

# Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials

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## Abstract

Impairment in mismatch negativity (MMN) generation is a robust biological marker of schizophrenia. Understanding the physiological and pharmacological processes involved in its generation may therefore advance our understanding of this complex disorder.

The present study tested if acute administration of nicotine modulates human auditory sensory memory as measured with MMN. ERP responses to tone duration deviants were recorded using a stimulation protocol with continuously changing (roving) standard stimuli in order to measure the effect of stimulus repetitions on encoding of new stimuli (MMN memory trace effect). Twenty healthy adult volunteers were randomly assigned to receive either a nicotine gum or placebo after a baseline ERP recording.

Nicotine administration augmented MMN amplitude in the treatment group compared to the baseline recording, while no MMN change was found in the placebo group. The drug effect was due to a selective enhancement of a frontal positive potential to standard stimuli (from 80–200 ms post-stimulus), while the negativity to deviants remained unaffected. Furthermore, under nicotine stimulation this repetition positivity showed a more marked increase with stimulus repetition compared to baseline and placebo.

These results have potential implications for schizophrenia by suggesting that nicotinic agonists could ameliorate patients' MMN deficits by improving stimulus encoding and sensory memory trace formation.

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## 1. Introduction

Cognitive impairments in patients with schizophrenia are increasingly recognized as core symptoms and are targets for therapeutic developments. They predict clinical prognosis and social outcome (Green, 1997), but their aetiology is insufficiently understood. Dysfunction of working memory and one of its more basic forms – auditory sensory memory – has been demonstrated reliably (Strous et al., 1995; Javitt et al., 1997). These behavioural findings are supported by deficits in an ERP correlate of auditory sensory (echoic) memory, the mismatch negativity (MMN) (Catts et al., 1995; Javitt et al., 1993; Shelley et al., 1991).

In the present study we explored the utility of MMN to elucidate the effects of nicotine on auditory sensory memory, as a putative, low-level marker of higher mnemonic functions. Nicotinic agonists are being considered as new treatments for schizophrenia and other neuropsychiatric disorders (Friedman, 2004; Singh et al., 2004; Martin et al., 2004). First, however, we will review the evidence that links MMN to cognitive dysfunction in schizophrenia and will outline evidence for neuronal and ERP correlates of echoic memory trace formation.

### 1.1. Neuronal and ERP correlates of auditory sensory memory formation

A candidate neuronal mechanism for echoic memory has been discovered in the cat primary auditory cortex (Ulanovsky et al., 2003), where stimulus specific adaptation (SSA) of

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single neuron firing was observed with repetition of frequent standard sounds, while responses to rare frequency deviants did not adapt. SSA developed rapidly, within a few seconds, but also showed adaptation at longer time scales (Ulanovsky et al., 2004). Indeed there are potential human ERP correlates of SSA in human auditory cortex (Nelken, 2004). First, the N1 component shows amplitude decrement with repetition (Butler, 1968; Näätänen and Picton, 1987). However, this effect is more determined by inter-stimulus interval (i.e., refractoriness) than stimulus repetition (Budd et al., 1998; Näätänen, 1992).

Furthermore, it is well established that MMN increases progressively with the number of repetitions of the standard stimulus (Sams et al., 1983; Näätänen, 1992; Imada et al., 1993; Javitt et al., 1998), suggesting that MMN reflects the strength of the underlying echoic memory trace, also called the *MMN memory trace effect*. However, MMN is elicited after a trace for preceding standards has been formed and it is so far not known which ERP changes correlate directly with the process of trace formation. A candidate ERP component for trace formation was observed in studies where the standard sounds were changed in frequency between consecutive stimulus trains (roving standard protocol introduced by Cowan et al. (1993) and Winkler et al. (1996)), which enabled us to study the rapid encoding of new auditory information. A fronto-central ERP positivity from 50–220 ms post-stimulus increased in amplitude with repetition of each new standard sound (Baldeweg et al., 2004). This repetition positivity (RP) was observed during both passive and active frequency discrimination tasks (Haenschel et al., *in press*) and accounted for the largest part of the MMN memory trace effect in those studies, suggesting that it may be a marker of the formation and strengthening of echoic memory traces. A different mechanism of adaptation, i.e., adaptation level theory, has been discussed in Ullsperger and Baldeweg (1991).

### 1.2. MMN as a marker of impaired cortical plasticity in schizophrenia

We considered these adaptation effects (RP) a basic form of cortical plasticity which could be a useful marker of aberrant synaptic function in schizophrenia (reviewed in Harrison and Weinberger, 2005). Specifically, we were interested if the short-term plasticity underlying MMN generation is correlated with measures of neuropsychological impairment, reflecting more widespread cortical deficits in this disorder (Baldeweg et al., 2004). The experimental emphasis on encoding of new auditory information is important, because one of the systems most consistently implicated in cognitive symptoms of schizophrenia is the NMDA type glutamate receptor (Javitt and Zukin, 1991). This receptor system is critical for activity-dependent plasticity (Singer, 1995), in particular in the early phase of stimulus encoding (Krystal et al., 1994) and the induction of cellular mechanisms of short- and long-term potentiation (Kandel, 2001). Furthermore, there is evidence for a role of NMDA receptor dependent neurotransmission in MMN generation (Javitt et al., 1996; Umbricht et al., 2000). This evidence led us to predict that MMN might be a suitable

*in vivo* marker of NMDA dependent neural deficits, such as in NMDA receptor gene expression (Humphries et al., 1996) and cortical dendritic spine density (Garey et al., 1998), the behavioural consequences of which are impairments in cognition.

In two subsequent studies (Baldeweg et al., 2004; Krljes et al., 2003) we indeed found the predicted relationship between the degree of patient's cognitive dysfunction and the efficacy of encoding new auditory information, as measured as a diminution of the MMN memory trace effect shown in Fig. 1. Let us first consider this MMN memory trace effect in more detail. It turned out that this effect (shown for the MMN difference waves in the insets above the graphs) was due to an increase in the negativity to deviants but also of a positivity to standards, visible in the control data. In contrast, the patient group showed a marked attenuation of both ERP effects, resulting in non-significant MMN responses even after 36 standard repetitions. However, the degree of attenuation was variable between patients, and approximately 50% of the variance in their cognitive performance level was accounted for by MMN slope (i.e., the relative increase in MMN from 2 to 36 standards). This correlation was strongest with tasks which required the encoding of new information into long-term memory (episodic memory) and short-term memory (digit span), compared to tasks which were based on retrieval of stored information (vocabulary). Negative correlations of MMN slope were found with markers of illness severity, such as number of hospital admissions and duration of illness. Weak stimulus encoding, as indicated by this study, may also account for the more rapid decay of memory traces as indicated by a study which varied intervals between stimulus trains (Minami and Kirino, 2005).

Our study suggested that the patient's deficits in echoic trace formation and MMN generation were correlated with a more widespread cortical dysfunction, which encompasses short- as well as long-term memory. Furthermore, a correlation between MMN and measures of functional status and levels of independence in living situations in schizophrenia patients has been reported recently (Light and Braff, 2005). Such correlations between a biological marker and illness severity is useful as it will aid in the search for disease modifying variables such as risk factors and drug treatments. In the present study we are beginning to address the question if pharmacological treatments could reverse or ameliorate the deficits in MMN generation and, by proxy, in auditory sensory memory and cognitive performance in this group of patients.

### 1.3. The aim of the present study

Given the consistency with which MMN impairment has been observed in schizophrenia (see meta-analysis and review in Umbricht and Krljes, 2005), it is surprising that only few studies have attempted to test which pharmacological agents could augment MMN (Inami et al., 2005; Engeland et al., 2002). Given the evidence of NMDA receptor dysfunction in schizophrenia (Javitt and Zukin, 1991; Harrison and Weinberger, 2005) and its role in MMN generation (Javitt et al., 1996;

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