Supplementary Online Content


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eAppendix. Methods and results
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This supplementary material has been provided by the authors to give readers additional information about their work.

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### Table: Task effects NoGo > Neutral ($p_{FWE} < .05$, 20 adjacent voxels)

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<th>Region</th>
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Methods

Sample
The initial sample consisted of 384 children of predominantly (>99.0%) European descent, born between 1986 and 1988. Infants were recruited from two obstetric and six children’s hospitals in the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and to control the risk status of the sample (factor 1 varying the degree of obstetric complications, and factor 2 the degree of psychosocial adversity, for full details c.f.[1,2]). To control for confounding effects of family environment and infant medical status, only firstborn children with singleton births and German-speaking parents were enrolled. Assessments were conducted at the age of 3 months and at regular intervals throughout development, most recently at age 25 years. From the initial sample of 384 participants, 18 (4.7%) were excluded due to severe handicaps, and 57 (14.8%) were dropouts, leaving a final sample of 309 for the 25-year assessment. From these, a subsample of N=182 right-handed individuals without current psychopathology were selected to participate in an fMRI session investigating inhibitory control. Exclusion criteria were the usual contraindications for MRI (such as heart pacemaker, neurological abnormalities, history of seizures, unconsciousness or head trauma), current psychiatric disorders as assessed by the Structured Clinical Interview for DSM-IV (SCID-I German version3), and psychotropic medication. Four participants were excluded due to movement artifacts (>2 mm) and systemic lupus erythematosus, respectively, resulting in a final sample of N=178 individuals (73 males, 105 females). 36.0% of this sample had a below-average level of educational attainment, while 2.8% were unskilled. 86.0% of the participants were still in training and 11.2% were students. With regard to maternal smoking during pregnancy, the dropout sample had a significantly higher proportion of smokers [p=.03; 33 (57.9%) were nonsmokers, 9 (15.8%) smoked 1-5 cigarettes per day and 15 (26.3%) smoked more than 5 cigarettes per day], whereas the fMRI sample comprised a significantly lower rate of males (45.9 vs. 60.4%, p=.03). No significant differences between the samples emerged regarding psychosocial / obstetric risk, prenatal stress and postnatal parental smoking.

Prenatal maternal smoking/ alcohol, drug consumption
In the standardized interview, mothers were asked, whether they a) did not smoke, smoked up to b) 5, c) 10, d) 20, e) 40 or f) more than 40 cigarettes per day. To avoid power problems due to small sample sizes, the latter groups (c-f) were pooled. No valid information about alcohol or drug consumption was available.

Postnatal parental smoking
Postnatal smoking of the parents was recorded within the framework of a standardized parent interview conducted at all assessments until the participants were aged 15 years. Smoking was defined as having smoked at least 5 cigarettes per day in any of the assessments (0=parents did not smoke, 1= at least one parent smoked until the offspring’s age of 15 years).

Psychosocial and obstetric adversity
Psychosocial adversity was assessed according to an ‘enriched’ family adversity index as proposed by Rutter & Quinton4 by a standardized parent interview conducted at the 3-month assessment. The index yields a sum score of the presence of 11 adverse family factors, covering characteristics of the parents, the partnership, and the family environment during a period of 1 year prior to the assessment2. An obstetric adversity score was obtained by counting the presence of nine adverse conditions during pregnancy, delivery and the postnatal period1.

Prenatal maternal stress
A standardized parent interview was conducted at the 3-month assessment. 11 questions were asked concerning worries, mood problems, as well as positive experiences during pregnancy. Mothers were requested to judge separately for the first and the second/third trimesters. As associations of prenatal stress in mid- and late pregnancy with behavioral outcome in the offspring have been reported to be largest5,6, only prenatal stress during the second and third trimester was included. Groups were defined according to the median of 3.0.

Lifetime nicotine dependence
Rates of nicotine dependence have turned out to be significantly higher in individuals exposed to tobacco during pregnancy7-9. As expected, lifetime nicotine dependence and maternal smoking during pregnancy were highly correlated (r=.247, p=.001). Lifetime nicotine dependence was measured with the Fagerström Test for Nicotine

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Dependence (FTND)\textsuperscript{10} at each assessment between the ages of 19 and 25 years and added up to a total score (FTND: M=2.38, SD=4.95). Missing values (N=3) were replaced by the mean FTND score.

**Lifetime alcohol abuse**
Additionally, the young adults completed the Alcohol Use Disorders Identification Test (AUDIT),\textsuperscript{11} a screening instrument for the detection of hazardous alcohol use, developed by the WHO. The AUDIT comprises 10 items, referring to the last 12 months, by which patterns of alcohol consumption (items #1–3), alcohol dependence (items #4–6) and adverse consequences of heavy drinking (items #7–10) are assessed. The AUDIT has shown reasonable reliability and validity in a German sample\textsuperscript{12}. Scores between 19 and 25 years of age were added up to a total score. Missing values (N=3) were replaced by the mean AUDIT score.

**Lifetime cannabis abuse**
We assessed lifetime cannabis use at ages 19 to 25 years by a standardized interview asking the participants whether they smoked marijuana during a prevalence period of the last 12 months (0=no, 1=yes) and, then, computed a sum score by adding up the values from each assessment. Missing values (N=3) were replaced by the mean cannabis abuse score.

**Lifetime ADHD symptoms**
The Mannheim Parent Interview (MEI) is a highly structured interview adapted from Rutter’s parent interviews\textsuperscript{13}, which was modified to include all symptoms related to major DSM-IV diagnoses. The K-SADS is a widely used structured diagnostic interview completed independently with parents and adolescents, and has an established body of reliability and validity\textsuperscript{14}. The number of ADHD symptoms present was calculated for each assessment between the ages of 2 and 15 years and sum scores were formed, indexing severity of lifetime ADHD symptoms.

**Novelty seeking**
The psychometric characteristics of the TCI were confirmed for the German version\textsuperscript{15}.

**fMRI parameters and data analysis**
For functional imaging, a total of 277 volumes with 36 slices (matrix 64x64, resolution 3.43x3.43x3 mm with 1-mm gap, repetition time=2210 ms, echo time=28 ms, flip angle=90\textdegree) covering the whole brain were acquired. The slices were inclined 20\textdegree from the anterior/posterior commissure level to minimize dropout artifacts in orbitofrontal and mediotemporal regions. The first 3 fMRI volumes were discarded to allow longitudinal magnetization to reach equilibrium. Preprocessing included slice time correction of the volumes to the first slice, realignment to correct for movement artifacts, coregistration of functional and anatomical data, spatial normalization to standard MNI (Montreal Neurological Institute) space and smoothing with a Gaussian kernel of 8-mm full-width-at-half-maximum (FWHM). Vectors comprising onsets and durations of either NoGo, incongruent, congruent, or neutral trials as well as errors were convolved with the SPM8 canonical hemodynamic response function in the context of a General Linear Model in order to model the BOLD time course. Furthermore, six movement parameters were included as regressors of no interest.

**Flanker task**
Subjects were instructed to press a button corresponding to the central arrow when flankers were other arrows (neutral condition) or squares, but not when flankers were crosses (NoGo condition). Flanking arrows were pointing either in the same (congruent) or opposite (incongruent) direction to the central arrow, thus allowing an investigation of conflict processing and interference. A total of 145 stimuli (33 NoGo) were randomly presented for 800 ms with an interstimulus interval (ISI) which varied between 2.2 and 8.1 seconds. During the ISI, a fixation cross was presented. The total duration of the task was 10 minutes 19 seconds.

**VBM**
T1-weighted images were acquired (192 slices covering whole brain, matrix 256x256, repetition time=2300 ms, echo time=3.03 ms, 50\% distance factor, field of view 256x256x192 mm, flip angle 9\textdegree). An average template from the data was created to which the images were registered. Additionally, the modulated images were affine-transformed to MNI space and smoothed with an 8-mm FWHM kernel. Total intracranial volume was calculated by adding the tissue probabilities of gray matter, white matter and cerebrospinal fluid.

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Mediation

Mediation analysis was applied in order to examine whether the impact of smoking during pregnancy on IFG activity was mediated by IFG volume. Therefore, mean activation and volume were extracted. Mediation was tested by means of the Sobel test\textsuperscript{16} according to Preacher and Hayes.\textsuperscript{17} All effects were adjusted for covariates.
Results

Effects of prenatal smoke exposure
A comparison of activation, adjusted for sex, in individuals exposed to prenatal smoke revealed a significantly lower response in the ACC ($t(175)=5.24$, $p_{FWE}<.001$) and the IFG (right $t(175)=4.50$, $p_{FWE}=.004$; left $t(175)=4.44$, $p_{FWE}=.005$) than among those non-exposed.

Due to missing ADHD symptoms in three participants, we repeated the analysis examining the effect of maternal smoking on the regions of interest (ACC: $t(165)=4.48$, $p_{FWE}=.003$; IFG right: $t(165)=3.71$, $p_{FWE}=.03$; left: $t(165)=4.07$, $p_{FWE}=.01$) in the smaller sample with the previously mentioned covariates. Again, activity in the SMG survived whole brain correction ($t(165)=5.01$, $p_{FWE}=.02$).

Effects of lifetime nicotine dependence
Using smoking in the offspring as a covariate of interest yielded no significant effects in the regions of interest (IFG: left $t(175)=2.66$, $p_{uncorr}=.004$, right $t(175)=3.01$, $p_{uncorr}=.001$, $p_{FWE}=.18$; ACC $t(175)=2.88$, $p_{uncorr}=.002$, $p_{FWE}=.30$). This was true irrespective of the inclusion of covariates (IFG: left $t(168)=1.71$, $p_{uncorr}=.04$, right $t(168)=2.21$, $p_{uncorr}=.01$; ACC $t(168)=2.56$, $p_{uncorr}=.006$).

Mediation
There was a significant effect of smoking during pregnancy on activity in the rIFG ($\beta=-.27$, $SE=.08$, $p=.001$). When including rIFG volume as a mediator, Sobel test revealed a non-significant indirect effect ($p=.88$), with a significant path between prenatal exposure to tobacco and rIFG volume ($\beta=-.03$, $SE=.01$, $p<.001$), but not between rIFG volume and rIFG activity ($\beta=-.12$, $SE=.78$, $p=.88$).

Effects of postnatal parental smoking
Comparison of individuals exposed vs non-exposed to postnatal parental smoking in the absence of prenatal smoking did not yield significant effects in the IFG (right: $t(131)=3.08$, $p_{FWE}=.16$; left: $p_{uncorr}>.05$). However, postnatal smoking was related to lower activity in the subgenual ACC ($t(131)=3.71$, $p_{FWE}=.04$). There was no overlap between this region and the dorsal ACC, which showed an effect of prenatal smoking.

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eReferences


