Effects of transdermal nicotine on cognitive performance in Down's syndrome

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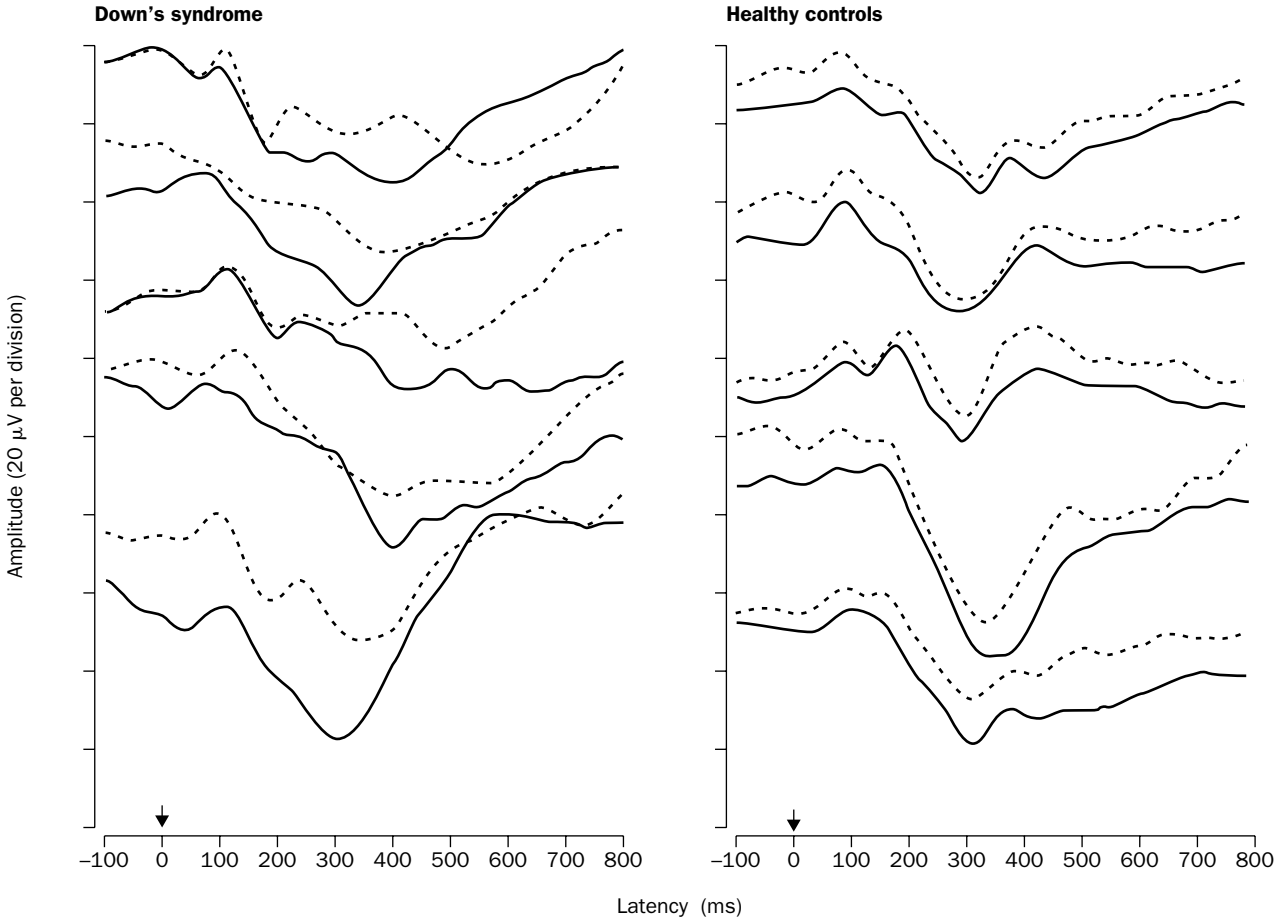
Down's syndrome involves age-dependent neuropathological and neurochemical changes similar to Alzheimer's disease, with cholinergic deficits being the most consistent. There is currently no proven treatment for Down's syndrome. We investigated the effect of nicotine-agonistic stimulation with 5 mg transdermal patches, compared with placebo, on cognitive performance in five adults with the disorder. Improvements possibly related to attention and information processing were seen for Down's syndrome patients compared with healthy controls. Our preliminary findings are encouraging, although not generalisable because of small numbers.

Down's syndrome combines developmental brain abnormalities resulting in early mental retardation with precocious, age-dependent, Alzheimer-like neurodegeneration.[1] Although neuropathological changes and cholinergic deficits similar to Alzheimer's disease are present,[2] only a third of adult patients with Down's syndrome have such progressive dementia, whereas non-demented older patients have selective impairments of recent memory and visuospatial functions. Besides inhibition of acetylcholinesterase, the nicotinic acetylcholine-receptors (nAChR) might represent a therapeutic target.[3] Nicotinergic agonists may combine direct stimulation of nAChRs with cascading effects via stimulation of release of other transmitters involved in cognitive function (acetylcholine, serotonin, dopamine, norepinephrine, γ-aminobutyric acid, and glutamate). Transdermal administration of nicotine has improved attention in Alzheimer's patients, but, as with acetylcholinesterase inhibition, did not improve memory.[3] In one study in Down's syndrome, workers reported improved communication, expressive language, attention, and mood stability after acetylcholinesterase inhibition, but nothing is known about nicotine-agonistic effects.[4]

To explore the acute cognitive effect of nicotinic stimulation, we administered a single dose of transdermal nicotine to five patients with Down's syndrome (aged 18–34 years) and five normal healthy volunteers (aged 20–34 years) in a single-blind randomised, placebo-controlled study with a within-subjects repeated-measures design. We selected ten families with non-institutionalised working adults who had Down's syndrome, of whom five were excluded because of impaired thyroid function (one), hearing impairment (two), unstable cardiac disease (one), and withdrawal (one). We also studied five healthy volunteers in a separate experiment to detect any unspecific solely arousal effect. We randomised the order of assignment of placebo or nicotine in two test sessions to keep learning effects to a minimum. Test sessions were separated by at least 1 week. 5 mg nicotine patches or placebo patches were attached to participants' arms for 2 h. Three Down's syndrome patients and two healthy volunteers received nicotine first. After removal of the patches, we measured auditory event-related potentials (P300) that used a standard active oddball paradigm. Down's syndrome patients



Individual auditory event-related potentials of 30 responses to rare infrequent stimuli for Down's syndrome patients and controls
Target tones of 2000 Hz with 20% probability of appearance and 100 ms duration at central electrode position Cz. Each couple of curves (from top to bottom) represents one individual—thick line=placebo, bold line=nicotine. P300 was the most postive peak between 260 ms and 550 ms. Arrows indicates time of stimulation (0) with 100 ms prestimulus time.

were asked to raise an index finger on each occurrence of the target stimuli (high tone=move finger), and healthy volunteers had to count the target stimuli silently. We also used several neuropsychological tests—digit symbol performance subtest from HAWIE-R (German version of WAIS-R), dot pattern exercise subtest from the Sonneville visual attention task (SVAT), and the Frankfurt attention inventory (FAIR)—done in a fixed order.

The study protocol was approved by the ethics committee of the University of Vienna and informed written consent obtained from the participants or the appropriate responsible people and authorities.

Data are given as mean (SE) and related samples Wilcoxon's signed-ranks test was used for all comparisons.

In the five patients with Down's syndrome nicotine improved P300 amplitude and latency at the central electrode position Cz (figure): mean amplitude (33·2 [SE 3·5, range 24–45] for nicotine *vs* 25·8 μV [3·3, 15·0–36·0] for placebo], p=0·039); mean latency (375 [21, 310–426] *vs* 437 ms [36, 356–554], p=0·042). No significant effect was found at Fz for amplitude (29·8 [3·0] *vs* 23·6 μV [2·7]) or latency (364 [26] *vs* 421 ms [32]), or at Pz for amplitude (28·2 [3·8] *vs* 23·4 μV [2·9]) or latency (376 [20] *vs* 442 ms [35]). Performance in digit-symbol subtest increased after nicotine compared with placebo (raw value 17·4 [3·8] *vs* 13·8 [2·9], p=0·042). SVAT and FAIR could not be done for all individuals and, therefore, were not analysed, which makes generalisation of these results impossible. Mean reaction times and error rate in dot-pattern exercise test improved in the two participants who did the maximum amount of series at the two test times, and another patient completed more series after nicotine, although with increased reaction time and error rate. In non-smoking healthy volunteers, nicotine did not affect latency or amplitude at any electrode site (figure) or any neuropsychological test parameter. Since the task difficulty differs between both groups, we did no between-subjects comparison. Except for slight nausea in one patient with Down's syndrome, no side-effects arose.

The event-related potential P300 is related to brain functions such as attention and information processing. Shorter latency in response to nicotine might reflect improved speed with which attentional resources can be allocated when immediate memory is updated, and P300 amplitude the updating of working memory. Neurochemically, direct glutamatergic triggering of P300 seems to be modulated by cholinergic neurotransmission (amplitude increase and latency decrease).[5] This possible improvement in attention and digit-symbol subtest (HAWIE-R) to measure psychomotor coordination and speed in Down's syndrome is encouraging. The absence of effects in non-smoking healthy volunteers suggest that effects were not solely arousal effects. There are, however, several limitations to interpretation of the observations. The small number of participants means that a beneficial effect can be assumed only for these five patients with Down's syndrome with no generalisability. Each patient received only a single nicotine dose and whether chronic administation would alter results or whether tolerance would develop is unclear. We did not measure nicotine concentrations. Cognitive effects observed to date might be attributed to attentional nicotinic effects, and other cognitive and behavioural benefits warrant further studies. We are not convinced that higher nicotine doses should be tried because of a steep dose-response curve and narrow therapeutic index.[3]

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Coronary heart disease mortality among Arab and Jewish residents of Jerusalem

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Information on coronary heart disease (CHD) in the Palestinian population is sparse. We compared mortality rates in the largely Palestinian Arab population of Jerusalem with the Jewish population of the district between 1984 and 1997 based on official Israeli statistics. CHD mortality and all-cause mortality rates were significantly higher among Arab residents than among Jewish residents aged 35-74 years. Whether the excess CHD mortality reflects increased incidence of events, higher case fatality, or both remains to be established. Possible explanations include a higher prevalence of conventional risk factors such as diabetes, obesity, and smoking in Palestinians, stress effects related to the complex political situation and socioeconomic inequalities, and suspected differences in medical care.

In the aftermath of the 1967 war Israel annexed east Jerusalem. Most of east Jerusalem's Arab residents did not become Israeli citizens, as opposed to the Israeli Arabs who became citizens in 1948. However, the Arab residents were accorded the legal status of permanent Israeli residents with social security benefits, access to health insurance (with full national health coverage since 1995), and access to the job market.

Information on the occurrence of cardiovascular disease in the Palestinian population is sparse. Using Israel Central Bureau of Statistics (CBS) data, we investigated mortality patterns in Arab and Jewish residents of the Israeli-demarcated Jerusalem district from 1984 to 1997. Deaths are notified to the Jerusalem district health office. We compared the cause of death as routinely coded by the CBS (International Classification of Diseases 9th revision codes 410–414 [coronary heart disease] and 140–208 [cancer]) for residents of the district aged 35–74 years. Attribution of cause of death becomes less valid at higher ages. The average study population during the defined period was 135 000 Jews and 34 200 non-Jews (subsequently termed Arabs, this non-Jewish population included a small number of non-Arab Christians and some Israeli Arabs residing within the pre-1967 Jerusalem district borders). Age-standardisation of rates was by the direct method weighted to the world standard population.

CHD mortality rates for Jerusalem were higher among Arab men than Jewish men (rate ratio [RR]=2·05 [95% CI 1·84–2·25] and women (RR=2·68 [2·34–3·01] (table),