Effect of Prenatal Exposure to Tobacco Smoke on Inhibitory Control
Neuroimaging Results From a 25-Year Prospective Study

Nathalie E. Holz, MA; Regina Boecker, MA; Sarah Baumeister, MA; Erika Hohm, MA; Katrin Zohsel, PhD; Arlette F. Buchmann, PhD; Dorothea Blomeyer, PhD; Christine Jennen-Steinmetz, PhD; Sarah Hohmann, MD; Isabella Wolf, PhD; Michael M. Plichta, PhD; Andreas Meyer-Lindenberg, MD, PhD; Tobias Banaschewski, MD, PhD; Daniel Brandeis, PhD; Manfred Laucht, PhD

**IMPORTANCE**
There is accumulating evidence relating maternal smoking during pregnancy to attention-deficit/hyperactivity disorder (ADHD) without elucidating specific mechanisms. Research investigating the neurobiological underpinnings of this disorder has implicated deficits during response inhibition. Attempts to uncover the effect of prenatal exposure to nicotine on inhibitory control may thus be of high clinical importance.

**OBJECTIVE**
To clarify the influence of maternal smoking during pregnancy (hereafter referred to as prenatal smoking) on the neural circuitry of response inhibition and its association with related behavioral phenotypes such as ADHD and novelty seeking in the mother’s offspring.

**DESIGN, SETTING, AND PARTICIPANTS**
Functional magnetic resonance imaging was performed for the offspring at 25 years of age during a modified Eriksen flanker/NoGo task, and voxel-based morphometry was performed to study brain volume differences of the offspring. Prenatal smoking (1-5 cigarettes per day [14 mothers] or >5 cigarettes per day [24 mothers]) and lifetime ADHD symptoms were determined using standardized parent interviews at the offspring’s age of 3 months and over a period of 13 years (from 2 to 15 years of age), respectively. Novelty seeking was assessed at 19 years of age. Analyses were adjusted for sex, parental postnatal smoking, psychosocial and obstetric adversity, maternal prenatal stress, and lifetime substance abuse. A total of 178 young adults (73 males) without current psychopathology from a community sample followed since birth (Mannheim, Germany) participated in the study.

**MAIN OUTCOMES AND MEASURES**
Functional magnetic resonance imaging response, morphometric data, lifetime ADHD symptoms, and novelty seeking.

**RESULTS**
Participants prenatally exposed to nicotine exhibited a weaker response in the anterior cingulate cortex ($t_{168} = 4.46$; peak Montreal Neurological Institute [MNI] coordinates $x = −2, y = 20, z = 30$; familywise error [FWE]-corrected $P = .003$), the right inferior frontal gyrus ($t_{168} = 3.65$; peak MNI coordinates $x = 44, y = 38, z = 12$; FWE-corrected $P = .04$), the left inferior frontal gyrus ($t_{168} = 4.09$; peak MNI coordinates $x = −38, y = 36, z = 8$; FWE-corrected $P = .009$), and the supramarginal gyrus ($t_{168} = 5.03$; peak MNI coordinates $x = 64, y = −28, z = 22$; FWE-corrected $P = .02$) during the processing of the NoGo compared to neutral stimuli, while presenting a decreased volume in the right inferior frontal gyrus. These findings were obtained irrespective of the adjustment of confounders, ADHD symptoms, and novelty seeking. There was an inverse relationship between inferior frontal gyrus activity and ADHD symptoms and between anterior cingulate cortex activity and novelty seeking.

**CONCLUSIONS AND RELEVANCE**
These findings point to a functional involvement of prenatal exposure to tobacco smoke in neural alterations similar to ADHD, which underlines the importance of smoking prevention treatments.

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About 22% of the European female population smokes,\(^1\) with approximately half of the female smokers continuing to smoke during pregnancy.\(^2-3\) Prenatal exposure to tobacco smoke is a well-established risk factor for adverse physical\(^4\) and mental outcomes in the offspring.\(^5,6\) In particular, a growing body of literature indicates that smoking during pregnancy may increase the risk of externalizing psychopathology, such as attention-deficit/hyperactivity disorder (ADHD).\(^7-13\) So far, however, there is controversy over whether this association is causal or mediated by genetic risk.\(^13,34\) Attention-deficit/hyperactivity disorder is characterized by symptoms of inattention, hyperactivity, and impulsivity.\(^55\) Research on the neuropsychological underpinnings of ADHD has revealed that individuals with this disorder exhibit poorer performance on tasks involving inhibitory control.\(^16,17\) In contrast, another study\(^38\) observed an increase in fractional anisotropy in the corpus callosum, as well as in frontal regions. As yet, research on the effect of maternal smoking on a functional level is rare. Only 2 studies\(^9,39\) with small samples reported increased activation in areas related to response inhibition during a NoGo task, which the authors interpreted as compensational recruitment. Likewise, increased activation of brain regions, such as the hippocampus during visuospatial memory\(^33\) and the superior temporal sulcus and the lingual gyrus during auditory attention,\(^32\) has been demonstrated in prenatally exposed offspring. However, a recent study\(^33\) observed less striatal and occipital activity during the anticipation of rewards in adolescents exposed to maternal smoking during pregnancy, in line with the reported hyposensitivity of the reward circuit during anticipation in ADHD.\(^34\)

Current evidence of the association between maternal smoking during pregnancy and different brain endophenotypes has been rather sparse with regard to critical neural functions such as inhibitory control. Moreover, interpretation has been equivocal owing to a failure to control for covarying factors such as prenatal and perinatal risks\(^35-37\) and psychosocial adversity.\(^38,39\) Also, it is likely that mothers who smoke during pregnancy continue smoking after childbirth, presenting another possible confounder. In addition, rates of substance abuse, such as nicotine dependence and excessive alcohol and cannabis consumption, have been found to be significantly higher for individuals exposed to tobacco during pregnancy.\(^40-42\) Critically, retrospective assessments of smoking during pregnancy\(^39-42\) may have distorted the results, highlighting the need for prospective studies.

Given the well-documented association of smoking during pregnancy with externalizing disorders such as ADHD, the present study aimed at clarifying the effect of prenatal exposure to tobacco smoke on the neural activity (in the IFG and ACC) implicated in these disorders (ie, inhibitory control as measured by the flanker/NoGo task\(^44-46\) using data from an epidemiological cohort sample of young adults followed since birth). Moreover, we intended to examine (1) whether the effect of maternal smoking during pregnancy also results in structural alterations and (2) whether a possible effect on neural activity is related to ADHD and to novelty seeking (NS), a temperamental characteristic associated with ADHD.\(^47,48\)

### Methods

#### Sample

This investigation was conducted in the framework of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study of the long-term outcome of early risk factors (for full details, see Laucht et al\(^49,50\); eAppendix in the Supplement). Our study was approved by the ethics committee of the University of Heidelberg, and written informed consent was obtained from all participants. The participants were financially compensated.

#### Assessments

**Prenatal Smoking**

Maternal smoking during pregnancy (hereafter referred to as prenatal smoking) was determined by a standardized interview with the mother conducted at the 3-month assessment. Of the 178 mothers, 140 (78.7%) were nonsmokers, 14 (7.9%) reported smoking 1 to 5 cigarettes per day, and 24 (13.5%) reported smoking more than 5 cigarettes per day (for further details, see eAppendix in the Supplement).

**Covariates**

The results were adjusted for several important confounders, such as sex, psychosocial and obstetric adversity, and prenatal maternal stress, which were assessed by a standardized parent interview conducted at the offspring’s age of 3 months. In addition, data on lifetime nicotine dependence (as measured by the Fagerström Test for Nicotine Dependence),\(^51\) lifetime alcohol abuse (as assessed by the Alcohol Use Disorders Identification Test),\(^52\) and lifetime cannabis abuse (12-month prevalence) of the offspring were collected at each assessment between the ages of 19 and 25 years. Furthermore, postnatal parental smoking was assessed until the offspring were 15 years of age (for further details, see eAppendix in the Supplement).

**Lifetime ADHD Symptoms**

For 175 participants, ADHD symptoms were assessed with the Mannheim Parent Interview\(^53\) at 2, 4, 8, and 11 years of age and with the German version\(^54\) of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)\(^55\) at 15 years of age. A sum score was computed to provide a measure of lifetime ADHD symptoms (see details in eAppendix in the Supplement).
Novelty Seeking

Novelty seeking was assessed at 19 years of age using the Temperament and Character Inventory,56 which captured 4 temperament traits (for more details, see eAppendix in the Supplement).

Functional Magnetic Resonance Imaging

Flanker Task

A validated flanker/NoGo task44,46 was applied. Participants saw an array of 5 shapes, including a central target arrow pointing either left or right, flanked by 2 shapes (arrows, squares, or crosses) on each side. They had to withhold their responses when the flankers were crosses (22.8% of the stimuli). Further details can be found in the eAppendix in the Supplement.

Functional Magnetic Resonance Imaging Parameters and Data Analysis

Functional magnetic resonance imaging (fMRI) was performed using a 3-T scanner (MAGNETOM Trio; Siemens) with a standard 12-channel head coil. The imaging protocol consisted of a localizer scan followed by a blood oxygenation level-dependent (BOLD)-sensitive T2*-weighted echoplanar imaging sequence and a structural T1-weighted sequence. The functional images were analyzed using Statistical Parametric Mapping version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.12. (MathWorks Inc) with standard preprocessing steps (eAppendix in the Supplement).

First-level contrast images revealing activation to NoGo vs neutral trials were entered into a second-level random-effects group analysis with smoking during pregnancy as a covariate of interest (0 = nonexposed, 1 = exposed to 1-5 cigarettes per day, and 2 = exposed to >5 cigarettes per day) and sex as a covariate of no interest. In a second step, we controlled for all covariates previously mentioned. Similar results were obtained when comparing nonexposed and less exposed (1-5 cigarettes per day) participants with those exposed to more than 5 cigarettes per day (not reported herein). For exploratory whole-brain analyses, a familywise error (FWE)-corrected P < .05 and a criterion of 20 adjacent voxels were set. According to previous research,57 the ACC and the IFG were defined as regions of interest using the corresponding automated anatomical labeling58 masks implemented in the Wake Forest University PickAtlas version 2.4,59 for which an FWE-corrected P < .05 was applied. For display reasons, the statistical threshold was set to P < .005 uncorrected in the regions of interest. To visualize and further analyze the effects using t tests and multiple regression, the mean contrast values of each participant were extracted from the significant clusters and exported to SPSS Statistics 20 (IBM). Given the previously reported association of ACC and IFG activity with ADHD,18 we examined whether brain activity in the significant clusters of the regions of interest and, on an exploratory level, in the supramarginal gyrus (SMG) was related to lifetime symptoms of this disorder, using Pearson correlations.

Voxel-Based Morphometry

To analyze the effects of maternal smoking during pregnancy on brain volume, the 1 × 1 × 1-mm T1-weighted anatomical images were bias-corrected and classified into gray matter, white matter, cerebrospinal fluid, and nonbrain tissue using the DARTEL (diffeomorphic anatomical registration using exponentiated Lie algebra) registration toolbox.60 For group statistics of gray matter images, the same analytic strategies, in-cluding all covariates as in the functional analysis, were performed while additionally controlling for total intracranial volume (eAppendix in the Supplement).

Results

Sample Characteristics

As expected, a higher rate of parental postnatal smoking and lifetime nicotine dependence was found in the group prenatally exposed to tobacco smoke (Table). Moreover, in line with previous research, this group exhibited significantly higher lev-
levels of psychosocial adversity and more lifetime ADHD symptoms. Task performance indicated a high level of accuracy and no group difference with regard to total errors, allowing us to specifically probe brain functions related to successful inhibition.

**Functional MRI**

**Task Effects**

Robust task activation related to inhibitory control emerged in the regions of interest ($t_{177} = 8.61$ for the ACC, $t_{177} = 16.33$ for the right IFG, and $t_{177} = 12.93$ for the left IFG; all FWE-corrected $P < .001$). Whole-brain activations are depicted in Figure 1 (eTable in the Supplement).

**Effects of Prenatal Exposure to Tobacco Smoke**

A comparison of activations in individuals exposed to tobacco smoke prenatally revealed a lower response in the ACC ($t_{168} = 4.46$; peak Montreal Neurological Institute [MNI] coordinates $x = −2$, $y = 20$, $z = 30$; FWE-corrected $P = .003$), the right IFG ($t_{168} = 4.09$; peak MNI coordinates $x = 44$, $y = 38$, $z = 12$; FWE-corrected $P = .04$), and the left IFG ($t_{168} = 4.09$; peak MNI coordinates $x = −38$, $y = 36$, $z = 8$; FWE-corrected $P = .009$) than among those unexposed, after controlling for psychosocial and obstetric adversity, lifetime nicotine dependence, parental postnatal smoking, and prenatal stress. Activation in the right SMG ($t_{168} = 5.03$; peak MNI coordinates $x = 64$, $y = −28$, $z = 22$; FWE-corrected $P = .02$) even survived exploratory whole-brain correction for multiple comparisons, irrespective of the inclusion of covariates (Figure 2). The results of prenatal exposure to tobacco smoke controlled for sex only can be found in the eAppendix in the Supplement.

Because some studies have provided evidence against a causal effect of maternal smoking on ADHD, we examined whether the results change when ADHD symptoms and NS are included as additional covariates. However, only marginal differences occurred (ACC: $t_{163} = 4.66$, FWE-corrected $P = .001$; right IFG: $t_{163} = 3.61$, FWE-corrected $P = .04$; left IFG: $t_{163} = 3.94$, FWE-corrected $P = .02$; SMG: $t_{163} = 5.02$, FWE-corrected $P = .02$) (further details are provided in the eAppendix in the Supplement). Likewise, we excluded that the effect of prenatal exposure to tobacco smoke was due to smoking among the offspring using lifetime nicotine dependence as a main predictor (further details are provided in the eAppendix in the Supplement).

**Association Between Neural Alterations and Behavioral Outcomes**

Significant correlations of NS with ACC activity ($r = −0.190$, $P = .01$) and left IFG activity ($r = −0.201$, $P = .01$), as well as correlations at a trend level with IFG activity ($r = −0.128$, $P = .09$) and SMG activity ($r = −0.142$, $P = .06$), were obtained, indicating that the levels of activity in these regions decreased with the level of NS. Furthermore, significant negative correlations of ADHD with left IFG activity ($r = −0.152$, $P = .04$) and
right IFG activity ($r = -0.158, P = .04$) but not with ACC activity ($r = -0.023, P = .76$) or SMG activity ($r = -0.081, P = .29$) were found, demonstrating a decreasing level of activity in the IFG with the number of ADHD symptoms (Figure 3).

Voxel-Based Morphometry
In the region-of-interest analysis, an effect of maternal smoking during pregnancy on the right IFG was obtained ($t_{167} = 4.47$; peak MNI coordinates $x = 46, y = 18, z = 21$; FWE-corrected $P < .001$).
Specifically, the participants who were exposed to tobacco smoke prenatally had significantly smaller volumes of the right IFG compared with those who were not exposed. Parallel volume differences emerged in the left IFG (uncorrected \( P = .002 \)) and in the ACC (uncorrected \( P = .001 \)); however, both regions of interest did not survive FWE correction. Volume differences in the right IFG did not significantly mediate the relationship between prenatal exposure to tobacco smoke and IFG activity (\( P = .88 \); eAppendix in the Supplement).

**Discussion**

The present study investigated the long-term effect of maternal smoking during pregnancy on the functional characteristics of inhibitory control in young adult offspring. Our findings, obtained from a 25-year prospective study, indicated that individuals prenatally exposed to tobacco exhibited less activity in the ACC, the IFG, and the SMG in a dose-dependent manner (except for activity in the right IFG) in response to NoGo vs neutral trials, irrespective of controlling for confounders, together with a decreased volume of the right IFG. Moreover, the differential activity in the ACC and the IFG proved to be inversely related to lifetime ADHD symptoms and NS, whereas no association was found for the SMG.

Although previous research has implicated the ACC in attention processes,\(^\text{61}\) response selection,\(^\text{62}\) and error monitoring,\(^\text{63}\) activity in the IFG has been linked more specifically to response inhibition.\(^\text{18}\) Accordingly, our finding of lower levels of ACC and IFG activity might be suggestive...
of a general lack of flexible cooperation between executive functions (ie, set shifting, monitoring, and inhibition). Functional deficits in both of these brain regions, as well as a thinner cortex in the IFG, have repeatedly been observed in ADHD. Moreover, we demonstrated that a reduced level of ACC activity was related to NS. High levels of this temperamental trait involving impulsiveness and irritability have been assumed to be dopaminergically modulated. Likewise, an association between dopaminergic neurotransmission and attention processes has been proposed. Thus, the observed effect of maternal smoking (ie, a reduced level of ACC activation) might represent a general lack of attention regulation, resulting in a temperament more prone to develop ADHD, which is in accordance with the reported association of ADHD with high levels of NS. In contrast, activity in the IFG was found to be negatively related to symptoms of ADHD, in line with studies demonstrating a specific impairment of the IFG in ADHD during inhibitory control. When controlling for ADHD and NS, both effects remained highly significant, suggesting that the effect of maternal smoking on brain activity cannot primarily be attributed to ADHD.

In addition to the effect of prenatal exposure to tobacco smoke on IFG and ACC activity, whole-brain analysis revealed enhanced deactivation in the SMG of the exposed group. The SMG has been implicated in the default mode network, with its deactivation probably being indicative of increased attentional focus. So far, evidence is lacking as to whether the SMG is compromised in ADHD during inhibitory control. Instead, Brieber et al found an increase in SMG gray matter in patients with autism compared with patients with ADHD and controls, with no difference between the latter 2 groups of participants. In addition, SMG volume appears to mediate the effect of early psychosocial deprivation on inattention. These results and the lack of an association with ADHD symptoms in our study may be interpreted as suggesting a potential compensatory attention pathway in individuals prenatally exposed to tobacco smoke, which is not typically observed in ADHD.

Previous research has highlighted the association between smoking during pregnancy and conduct disorder. In our study, we refrained from including conduct disorder as a behavioral phenotype because our flanker paradigm measured “cool” inhibition (ie, pragmatic decision without affect component). In contrast, conduct disorder has been consistently associated with deficits in emotion regulation and differential activation in hot regulatory regions during emotion processing. Accordingly, Rubia et al identified the inferior prefrontal cortex to be specifically hypoactivated in ADHD compared with conduct disorder during inhibitory control.

Animal research on the neurobiological pathways underlying the effect of smoking during pregnancy on the fetus has emphasized the negative consequences of nicotine on acetylcholine receptors and cholinergic neurotransmission resulting in a short-term upregulation of nicotinic acetylcholine receptor binding sites followed by cholinergic hypoactivity in adolescence and adulthood. Moreover, a high density of nicotinic acetylcholine receptors has been found in the ACC and the insula, the latter being next to the IFG. This finding is well in line with our results suggesting that these areas are neural targets of the detrimental effects of prenatal exposure to nicotine. One may speculate that a postnatal “withdrawal” effect in the offspring might result in an understimulation of those receptors in the ACC, which, in turn, may lead to a higher level of NS.

In line with evidence indicating an increased risk of nicotine dependence in the offspring of mothers who smoked during pregnancy, lifetime nicotine dependence was positively related to prenatal exposure to tobacco smoke in our sample (eAppendix in the Supplement). It has been suggested that exposure to nicotine may alter brain development, presumably in prefrontal areas. Accordingly, Galván et al reported a negative association between smoking behavior and prefrontal function during response inhibition. By controlling for lifetime nicotine dependence, we ruled out that smoking among the offspring might account for the observed effects.

Recent research has discussed the fetal programming hypothesis, which is the adjustment of the fetus to an adverse environment as a consequence of adversities, such as poor nutrition during pregnancy. If the maternal forecast contradicts the actual postnatal environment, which, for example, is rich, maladaptation results in negative consequences for the
offspring.88-90 Such fetal programming can, for example, be assessed through epigenetics. Indeed, there is evidence for global methylation,91 as well as gene-specific methylation alterations,92,93 as a consequence of prenatal nicotine exposure. Future studies should investigate how methylation patterns change in candidate genes previously associated with ADHD, such as the dopamine transporter94 or the catechol-O-methyltransferase,95 after maternal smoking during pregnancy. Interestingly, methylation of the catechol-O-methyltransferase promoter has already been demonstrated to be a function of nicotine exposure.96

In contrast to previous studies99,35 reporting higher activity following prenatal exposure to tobacco, we found lower activity in areas related to inhibitory control. Several reasons may be responsible for this discrepancy, such as differences in sample composition, with our sample being substantially larger and consisting of adults only. Furthermore, we controlled for a number of covariates previously reported to be related to smoking during pregnancy. Moreover, we used a more difficult flanker/NoGo paradigm, in which NoGo stimuli occurred less frequently. In addition, our results were corrected for multiple comparisons, thus decreasing the likelihood of false-positive findings. Finally, we were able to demonstrate behavioral correlates of the observed region-of-interest activation.

In the present study, a validated fMRI paradigm was used to assess inhibitory control under conditions of high accuracy. Although group differences at the functional level were obtained, individuals prenatally exposed to tobacco did not significantly differ from those unexposed with regard to task performance. One reason for this could be that the difficulty level of the task was not sufficiently high for group differences to emerge. However, the present approach enabled us to focus on brain activity during successful inhibition. In contrast, during stop signal tasks yielding a significant number stop failures, additional error-related processes can be studied. Hence, future studies should examine whether, during a stop signal task, group differences also occur during error processing or at the level of task performance.

The present study has several limitations that have to be taken into account. First, relatively few participants had been exposed to prenatal nicotine in comparison with other studies (eg, see Müller et al97). However, in contrast to most of the published studies using fMRI, we assessed smoking during pregnancy shortly after birth, thus minimizing confounders such as recall bias. Second, self-report data have been shown to underestimate the proportion of mothers smoking during pregnancy (eg, see Lindqvist et al97). The measurement of cotinine (a metabolite of nicotine) in blood, saliva, or urine would have allowed us to validate the amount of exposure to nicotine.98 Third, no data were available on paternal smoking during pregnancy, which has been related to a decrease in the level of attentional control in children with ADHD.99 However, this effect remains equivocal because another study39 was unable to establish a relationship between passive smoking during pregnancy and ADHD. Fourth, every individual who was exposed to maternal smoking during pregnancy has also been exposed to parental smoking after pregnancy. As a consequence, the reported effects of regression analyses adjusted for postnatal smoking represent the effects of prenatal maternal smoking in the presence of postnatal parental smoking. The effect of prenatal smoking in the absence of postnatal smoking cannot be estimated with our data. It is, however, assumed that this type of maternal smoking behavior is rather rare (eg, see Xu et al100). Moreover, a comparison of groups exposed vs not exposed to postnatal smoking (both groups without prenatal smoking) did not yield significant effects in our regions of interest (see details in eAppendix in the Supplement). Fifth, NS and lifetime ADHD symptoms were not assessed simultaneously with fMRI activation. However, the personality trait of NS has been suggested to exhibit a considerable stability.101 Likewise, ADHD is a disorder with high heritability that is rooted in childhood. Hence, problems related to non-simultaneous assessment of behavioral outcomes and neural phenotypes should be minimized. Sixth, current research discusses the possibility as to whether the association between smoking during pregnancy and ADHD might be mediated by inherited effects.14 Because data on maternal ADHD and NS were not available in the present study, we were unable to control for these possible confounders. However, although ADHD and NS exhibit high heritability,101,102 our results cannot, for the most part, be accounted for by these characteristics. Thus, smoking during pregnancy appears to exert more extensive effects on brain activity than can be solely attributed to inherited effects.

Conclusions

In conclusion, our results suggest that smoking during pregnancy may have widespread long-term effects on neural activity and development independent of prenatal and postnatal adversity, as well as substance abuse, among the offspring. Therefore, our findings strengthen the importance of smoking cessation programs for pregnant women and women planning to become pregnant, to minimize prenatal exposure to tobacco smoke by the offspring.
for the integrity of the data and the accuracy of the data analysis. Drs Brandeis and Laucht contributed equally to this work.

Study concept and design: Buchmann, Pichla, Meyer-Lindenberg, Banaschewski, Brandeis, Laucht.

Acquisition, analysis, or interpretation of data: Holz, Boecker, Baumeister, Hohm, Zohsel, Buchmann, Blomery, Jennen-Steinmetz, Hohm, Wolf, Banaschewski, Brandeis.

Drafting of the manuscript: Holz, Baumeister, Laucht.

Critical revision of the manuscript for important intellectual content: Boecker, Hohm, Zohsel, Buchmann, Blomery, Jennen-Steinmetz, Hohm, Wolf, Pichla, Meyer-Lindenberg, Banaschewski, Brandeis.

Statistical analysis: Holz, Hohm, Zohsel, Jennen-Steinmetz, Brandeis.

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