (as a rule of thumb, n trials reduce the background activity by $\sqrt{n}$).



Trial 1 contains event-related brain potential (ERP)+background activity 1. Trial 2 contains ERP+background activity 2 (counterphase, as illustrated in the combined plot in the lower right panel). The average is point by point and reveals the exact ERP.

Box 2 Multichannel magnetoencephalogram (MEG) and magnetic resonance imaging (MRI)-constrained sources

During recent years, the instrumentation of MEG devices has been developed and over 300 channel whole-head devices have been built. Especially these devices can be used to compute the distribution of cerebral activity accurately as a function of time. MEG's unique combination of characteristics include its non-invasiveness, simple and quick procedures, good accuracy in locating sources, and excellent time resolution. MRI-constrained MEG-source modeling helps in localization of the activation of specific cortical structures.



The figure shows group statistical parametric maps (SPM) of the eyes closed vs. eyes open contrasts with and without lorazepam administration recorded with MEG in the medial cortical surfaces. The parieto-occipital α-activity, which is evident in the placebo condition, is strongly attenuated by lorazepam. Abbreviations: CS, calcarine sulcus; POS, parieto-occipital sulcus. Adapted from Ahveninen *et al.* (2007).

TABLE 1 Overview of ERP/ERF Paradigms

Paradigm	Global function tested	Global anatomy	Use of MEG?
P50 suppression	Inhibition ('gating')	Sensory cortex, influence by top-down signal	Yes (not yet in psychopharmacology)
LDAEP	Inhibition of response to excessively intense stimulation	Sensory cortex	Yes
MMN	Bottom-up detection of change	Sensory cortex+frontal component	Yes
Selection potentials	Top-down modulated feature processing	Sensory cortex+frontal component	No
P300	Attention to relevant or salient events, memory updating	Temporal/frontal parietal/posterior cingulate cortex	No
Mental chronometry (AFM-ERP)	Mental chronometry; structure of information processing	See P300; motor cortex	No
Inhibitory control (stop task)	Inhibition of ongoing motor preparation	Sensory motor connections; (modulated by) superior and inferior frontal inhibition mechanisms)	Hardly
Conflict monitoring	Detection of conflicting response tendencies, response errors, negative reinforcement	Anterior cingulate cortex	No

Abbreviations: AFM, additive factor method; ERF, event-related magnetic field; ERP, event-related potential; LDAEP, loudness-dependent auditory evoked potential; MEG, magnetoencephalogram; MMN, mismatch negativity.

Box 3 Pitfalls in psychopharmacology

There are many ways to obscure, bias, or contaminate drug effects on behaviour and brain function. In this respect 'electropsychopharmacology' is not different from psychopharmacology. Here some potentials pitfalls are mentioned that are relevant to the remainder of the text.

Practice effects. Psychopharmacological research often employs within-subject crossover designs. Depending on the number of substances and dosages the number of repeated measurements (drug-/dosage-condition sessions) can grow substantially. This may yield practice effects that may confound the drug effects of interest. One approach to this problem was presented by Shelley *et al* (1991b). These authors demonstrated that over 6 weekly repeated sessions, an attention-related brain potential decreased especially from the first to the second session. Consequently, a subsequent psychopharmacological application of their design included an initial, additional placebo condition that preceded all conditions of the psychopharmacological design (including the 'true' placebo condition). The initial placebo condition served merely to wash out the practice effect and was not included in the data analysis (see section on 'Top-down selective attention'). Obviously, such special adjustments should be supplemented by appropriate counter-balancing of the drug conditions of interest across participants.

Room for change. Floor effects can obscure drug effects. Administering agonists (eg, of dopamine) to healthy volunteers may not yield the expected effect because neurotransmitter function is already optimal under placebo conditions. In that case, to establish a relation between a neurotransmitter system and brain function, antagonists are better suited. For individuals with suboptimal brain function (eg, patients or deprived smokers), agonists may at times be an appropriate choice. In addition, there are numerous reports on healthy individuals with a low baseline score for a certain function that respond favourable to agonistic manipulation, whereas individuals with high-baseline scores do not (de Wit *et al*, 2002; Mehta *et al*, 2000).

Limited dose range. The present review contains many examples of single-dose studies, which may fail to uncover the full range of possible effects of a substance. This should always be kept in mind when interpreting the results of such studies. One way to accommodate the possible restricted effect range is to use single dosages for which effects on cognition or brain function have been established in previous studies.

Specificity of effects. Drug effects may reflect global sedation or activation, rather than the specific neurotransmitter-function modulation they were aimed at. For example, anti-cholinergics reduce memory function and memory-related event-related brain potentials, but this may also be an indirect effect of their sedating quality. One approach to this problem is to include an additional control condition with another sedating substance that however targets a different neurotransmitter system that is not implicated in memory function (see discussion of the Curran *et al* (1998) study in the section on P300).

Box 4 Human electrophysiology as indices of a 'unified brain theory'?

In its attempt to provide a comprehensive overview of 'electropsychopharmocology', the present review may at times appear broad and unfocussed. However, the various electrocortical markers that are discussed all fit quite well in a 'unified brain theory' (UBT) framework (Friston, 2010). Briefly, UBT postulates that the brain continuously strives to reduce 'surprise'. Surprise, or the inverse of positive value, results from 'prediction errors' given the representation of expected events (ie, the prediction) and the actual event as it happens. To reduce prediction errors, the brain continuously attempts to increase 'precision' of the prediction, by selectively adjusting synaptic gains through top-down or more local feedback signals. According to UBT, this limited set of principles describes all brain function in widely different domains, ranging from sensory processing to action selection, and as implemented in a multitude of local or more global anatomical connections, that utilize a similar multitude of different neurochemical messengers.

For example, referring to Table 1, P50 suppression is the result of increased precision based on an immediately preceding experience. MMN is a typical prediction-error signal instrumental in increasing precision (Garrido *et al*, 2009). Selection potentials are the result of increased precision in the sense of selective adjustment of synaptic gain in some pathways over others. Finally, conflict-monitoring potentials may be viewed as pre-eminently reflecting surprise or negative value, resulting from insufficient precision (conflicting response tendencies), or from prediction errors (performance errors or negative feedback).

EXOGENOUS POTENTIALS: GATING AND LOUDNESS-DEPENDENCY

P50 SUPPRESSION

P50 suppression refers to a simple contextual effect: repetition, after 500 ms, of one auditory stimulus results in a smaller auditory evoked potential to that stimulus; this attenuation is visible as early as 50 ms after the stimulus, as a reduced positive deflection over the auditory cortex. Accounts of P50 suppression emphasize top-down influences, but a bottom-up, intrinsic auditory-cortex mechanism cannot be ruled out. The milestone study by Knight

et al (1999) convincingly showed that P50 is actually larger for patients with lateral prefrontal lesions, not different for parietal lesions, and smaller for temporal lesions. This can only be understood by assuming inhibitory signals from frontal to auditory cortex, which would suppress P50 especially with numerous repetition of the same, utterly neutral auditory stimulus. Electrical source localization studies have identified a superior frontal response to the first (conditioning) stimulus, in addition to auditory cortex activation (Oranje *et al*, 2006a; Weisser *et al*, 2001); this superior frontal activation may embody an inhibitory signal to the auditory cortex, which may suppress the auditory cortex response to the second (test) stimulus. Such top-down signals may also be instrumental in the sensitivity of P50-like responses to voluntarily directed attention (Woldorff *et al*, 1993).

Dopamine. Deficient P50 suppression is thought to represent a deficiency in gating or filtering out stimuli that lack novelty, threat or other salience. Such a deficiency may induce overload and may be central to especially symptoms of schizophrenia. Indeed, schizophrenic patients exhibit reduced P50 supression (as do heavy marihuana users; Patrick *et al*, 1999), although the robustness of this effect depends to some extent on the exact experimental parameters (de Wilde *et al*, 2007). Conspicuously, typical antidopaminergic (antipsychotic) 2–4 weeks medication does not alter this (Adler *et al*, 1990), arguing against a straightforward dopaminergic mechanism for the reduced P50 suppression in patients. In healthy volunteers, P50 suppression was affected by neither the dopamine precursor L-dopa (300 mg), nor the dopamine-2 agonist bromocriptine (1.25 mg; Oranje *et al*, 2004). In another study with healthy volunteers, acute tyrosine/phenylanaline depletion (ATPD), intended to reduce dopamine levels, did also not affect P50 suppression (Mann *et al*, 2007). These nil effects are inconsistent with a straightforward dopaminergic (D2) explanation of deficient P50 suppression. In an older study, acute treatment with 2 mg haloperidol (a typical antidopaminergic antipsychotic) in healthy volunteers treated with ketamine (0.3 mg, i.v.) resulted in disrupted P50 suppression (Oranje *et al*, 2002). Reduction of P50 suppression was also found for amphetamine, which promotes synaptic dopamine and (NE), with an acute dosage of 0.3 mg/kg in healthy volunteers (Light *et al*, 1999).

Given the absent or even negative relation between dopamine and P50 suppression in the other studies, the amphetamine effect is perhaps best understood in terms of a specific noradrenergic mechanism in P50 suppression (see also below). On the other hand, numerous studies have shown that cognitive effects of 1.25 mg bromocriptine depend on baseline individual characteristics. The balance between reward and punishment sensitivity is different for individuals with low *vs* those with high baseline striatal DA levels, and so is the effect of bromocriptine (Cools *et al*, 2009), and acute 1.25 bromocriptine benefits task performance in individuals with a low short-memory span, but reduces it in high-span individuals (Gibbs and D'Esposito, 2005; Kimberg *et al*, 1997). The mechanism underlying these differences in responsivity may involve highly sensitive postsynaptic D2 receptors in low-dopamine/low-span individuals, combined with more pronounced presynaptic D2 effects in high-dopamine/high-span individuals (Cools *et al*, 2009). This dependence of dopaminergic effects on individual differences should be addressed for P50 suppression as well, before definitely concluding that dopamine has no role in the P50 suppression mechanisms.

In contrast to the absent effects of classical antipsychotics, 1-month treatment with the atypical antipsychotic clozapine does restore P50 suppression in the majority of schizophrenic patients to normal values (see Figure 2), along with superior improvement on (brief) psychiatric rating scales (Nagamoto *et al*, 1996). This may be related to clozapine's antagonistic actions on 5-HT-2/3 and D4 receptors, rather than the D2 receptors that are antagonized by typical antipsychotics.

Serotonin. Consistent with a role of 5-HT-2 receptors in the effects of clozapine, a reduced P50 suppression has been reported for ayahuasca, which contains the 5-HT-2a/2c agonist *N*,*N*-dimethyltryptamine (Riba *et al*, 2002). Rather inconsistently however, acute tryptophane depletion (ATD; reducing serotonin synthesis in the brain) in healthy volunteers reduced P50 suppression (whereas ATPD did not; Mann *et al*, 2007). It should be noted that the reduction of P50 suppression by ATD was pronounced but not statistically significant, suggesting substantial individual differences in the exact effects of ATD; this in turn may reflect individual differences in the distribution of diverse 5-HT receptors. Non-specific modulation of serotonin levels

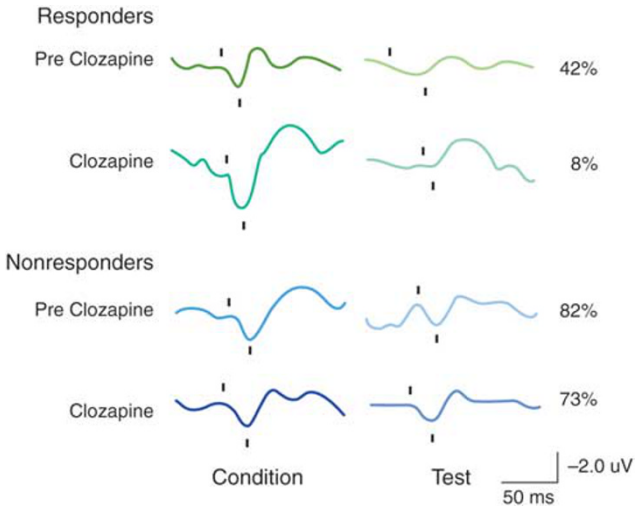


Figure 2. Auditory P50 recorded from vertex, averages for six clinical responders and three non-responders. The P50 is indicated by the tics below the waveforms. Stimulus onset at the beginning of the trace. The lower the percentage, the more P50 suppression after the second stimulus, relative to the P50 to the first stimulus. Adapted from (Nagamoto *et al*, 1996).

by using an acute selective serotonin reuptake inhibitor (SSRI; escitalopram 10 mg) did not affect P50 suppression in healthy volunteers (Jensen *et al*, 2008). A further clue is that the P50-suppression enhancing effects of clozapine were not observed for either olanzapine, risperidone, or quetiapine (Adler *et al*, 2004). One possibility raised by the latter authors is that clozapine's interactions with the 5-HT3 receptor are critical. Consistently, acute administration of 16 mg ondansetron, a 5-HT-3 blocker, augmented P50 suppression in typically medicated schizophrenic patients (Adler *et al*, 2005).

Acetylcholine (ACh). Clozapine's interactions with the 5-HT3 receptor have also been linked to the enhancement of α-7-nicotinergically mediated ACh transmission (Adler *et al*, 2004). Specifically, clozapine blocks 5-HT-3-mediated inhibition of prefrontal neurons in rats (Kinon and Lieberman, 1996). It is possible that these prefrontal neurons are involved in P50 suppression through cholinergically mediated signals; there is *in vitro* evidence that cortical ACh release is inhibited by 5-HT-3 receptor activity, with a mediating role for $GABA_A$ receptors (Rámirez *et al*, 1996). Direct augmentation of nicotine receptor activity also restores P50 suppression in schizophrenic patients (Adler *et al*, 1993), and recently the partial α-7 nicotine agonist DMBX-A (150 mg, 4-weeks regime) reduced hippocampal activation in patients during smooth pursuit (Tregellas *et al*, 2009).

Norepinephrine. Another possibility refers to clozapine's antagonistic affinity for noradrenergic α-1-receptors (Kinon and Lieberman, 1996), which seems to be less obvious for the other atypical antipsychotics. As mentioned above, acute effects of amphetamine may also be consistent with a noradrenergic mechanism. Furthermore, yohimbine, an α-2 antagonist that effectively stimulates noradrenergic transmission, reduces P50 suppression acutely in healthy volunteers in a dosage of 0.4 mg/kg (Adler *et al*, 1994). Also, 50 mg imipramine acutely disrupted P50 suppression in healthy volunteers, consistent with a role for augmented NE availability (Hammer *et al*, 2007). In sum, modulating NE transmission directly or indirectly has revealed a negative relation with P50 suppression.

P50 suppression constitutes an interesting paradigm, especially if one accepts the involvement of prefrontal mechanisms in producing the suppression. Malfunctioning of this system could result in either overload of stimulation resulting in misattribution as to sources of this information (positive symptoms), or in excessive blunting or saturation of the system, which may be related more to negative symptoms. It is in this respect telling that only a substance that remedies both negative and positive clinical symptoms also restores impaired P50 suppression in patients. As discussed, clozapine constitutes one handle to modulate a delicate network in which cholinergic transmission must overcome the inhibitory effects of 5-HT-3 and perhaps -2 activity, as well as of $GABA_A$, and in addition, the opposing effects of NE transmission.

The significance of the P50 suppression paradigm could be enhanced by a better understanding of brain networks, possibly external to auditory cortex, that mediate 'active inhibition' as a consequence of repeated stimulus interpretation. These networks could involve (superior) prefrontal neurons that use cholinergic signaling. That is, activation in such a network should increase with increasing P50 suppression. An indirect approach to this issue used a comparison between the fMRI–BOLD response to nine click repetitions, separated by 500 ms, with that to a single click, in a group of schizophrenic patients as well as in controls (Tregellas *et al*, 2007). EEG P50 suppression was reduced in the patients but, contrary to expectations, the BOLD response in a network consisting of dorsolateral prefrontal cortex, hippocampus, and thalamus, was increased. Still more unexpectedly, in controls as well as in patients, activation in this network correlated negatively with P50 suppression. Possibly, the low temporal resolution and the indirectness of fMRI limit its usefulness in understanding P50 suppression. An alternative approach would focus on the frontal electrical sources discussed above, and investigate whether the strength of the frontal response to the conditioning stimulus could predict the suppression of the P50 to the test stimulus.

A final point concerns the possibility to address other responses of auditory cortex, such as the negative potential following P50 in time, 'N1'. Usually N1 has a better signal-to-noise ratio, and like P50 it is very sensitive to stimulus repetition. For example, in the study by Mann *et al* (2007), N1 at about 100-ms latency seemed to exhibit 'N1 suppression' in placebo; this suppression seemed absent under ATPD but present again with combined ATPD and ATD, and seemed actually larger with ATD alone. Deficient modulation from prefrontal cortex of N1 has also been implicated in deficient inhibitory motor-control as manifest in, eg, attention-deficit hyperactivity disorder (ADHD; see discussion of motor inhibition below).

Loudness-Dependent Auditory Evoked Potential

The classical auditory evoked potential consists of two prominent peaks, N1 (100-ms latency) and P2 (200-ms latency). The strength of this N1-P2 complex increases with stimulus intensity, but levels off with very high intensities. This is thought to reflect a regulatory inhibitory mechanism that protects the system from over-stimulation.

Serotonin. This loudness dependence of the auditory evoked potential (LDAEP) has been related to the activity of serotoninergic neurons in the primary auditory cortex, with low serotoninergic activity leading to a high intensity dependence and vice versa (Hegerl and Juckel, 1993; Hegerl *et al*, 2001; Juckel *et al*, 1997; Juckel *et al*, 1999). The most convincing evidence for a direct relationship between serotoninergic function and low LDAEP has come from

animal studies. For example, Juckel *et al* (1999) reported differential effects of microinjection of a 5-HT_{1A} agonist and a 5-HT_{1A} antagonist into the dorsal raphe nucleus on the intensity dependence of auditory evoked potentials recorded epidurally from the primary and secondary auditory cortex in behaving cats. Futhermore, Wutzler *et al*, 2008 showed that the increase of serotonin levels after citalopram application in rats was significantly related to a decrease of LDAEP of the N1 component.

Evidence in humans for the relation between serotonin and LDAEP is inconsistent. Proitti-Cecchini *et al* (1997) showed that a single-dose of zolmitriptan, a 5-$HT_{1B/1D}$ agonist, increased the intensity dependence of auditory N1/P2 amplitudes, whereas fenfluramine decreased it. Studies with single doses of SSRIs have yielded inconsistent results; some found a decreased slope of the LDAEP (ie, weaker LDAEP) after citalopram (Nathan *et al*, 2006; Segrave *et al*, 2006; see Figure 3), others did not find any effects after citalopram, escitalopram or sertraline administration (Guille *et al*, 2008; Uhl *et al*, 2006).

One way to establish a relationship between serotonergic function and LDAEP is utilization of ATD, which causes a rapid decrease of serotonin synthesis in the brain (Nishizawa *et al*, 1997). As in the case of SSRI challenges, studies with ATD are also inconsistent in relating serotoninergic function to intensity dependence of N1/P2 components. In one study, the slope of the N1/P2 intensity-dependence function was decreased after ATD (Dierks *et al*, 1999). A similar result was reported by Kähkönen *et al* (2002) with MEG; in this study, the effect was significant only for the contralaterally stimulated ear (Kähkönen *et al*, 2002). However, in other studies ATD did not modulate the LDAEP (Debener *et al*, 2002; Massey *et al*, 2004; Norra *et al*, 2008; O'Neill *et al*, 2008).

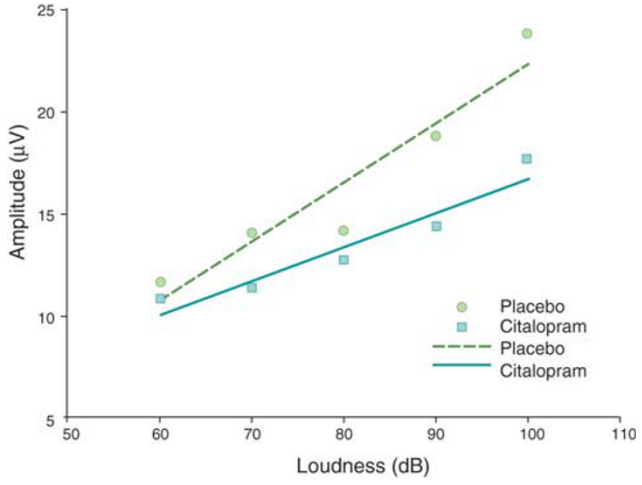


Figure 3. The amplitude of the auditory evoked potential increases with loudness, and this effect is reduced by acute citalopram. Adapted from Nathan *et al* (2006).

Dopamine. It has been suggested that the LDAEP is not only influenced by serotonin but also by dopaminergic neurotransmission (Juckel *et al*, 1997). Although the dopamine receptor agonists pergolide (D1/D2) and bromocriptine (D2) had no effect on the LDAEP, dopamine transporter availabilities correlate with LDAEP (Juckel *et al*, 2008), indicating that synaptic dopamine levels may modulate LDAEP. However, dopamine depletion did not modulate LDAEP (O'Neill *et al*, 2008).

Glutamate. O'Neill *et al* (2007) also studied the effects of high-dose glycine, a modulator of NMDA receptors on LDAEP. They showed a weaker LDAEP (a pronounced decrease in the slope of the N1/P2 with increasing tone loudness) after glycine administration. The authors concluded that glycine may have an inhibitory effect in the cortex, possibly via activation of NMDA receptors on GABA interneurons or inhibitory glycine receptors.

Summarising the findings, direct pharmacological manipulations in healthy humans do not consistently confirm that low sertoninergic activity leads to a high intensity dependence of N1/P2 or vice versa. However, long-term administration of serotonin-related agents may have different effects in healthy subjects on LDAEPs. Other neurotransmitter systems, such as glutamate/NMDA, may also modulate the slope of N1/P2 for intensity-dependence function.

BOTTOM-UP AND TOP-DOWN ATTENTION

Bottom-Up: Change Detection

Mismatch negativity (MMN) and its magnetic counterpart (MMN*m*) are auditory evoked responses, which are time-locked to changes in the EEG or MEG to auditory stimuli. MMN and MMN*m*, peaking at about 150–200 ms after stimulus onset, are elicited when infrequent deviant sounds are embedded among frequent standard tones, but also in response to any violation of auditory regularity (see Figure 4). MMN is believed to have several overlapping

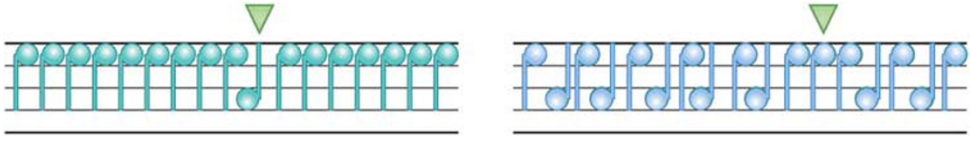


Figure 4. Two ways to elicit MMN in auditory cortex. Each note is a stimulus. Stimuli are presented in a sequence, spaced by a (fraction of) a second or so. Arrows indicate the stimuli that elicit MMN, relative to the other stimuli. MMN develops at about 100 ms after stimulus onset. In the left panel it is elicited by simple physical deviance. In the right panel it is elicited by the violation of regular repetition.

subcomponents that reflect different phases of detection and orienting to novel stimulus features (Näätänen *et al*, 2007). The detection of a sound change or other regularity violation is proposed to elicit a temporal MMN subcomponent, which can be detected by both MEG and EEG, because it has a tangentially located source in the auditory cortex (Näätänen, 1992). The subsequent initiation of an involuntary attention shift to this regularity violation is probably reflected by a later frontal MMN subcomponent (Näätänen, 1992, Rinne *et al*, 2000). The frontal subcomponent might be radially oriented, judging from the fact that MEG does not detect it (Rinne *et al*, 2000). Because of the different orientation of sources involved in the attentional processing of auditory stimuli, the combination of MEG with EEG makes it possible to differentiate neural events related to involuntary attention. The MMN has been used extensively as a model in human psychopharmacology (see Tables 2 and 3). The various applications are discussed right below, sorted with respect to neurotransmitter systems.

Glutamate. In monkeys, MMN generation has been linked to the NMDA receptor subtype of glutamate neurotransmission (Javitt *et al*, 1996). It was shown that a sub-anesthetic dose of ketamine, an NMDA-receptor antagonist, specifically diminishes MMN amplitude to frequency and duration changes in humans, but does not alter other sensory ERPs of similar latency (Umbricht *et al*, 2000a). Further, Kreitschmann-Andermahr *et al* (2001) demonstrated that ketamine increased the MMN*m* latency and decreased the dipole moment of the MMN*m* without affecting the latency and dipole moment of the N1 m, suggesting that the supratemporal MMN component is specifically affected. However, this study was not placebo controlled and therefore the role of NMDA receptors in supratemporal MMN regulation in humans remains speculative. Furthermore, Umbricht *et al* (2002a) analyzed the correlations between MMN recorded before ketamine administration and after that. Smaller MMNs to both frequency and duration deviants were significantly correlated with stronger ketamine effects. Moreover, glycine, which augments NMDA receptor function via stimulation of the glycine modulatory site of the NMDA receptor, significantly attenuated the MMN amplitude at frontal sites, but not at the mastoid sites (Leung *et al*, 2008). Although no source modeling was used, it is possible that glycine has different effects on supratemporal *vs* frontal MMN generators, which may explain the unexpected findings. Korostenskaja *et al* (2007) showed that the NMDA antagonist memantine increased MMN amplitude without otherwise changing ERP components. This effect of memantine was observed only in EEG but not in MEG, suggesting that memantine has effects on frontal but not temporal MMN components.

GABA. Lorazepam decreased MMN*m* source activity to frequency, duration and intensity changes (Rosburg *et al*, 2004). Propofol, which is used as an anesthetic, also decreased MMN (Koelsch *et al*, 2006). The role of GABA in MMN modulation was confirmed by a study in which alcohol reduced MMN*m* amplitudes (Jääskeläinen *et al*, 1996; Jääskeläinen *et al*, 1995, Kähkönen *et al*, 2005a). As the MMN reduction was found in MEG and EEG, alcohol can decrease both temporal and frontal MMN components. Interestingly, acute alcohol (0.05% BAC) also reduced the visual counterpart of MMN, or the 'rareness-related negativity' (Kenemans *et al*, 2010). Flumazenil did not change MMN when an active paradigm was used (Smolnik *et al*, 1998).

Serotonin. Studies on pre-attentive auditory change detection have indicated that ATD increased MMN amplitudes, and shortened MMN*m* latencies, so it appears to affect both the temporal and the frontal MMN components (Kähkönen *et al*, 2005a, b); however, source modeling of EEG data is needed to confirm these findings. The serotonin reuptake inhibitor escitalopram increased MMN amplitude (Oranje *et al*, 2008; Wienberg *et al*, 2009). The specific mechanisms remain to be established as psilocybin and dimithyltryptamine, agonists of serotonin 5-HT2a-receptors, have yielded opposite effects (Heekeren *et al*, 2008; Umbricht *et al*, 2002a, b).

Acetylcholine. Scopolamine reduced MMN*m* amplitudes in response to frequency, but not to duration change (Pekkonen *et al*, 2001). Nicotine decreased MMN latencies and increased amplitudes (Baldeweg *et al*, 2006; Inami *et al*, 2005), but recently Knott and colleagues were not able to confirm these findings (Knott *et al*, in press). This may be related to a different route of nicotine administration or paradigm used.

Dopamine. A number of studies with healthy volunteers have evidenced a weak association between dopaminergic activity and MMN generation. First, Hansenne *et al* (2003) indirectly demonstrated the lack of implication of DA and NA activities, as assessed by the growth hormone response to apomorphine and clonidine, in the generation or modulation of MMN. Moreover, a study by Leung *et al* (2007) failed to show any significant effect of dopamine D2 and D1/D2 receptor stimulants bromocriptine and pergolide on MMN generation. Korostenskaja *et al* (2008) demonstrated no significant effect of methylphenidate, working through DA and noradrenaline systems, on MMN. Finally, tyrosine/phenylalanine depletion did not affect the MMN latencies or amplitudes (Leung *et al*, 2010). Haloperidol, a dopamine-2-receptor antagonist, shortened MMN*m* latencies to frequency change whereas no effects on amplitudes or latencies to duration change were observed (Pekkonen *et al*, 2002). As the only study to contradict the idea that dopamine is not involved in MMM generation, Kähkönen *et al* (2001) showed that, in a dichotic listening task, haloperidol, increased MMN amplitudes in the EEG, but not in the MEG, suggesting some involvement of DA in frontal-MMN generation.

In summary, main excitatory and inhibitory neurotransmitters systems, glutamate and GABA, respectively, are

TABLE 2 Drug Effects on Mismatch Negativity (MMN; EEG)

Drug	Neuro transmitter system	MMN paradigm	Latency	Amplitude	Comments	Reference
Escitalopram	Serotonin	Frequency change	0	↑		Wienberg *et al* (2010)
Nicotine	Acetylcholine	Frequency change	0	0	Distraction task; nicotine gum	Knott *et al* (in press)
Tryptophan depletion	Serotonin	Duration change	0	0		Leung *et al* (2010)
Tyrosine/phenylalanine depletion	Dopamine	Duration change	0	0		Leung *et al* (2010)
Ketamine/ dimethyltryptamine	Glutamate/serotonin	Duration/ frequency change		Both drugs decreased MMN		Heekeren *et al* (2008)
Methylphenidate	Dopamine/noradrenaline	Duration/ frequency change	0	0		Korostenskaja *et al* (2008)
Escitalopram	Serotonin	Frequency change	0	↑		Oranje *et al* (2008)
Glycine	Glutamate	Duration change	0	↓		Leung *et al* (2008)
Cannabis	Cannabinoid	Frequency change		↑	No effect from delta(9)-THC	Juckel *et al* (2007)
Bromocriptine	Dopamine	Duration change	0	0		Leung *et al* (2008)
Pergolide	Dopamine	Duration change	0	0		Leung *et al* (2008)
Memantine	Glutamate	Duration/ frequency change	0	↑		Korostenskaja *et al* (2007)
Propofol	GABAa	Frequency/timbre/ omission change	↓			Koelsch *et al* (2006)
Nicotine	Acetylcholine	Duration change		↑	Roving paradigm	Baldeweg *et al* (2006)
Nicotine	Acetylcholine	Frequency change	↓	0	Transdermal administration	Inami *et al* (2005)
Ethyl alcohol	GABA	Frequency change	0	↓		Kähkönen *et al* (2005a,b)
Propofol	GABA	Frequency change		↓		Heinke *et al* (2004)
Psilocybin	Serotonin	Duration/ frequency change	0	0		Umbricht *et al* (2002b)
Apomorphine	Dopamine/noradrenaline	Duration change	0	0	Correlations with growth hormone responses and MMN	Hansenne *et al* (2003)
Clonidine	Dopamine/noradrenaline	Duration change		0	Correlations with growth hormone responses and MMN	Hansenne *et al* (2003)
Haloperidol	Dopamine	Frequency change	0	0	Active paradigm	Kähkönen *et al* (2002)
Haloperidol	Dopamine	Frequency change	0	↑	Dichotic listening task	Kähkönen *et al* (2001)
Ketamine	Glutamate	Duration/ frequency change	↓	In both conditions MMN was decreased		Umbricht *et al* (2000)
Ketamine	Glutamate	Frequency change	0	0	Dichotic listening task	Oranje *et al* (2000)
Nitrous oxide	Glutamate	Frequency change		↓	Dichotic listening task	Pang and Fowler (1999)
Vasopressin	Antidiuretic hormone	Frequency change		↑		Born *et al* (1998)
Flumazenil	GABA	Frequency change	0	0	Dichotic listening task	Smolnik *et al* (1998)
Ethyl alcohol	GABA	Duration change	0	↓		Jääskeläinen *et al* (1996)
Chlorpheniramine	Histamine	Frequency change		↓	Effect was found in the ending phase of MMN	Serra *et al* (1996)
Ethyl alcohol	GABA	Frequency change	0	↓		Jääskeläinen *et al* (1995)
ACTH 4–10	Corticotropin hormone	Frequency change	0	0	Dichotic listening task	Born *et al* (1990)

Abbreviations: EEG, electroencephalogram; MMN, mismatch negativity.
Note: arrow indicates increase (↑) or decrease (↓), 0 indicates no effect.

involved in MMN generation. In addition to these, at least serotonin and ACh may modulate MMN, possibly indirectly. In the future, combined neurotransmitter studies (eg, glutamate and serotonin) are needed to establish more exactly the mechanisms of MMN regulation. Combined MEG and EEG studies with novel multifeature MMN paradigms (Pakarinen *et al*, 2007) may help in understanding the role of different MMN sources in MMN

TABLE 3 Drug Effects on Mismatch Field

Drug	Neurotransmitter system	MMN paradigm	Latency	Amplitude	Comments	Reference
Methylphenidate	Dopamine/ noradrenaline	Duration/ frequency change	0	0	Combined MEG/EEG	Korostenskaja *et al* (2008)
Memantine	Glutamate	Duration/ frequency change	0	0	Combined MEG/EEG	Korostenskaja *et al* (2007)
Tryptophan depletion	Serotonin	Duration/ frequency change	↑	Combined MEG/ EEG		Kähkönen *et al* (2005a, b)
Tryptophan depletion	Serotonin	Frequency change			Discirimination task	Ahveninen *et al* (2002)
Ethyl alcohol	GABA	Frequency change	0	↓	Combined MEG/EEG	Kähkönen *et al* (2005a, b)
Lorazepam	GABA	Duration/ frequency/intensity change	↓	Effect was found in all conditions		Rosburg *et al* (2004)
Haloperidol	Dopamine	Frequency change	0	0	Combined MEG/EEG; active paradigm	Kähkönen *et al* (2002)
Haloperdol	Dopamine	Duration/ frequency change	↓	0	Combined MEG/EEG; passive paradigm	Pekkonen *et al* (2002)
Ketamine	Glutamate	Duration/ frequency/intensity change	↓	↓	Pre-post design; effect was not found only in intensity change condition	Kreitschmann-Andermahr *et al* (2001)
Scopolamine	Acetylcholine	Duration/ frequency change	↓		Effect was found only in frequency change condition	Pekkonen *et al* (2001)

Abbreviations: EEG, electroencephalogram; MEG, magnetoencephalogram; MMN, mismatch negativity.
Note: arrow indicates increase(↑) or decrease (↓), 0 indicates no effect.

regulation. These studies also help in understanding the mechanisms underlying MMN changes observed in clinical conditions, such as in schizophrenia. Since the first report of the abnormal MMN in schizophrenia (Shelley *et al*, 1991a), there have been at least 40 additional studies on the MMN in schizophrenia. The results of a meta-analysis indicate that the MMN deficits are robust in patients with chronic schizophrenia (Umbricht and Krljes, 2005). As MMN can be measured even in animals such as the rat (Astikainen *et al*, 2006, Tikhonravov *et al*, 2008) and the mouse (Umbricht *et al*, 2005), use of MMN should facilitate the selection of potential drugs in the preclinical phase before testing them in healthy human subjects and in schizophrenia patients.

Top-Down: Selective Attention

Selective attention refers to the focussing, and maintaining that focus, on a limited part of the available information. A common methodology is to present participants with streams of stimuli, which differ in one or two features. Attention has to be selectively directed only to stimuli with one specific feature (eg, attend to the blue patterns, ignore all the yellow ones; attend to tones in the left, ignore those in the right ear). ERP/Fs are recorded to attended (relevant) and to ignored (irrelevant) stimuli, and the difference between these ERP/Fs indexes the effect of the attentional manipulation. Such difference or 'selection potentials' usually take the form of time-varying potential distributions, which reflect the sequential selective activation of different cortical areas, eg, Kenemans *et al* (2002) found that selective attention to specific visual spatial frequencies caused a sequence of selective activations in relatively dorsal–posterior cortex, followed by relatively ventral–posterior, followed by relatively medial–frontal cortex, all within an interval of 100–300 ms after the stimulus. The auditory counterpart of these visual selection potentials is the so-called 'processing negativity'.

NE and dopamine. In a seminal study, Shelley *et al* (1997) investigated the effects of net norepinephrinergic (clonidine 1.5 μg/kg i.v.) and dopaminergic antagonism (droperidol 15 μg/kg i.v.) on the processing negativity (between 200 and 400 ms poststimulus). Both manipulations distorted the processing negativity, but in rather different ways. Droperidol completely annihilated the processing negativity for relevant *vs* irrelevant pitches; in contrast, clonidine resulted in pronounced processing negativites for pitch as presented on both relevant and irrelevant locations (ie, ear of presentation). Under saline, processing negativity for relevant *vs* irrelevant pitches was observed only for relevant locations. Jonkman *et al* (1997a, b) found processing negativity (200–400 ms after the stimulus) to be reduced in children with ADHD compared with healthy controls. Acute methylphenidate (15 mg) partly but significantly restored the processing negativity in these ADHD children (a similar result was found for the visual medial–frontal selection potential; Jonkman *et al*, 1997a, b). Later source analysis revealed that the cortical area's involved in producing the processing negativity were slightly different

under methylphenidate from those in control children (although in both cases in the vicinity of auditory cortex; Kemner *et al*, 2004). In healthy volunteers, auditory processing negativity was not affected by acute 1.25 mg bromocriptine, nor by 300 mg L-Dopa (Oranje *et al*, 2006a, b). This may suggest that the methylphenidate effects in ADHD are norepinephrinergically mediated. However, the results from the Shelley *et al* (1997) study discussed above did reveal an effect of a dopaminergic antagonist. An alternative interpretation therefore is that in healthy volunteers there is not much room for improvement when using agonists, and the pharmacology of selective processing is better investigated using antagonists.

Only a few other studies are available that address pharmacological effects on selection potentials. Visual selection potentials have been found to be enhanced by caffeine, depending on task demands (Kenemans and Lorist, 1995; Lorist *et al*, 1994b), and to be insensitive to CBR1 agonists (Böcker *et al*, 2010). One interesting manipulation would be that of cholinergic substances, especially when contrasted with noradrenergic ones. This is especially relevant when the process of attentional modulation (as reflected in selection potentials) is experimentally separated from that of 'attentional control', the brain mechanism that directs attention to specific information, by creating a 'bias' among cortical representations for relevant *vs* irrelevant features. For attention to specific locations in visual space, an additional mechanism has been described, commonly referred to as 'disengagement'. Disengagement is a brain mechanism instrumental to shifting attention in space to a previously ignored location. In visual–spatial cuing tasks, a first stimulus cue indicates the most likely location of the subsequent target. The location of the subsequent target then turns out to be either validly or invalidly cued. Reaction times (RTs) in the latter condition are slower: The validity effect. The validity effect then is thought to increase with a stronger effect of attentional control (in response to the cue), but to be reduced again with a more effective disengagement response (in response to an invalidly, as opposed to a validly cued target).

An important theory states that attentional control is based in a dorsal parietofrontal network and depends on neurotransmission involving ACh; disengagement, based in the temporal–parietal junction would depend on neurotransmission involving NE (Corbetta and Shulman, 2002; Marrocco, 1998). However, the relevant empirical behavioral evidence in this case presents a seemingly contradictory picture. Substances with sedating effects degrade task performance in general. Some sedating substances (clonidine, droperidol) reduce the validity effect (Clark *et al*, 1989). On the other hand, stimulants (nicotine), which have general performance effects exactly opposite to sedators, also reduce the validity effect (Witte *et al*, 1997). Clonidine effectively reduces available synaptic NE, therefore antagonizes noradrenergic transmission. Nicotine mimics effects of ACh, therefore amplifies ACh transmission. Thus, two substances with opposing effects on general information processing have identical effects on selectivity of attention. We have previously proposed a solution of this apparent contradiction (Kenemans *et al*, 2005), resting on two assumptions: clonidine (NE reduction) mainly reduces attentional control, therefore reduces the validity effect; nicotine (ACh enhancement) mainly facilitates disengagement, therefore reduces the validity effect. For a true test for this hypothesis however, it is necessary to use separate ERP correlates for attentional control and disengagement, respectively, which have indeed been described, eg, cue-locked attention-directing negativity and positivity (van der Lubbe *et al*, 2006) and the late-positive deflection that is larger to invalid than to valid targets (Mangun and Hillyard, 1991). Such a late-positive deflection has indeed been reported to be enhanced by acute nicotine (2 mg Nicorette) in healthy volunteers (Meinke *et al*, 2006).

'ATTENTION' AND MEMORY UPDATING: P300

The P300 is a deflection in the ERP that peaks between 300 and 600 ms after the stimulus and is maximal over the medial–parietal region. It is elicited by events that are surprising or relevant, and preferably both (Figure 5). They may be surprising because they consist of an infrequent deviation from a monotonous background, and they may be relevant because of the subject's task. For example, a sequence of words contains an occasional word that differs in letter size, and this 'oddball' target has to be detected. Relative to the non-targets, the targets typically elicit a large P300 response. Such a P300 is generally considered to be a cortical correlate of attention being attracted to a salient event.

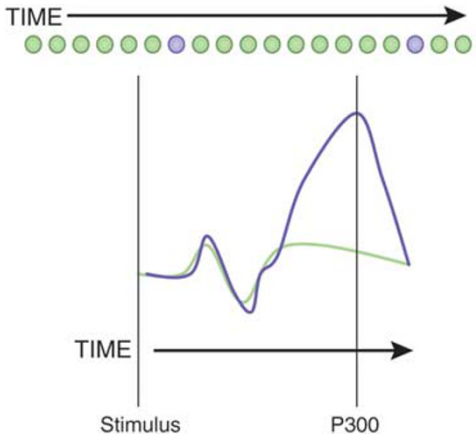


Figure 5. Typical P300 set-up and response. Averaging the event-related brain potentials to successive frequent green dots and infrequent purple dots yields the average signals in the corresponding colors. The P300 peak occurs some 300–500 ms after the stimulus, mainly over parietal areas. It is especially pronounced when the infrequent stimulus is a target for behavioural response.

Donchin and colleagues hypothesized that the process reflected in P300 concerns 'context updating': On the basis of salient, often novel information, certain memory traces are modified. In other words, an attention-related process would influence a memory-related process. Indeed, P300 was reported to be larger for word items that were later recalled *vs* that were not (Fabiani *et al*, 1986), and this phenomenon has been replicated many times. Later varieties included fMRI and TMS rather than ERP and revealed contributions from temporal cortex (fusiform and parahippocampal gyrus), as well as inferior frontal gyrus (Kohler *et al*, 2004; Wagner *et al*, 1998). Thus P300, or any other difference potential related to later retrieval ('Dm'), can be used to track processes of encoding during the initial exposure to information in relation to later retrieval.

A related phenomenon is the 'old/ new' effect, or 'retrieval positivity'. This refers to the phenomenon that during subsequent retrieval tests with a mixture of previously presented (old) items and new items, items that are recognized as 'old' elicit a larger positive ERP deflection than new items do (Rugg, 1995). This 'retrieval positivity' is even elicited by items that are incorrectly designated as old (Bentin *et al*, 1992). It has a latency of about 400 ms post-item and a scalp distribution that at least superficially resembles that of P300 or Dm (Besson and Kutas, 1993), suggesting at least partly overlapping intracranial generators, although sometimes a left hemisphere dominance is reported for verbal materials (McAllister-Williams *et al*, 2002). In general, it should be noted that there are substantial procedural differences in the various paradigms used tot elicit P300, which may interact with the effects of various drugs. However, a study that used two rather different P300 paradigms found similar patterns of drug effects in both versions (Curran *et al*, 1998; see below).

From these characteristics it can be inferred that P300 is to a large extent related to the anticipation of future events. Therefore, it can easily be dissociated from direct performance as affected by diverse manipulations, including drug interventions. Wester *et al* (2010) recently showed that while performance measures were affected by blood–alcohol concentrations of 0.05% and higher, P300 amplitude was already reduced with a BAC of 0.02%. Another dissociation was reported in a study by Van Laar *et al* (2002) on the effects of the tricyclic antidepressant amitriptyline (25 mg). Healthy volunteers had to search for visual targets in conditions that varied in short-term memory load and attentional-focussing demands. Performance (RTs, target-detection rates) was disrupted by amitriptyline as an acute single-dose effect, but this did not affect P300. After repeated dosages (50 + 25 mg daily) across 8 consecutive days, performance was no longer affected, relative to placebo, but P300 was significantly smaller (van Laar *et al*, 2002). The authors' interpretation is in terms of tolerance for histaminergic and/or adrenergic antagonism that affects performance, and cholinergic receptor antagonism more related to higher cognitive processes: The increase in P300 across the 8 days was only observed under placebo, not under amitryptiline.

Acetylcholine. Also implicating cholinergic factors in P300, Neuhaus *et al* (2006) reported reduced P300s in both current smokers (for about 20 years) and former smokers (about 12 years abstinence), relative to never smokers. This may point to a relatively strong disposition to indulge in smoking behavior in low-P300 individuals, perhaps to compensate low natural cholinergic transmission; or chronic smoking alters the cholinergic system and thereby P300 in an irreversible manner, perhaps through receptor desensitization. Also acute nicotinergic effects on P300 amplitude have been reported. A study into the effects of smoking a non-nicotine-yielding cigarette *vs* smoking a nicotine-yielding (1.1 mg) one reported faster RTs as well as larger P300 amplitudes to test probes in a memory scanning task (Houlihan *et al*, 2001). A multidose i.v. nicotine study by Lindgren *et al* (1999) found similar effects of nicotine on P300 amplitude and on RT (to infrequent oddball targets), although these effects were not significant. An older study had already reported a significant reduction in P300 amplitude by muscarinergic receptor antagonism (Curran *et al*, 1998).

In all, acute cholinergic effects on P300 do seem to be real, and therefore may also have been present in the study by Van Laar *et al* (2002; see above). One possibility is that amitriptyline yields combined cholinergic antagonism and norepinephrenergic agonism, which may have opposite effects on P300 (see below).

ACh vs *GABA and histamine.* A comprehensive analysis of the acute effects of scopolamine (muscarinergic antagonist, 0.6 mg s.c.), lorazepam (GABAergic agonist, 2 mg), and diphenhydramine (histamine-1 antagonist, 25 and 50 mg) was provided by Curran *et al* (1998). P300 was recorded in both oddball (see Figure 5) and old/new paradigms. The latter allowed for the assessment of memory effects, including the contribution of effects on both encoding and retrieval stages. Rather unexpectedly, drug effects on the retrieval positivity were not analyzed. The memory retention reductions were largest for lorazepam, somewhat smaller for scopolamine, and not significant for diphenhydramine. In both paradigms, the reducing effects of scopolamine on P300 were the largest, those of lorazepam somewhat smaller, and those of diphenhydramine negligible (see Figure 6). On objective and subjective measures of sedation, the effects of scopolamine, lorazepam, and diphenhydramine (50 mg) were comparable. This dissociating pattern of effects suggests interesting conclusions. First, sedation was observed equally for muscarinic–cholinergic and histaminergic (H1) antagonism, as well as GABAergic agonism, but the P300 and memory effects dissociated from sedation in that they were hardly affected by H1 antagonism. Second, P300 again turned out to be the measure most sensitive to muscarinic–cholinergic manipulation, whereas memory performance was most sensitive to GABAergic

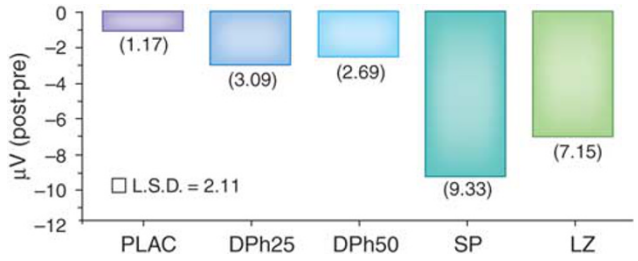


Figure 6. The difference between post- and pretreatment P300 for placebo (PLAC), diphenhydramine (DPh 25 and 50 mg), scopolamine (SP), and lorazepam (LZ). LSD is least significant difference: histograms differing by more than this are significantly different ($P < 0.05$; Curran *et al*, 1998).

agonism. This suggests that the encoding aspects of memory, as reflected in P300 especially during the oddball, are relatively specifically affected by cholinergic manipulation, whereas GABAergic agonism induces at least additional effects on retrieval. The lack of P300 effects of H1 antagonists are consistent with the lack of effect of tripolidine and terfenadine reported earlier (Swire *et al*, 1989). The reducing effects of a benzodiazepine are consistent with the reducing effects reported for triazolam (0.125 mg; Urata *et al*, 1996) and for oxazepam (20 and 40 mg; Van Leeuwen *et al*, 1994; Van Leeuwen *et al*, 1995).

NE and dopamine. Nieuwenhuis *et al* (2005) reviewed results from both both animal and human studies that convincingly indicate a stimulating contribution of the ascending noradrenergic locus–cereleus system in generating P300. Furthermore, P300 as the prototypical attentional response to relevant or salient stimuli has been found to be deficient in numerous psychopathologies, especially when catecolaminergic deficiencies may play a role. In children with ADHD, P300 is generally smaller, relative to controls, and augmented again by standard dosages of methylphenidate (Jonkman *et al*, 2000; Klorman, 1991; Seifert *et al*, 2003). In the Jonkman *et al* study two levels of task difficulty of the task were presented. ADHD children emitted smaller P300s especially in the harder condition, in which they failed to augment P300 as the controls did. Methylphenidate resulted in larger P300s for both levels of difficulty, but did not specifically enhance the P300 in the hard condition. This was interpreted as ADHD being characterized not by diminished capacity of attention, but by an inability to allocate it when the demands were higher. Methylphenidate only partly remedied this pattern, in that it increased general capacity, but not the response to task-specific demands. In later sections we will encounter more examples of how ERPs reveal specific neurocognitive deficits in ADHD that only partially map on the effects of methylphenidate.

Serotonin. Results for the serotoninergic modulation of P300 are mixed. The study by Van Laar *et al* mentioned above also included the SSRI paroxetine (30 mg) and the non-specific 5-HT2 antagonist nefazodone (200 mg) but did not find any effect. Consistent acute nil effects have also been reported for 15 mg escitolapram (Wienberg *et al*, 2010), as well as in older studies using methysergide (Meador *et al*, 1989), and fenfluramine (Pritchard *et al*, 1987). Inconsistently, McAllister-Williams *et al* (2002) found larger P300s after ATD. Although ATD did not affect the retrieval positivity, it significantly reduced episodic source memory. This was interpreted as reflecting a specific effect of ATD on the encoding stage of memory performance; however, an alternative explanation holds that the initiation of the recognition response (reflected in performance) is disturbed, but once initiated it proceeds in an unimpaired manner (as reflected in the retrieval positivity). In all, the evidence for a relation between general serotonin and P300 is weak.

To the extent that P300 is stimulated by catecholaminergic manipulation, but may be reduced by serotoninergic manipulation, mixed catecholoamine and 5-HT antagonists may produce mixed effects, which may explain the insensitivity of P300 to acute olanzapine (2.5 or 5 mg) in healthy volunteers (Hubl *et al*, 2001). Although P300 is also generally reduced in patients with schizophrenia, neither a clozapine nor an olanzapine 4-week treatment augmented P300 in patients, even although clinical parameters did improve (Gallinat *et al*, 2001).

Summarizing, the P300 reflects a relatively high-level cognitive mechanism, involved in the allocation of attention to relevant events, and instrumental in creating, and possibly retrieving, long-tem memories. Not surprisingly, the cortical generators of P300 include temporal, frontal, and probably also parietal and posterior-cingulate regions. Equally non-surprising is its sensitivity to manipulations of various neurotransmitter systems. Some of these effects may be relatively specific, especially the augmenting (reducing) effects of cholinergic stimulation. Relatively specific is also the P300-reducing effect of GABAergic agonism. Finally, there is good evidence for a positive relation between P300 and the activity in the ascending noradrenergic locus-cereleus system The complementary contribution of this system and especially the cholinergic system should be scrutinized in future research.

MOTOR-RELATED PROCESSES, MENTAL CHRONOMETRY, AND INHIBITION

This section addresses research into the pharmacology of human motor preparation in its broadest sense. First, we introduce a typical human electrophysiology approach to identifying motor preparation that is selective for a specific planned response ('lateralized readiness potential (LRP)'). This measure can be used to separate motor preparation in relation to a specific stimulus demanding a specific overt response, from preceding stages in the stimulus-response interval that are of more perceptual nature. Hence, it can be used to assess the extent to which a drug affects stages in

the processing of stimulus information that are more perceptual in nature, or stages that are contingent upon response choice (the formal analysis of such information-processing stages is termed 'mental chronometry'). Importantly, the structure of information processing in a given task situation is per definition controlled by top-down processes. These latter processes determine, at a general level, the trade-off between speed and accuracy, as can be derived from individual performance data. At a more specific level, top-down mechanisms control how much (perceptual) information about the stimulus is accrued before motor preparation for a specific response commences. Such top-down influences may be sensitive to pharmacological manipulation, which would then change the structure of information processing. LRP and related methodology is eminently suitable to uncover this kind of effect. Briefly, the LRP ('lateralized readiness potential') is derived by averaging the difference in ERP amplitude (larger over the left than over the right motor cortex) for right-hand responses, with the inverse difference in ERP amplitude (larger over the right than over the left motor cortex) for left-hand responses. This yields a time-varying reflection of cortical activation specifically related to the preparation of the response hand. The LRP may start hundreds of milliseconds before the overt response can be observed.

Second, given central motor preparation of any kind, a classical idea is that there are dedicated central mechanisms for suppressing ongoing response tendencies: inhibition. Inhibitory mechanisms are especially taxed in the face of violations of contextually derived regularities or sudden changes in environmental task demands. We argue that weak inhibitory control is an important aspect of impulsivity and impulsivity-related disorders. Specifically, ERP(F) research, in combination with patient and fMRI work, strongly suggests a dedicated top-down mechanism that flexibly controls inhibitory connections within the brain, based in a specific region of prefrontal cortex. This inhibitory control mechanism is impaired in certain populations and sensitive to pharmacological manipulation.

Third, a variety of neuroimaging methods (including ERP/ERF) has uncovered a mesocortical mechanism specifically dedicated to the processing (and hopefully learning from) unfavorable events in general, in particular self-emitted errors and negative feedback about performance. This error- or conflict-processing mechanism has been hypothesized to inform and direct the top-down control mechanisms as described above, but this is a conjecture that still awaits definitive empirical confirmation. The ERP/ERF correlate of this mechanism shows a clear temporal relationship to the time point of the committed error or the negative feedback information. Its very existence has also inspired a host of psychopharmacological research, especially motivated by the presumed dopaminergic involvement in learning from errors and negative feedback (Holroyd and Coles, 2002).

Mental Chronometry

Mental chronometry relies on decision choice reaction-time (RT) designs, in combination with dedicated task manipulations, aimed at affecting isolated information-processing stages. The most straightforward examples are stimulus degradation, assumed to specifically affect a perceptual stage, and response complexity, assumed to specifically affect a motor stage later in post-stimulus time (see Figure 7). So-called superadditive interactions between the effects on RT of a drug and these task variables are interpreted as specific effects of the drug on the information-procesing stages that correspond to the task manipulations (this is the logic of the additive factor method (AFM)). For example, if the effect of stimulus degradation on RT becomes larger under the drug, the latter is said to specifically lengthen a perceptual information-processing stage. Because such conclusions are ultimately based on unproven assumptions, any independent additional source of information about stimulus processing and response preparation, including ERPs or ERFs, could be valuable. A pure measure of selective response-choice dependent cortical activation is the LRP. If a substance lengthens RT, it may also affect the interval between stimulus and LRP onset (derived from the stimulus-locked or S-locked LRP signal), or the interval between LRP onset and RT (derived from the response-locked or R-locked LRP signal), or both. This yields relatively straightforward indices of whether the drug affects information-processing stages that precede response decision (and could therefore be 'perceptual'), or stages that succeed response decision ('motor preparation'), or both (see Figure 7). Another popular measure is the latency of the P300 peak, assumed to reflect 'stimulus evaluation', which is also generally viewed as a collection of perceptual stages (Smulders *et al*, 1995). The added value of ERP(F)s within the context of AFM-ERP logic rests on their quality as indices of stage durations independent of those identified by AFM logic. For example, if a drug effect on RT interacts superadditively with stimulus degradation, the inference that the drug affects a perceptual stage also requires an effect of the drug on S-locked LRP and P300 onset latencies. Furthermore, it is possible that a drug does not affect RT but results in reduced choice accuracy. As will be discussed below, the drug may also shorten S-locked LRP latency, indicating that the drug speeds up perceptual stages at the cost of degraded output from these stages, the latter having the result of no reduction of total processing time

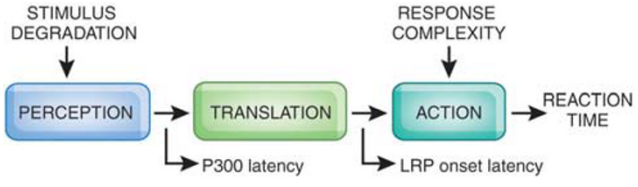


Figure 7. Simple stage model, including specific sensitivity of ERP latency measure to stage durations, and putative selective experimental effects on stage durations.

(RT) in combination with reduced behavioral output accuracy. In such a case, the inference is that the drug actually changes the structure of information processing, in that it modulates the output quality of a certain stage, which has direct repercussions for the duration of subsequent stages.

In analogy, latency-resolved fMRI has been proposed as a method to combine the spatial accuracy of fMRI with mental chronometry. Some initial results looked promising, in that the onset latency of the fMRI–BOLD response in V1 in one hemisphere, relative to the other, closely followed the delay in stimulus timing in the corresponding hemifield (Menon *et al*, 1998). More generally, experimental effects on RT of 125 ms or more, as well as individual differences in RT in the order of 50 ms, could be traced back to parallel timing effects in V1 and M1, opening the possibility to use these localized differences in timing as the neurophysiological translation of the more arbitrarily defined information processing stages. However, the initial report by Menon and colleagues has hardly been followed on, and certainly not in the context of psychopharmacology or pathology. A lack of applications in psychopathology also characterizes the AFM-ERP approach as such. This may be viewed as a missed opportunity: in analogy to whole-brain scans as obtained with fMRI, AFM-ERP may yield 'whole-information-processing' scans, with a functional resolution that depends on the number of parallel or crossed experimental manipulations. This could yield maps of specific deficits of even individual pathology, as well as maps of selective effects of drugs and of other interventions, which could then be scrutinized for overlap so as to point the way to possible new treatments. In this study, we look at some examples of selective drug effects as revealed using combined AFM-ERP logic.

Histamine. Van Ruitenbeek *et al* (2009a) investigated the effect of L-histidine depletion (assumed to reduce central histamine availability). Stimulus degradation and response complexity slowed down RT additively, but these effects did not interact with those of treatment, nor was their any main effect of treatment (this also held for accuracy). S-locked LRP and P300 latency were lengthened only by stimulus degradation. R-locked LRP latency was lengthened by response complexity, not by stimulus degradation. In addition, L-histidine depletion increased the effect of response complexity on R-locked LRP latency. These results show that chronometric ERP measures may be more sensitive than performance measures, but at the same present something of a puzzle, in that the pharmacological ERP effects are not paralleled by pharmacological performance effects.

Ignoring the absence of the performance effects, the ERP-latency effects in this study are consistent with a seemingly specific effect of L-histidine depletion on a motor preparation stage. However, the results of a companion study by the same group suggest that a global decrease in the availability of histamine in fact induces a complex mixture of effects, probably related to interactions with different receptor subtypes. In the latter study, the H1 antagonist dexchlorpheniramine (4 mg) prolonged RT additively with effects of stimulus degradation and response complexity (Van Ruitenbeek *et al*, 2009b). The effect of stimulus degradation on P300 latency was augmented by the H1 antagonist, and S-locked LRP latency was lengthened independently of task condition, whereas there were no R-locked LRP effects. This pattern of results is consistent with a specific perceptual-stage effect of the H1 blocker. This contrasts with the motor-stage effects in the L-histidine depletion study, and suggests that the latter manipulation may indeed have produced a combination of effects, with H1 perceptual effects being masked by effects mediated by other H-receptor subtypes, that may also have been involved in producing the motor-stage effects.

GABA. In the same study (Van Ruitenbeek *et al*, 2009b), also the effects of 1 mg lorazepam (a relatively low dose) were investigated. Lorazepam lengthened RT additively to response complexity, but super-additively with stimulus degradation. It did not have any effect on P300 or R-locked-LRP latency, but it lengthened S-locked-LRP latency. This pattern is consistent with lorazepam affecting a processing stage that is not affected by stimulus degradation, nor reflected in P300 latency, but nevertheless precedes LRP onset in time, and therefore may involve 'the transition between feature extraction and response programming' (p. 83). However, the over-additive interaction between the lorazepam effect and that of stimulus degradation on RT, but not on P300 or S-locked LRP latency, points to a second perceptual stage affected by lorazepam that is separable from the one that was affected so as to produce the main effect on S-locked LRP latency. Studies using relatively high benzodiazepine doses did report delaying effects of alprazolam (1 mg) on both RT, as well as P300 latency and S-locked LRP onset latency (Riba *et al*, 2005a), as well as of triazolam (0.25 mg) on both RT and P300 latency (LRP not recorded; Pang and Fowler, 1994). Thus, benzodiazepine effects seem to be predominantly premotor, with higher doses leading to an increasing number of affected information-processing stages. Overall, reducing histaminergic transmission and promoting GABAergic transmission have similar global performance impairing effects. However, ERP results indicate that these declines in performance reflect rather different relations of these two neurotransmitter systems with specific stages of information processing. That is, GABA is more involved in perceptual and other premotor stages, whereas histamine concerns either perceptual (H1) or motor stages (other receptors).

Dopamine. The study by Van Ruitenbeek *et al* (2009a) discussed above also applied L-tyrosine/L-phenylalanine depletion (assumed to reduce central dopamine availability). This manipulation shortened the interval between R-locked LRP and the response, indicating an accelerated motor-processing stage. Quite similar to the histamine

results, acute dopaminergic receptor-agonism manipulations yield results that were different from those obtained with depletion paradigms. Whereas L-tyrosine/L-phenylalanine depletion speeded up a specific motor stage (Van Ruitenbeek *et al*, 2009a), the effects of the mixed D1/D2 receptor agonist pergolide appear to affect a perceptual stage. Specifically, pergolide (0.075 mg) shortened S-locked but not R-locked LRP onset, reduced RT variability without affecting mean RT, and resulted in an increase of choice–error rate (Rammsayer and Stahl, 2006). This pattern of results clearly points to a more rigid, overly rapid stimulus identification process under pergolide, which translates into an increase in decision errors at the behavioral level. It is perhaps the prime example to show how ERPs can reveal that a drug induces a (top-down driven) change in the structure of information processing: a shorter perceptual stage at the cost of degraded output of this stage to subsequent stages of response selection and motor preparation.

Effects of D1/D2 agonism may at least partly overlap with those of caffeine; adenosine and D1/D2 receptors exhibit considerable colocalization, and a substantial part of caffeine's neurocognitive effects are believed to be dopaminergically mediated. However, from studies using AFM-ERP or related logic, it appears that caffeine speeds up both perceptual and later motor stages, resulting in generally shorter RTs that do not come at the cost of increased error rates (Kenemans and Lorist, 1995; Lorist *et al*, 1994a). This may reflect that the adenosine system interacts with additional DA receptors as well, and with other transmitter systems to mediate the complete pattern of neurocognitive caffeine effects.

Inhibition

Inhibition is mostly probed using the 'stop-signal task'. Briefly, participants perform a choice–RT task, eg, two alternative visual stimuli mapped on two alternative responses. Occasionally, the current choice stimulus is succeeded, within some 100–300 ms, by a third stimulus (eg, a tone) that dictates that the behavioral response should be suppressed. Using specialized digital signal processing procedures, the ERP to the stop signal can be isolated from that to the go stimulus (Bekker *et al*, 2005b); an ERF equivalent has also recently been reported (Boehler *et al*, 2009). Stop ERP(F)s have revealed a link between the impact of the stop signal in sensory cortex (eg, of a stop tone in auditory cortex) and the probability of successful stopping ('stop N1' effect; Bekker *et al*, 2005b). Individuals diagnosed as being excessively impulsive (attention deficit/hyperactivity disorder or ADHD) are known to have weak stopping abilities, and also, when off-medication, lack the link between sensory cortex activation and chances of stopping (Bekker *et al*, 2005c). Damage in the right hemisphere inferior frontal gyrus (R-IFG) has been reported to specifically impair stopping performance (Aron *et al*, 2003), and therefore, this prefrontal cortex region could implement the top-down control of the inhibitory link between sensory cortex and the motor system. This notion is consistent with results obtained using neuroimaging techniques (eg, fMRI) that are not as apt for separating processes in time, but fare much better with respect to spatial localization (Aron and Poldrack, 2005). Stop-ERP studies thus far have only concerned methylphenidate and paroxetine, but as will be argued below, they offer great promise in assess the possibilities of other treatments.

The standard medication for ADHD, methylphenidate (0.6 mg/kg in adults) restores the failed sensory motor inhibitory connection in ADHD, presumably through its effect on R-IFG activity (Overtoom *et al*, 2009), as well as improves stopping performance (for both parameters this was contrasted with 20 mg paroxetine which had no effect).

Stop-ERP studies have also revealed situations in which R-IFG, rather than instigating and maintaining the inhibitory sensory motor link, is activated on the presentation of the stop signal, and manifests as 'stop N2' (Schmajuk *et al*, 2006). Additionally, this stop-signal contingent R-IFG activation is reduced in ADHD (Liotti *et al*, 2007), and restored in turn by methylphenidate (individually titrated dosage, subchronical regime in children; Pliszka *et al*, 2007). Furthermore, a second mechanism related to stopping performance has been reported to be reflected in the so-called 'stop P3' (De Jong *et al*, 1990). The stop-P3 might very well originate from the superior frontal gyrus (Floden and Stuss, 2006). It is also reduced in ADHD, although still significantly present (Bekker *et al*, 2005c), and, in contrast to the sensory motor inhibitory link, also reduced in healthy poor stoppers, as compared with healthy good stoppers (Lansbergen *et al*, 2007b). Importantly, it is not affected by methylphenidate (Overtoom *et al*, 2009). This opens a range of possibilities for evaluating the suitability of treatments (eg, methylphenidate *vs* alternatives) for different individuals; eg, impaired stopping performance could be paralleled by an impaired inhibitory sensory motor connection, or by a reduced stop P3, and this would have profound implications for the choice of treatment. A pertinent question then is whether alternatives to methylphenidate such as atomoxetine (60 mg), known to improve stopping performance (Chamberlain *et al*, 2007), and amphetamine (20 mg; de Wit *et al*, 2002), also restore sensory motor inhibitory connections and/or the stop P3.

A related phenomenon is the 'novelty-P3' or P3a (Muller-Gass *et al*, 2007). One hypothesis is that both the stop P3 and the P3a implement a behavioral interrupt signal, perhaps based in medial–superior frontal regions. P3a reducing effects of acute moderate alcohol (0.05% BAC) were recently described (Wester *et al*, 2010). Acute alcohol (0.08%) also lengthens stop signal RTs (Loeber and Duka, 2009), and a remaining question is whether this impaired stopping is associated also with reductions in the stop P3, given that the stop P3 is similar to the P3a in reflecting a behavioral interrupt signal. In a stop-task fMRI study, the one region that was activated more for successful than for failed stops was located in superior/middle frontal gyrus

(Aron and Poldrack, 2006). All his serves to illustrate that on the one hand common mechanisms may be at stake in different task situations, but on the other hand performance in one and the same task (eg, stopping) may reflect the contribution of multiple cortical mechanisms. Understanding these mechanisms could help to better specify what exactly is compromised in different individuals within the same diagnostic category (eg, in ADHD: is it stop N1 or stop P3) and help selection of adequate treatment. It could also clarify the brain mechanisms of impaired stopping in other populations, as in, eg, schizophrenia (Huddy *et al*, 2009).

Error and Conflict Processing

There is considerable consensus about a class of brain potentials specifically related to 'conflict monitoring'. This class includes (1) the ERN (Gehring *et al*, 1993) or N_e (Falkenstein *et al*, 1991); (2) the feedback-related negativity (FRN; Gehring and Willoughby, 2002); (3) the Nogo N2 (Bekker *et al*, 2005a); and (4) the 'incongruence negativity' (N_i; Van Veen and Carter, 2002). 'Conflict monitoring' refers to a brain mechanism that is activated as part of the detection of conflicting response options, or perhaps more generally conflicting neuronal representations (Carter *et al*, 1998). Such conflicts may pertain to erroneous responses (conflicting with the correct response, ERN), reward-prediction errors (FRN), nogo demands in a context of prepotent go responses (nogo N2), and color-naming responses to incongruent color words (N_i). All these potentials are thought to be generated in the anterior part of the cingulate cortex (ACC; Dehaene *et al*, 1994; Lansbergen *et al*, 2007a; Van Veen and Carter, 2002; see Figure 8). The function of this mechanism is thought to be to provide a signal to other brain regions so that top-down control can be adjusted in anticipation of future conflicts, but this has actually never been established. Nevertheless, conflict potentials provide a direct window on a brain mechanism that is reflected in performance measures only indirectly (eg, through slowing down or favoring accuracy over speed after an error or high-conflict trial). Therefore, these potentials may have explicit added value to inform the psychopharmacology of cognition and affective processes. A summary of results is provided in Table 4.

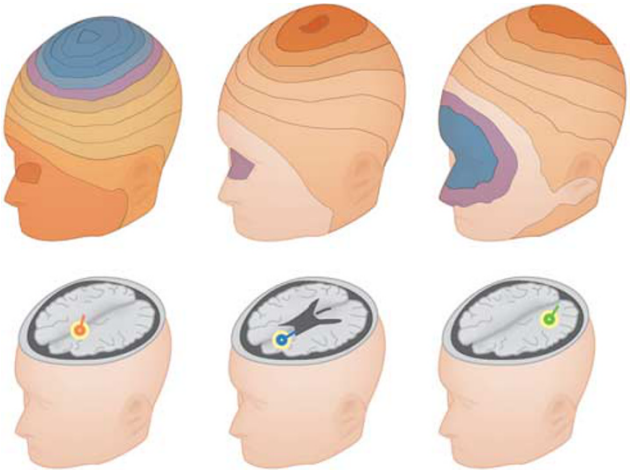


Figure 8. Top row, left to right: scalp distributions for ERN (about 60 ms after the error), and the early (188 ms), and late (298 ms) phase of the P_e. Bottom row: the red, caudal ACC dipole explains ERN and early P_e; the blue, rostral ACC dipole, combined with the green posterior dipole, explains the late P_e. Adapted from Van Veen and Carter (2002).

Dopamine. Part of the psychopharmacological research involving conflict processing has been motivated by the theory that conflict potentials strongly depend on the fluctuations in dopamine release. Specifically, errors, negative feedback, or other conflict-inducing events may result in a transient dip in dopamine release from neurons in the ventral tegmental area or (ventral) striatum. These dips may directly or indirectly produce a transient hyperactivity in ACC neurons, which would manifest as the conflict potential (Holroyd and Coles, 2002). Dopamine dips can be thought to be especially pronounced with high tonic dopamine levels, when there is a relatively unrestricted range for the phasic dip response (for a similar logic, see Cools *et al*, 2008). Consistently, the ERN was acutely enhanced by 15 mg D-amphetamine (Figure 9; De Bruijn *et al*, 2004), and reduced by 2.5 or 3 mg haloperidol (Figure 10; De Bruijn *et al*, 2006; Zirnheld *et al*, 2004).

However, results of ERN studies in patients with Parkinson's disease are not entirely consistent with the dopamine hypothesis. *De novo* patients, as well as long-term patients off medication, can be assumed to have reduced dopamine levels, and indeed samples from both populations

TABLE 4 Summary of Acute Drug Effects on Conflict-Related Potentials in Healthy Volunteers

Drug	ERN	P_e	FRN	N_i	Reference
D-Amphetamine	↑			0	De Bruijn *et al* (2004)
Haloperidol	↓			0	De Bruijn *et al* (2006)
Haloperidol	↓				Zirnheld *et al* (2004)
Yohimbine	↑	0		0	Riba *et al* (2005b)
Alprazolam	↓	↑		0	Riba *et al* (2005a)
Lorazepam	↓			↓	De Bruijn *et al* (2004)
Oxazepam	↓				Johannes *et al* (2001)
Olanzapine	↓			0	De Bruijn *et al* (2006)
Paroxetine	0			0	De Bruijn *et al* (2006)
Tryptophane depletion			0		van der Veen *et al* (2008)
Diphenhydramine	0				Zirnheld *et al* (2004)
Mirtazapine	0			0	De Bruijn *et al* (2004)
Alcohol	↓			0	Ridderinkhof *et al* (2002)
Caffeine	↑	↑			Tieges *et al* (2004)

Abbreviations: ERN, error-related negativity; FRN, feedback-related negativity. See text for explanation. Note: arrow indicates increase (↑) or decrease (↓), 0 indicates no effect.

exhibit substantially reduced ERNs (Willemssen *et al*, 2008; Willemssen *et al*, 2009). However, the long-term group, when given medication (L-dopa or DA-receptor agonists), still showed a similarly reduced ERN (Willemssen *et al*, 2008), whereas clinical symptoms improved as expected. This suggests that adequate dopamine levels are necessary for a normal ERN, but not sufficient. Parkinson's patients on L-dopa also manifest as 'positive learners': They learn more from positive than from negative feedback, apparently because elevated dopamine levels make them more sensitive to reward (Frank *et al*, 2004). In contrast, patients off medication present as negative learners. Healthy positive learners have been shown to have reduced ERNs (and FRNs), relative to negative learners (Frank *et al*, 2005). Thus, positive learning is associated with dopamine in patients, and with small ERNs in healthy volunteers. This latter relation may have also have a role in the reduced ERNs in the patients even when they were on medication. Furthermore, the smaller ERNs for positive learners are inconsistent with the notion outlined above, that high tonic dopamine is favorable for large ERNs. To possibly resolve this issues, future research should address positive learning in relation to the ERN in both patients and healthy controls.

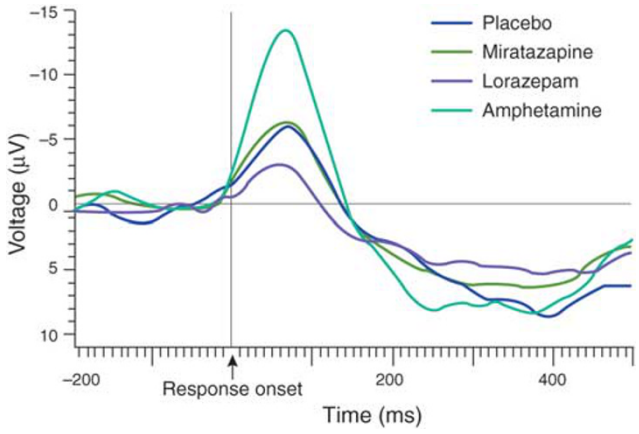


Figure 9. Enhancement of ERN under amphetamine, as well as reduction under lorazepam, and lack of effect of the ant-depressant mirtazepine. Adapted from De Bruijn *et al* (2004).

Norepinephrine. Riba *et al* (2005b) reasoned that the ACC is also innervated by noradrenergic projections from the locus cereleus. Consistently, administering 30 mg oral yohimbine, an NE-α2-receptor antagonist with a net effect of augmenting NE transmission, resulted in a significant increase in ERN. This was interpreted as a general modulating effect via these projections on ACC functioning. Yohimbine also reduced the number of performance errors in the Eriksen flanker task, which may have been instrumental in increasing the ERN (there is a negative correlation between ERN amplitude and error rate). However, after including error rate as a covariate for the ERN effect the latter still remained significant. No effect of yohimbine was found for the N_i, indicating that ERN and N_i reflect mechanisms with different biochemical signatures. A nil effect was also observed for 'P_e' or 'error-related positivity'. This is a second phase in the error-related potential, starting after 100 ms after the error, and at least partly reflecting activity in more posterior deep cortical regions (Figure 8; Van Veen and Carter, 2002), and perhaps more conscious recognition of the error (Overbeek *et al*, 2005).

GABA. Alprazolam (1 mg) reduced ERN but enhanced P_e (Riba *et al*, 2005a). Consistent results for ERN under lorazepam were reported in the study by De Bruijn *et al* (2004; see Figure 9), and for 30 mg oxazepam (Johannes *et al*, 2001). A later study by De Bruijn *et al* (2006) also

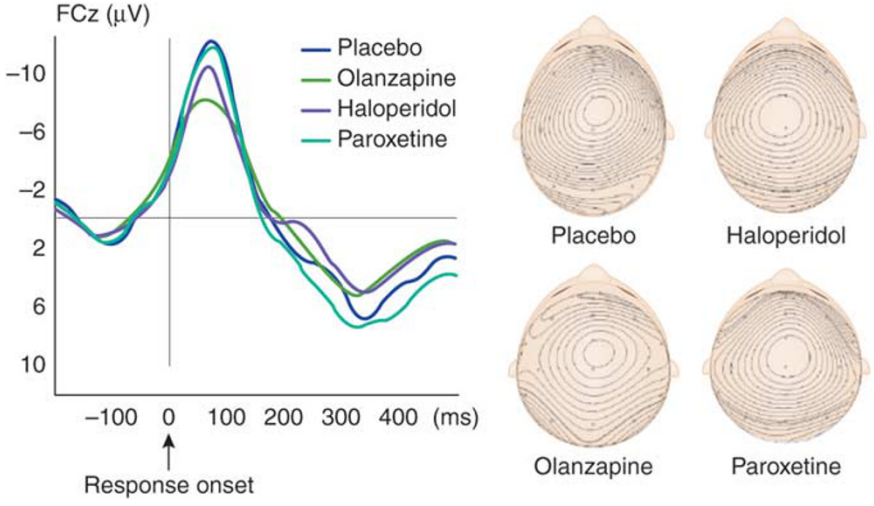


Figure 10. Reduction of ERN by haloperidol, but even more so by olanzapine, perhaps due its additional $GABA_A$ agonism. Note absence of effect of paroxetine, and the qualitative identity of the ERN topographies in the four drug conditions. Adapted from De Bruijn *et al* (2006).

noted ERN reducing effects of acute olanzapine (10 mg; see Figure 10), which can be explained by olanzapine's agonistic action at $GABA_A$.

Serotonin. Relatively pure manipulations of 5-HT (paroxetine 20 mg) do not affect the ERN (Figure 10; De Bruijn *et al*, 2006), nor the FRN as revealed in a recent ATD study (van der Veen *et al*, 2008).

These results suggest that the ERN may reflect a transient dopaminergic signal, the strength of which can be modulated by manipulation of other neurotransmitter systems in more or less non-specific ways. Indeed, ERN has been reported to be affected by substances known to exert widespread effects throughout the central nervous system, especially by interacting with a variety of neurotransmitter systems. ERNs are reduced by acute moderate alcohol (Ridderinkhof *et al*, 2002) and benzodiazepines (see above), and enhanced by caffeine (Tieges *et al*, 2004). ERNs were however not affected by 15 mg mirtazapine, a mixed NE-agonist/ non-specific 5-HT antagonist/ H1 antagonist (De Bruijn *et al*, 2004), nor by the specific H1 antagonist diphenhidramine (25 mg; Zirnheld *et al*, 2004).

As can be seen in Table 4, N_i is generally not affected by drug manipulations. This could be taken to suggest that N_i is not as sensitive as ERN to such manipulations. This in turn indicates that the neural ensembles involved in generating either potential are not completely overlapping. Finally, the few P_e results are paradoxical, as it is enhanced by both a sedating and a mildly stimulating substance.

WRAPPING UP ELECTROPSYCHOPHARMACOLOGY

This review surveyed human electrocortical neurophysiology in relation to cognition, its magnetic counterparts, and how they have been or may be applied in psychopharmacology. The discussed paradigms ranged from almost completely bottom-up determined sensory-processing mechanisms up to higher-order mechanisms of top-down control of attention and inhibition.

A first group of paradigms unravels stimulus-driven processing, in interaction with basic regulating mechanisms and internal representations of the context; all of these paradigms are completely independent of any task-directed behavior or performance, and therefore can be applied in almost any human population. Perhaps the most basic phenomenon is the LDAEP: a reduced slope of this function can be thought of as being protective for the information-processing system, as the result of a kind of stimulus-driven inhibitory mechanism; although in terms of protective actions a reduced LDAEP might rather reflect a lack of sensitivity to the threatening qualities of highly intense stimulation. Also primarily based in sensory cortex is P50 suppression, or the filtered sensory-cortex response to the repetition of irrelevant information, although in this case the existence of regulating frontal signals that regulate the suppression is plausible and can be made visible in the ERP/F (Oranje *et al*, 2006a; Weisser *et al*, 2001). A related phenomenon is the MMN, reflecting the more or less automatic signaling within sensory cortex of an unexpected change in stimulation (more technically: any violation of stimulus regularities). There is evidence that a change of stimulus rather than a repetition in the P50 suppression paradigm elicits the MMN (Sams *et al*, 1984). Detection of the violation of regularities also results in secondary frontal activation, presumably related to orienting of attention to the conspicuous event (frontal MMN) or perhaps constituting a behavioral interrupt signal (novelty P3a).

A second group of paradigms refers to explicitly goal-directed behavior in well-defined task contexts. Top-down modulated electrocortical processing in sensory and frontal cortex ('selection potentials') has been described extensively in the context of selective attention, but has thus far found only limited application in psychopharmacology. Furthermore, we argued that this approach should be supplemented by imaging the top-down signals that cause the attentional modulation (van der Lubbe *et al*, 2006). In this context ERP/F methods are especially suitable to track split-second changes in attentional settings as conveyed by equally rapidly changing environmental or task demands. A similar point can be made with respect to inhibitory control, as commonly assessed within the context of the stop task. ERP/F analysis strongly suggests that the successful suppression of on-going behavior depends at least partly on a potentiated inhibitory link between sensory cortex and the motor system ('stop N1'), and it would be very much worth while to chart the signal that controls this potentiation as it instantiates in (presumably) prefrontal cortex. ERP/F analysis has additionally revealed two other mechanisms that are associated with successful stopping, stop N2 and stop P3, as well as dissociations between the three mechanisms with respect to the effects of methylphenidate and differences between pathologically and healthy slow stoppers. In effect then, we see a pattern of variation in uniform performance that may be associated with different electrocortical mechanisms, each of which passes again on a split-second time scale.

A third group contains P300 and conflict potentials. P300 is interesting in relation to especially the encoding aspects of memory, to the extent that its strength as it is elicited by initial presentation of information, can be used to predict later retrieval performance. This variation in P300 during encoding at least partly reflects variation in attention (Fabiani *et al*, 1986), and possibly the involvement of working memory-related mechanisms (Kohler *et al*, 2004; Wagner *et al*, 1998), and these contributions may have anatomical correlates in temporal and frontal regions, respectively. This goes to demonstrate that also P300 is suitable to track covert internal operations (eg, encoding), and this characteristic applies even more to the set of conflict potentials (most notably ERN). This refers to a set of brain mechanisms that are activated as part of the detection of conflicting response options, downright

errors, or negative reinforcement, and are generated in medial–frontal regions. These conflict mechanisms are generally seen as instrumental in 'controlling the control' (Cohen *et al*, 2004): They are assumed to signal to other regions that adjustments in attentional or inhibitory settings are in order, hence extending the chain of information-processing control signals with a conflict signal to attention–control mechanisms (prefrontal cortex), that in turn signal to sensory or motor areas to amplify some representations and attenuate others, which is turn leads to newly modulated responses to subsequent information and events.

A final set of paradigms was headed by 'mental chronometry' and 'AFM-ERP'. These techniques typically reveal 'the locus of effect' of drugs or any other state or trait factor in terms of stages of information processing. In principle the locus of effect is expressed in terms of the effect being more perceptual, or premotor, or motor, but the resolution of this localization can be extended substantially by including more appropriate task manipulations. ERP/F chronometric measures (LRP, P300 latency) have been used to further refine or constrain the stage analysis as based on performance analysis.

It was suggested that mental chronometry may yield 'whole-information processing' scans, involving maps of specific deficits of even individual pathology, as well as maps of selective effects of drugs and of other interventions, which could then be scrutinized for overlap so as to point the way to possible new treatments. We venture to extend this principle to the complete human electrophysiology approach to psychopharmacology and pathology as reviewed here. This consideration reflects that the present 'electropsychopharmacological' approach covers many domains of mental processes and information processing in general, and can be extended into additional domains such as language and affective and social processing (see also Table 4). Furthermore, it provides a window on many cortical processes and mechanisms that are principally covert, or reflected in behavioral performance only very indirectly, and therefore provides important additional constraints for theoretical modeling of behavior.

WRAPPING UP NEUROTRANSMISSION, DRUGS, AND CORTICAL PROCESSING

Table 5 presents a somewhat speculative and preliminary survey of the involvement of the major neurotransmitter systems in cortical mechanisms of information processing, as inferred from the reviewed data. The following paragraphs highlight some of these insights, ordered by neurotransmitter system.

Dopamine. Evidence for the involvement of the dopamine system in more bottom-up driven processing (P50, LDAEP, MNN) as well as in P300 mechanisms is weak. With respect to mental chronometry, dopaminergic effects seem to be receptor dependent. Overall depletion has been associated with speeding up motor preparation, while specific D1/D2 agonism speeds up perceptual processes at the cost of accuracy. DA is highly implicated especially in the subcortical control of conflict monitoring. Hypotheses about its role in the cortical control of inhibitory sensory motor links and other mechanism of inhibitory control rest mainly on the observed effects of methylphenidate, and further tests are needed to dissociate DA contributions to these effects from those of NE. The NE reuptake inhibitor atomoxetine also improves stopping (Chamberlain *et al*, 2006, 2007), as well as increases R-IFG activation during stopping (Chamberlain *et al*, 2009). If indeed the the stop-N1 effect is the result of signals from R-IFG that potentiate the inhibitory sensory motor link, than the stop N1 should be enhanced by atomoxetine, just as it is by methylphenidate. Atomoxetine selectively blocks the NE reuptake transporter, and thus the improvement in stopping would suggest that stopping does not depend on dopaminergic function. However, in prefrontal cortex atomoxetine also increases available extracellular dopamine, which may as well account for the improvement in stopping (Bymaster *et al*, 2002).

Norepinephrine. The involvement of NE in the currently reviewed neurocognitive mechanisms has not been investigated, or is weakly supported (except for P300). One study

TABLE 5 Summary of Inferred Relationships between ERP/ERF Variables and Neurotransmitter Activity

	P50 suppression	LDAEP	MMN	P300	Chronometry	Inhibition	Conflict potentials (ERN)
Dopamine	R, N	N	R?	A?	M	A?	A
Norepinephrine	R?	O	N?	A	O	A?	A, I
Serotonin	M	M	M	N?	O	N	N
Acetylcholine	A, I	O	A-temp, A-fro	A	O	O	O
Glutamate (NMDA)	O	R	A-temp, R-fro	O	O	O	O
$GABA_A$	O	O	R-temp, R-fro	R	R, perceptual	O	R
Histamine	O	O	O	N	A, mixed	O	O

Abbreviations: ?, weak evidence; A, augmenting effect of neurotransmitter; fro, frontal component; ERF, event-related magnetic field; ERP, event-related brain potential; I, indirect; M, mixed effect; MMN, mismatch negativity; N, no effect; O, open for investigation; R, reducing effect; temp, temporal component.
For mental chronometry, the terms perceptual, motor, and mixed perceptual motor are additionally used.

found an enhancing effect of yohimbine on the ERN (Riba *et al*, 2005b). This was interpreted as an 'indirect effect', but perhaps it is more appropriate to conclude that NE projections to the ACC modulate the signal strength within projections to the ACC that use other neurotransmitter systems. A similar scenario may hold for the relation between NE and P300 (Nieuwenhuis *et al*, 2005).

As noted in the discussion of the selection potentials, NE could be important in top-down signals from parietal and frontal regions that modulate processing in sensory and motor cortices. One PET study reported that parietal activation specifically related to orienting in visual space was reduced by acute clonidine, an α-2 agonist that works mainly presynaptically in common dosage, and therefore effectively as an NE antagonist (Coull *et al*, 2001). As indicated, electropsychopharmacology should help to separate such an attentional control component from more bottom-up driven ones such as 'disengagement'. Furthermore, excessive NE transmission could be implicated in certain symptoms of schizophrenia, that are related to reduced sensory gating and readily remediated by clozapine (not but by other antipsychotics, either typical or atypical).

Serotonin. With respect to relatively more bottom-up driven mechanisms (P50 suppression, LDAEP, MMN), the effects of acute enhancement of 5-HT transmission are generally mixed. These mixed results may reflect receptor specificity of various effects, as well as individual differences in the distributions of receptor subtypes. Results on the relation between serotoninergic transmission and the P300 process are also mixed, whereas serotonin has a stimulating effect on certain aspects of memory performance, consistent with behavioral studies (Cools *et al*, 2008; Mendelsohn *et al*, 2009). Studies explicitly addressing 5-HT influences on motor inhibition and conflict processing have not yielded significant effects. This pattern of either negative or no effect of 5-HT manipulations may reflect the more neuro-cognitive, rather than neuro-affective nature of the presently reviewed paradigms. Furthermore, 5-HT may be more involved in punishment than in reward processing and learning (Cools *et al*, 2008). Finally, the emphasis here is mainly on acute effects, which may be rather different from those of the chronic regimes as commonly aimed at in clinical applications.

Acetylcholine. Cholinergic transmission is an important determinant of P300 amplitude, a reflection of attention allocation predictive of subsequent memory, and probably based in a posterior cortical network, including temporal and parietal areas, as well as well possibly posterior cingulate cortex (Neuhaus *et al*, 2006). ACh further augments MMN (temporally and frontally) as well as P50 suppression, although the latter effect is believed to be indirect (Adler *et al*, 2004). ACh-enhanced P50 suppression by all means involves the nicotine receptor, whereas MMN as well as P300 modulation have been linked to both nicotinic and muscarinic mechanisms. The involvement of the ACh system in mechanisms of motor preparation, inhibition, and conflict monitoring is still very much open to investigation.

Other neurotransmitter systems. As Table 5 shows, there is limited information from human ERP/F work on the effects of a number of other neurobiochemical systems. Generally reducing effects of benzodiazepines ($GABA_A$ manipulation) have been reported for MMN, P300, conflict processing, and mainly perceptual stages of information processing. In one case the reducing effect (on P300) was dissociated from the generally sedating effects of H1 antagonism, which had no effect on P300. In terms of mental chronometry, also H1 antagonism can have a relatively specific effect on perceptual processes, whereas acute general depletion of histamine has more motor-related effects. Finally, some limited results on Glu/ NMDA transmission were noted. The NMDA agonists glycine reduces LDAEP, but also the frontal component of the MMN, which is actually enhanced by memantine, an NMDA antagonist. The MMN-temporal component appears to have a positive relation with NMDA transmission.

FUTURE DIRECTIONS AND CLINICAL APPLICATIONS

The preceding summary is preliminary and at times speculative, and refers to numerous open questions. Especially the distinction between direct receptor interactions and indirect effects, as well as between acute and chronic effects, needs further clarification. An important topic for future research concerns the further specification of top-down signals that modulate processing in sensory-motor pathways, in terms of both electro- and magnetoencephalographic time course and biochemical characteristics. One example is the putative signal from frontal areas that is instrumental in P50 suppression, and may be of crucial importance with regard to disorders such as schizophrenia. Another case is formed by the top-down signals from frontal and parietal areas that implement selective attention to specific environmental inputs. A better understanding of these pathways and their biochemistry (especially NE transmission) may prove to be crucial for the treatment of attention-related disorders such as ADHD.

Such further specification is also needed for adaptive control or 'controlling the control': conflict-processing signals, or bottom-up driven responses to salient events outside the current task settings that trigger new control settings that are implemented through the frontal and parietal top-down signals. This principle can be extended to P300 paradigms, as typical electrocortical windows on how relevant and/or salient events attract attention and result in memory updating. Especially the incidental-learning paradigm, in which salience is manipulated and its effect on subsequent memory has been established, should be useful to further characterize the cortical pathways underlying

these behavioral effects (Fabiani *et al*, 1986), as well as their biochemistry (especially ACh and NE transmission) and the way they are disturbed in various disorders.

A direct handle for clinical application may be the observation that one and the same behavioral phenotype (eg, deficient stopping or inhibitory control in ADHD) may be associated with different electro- or magnetocortical phenotypes (eg, stop N1 *vs* stop P3). A better understanding of the biochemistry of these neurophysiological phenotypes may directly inform possible treatment, as the behavioral phenotype may be paralleled by one neurophysiological phenotype for one individual, and by the other for another individual. It is also an open question whether these same mechanisms contribute to impulsivity in other disorders such as schizophrenia. Another starting point is the modest misalignment between neurocognitive deficits in a certain disorder on the one hand, and the precise effect of conventional medication on the other. For example, ADHD is marked by a reduced stop P3 and an aberrant allocation of attention as manifest in P300 in difficult task conditions. However, methylphenidate does not restore the reduced stop P3 (although it does restore the reduced stop N1 as well as stopping performance), and increases attentional capacity as reflected in P300 equally in easy and in difficult task conditions (Jonkman *et al*, 2000; Overtoom *et al*, 2009). Especially the latter result is reminiscent of the recent finding that ADHD is marked by a reduced adjustment of decision strategy to amount of available information, whereas methylphenidate affects decision strategy independent of available information (DeVito *et al*, 2008). Such partial misalignment between the neurocognitive endophenotypes of a disorder and the effects of treatment may lead the way to more optimization, and perhaps even personalization of treatment. Such an endeavor could be complemented by a combination of behavioral and EEG/MEG phenotypes that are valuable in predicting the individual response to medication and other treatment (Clarke *et al*, 2002; Sangal and Sangal, 2005). These phenotypes should not be limited to the presently discussed ERP and ERF measures, but also include spontaneous, as well as emitted and induced oscillations (see Figure 2; Ahveninen *et al*, 2007; Böcker *et al*, 2010; Jensen, 2006).

DISCLOSURE

The authors declare no conflicts of interest.

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