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Letter to the editor

Nicotine effect on mismatch negativity in smoking and nonsmoking patients with schizophrenia

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Dear editors,

A fundamental reduction in nicotinic receptor signaling has been associated with schizophrenia, and cigarette smoking could be a form of 'self-medication' for them (Esterlis et al., 2014; Mexal et al., 2010; Smucny and Tregellas, 2017). Patients with schizophrenia show decreased α7 nicotinic acetylcholine receptor (nAChR) expression in several regions, including the cingulate cortex, hippocampus, and thalamus (Freedman et al., 1995). An event-related potentials (ERP) component, mismatch negativity (MMN), is a leading candidate among biological markers for schizophrenia (Naatanen and Alho, 1995a, 1995b). At presynaptic nAChR, nicotine facilitates release of glutamate, and γ-aminobutyric acid (GABA) (Picciotto et al., 2000). In schizophrenia, the *N*-methyl-D-aspartate (NMDA) deficiencies could trace to disrupted MMN generation (Javitt et al., 1995, 1998). MMN and nicotine both may be substrates of cognitive dysfunction in schizophrenia, even though how they might relate to one another is unclear. In this study, we examined the effect of nicotine on MMN in smokers and nonsmokers with and without schizophrenia.

Eighteen patients with schizophrenia (10 nonsmoking; 27.7 ± 6.7, 8 years old 5 males, 8 smoking 32.0 ± 8.3 5m,) and 22 unaffected participants (11 nonsmoking; 30.0 ± 4.9 6m, 11 smoking; 29.0 ± 3.8 6m) underwent three sessions of a frequency MMN paradigm. Each participant gave written informed consent following presentation of a complete study description, and the Institutional Review Board of the Juntendo University Koshigaya Hospital approved the study protocol. The study consisted of a baseline session plus two testing sessions, administered respectively over 3 days, consecutively, at the same time of day. For the baseline session on day 1, participants receive neither placebo nor nicotine, and on days 2 and 3, they received either placebo or nicotine, which were counter-balanced. The skin patch (Nicotinell® TTS® 20) used in this study covers 20 cm^2 of skin, has a total nicotine content of 35 mg. We used an oddball paradigm for ERP recording. Frequencies for deviant (probability = 0.05) and standard (probability = 0.95) tones were respectively 1050 and 1000 Hz, with an onset–onset interval of 600 ms. The experimental task was a single 2000-tone block. A Brain Atlas 2® (Bio-Logic) system was used for recording and analyzing electroencephalography (EEG) data. Repeated-measures analysis of variance (ANOVA) was used for comparing MMN latencies at Fz/Cz sites and we used Dunnett's post hoc tests for intra-group comparisons.

Both group [$F(3, 108) = 6.831$, $p = 0.001$, effect size = 0.754, power $(1 - \beta) = 0.962$] and drug [$F(2, 72) = 13.785$, $p < 0.001$, effect size = 0.612, power $(1 - \beta) = 0.999$] affected MMN latency, and the two factors interacted [$F(6, 216) = 3.314$, $p = 0.006$, effect size = 0.526, power $(1 - \beta) = 0.996$]. In nonsmoking and smoking participants without schizophrenia, transdermally administered nicotine shortened MMN latencies, but it did not do so in nonsmoking participants with schizophrenia. Among participants with schizophrenia who smoked, smoking cessation led to prolonged MMN latencies that returned to baseline after nicotine administration (Fig. 1).

To our knowledge, this study offers the first comparison of nicotine's effects on MMN between smoking and nonsmoking patients with schizophrenia. Our finding of shortened MMN latencies with nicotine administration in nonsmoking and smoking controls but not in nonsmoking participants with schizophrenia suggests that nicotine administration might not ameliorate deficits in nicotinic cholinergic signaling in patients with schizophrenia as readily as in healthy controls. The implication is that the deficient functions of α7 nAChRs are partially irreversible. On the other hand, among smoking patients, MMN latencies were prolonged by smoking cessation but recovered to baseline levels after nicotine administration. Thus, the effects of "self-medication" with chronic nicotine exposure were evident among the smoking patients. These effects may contribute to the potentiation and maintenance of the activation and plasticity of α7 nAChRs in patients with schizophrenia, who otherwise would experience deficient neurotransmission because of low expression levels. This finding suggests that nicotinic cholinergic systems are partially reversible and could potentially be restored by nicotine administration in these patients. In analogy with our findings, Dulude et al. (2010) reported that nicotine increased the amplitude of duration MMN in patients with schizophrenia and concluded that α7 nAChR activation might mediate this effect.

In conclusion, nicotine administration could not ameliorate deficits in nicotinic cholinergic signaling in participants with schizophrenia as readily as in unaffected participants. This finding suggests that deficient nAChR function is partially irreversible in schizophrenia. However, the nicotinic cholinergic system also was partially reversible because it was restored with nicotine administration in the participants with schizophrenia who were smokers. These "self-medication" effects of nicotine may contribute to potentiating or maintaining the activation and plasticity of nAChRs. Our work provides the first comparison of how nicotine affects the MMN in smokers and nonsmokers with schizophrenia. MMN might be useful for elucidating the neural effects of treatments targeting the nicotinic receptor.

Conflict of interest

The authors declare no conflicts of interest.

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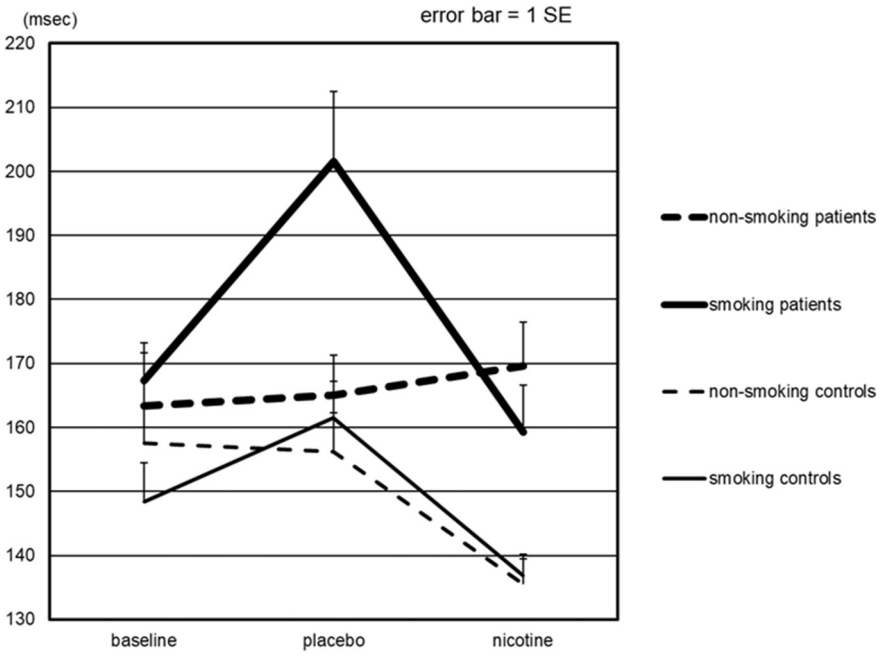

Fig. 1. MMN latencies measured at the Fz site on the scalp. Nicotine shortened the MMN latencies in nonsmoking controls and smoking controls, but not in nonsmoking patients. MMN latencies of smoking patients were prolonged during smoking cessation (placebo), but recovered to baseline levels after nicotine administration. Error bars indicate 1 SE.

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