European Neuropsychopharmacology (2019) 29, 235–246

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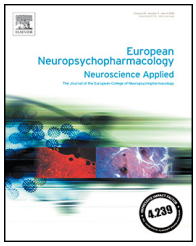

Effects of nicotine and atomoxetine on brain function during response inhibition

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Received 25 June 2018; received in revised form 21 November 2018; accepted 1 December 2018

KEYWORDS
Nicotine;
Atomoxetine;
Cognitive control;
Inhibition;
Neuroimaging;
Impulsivity

Abstract
The nicotinic acetylcholine receptor (nAChR) agonist nicotine and the noradrenaline transporter inhibitor atomoxetine are widely studied substances due to their propensity to alleviate cognitive deficits in psychiatric and neurological patients and their beneficial effects on some aspects of cognitive functions in healthy individuals. However, despite growing evidence of acetylcholine-noradrenaline interactions, there are only very few direct comparisons of the two substances. Here, we investigated the effects of nicotine and atomoxetine on response inhibition in the stop-signal task and we characterised the neural correlates of these effects using blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) at 3T. Nicotine (7 mg dermal patch) and atomoxetine (60 mg per os) were applied to $N = 26$ young, healthy adults in a double-blind, placebo-controlled, cross-over, within-subjects design. BOLD images were collected during a stop-signal task that controlled for infrequency of stop trials. There were no drug effects on behavioural performance or subjective state measures. However, there was a pronounced upregulation of activation in bilateral prefrontal and left parietal cortex following nicotine during successful compared to unsuccessful stop trials. The effect of nicotine on BOLD during failed stop trials was correlated across individuals with a measure of trait impulsivity. Atomoxetine, however, had no discernible effects on BOLD. We conclude that nicotine effects on brain function during inhibitory control are most pronounced in

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https://doi.org/10.1016/j.euroneuro.2018.12.004

individuals with higher levels of impulsivity. This finding is compatible with previous evidence of nicotine effects on stop-signal task performance in highly impulsive individuals and implicates the nAChR in the neural basis of impulsivity.

1. Introduction

The ability to stop oneself from acting if demanded by situational contexts is an important function of inhibitory control and has been experimentally modelled with the stop-signal task (SST) (Verbruggen and Logan, 2008). The SST requires participants to make frequent responses to stimuli in a choice reaction task but to cancel their response on a minority of trials when a stop signal occurs shortly after the imperative stimulus. Functional magnetic resonance imaging (fMRI) studies have shown that frontal and striatal structures are activated when participants perform the SST (Verbruggen and Logan, 2008; Sebastian et al., 2018), with recent research aiming to dissect this network into functional roles pointing to the importance of controlling for stimulus infrequency of stop-signal trials (Sharp et al., 2010). The neurotransmitter systems underlying response inhibition are not fully understood, but cholinergic, noradrenergic and dopaminergic systems have been shown to play a role (Bari and Robbins, 2013; Schmidt et al., 2017).

The nicotinic acetylcholine receptor (nAChR) agonist nicotine has beneficial effects on SST performance in populations with inhibitory impairment (for review, see Ettinger and Kumari, 2018). Specifically, nicotine improves performance in non-smoking adolescents and adults with attention deficit hyperactivity disorder (ADHD) (Potter and Newhouse, 2004, 2008) and in impulsive non-smoking adults (Potter et al., 2012). Beneficial effects have also been observed in cigarette-withdrawn smokers following smoking as usual compared to abstinence (Ashare and Hawk, 2012; Charles-Walsh et al., 2014; Tsaur et al., 2015). Effects in non-impaired, non-smoking adults, however, are mostly negative (Ettinger and Kumari, 2018). Concerning neural effects, in the only available fMRI study, nicotine increased anterior cingulate activation during inhibition failures in both schizophrenia patients and healthy controls and caused up-regulation of activation in right caudate during inhibition failures in patients (Moran et al., 2018).

Regarding noradrenaline, several studies have focussed on atomoxetine, a noradrenaline transporter blocker used in the treatment of ADHD (Clemow and Bushe, 2015). Single-dose administration of atomoxetine has been found to improve SST performance in studies of healthy adults (Chamberlain et al., 2006, 2009), adults with ADHD (Chamberlain et al., 2007) and Parkinson's disease patients (PD) (Kehagia et al., 2014; Rae et al., 2016). Other studies, however, have failed to observe effects in healthy adults (Nandam et al., 2011) or boys with ADHD (Cubillo et al., 2014). fMRI studies have reported that atomoxetine increases right IFC activation during stop-trials in healthy adults (Chamberlain et al., 2009) and normalises otherwise dysfunctional brain functional networks in boys with ADHD (Cubillo et al., 2014) and PD patients (Rae et al., 2016).

Both nicotine and atomoxetine are studied widely due to their propensity to alleviate cognitive deficits in neuropsychiatric patients and to enhance cognitive function in healthy adults. However, whilst beneficial effects of the two substances have been described separately in previous studies, their effect profiles in these populations have not been directly compared. However, evidence from direct comparisons is essential for a number of reasons. First, such data are needed in clinical practice to inform decision making about which types of drugs are likely to best act on specific domains of dysfunction in patients. Second, basic research has generated theories on the specific roles of different neurotransmitter systems in cognition (Robbins, 2013), which require multi-drug comparison studies for substantiation.

However, only very little evidence exists to compare and contrast the cognitive effects of nicotine and atomoxetine (Gould et al., 2005) and no fMRI study has compared the substances' effects on brain function. Head-to-head comparisons are particularly called for regarding these two substances, given evidence of interactions between the cholinergic and noradrenergic systems. For example, the cognitive symptoms of ADHD have been argued to resemble those observed during nicotine withdrawal, and atomoxetine has been found to reverse nicotine-withdrawal induced deficits in contextual fear conditioning in mice (Davis and Gould, 2007) and abstinence-induced withdrawal symptoms in smokers (Ray et al., 2009). Further, in mice prenatally exposed to nicotine, cognitive deficits in adulthood are reversed by atomoxetine (Alkam et al., 2017).

Therefore, the aims of the current study were to compare the effects of nicotine and atomoxetine on behavioural performance in the SST, on subjective state measures, and on brain function during a variant of the SST that controls for the effects of stimulus infrequency (Sharp et al., 2010). Given previous findings of nicotine effects on error processing in the SST (Moran et al., 2018), we also explored drug effects on post-error slowing in reaction times following inhibition failures. Given evidence of beneficial effects of nicotine and atomoxetine in impaired or impulsive samples (Ettinger and Kumari, 2018), we additionally explored whether individual differences in trait impulsivity are associated with the magnitude of the drug effects.

2. Experimental procedures

2.1. Participants

Healthy participants were recruited through mailing lists, online job platforms and advertisements at the University of Bonn, Germany. We applied the following inclusion criteria: German-speaking, right-handed (Oldfield, 1971), normal or corrected-to-normal vision, aged 18–35 years, weight 50–120 kg. Exclusion criteria were pregnancy, hypertension, chronic and severe disease, psychiatric disorder as assessed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), relatives (up to third grade) with psychosis or bipolar disorder, current intake of

medication affecting the CNS, smoking more than 20 cigarettes/lifetime, or drug abuse. Further exclusion criteria concerned MRI contraindications to assure participant safety and to avoid disturbances in image acquisition (e.g., claustrophobia, metallic implants). Before commencing the study procedures, participants underwent an examination by the study physician to ensure physical health.

The study was approved by the research ethics committee of the Department of Psychology at the University of Bonn. Participants gave written informed consent and received reimbursement for their time.

2.2. Procedure

A double-blind, placebo-controlled, cross-over, within-subjects design was employed. Order of drug administration was varied between participants using a Latin-square design (Supplementary Table 1). Assessments took place on the same weekday at the same time of day for each participant for three consecutive weeks. On each occasion, participants received a dermal patch 180 min prior to scanning and a capsule ingested with water 90 min prior to scanning. Sessions were counter-balanced with regard to substance and task order (another task was administered, not reported here).

The dermal patch was either nicotine (NiQuitin Clear®, 7 mg, GlaxoSmithKline, Germany) or placebo (Rheumaplast, 4.8 mg, Hansaplast, Germany) and was applied to the left shoulder. The capsule either contained atomoxetine (Strattera, 60 mg, Eli Lilly and Company) or placebo (Mannitol with 0.5% AEROSIL®). Drug administration was randomised such that in each session a participant received either one of the two active substances and a placebo or two placebos, but never both active substances. Study staff applying the patch did not collect and analyse data, thereby ensuring double-blindness.

Dosage and administration time of nicotine were chosen following earlier studies in non-smokers (Potter et al., 2012; Petrovsky et al., 2012; Ettinger et al., 2017) and treatment guidelines reporting the plasma concentration of nicotine to achieve a plateau within 2–4 h after transdermal application (Summary of Product Characteristics of NiQuitin Clear). Similarly, atomoxetine has been shown to produce behavioural effects at the selected dose and reaches peak plasma levels within 1–2 hours after application (Chamberlain et al., 2009).

Participants were asked to abstain from alcohol, orange and grapefruit juice the evening before and on the day of the scanning session and to maintain their habits regarding caffeine consumption, nutrition, physical activity as well as bed and waking times. After drug administration, participants rested in a quiet room and fasted (except for water) until the start of the scan. During the waiting period, data on handedness (Edinburgh Handedness Inventory, EHI; Oldfield, 1971), verbal intelligence (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B; Lehrl, 2005), and impulsivity (Barratt Impulsiveness Scale, BIS-11; Patton et al., 1995) were collected. The BIS-11 is a 30-item self-report questionnaire. BIS-11 items are answered using a four-point response format of rarely/never (1), occasionally (2), often (3), and almost always/always (4). The BIS-11 total score was computed, with higher scores indicating higher levels of impulsivity (possible range, 30–120).

Subjective measures of mental states were obtained using visual analogue scales (VAS) (Bond and Lader, 1974) immediately before patch administration (T1), before scanning (T2) and after scanning (T3). From these VAS, three subjective measures for each participant and time point were obtained: alertness, contentedness and calmness, where higher scores indicate less alertness, contentedness and calmness.

2.3. Behavioural task

Participants performed a modified version of the SST. The SST used in this study (Supplementary Figure 1) comprised three conditions (Sharp et al., 2010), i.e., (1) Go (280 trials), (2) Stop (60 trials) and (3) Continue (60 trials). The basic task was a choice reaction time task. A trial started with a white fixation cross on a black screen (500 ms) and continued with the appearance of three white arrows (1400 ms) pointing either left or right. Participants had to press their left or right index finger on the response devices (ResponseGrip, NordicNeuroLab, Bergen, Norway) corresponding to the direction of the arrows. A black screen (200–800 ms) was presented at the end of the trial, resulting in an average trial duration of 2500 ms.

In 15% of trials, the middle arrow turned yellow after a short delay, which was the signal to withhold the motor response (stop signal). This stop signal delay (SSD) was initially 250 ms and then changed according to a stair-case procedure. To achieve successful inhibition of approximately 50% in each session, the SSD was increased by 50 ms in the trial following a successful stop signal trial and decreased by 50 ms following an unsuccessful stop signal trial.

Additionally, in 15% of trials, the middle arrow turned blue with the same timing as the stop signal. Participants were instructed no to alter their response and continue with their go response in that case. The duration for both stop and continue cues was 1400 ms minus the current SSD. These continue trials served as control condition for attentional capture of unpredictable perceptual events (Sharp et al., 2010). Participants completed a few training trials to make sure that they comprehended the task before starting the actual scanning procedure. The task lasted approximately 17 min.

The stop signal reaction time (SSRT) was calculated according to the blocked integration method (Verbruggen et al., 2013). Additionally, we calculated post-error slowing (PES) using the robust method suggested by Dutilh et al. (2012) for trials following commission errors on stop trials. PES was computed by averaging the difference between reaction time of go trials after (E + 1) and the reaction time of the go trial before (E − 1) a failed stop trial (E). Additionally, mean and intra-individual coefficient of variation of reaction time (ICV; Nandam et al., 2011), a measure of the variability of task performance, were calculated for go, continue and commission errors of stop trials.

2.4. Statistical analysis of behavioural and subjective measures

Trials with reaction time below 200 ms or higher than 1600 ms were excluded from behavioural and neuroimaging analysis (mean = 4.27% (SD = 6.04) for nicotine, mean = 4.23% (SD = 4.49) for atomoxetine, mean = 3.78% (SD = 4.54) for placebo). Exclusion criteria for participants regarding outliers in task performance were taken from Congdon et al. (2012): (1) percent successful inhibition on stop trials $<25\%$ or $>75\%$; (2) percent correct go/continuous-response $<60\%$; (3) percent go errors $>10\%$; and (4) SSRT that is negative or <50 ms. Statistical analysis of behavioural data was performed with SPSS Statistics 24 (IBM, Armonk, NY, USA). Normality of distribution was assumed when skewness was between -1 and $+1$ for at least two of the three conditions (nicotine, atomoxetine, placebo) and only slightly below or above for the third condition. Log-transformation was applied otherwise. Where sphericity assumption was violated, results were Greenhouse-Geisser corrected and uncorrected degrees of freedom and Greenhouse-Geisser epsilon are reported (Jennings, 1987).

Mean reaction times and ICVs were analysed with a 3×3 analysis of variance (ANOVA) with Trial Type (go, continue, failed stop) and Drug (nicotine, atomoxetine, placebo) as within-subject

factors. The influence of Drug on SSRT and PES was examined with a one-way ANOVA.

Subjective measures (VAS) were analysed using a 3×3 repeated-measures ANOVA with Time (T1, T2, T3) and Drug (nicotine, atomoxetine, placebo) as within-subject factors.

Effect sizes for repeated measures ANOVA were calculated using partial eta squared (partial η^2). For post-hoc comparisons, Cohen's d was calculated as measure of effect size (Morris and DeShon, 2002).

2.5. fMRI data acquisition

Imaging data were collected on a 3-Tesla field strength Magnetom Tim-Trio scanner (Siemens, Erlangen, Germany). Earplugs (OHROPAX, Wehrheim, Germany) and foam pads were used for noise protection and for minimising head movements. The signal was received with a 12-channel head coil. The SST was implemented with in-house software. Stimuli were presented via VisualSystem video goggles and responses were recorded using ResponseGrip hardware (NordicNeuroLab, Bergen, Norway).

T2*-weighted MR echo-planar images (EPI) with blood-oxygenation-level-dependent (BOLD) contrast of the whole brain were acquired (repetition time = 2500 ms, echo time = 30 ms, field of view = 192 × 192, flip angle = 90°, matrix size 96 × 96). Thirty-seven axial slices covering the whole brain were collected in descending order parallel to the AC-PC line, each with a thickness of 3 mm and an inter-slice gap of 0.3 mm leading to a voxel size of $2 \times 2 \times 3.3$ mm and an in-plane resolution of 2×2 mm^2. A total of 400 images were acquired in one session. The first five images were discarded to reach steady-state magnetisation.

Subsequently, a whole brain high-resolution T1-weighted anatomical scan with 192 slices was acquired using a gradient-echo sequence with inversion recovery (GR/IR) sequence (repetition time = 1660 ms, echo time = 2.54 ms, flip angle = 9°, field of view = 256 × 256 mm^2, matrix size 320 × 320) resulting in a voxel size of $0.8 \times 0.8 \times 0.8$ mm.

2.6. fMRI data analysis

fMRI data were pre-processed and analysed using Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running in MATLAB R2015b (The MathWorks, Inc., Natick, MA, USA).

First, movement correction was applied by realigning each participant's functional images to their mean using a least squares approach and a six parameter rigid body transformation (x, y, z, pitch, roll, yaw). Unwarping was performed by means of SPM12 default settings. Second, T1-weighted images were segmented into white matter, grey matter and cerebrospinal fluid using mutual information and a priori tissue probability maps. The T1-weighted high-resolution scan was coregistered to the mean T2*-weighted image of the preceding realign and unwarp process by maximising normalised mutual information using a rigid body transformation. The resulting normalising parameters were used to project the anatomical and functional images via non-linear transformations on the Montreal Neurological Institute (MNI) template with a voxel size of $2 \times 2 \times 2$ mm. Finally, the normalized images were smoothed using an 8 mm full-width at half maximum (FWHM) Gaussian kernel (Mikl et al., 2008). Furthermore, the six movement parameters were used to calculate the total displacement (TD) parameter which contains information about the overall movement for each participant. This was done using the Motion Fingerprint Toolbox (Wilke, 2012) with standard cortical distance (davg) of 65 mm. Participants were excluded if TD exceeded voxel size (TD > 3 mm; Wilke, 2012).

First-level analyses were carried out by means of general linear models. Data were high-pass filtered (128 s). Stimulus onsets were modelled as events, with SSDs as durations. The following regressors were modelled by convolution with a canonical hemodynamic response function: (1) successful stop, (2) failed stop, (3) correct continue and (4) a residual category containing omissions and directional errors of go and continue trials, as well as invalid trials (RT < 200 ms or >1600 ms). Go trials were not modelled and thus served as implicit baseline (Chamberlain et al., 2006; Kasparbauer et al., 2015). Additional regressors included the six individual realignment parameters. The following contrasts were calculated at the first level: (a) successful stop vs. correct continue, (b) failed stop vs. correct continue.

At the second level, first-level contrasts (a) and (b) were entered into a flexible factorial model. Drug (nicotine, atomoxetine, placebo) and Inhibition (successful stop, failed stop) served as within-subject factors. Total displacement was included as covariate. An omnibus F-test was performed to detect clusters with main effects and interaction effects. The F-tests were masked with post-hoc t-comparisons in order to determine direction of the effects.

Post hoc *t*-tests were used to explore the direction of the observed effects and were focused on clusters of the prior F-test that survived correction for multiple comparison. For all analyses, the statistical height-threshold was set to $p < 0.001$ and a cluster-level correction (family wise error at $p < 0.05$) was used at whole-brain level.

Anatomical locations were determined using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) of the WFU PickAtlas toolbox (http://www.ansir.wfubmc.edu/) running in Matlab R2015b. Mean local signal change of clusters of interest was extracted using MarsBaR (MarsBaR region of interest toolbox for SPM, RRID:SCR_009605).

In order to explore associations between drug effects at levels of behaviour and BOLD, Pearson correlations were carried out between change scores of BOLD in clusters that showed significant drug effects and change scores of behavioural variables. Additionally, in order to investigate whether individual differences in impulsivity are associated with the magnitude of drug effects (Ettinger and Kumari, 2018), Pearson correlations were carried out between the BIS-11 total score and variables showing a significant drug effect. All correlations were Bonferroni corrected.

3. Results

3.1. Behavioural data and subjective measures

Forty-two participants were enrolled into the study, of whom five did not complete all fMRI sessions due to nausea ($N = 2$) or technical or scheduling reasons ($N = 3$). Seven participants were excluded due to insufficient task performance (>10% go errors, $N = 1$; <60% go/continue responses, $N = 6$). One participant was excluded due to excessive motion (TD > 3 mm) and three participants' data were discarded due to incomplete image acquisition. Characteristics of the final sample ($N = 26$) are in Table 1. Descriptive statistics of performance variables, TD and subjective ratings are in Table 2.

There was a main effect of Trial Type ($F[2,50] = 107.48$, $p < 0.001$, $\eta p^2 = 0.81$; $\varepsilon = 0.623$) on mean reaction times. Reaction times with a continue signal were 53.72 ms higher than go reaction times ($p < 0.001$), whereas stop signal errors were significantly faster than both continue and go trials (both $p < 0.001$). There was no main effect of Drug and

Table 1 Sample characteristics.

Gender (% female)	50.00	-
Age (years)	23.69	±3.65
Height (cm)	176.04	±10.47
Weight (kg)	70.50	±13.81
IQ	112.38	±12.53
BIS-11	61.31	±8.57

Data are presented in means ± standard deviation unless otherwise stated. IQ: Intelligence quotient based on MWT-B (Lehrl 2005). BIS-11: Barratt Impulsiveness Scale total score (Patton et al., 1995). $N = 26$.

no interaction between Drug and Trial Type on mean reaction times (both $p > 0.87$). There were no main or interaction effects on ICVs ($p > 0.15$).

SSRT was numerically lower with both atomoxetine and nicotine than placebo (Table 2), but there was no statistically significant effect of Drug ($p = 0.46$). Similarly, there was no effect of Drug on post error slowing ($p = 0.20$).

For subjective measures (VAS), there was a main effect of Time on alertness ($F[2,50] = 10.79$, $p < 0.001$, $\eta p^2 = 0.30$). Subjectively experienced alertness was significantly lower after scanning (T3) as compared to T1 ($p < 0.01$) and T2 ($p < 0.01$), but the effect was independent of Drug ($p = 0.45$) and there was no main effect of Drug ($p = 0.65$). There were no main or interaction effects on subjective measures of contentedness and calmness ($p > 0.27$).

3.2. fMRI data

3.2.1. Task effects

Inhibition-related activity was determined by an omnibus F-test. The observed network of significant clusters was mostly due to higher response to successful stop than failed stop trials. Greater BOLD signal was observed during successful stop than failed stop trials in bilateral putamen, fronto-parietal structures (inferior and superior frontal and parietal gyri), motor and sensory areas (precentral and postcentral gyri) and occipital regions (Table 3; Fig. 1). Failed stop compared to successful stop trials elicited higher BOLD in medial frontal cortex (Table 3; Fig. 1).

3.2.2. Drug effects

There were no significant clusters showing a main effect of Drug as investigated by an omnibus F-test. However, there were clusters showing an interaction between Inhibition and Drug in left superior frontal gyrus (SFG) and middle frontal gyrus (MFG), right SFG, and left superior parietal lobule (SPL) and inferior parietal lobule (IPL) as well as occipital cortex (Table 3). These clusters overlapped partly with the inhibition network (Fig. 1). Locations of clusters showing Drug x Inhibition interactions and mean local signal change for each cluster according to Drug condition are in Fig. 2. To examine these interactions, mean local signal change of these clusters was extracted and analysed with post-hoc *t*-tests, using a threshold of $p < 0.006$ after Bonferroni correction.

Table 2 Descriptive statistics of behavioural results, subjective measures, and displacement data.

		Nicotine		Atomoxetine		Placebo	
		Behavioural results					
Go mean RT (ms)		711.91	±178.95	708.02	±190.81	715.65	±181.40
ICV Go		0.20	±0.05	0.21	±0.05	0.21	±0.04
Continue mean RT (ms)		768.81	±185.67	760.35	±203.87	767.58	±188.40
ICV continue		0.20	±0.06	0.19	±0.05	0.20	±0.05
Failed stop mean RT (ms)		658.68	±171.68	646.33	±187.49	650.38	±175.19
ICV failed stop		0.20	±0.09	0.19	±0.07	0.19	±0.07
SSRT (ms)		310.82	±59.80	313.41	±45.87	323.37	±49.72
PES (ms)		2.29	±52.40	−14.62	±55.14	6.19	±42.98
Accuracy go trials (%)		96.09	±6.06	95.81	±5.15	96.59	±4.98
Accuracy continue trials (%)		96.57	±6.88	96.55	±5.38	97.52	±4.98
Accuracy on stop trials (%)		52.38	±6.82	52.76	±5.46	52.63	±5.62
		Subjective measures (VAS)					
Alertness	T1	3.12	±0.75	3.12	±0.65	3.04	±0.69
	T2	3.31	±0.55	3.22	±0.72	3.07	±0.69
	T3	3.50	±0.59	3.46	±0.64	3.49	±0.58
Contentedness	T1	2.82	±0.72	2.70	±0.76	2.70	±0.70
	T2	2.86	±0.74	2.78	±0.94	2.67	±0.75
	T3	2.89	±0.87	2.76	±0.78	2.75	±0.69
Calmness	T1	2.75	±0.93	2.67	±0.88	2.70	±0.77
	T2	2.91	±1.11	2.84	±0.83	2.67	±0.79
	T3	3.02	±0.92	2.83	±0.96	2.75	±0.59
		Displacement Data from fMRI					
Scan to scan displacement		0.09	±0.05	0.08	±0.04	0.09	±0.04
Total displacement		1.06	±0.67	1.53	±1.21	1.25	±0.54

Data are presented in means ± SD. RT: reaction time; ICV: intraindividual coefficient of variation; SSRT: stop signal reaction time; PES: post error slowing; VAS: visual analogue scales (Bond and Lader 1974).

Table 3 fMRI results.

Label	Side	Cluster size	*x*	*y*	*z*	*Z*
Main effect of inhibition (F-test)						
Successful stop > failed stop						
Putamen	Right	1022	16	8	−8	7.40
Putamen	Right		26	−6	8	4.11
Putamen	Right		22	−2	18	3.60
Putamen	Right		28	−14	6	3.52
Putamen	Left	859	−24	8	−4	6.39
Putamen	Left		−12	8	−10	6.01
Putamen	Left		−28	−8	2	4.61
Putamen	Left		−20	22	−16	3.33
Precentral gyrus	Left	10,389	30	−6	54	5.63
Postcentral gyrus	Right		36	−34	44	5.39
Postcentral gyrus	Right		32	−34	46	5.22
Superior frontal gyrus	Right		−28	−8	60	5.17
Superior parietal lobule	Left		22	−64	56	5.04
Superior Parietal Lobule	Right		24	−68	54	5.00
Postcentral gyrus	Right		−40	−36	50	4.96
Middle frontal gyrus	Left		30	8	58	4.94
Middle occipital gyrus	Right		38	−76	34	4.87
Superior parietal lobule	Right		−18	−64	52	4.87
Inferior parietal gyrus	Left		28	−50	50	4.70
NA	Left		−22	−6	46	4.69
Middle occipital gyrus	Right		42	−76	0	4.66
Precentral gyrus	Left		−26	−24	64	4.61
NA	Right		22	−52	50	4.58
Superior frontal gyrus	Right		26	24	54	4.57
Middle occipital gyrus	Left	448	−32	−78	32	4.31
Superior occipital gyrus	Left		−26	−82	30	4.13
Middle occipital gyrus	Left		−26	−76	32	4.12
Middle occipital gyrus	Left		−30	−70	26	3.74
Superior occipital gyrus	Left		−18	−92	20	3.32
Middle occipital gyrus	Left		−22	−94	16	3.31
Superior occipital gyrus	Left		−16	−88	18	3.26
Middle occipital gyrus	Left		−24	−90	10	3.24
Middle occipital gyrus	Left	225	−26	−92	16	3.23
Superior temporal gyrus	Right		64	−20	4	4.11
Superior temporal gyrus	Right		62	−14	2	4.09
Superior temporal gyrus	Right	256	60	−4	−6	3.83
Middle occipital gyrus	Left		−36	−84	0	3.92
Middle occipital gyrus	Left		−40	−86	0	3.86
Middle occipital gyrus	Left		−42	−76	4	3.64
Middle occipital gyrus	Left		−40	−64	6	3.63
Middle occipital gyrus	Left		−40	−70	8	3.34
Failed stop > successful stop						
Medial frontal gyrus	Right	270	2	52	26	4.51
Medial frontal gyrus	Left		−6	50	24	4.28
Interaction drug X inhibition (F-test)						
Superior frontal gyrus	Right	221	24	20	58	3.91
Superior frontal gyrus	Right		26	8	58	3.78
NA	Right		24	2	48	3.71
NA	Right		20	−2	46	3.49
Middle frontal gyrus	Left	212	−26	12	64	4.07
Middle frontal gyrus	Left		−24	18	62	4.01
Middle frontal gyrus	Left		−26	8	60	3.90
Superior frontal gyrus	Left		−18	16	56	3.87
Middle frontal gyrus	Left		−26	4	50	3.18
Precentral gyrus	Left		−28	2	46	3.18

(*continued on next page*)

Table 3 (*continued*)

Label	Side	Cluster size	*x*	*y*	*z*	*Z*
Middle occipital gyrus	Left	301	−30	−70	36	3.85
Inferior parietal lobule	Left		−32	−68	44	3.82
Inferior parietal lobule	Left		−38	−58	50	3.38
Superior parietal lobule	Left		−26	−74	44	3.32
Inferior parietal lobule	Left		−34	−54	38	3.16

Cluster size is given in number of voxels. Coordinates are in MNI space. Results are corrected for multiple comparison at FWE cluster-level $p < 0.05$. $N = 26$.

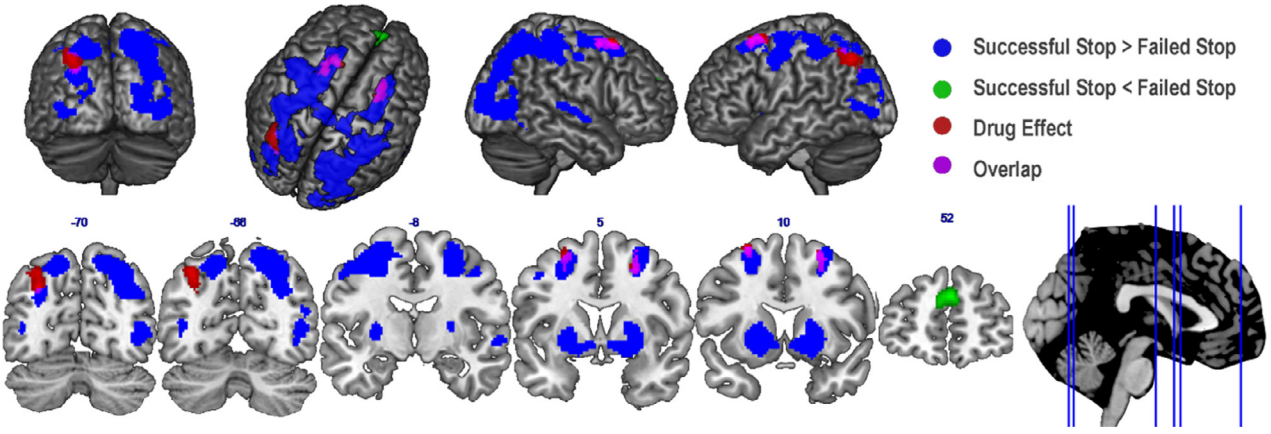

Fig. 1 Task and drug effects on BOLD. The figure shows the task and drug effects on BOLD (also see Table 3). Blue depicts higher BOLD response to successful inhibition as compared to failed inhibition trials. Green illustrates higher BOLD response in trials of failed inhibition as compared to successful stop trials. Red shows the observed drug effect. Purple illustrates the overlap between Drug Effect and Successful Stop > Failed Stop. Images are shown in neurological convention. *Y*-coordinates of images in bottom row are given in MNI space, from left to right: −70, −66, −8, 5, 10, 52. $N = 26$.

In left SFG/MFG, nicotine elicited significantly lower signal than placebo for failed stop trials ($t(25) = -4.31$, $p < 0.001$, $d = -0.85$), and signal was higher for successful than failed stop trials during nicotine ($t(25) = 5.36$, $p < 0.001$, $d = 1.05$). No further comparisons were significant after Bonferroni correction.

In right SFG, the identical pattern was observed: nicotine elicited significantly lower signal than placebo for failed stop trials ($t(25) = -4.93$, $p < 0.001$, $d = -0.97$), and signal was higher for successful than failed stop trials during nicotine ($t(25) = 4.90$, $p < 0.001$, $d = 0.96$). No further comparisons were significant after Bonferroni correction.

The same pattern was also observed in left SPL/IPL: nicotine elicited significantly lower signal than placebo for failed stop trials ($t(25) = -3.00$, $p = 0.006$, $d = -0.59$), and signal was higher for successful than failed stop trials during nicotine ($t(25) = 6.28$, $p < 0.001$, $d = 1.23$). No further comparisons were significant after Bonferroni correction.

Next, the behavioural correlates of these clusters were investigated using Pearson correlations. BOLD difference scores between the nicotine and placebo conditions were correlated with difference scores of all behavioural measures for the comparison between nicotine and placebo. No significant correlation was observed (all $p > 0.01$, n.s. after Bonferroni correction).

Finally, in investigating the relationship between nicotine effects in these clusters and trait impulsivity, a significant negative Pearson correlation emerged between BIS-11 total score and BOLD difference between nicotine and placebo in left SFG/MFG during failed stop trials ($r = -0.78$, $p < 0.001$, significant after Bonferroni correction) (Fig. 3). This finding indicates that the reduction in left SFG/MFG BOLD that is observed with nicotine in the entire group (Fig. 2) is particularly pronounced for individuals with higher levels of impulsivity. No further correlations with BOLD difference scores were significant (all $p > 0.2$, n.s. after Bonferroni correction) and there were no significant correlations between BIS-11 and change scores in behavioural variables (all $p > 0.01$, n.s. after Bonferroni correction).

4. Discussion

The main finding of this study is that nicotine caused an upregulation of fronto-parietal BOLD during successful compared to unsuccessful inhibition trials. Further, the magnitude of BOLD change due to nicotine in left prefrontal cortex was related to trait impulsivity, with stronger BOLD reductions with nicotine during failed stop trials observed in those with higher levels of impulsivity. Nicotine effects were

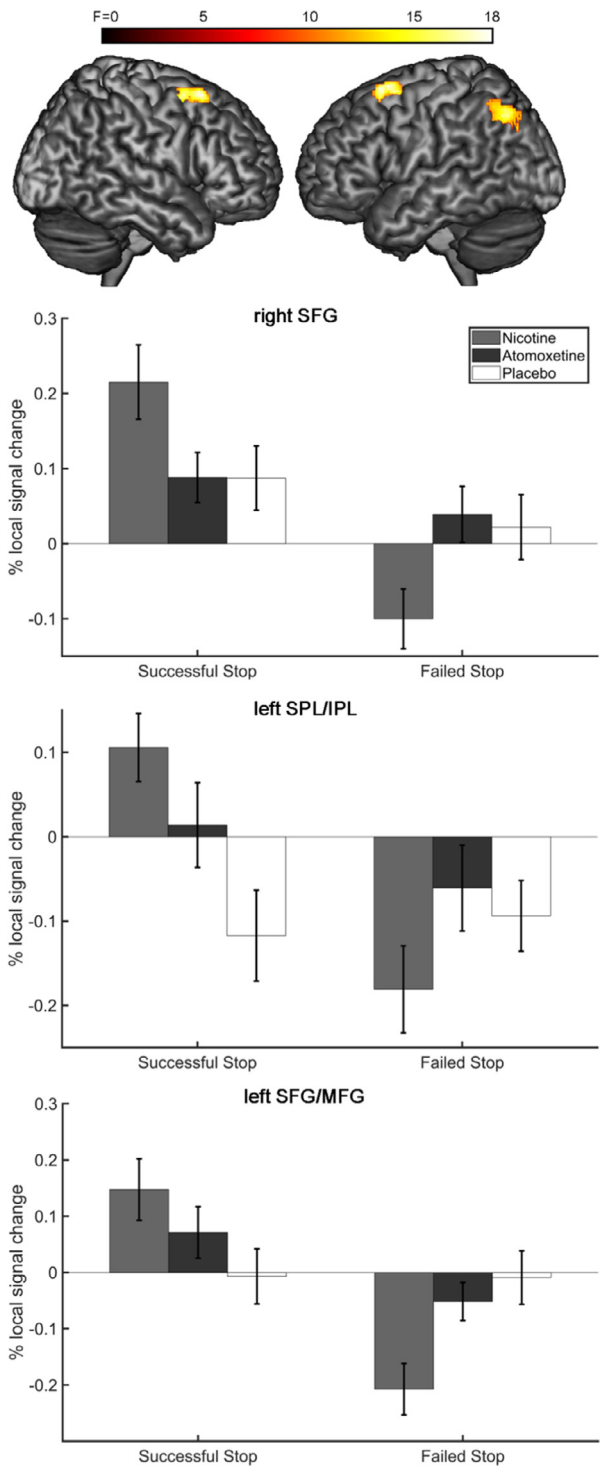

Fig. 2 Drug effects as a function of inhibition performance. Graphs depict mean percent local signal change, and error bars represent SEM. SFG is superior frontal gyrus. MFG is middle frontal gyrus. SPL is superior parietal lobule. IPL is inferior parietal lobule. $N = 26$.

independent, however, of the substance's behavioural effects.

Nicotine effects on response inhibition in humans have been investigated in a number of single-dose administration studies. Ettinger and Kumari (2018) recently reviewed this literature and concluded that these effects are task-dependent, with the majority of studies observing nicotine-induced improvement on the antisaccade task, whereas findings on other inhibitory tasks e.g., the go/no-go and Stroop tasks are less consistent. Beneficial effects of nicotine on SST performance are found particularly in people with impulsivity or inhibitory impairments such as ADHD patients or cigarette-withdrawn smokers. Experimentally controlled applications of nicotine to healthy individuals, however, appear not to reliably enhance SST performance (Ettinger and Kumari, 2018).

In the present study of healthy non-smokers, nicotine did not affect any aspect of SST performance, including inhibitory control, go-responding or post-error slowing, and had no effect on subjective measures. However, nicotine had a pronounced effect on fronto-parietal BOLD during successful compared to unsuccessful inhibition trials. The pattern of effects suggests that the substance enhanced the difference in activation between successful and unsuccessful trials in these areas. As can be seen from Fig. 2, these areas tended not to differ between successful and unsuccessful stop trials under placebo or atomoxetine. With nicotine, however, successful inhibition was associated with enhanced BOLD in these areas, whereas inhibition failures were associated with lower BOLD. Given the low temporal resolution of BOLD fMRI, it cannot be discerned whether these are causes of successful inhibiting or consequences of processing the resulting performance. Whilst nicotine was recently shown to upregulate BOLD during inhibition errors on the SST (Moran et al., 2018), reductions in activation following nicotine have also previously been observed (Hahn et al., 2007; Ettinger et al., 2009; Kasparbauer et al., 2016).

An intriguing finding that may further aid the interpretation of the nicotine effect observed here was the correlation between nicotine-induced BOLD changes in left SFG/MFG and BIS-11 total score. The correlation indicates that the effect that was observed at group level, i.e., a nicotine-induced BOLD reduction in this area, was more pronounced in individuals with higher levels of trait impulsivity. The rationale behind investigating the association of drug effects on stop-signal task performance and BOLD was previous evidence that nicotine improves SSRT particularly in individuals with higher levels of impulsivity (Ettinger and Kumari, 2018). Specifically, previous studies have provided evidence of beneficial nicotine effects on SSRT particularly in non-smoking adolescents (Potter and Newhouse, 2004) and adults (Potter and Newhouse, 2008) with ADHD and non-smoking young adults with high levels of impulsivity (Potter et al., 2012). Replicable evidence of beneficial nicotine effects on SSRT is also obtained in smokers in a state of abstinence (Ashare and Hawk, 2012; Charles-Walsh et al., 2014; Tsaur et al., 2015; however, see Austin et al., 2014). Studies of healthy, non-deprived individuals, however, are largely negative (Bekker et al., 2005; Wignall and De Wit, 2011; Logemann et al., 2014a, 2014b; Ettinger et al., 2017). Overall, it may be concluded that nicotine improves the SSRT in

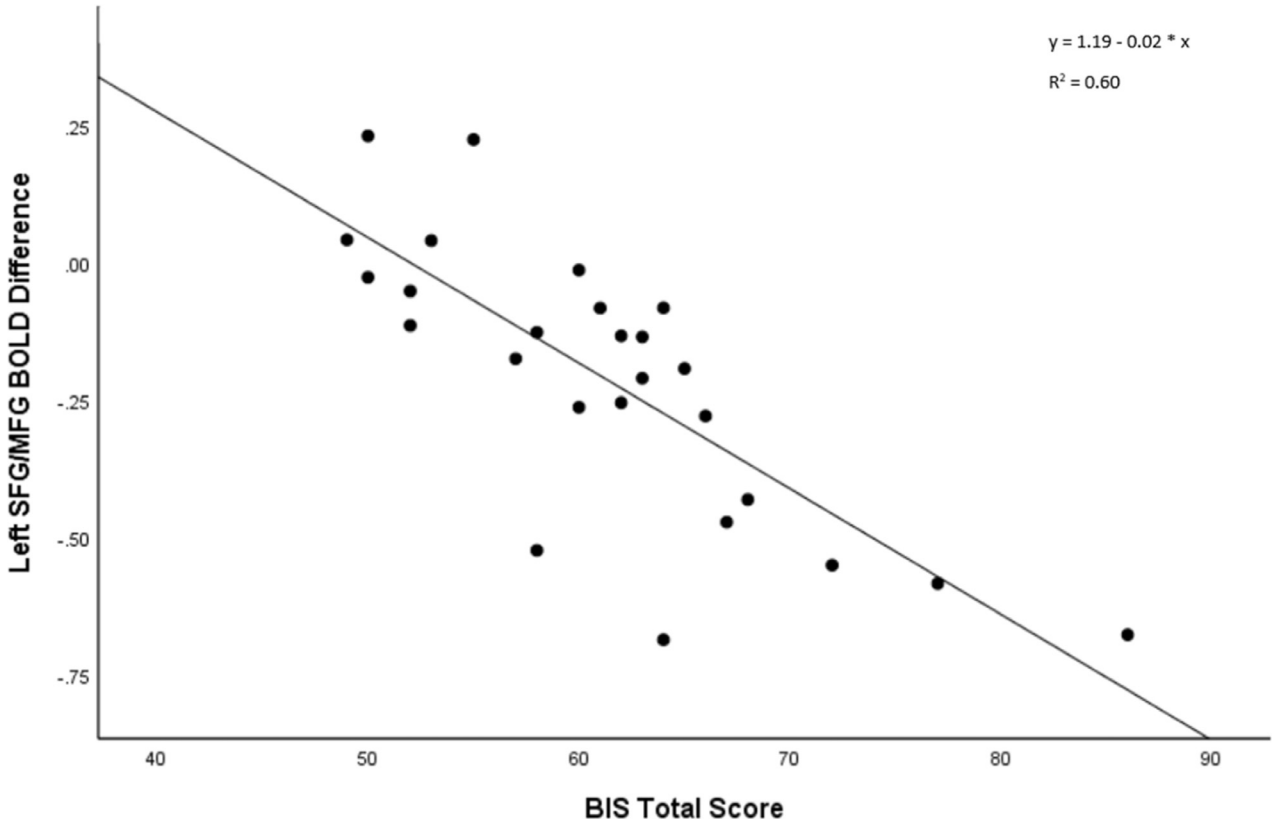

Fig. 3 Scatterplot for the association between impulsivity and nicotine effects on BOLD. The figure illustrates the correlation between the difference score in BOLD between nicotine and placebo in left SFG/MFG during failed stop trials and BIS-11 total score. SFG is superior frontal gyrus. MFG is middle frontal gyrus. BIS is Barratt Impulsiveness Scale (Patton et al., 1995). $N = 26$.

individuals with state or trait impairments in inhibitory control, compatible with previous conjectures on the baseline-dependency of nicotine effects (Perkins, 1999). The current data extend these findings to the level of BOLD, by showing that trait impulsivity may be a predictor of the substance's effects on brain function, even though no association with behavioural effects was observed here. As such, the current findings also support theories of a role of the nAChR in the neural basis of impulsivity (Ohmura et al., 2012).

The precise molecular mechanisms underlying the observed effects are likely to be complex and cannot be fully reconstructed from this study alone. Nicotine is a non-selective nAChR agonist. The nAChR is an ionotropic receptor of pentameric composition, i.e., it contains five subunits (identified as α, β, γ, δ and ε), which in different combinations make up several receptor subtypes. Neuronal nAChR contains only the α and β subunits, with the $\alpha4\beta2$ and $\alpha7$ receptor subtypes being currently under particular investigation for potentially mediating pro-cognitive cholinergic effects of nicotine and other ligands (Levin, 2002; Leiser et al., 2009; Lewis et al., 2017).

Importantly, activation of the presynaptic nAChR by nicotine increases release of not only acetylcholine, but also other neurotransmitters such as dopamine, serotonin, gamma-aminobutyric acid (GABA), histamine, glycine and glutamate (Di Matteo et al., 2007; Dani and Bertrand, 2007). Adding to the complexity of these multiple neurotransmitter effects of nicotine, the architecture of the cholinergic system itself is also widespread and complex, with three major subsystems innervating essentially the entire brain (Woolf, 1991; Dani and Bertrand, 2007). A first system consists of cholinergic interneurons in striatum, which likely play an important role in motor control. Second, there is widespread cholinergic innervation of cortex, hippocampus and limbic areas by basal forebrain neurons, a system thought to influence diverse cognitive functions. A third important projection of cholinergic neurons emerges from the laterodorsal and pedunculopontine tegmental nuclei and innervates midbrain dopaminergic cells, thereby likely playing a role in the reinforcing effects of nicotine.

An interesting hypothesis regarding the mechanisms of nAChR agonist effects on cognition was proposed by Sarter et al. (2009). The hypothesis argues that detection of cues, a process that is fundamental to attentional and other cognitive functions (Posner et al., 1980), is mediated by cue-evoked increases in prefrontal cholinergic activity. It is argued further that nAChR agonists, particularly at the $\alpha4\beta2$ receptor subtype, enhance the neuronal control of cue detection through augmentation of these transient cholinergic activations, a process thought to involve local glutamatergic-cholinergic microcircuitry. This hypothesis may be drawn upon to explain the pattern of nicotine effects on BOLD in our study, which essentially showed that nicotine enhanced the difference in BOLD between successful and failed stop trials. The detection of a cue or signal, viz. the stop signal, is undoubtedly a process critically

required for successful performance on the task (Sharp et al., 2010; Hampshire, 2015). Nicotine administration may thus have shifted the processing of the stop signal in cortex towards a mode that relies more heavily on the cholinergic mechanisms underlying signal detection as described by Sarter et al. (2009), yielding the observed pattern of enhanced BOLD differences between successful and failed stop trials.

However, these speculations are subject to a number of limitations. First, it should be noted that nicotine binds not only to the $\alpha 4\beta 2$ receptor subtype that is in the focus of Sarter and colleagues' hypothesis. Additionally, cholinergic projections are widespread and there are effects of nAChR stimulation on other neurotransmitter systems in addition to acetylcholine (Woolf, 1991; Di Matteo et al., 2007; Dani and Bertrand, 2007). Therefore, the BOLD changes in frontal and parietal areas observed here may not be unequivocally ascribed to a particular cholinergic projection or mechanism. Multi-drug interaction studies and pharmacogenetic approaches may help to clarify this important issue.

Atomoxetine had no discernible effects in this study. Whilst some previous studies of comparable doses of atomoxetine have observed improved SSRT in healthy adults, adults with ADHD and patients with PD (see Introduction), other studies have failed to observe beneficial effects in healthy or ADHD participants (Nandam et al., 2011; Cubillo et al., 2014). Atomoxetine has also been shown to increase BOLD in right IFC in healthy adults (Chamberlain et al., 2009) and to normalise brain networks in ADHD and PD (Cubillo et al., 2014; Rae et al., 2016). The reasons for our failure to observe effects of atomoxetine on performance and BOLD are unknown, but may relate to the control for infrequency effects in our SST. Additionally, our careful selection of participants may have resulted in high-performing individuals whose performance is difficult to improve further.

4.1. Limitations and future directions

A number of limitations of our study have to be raised. First, our selection of the doses of nicotine and atomoxetine was based both on safety considerations and on previous experimental studies. As we employed only a single dose of each compound we are unable to identify whether the substances studied here may have had beneficial effects on task performance at other doses. This remains to be determined in future multi-dose studies.

Another limitation is that we did not obtain physiological measures, such as blood pressure or pulse. Such measures may have been useful to more comprehensively quantify the effects of the investigated substances.

Finally, whilst the present study allowed us to directly compare, within the same sample, the effects of nicotine and atomoxetine, this work should be extended in the future to include a condition in which both substances are administered. Such a condition would allow the direct investigation of interactions between the noradrenergic and cholinergic systems in their effects on cognition and brain function (Davis and Gould, 2007; Ray et al., 2009; Alkam et al., 2017).

5. Conclusions

To conclude, we observed that nicotine led to an enhancement of the BOLD contrast between successful and unsuccessful inhibition in fronto-parietal cortex. Correlational analysis suggested that this effect was more pronounced in participants with higher levels of impulsivity. This finding is compatible with previous evidence of the baseline dependency of nicotine effects on performance of the stop-signal task and implicates the nAChR in the neural basis of impulsivity.

Acknowledgements

We are grateful to thank Alena Grimm, Rebekka Heinen and Hannah Kilian for their support in data collection. We would like to thank all volunteers for their participation in this study.

Funding and disclosure

We gratefully acknowledge funding of this study by the Gielen-Leyendecker-Stiftung. The funding body had no role in the design of the study, collection and analysis of data or decision to publish.

Conflict of interest statement

The authors do not report any financial or other interests in relation to the work described in this manuscript.

Contributors

Anna-Maria Kasparbauer, Nadine Petrovsky, Peter Trautner, Bernd Weber and Ulrich Ettinger designed and planned the study.

Anna Kasparbauer, Nadine Petrovsky, Pia-Magdalena Schmidt and Birgitta Sträter carried out participant recruitment, screening, data collection, and data analysis.

All authors interpreted the data and contributed to the write-up.

All authors agreed on the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.12.004.

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