NeuroImage: Clinical 15 (2017) 753–760

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Automatized smoking-related action schemata are reflected by reduced fMRI activity in sensorimotor brain regions of smokers

Ayse Ilkay Isik[a,b,1], Marcus J. Naumer[b], Jochen Kaiser[b], Christian Buschenlange[b], Sandro Wiesmann[b], Stefan Czoschke[a,b], Yavor Yalachkov[b,c,*,1]

[a] Max Planck Institute for Empirical Aesthetics, Frankfurt am Main, Germany
[b] Institute of Medical Psychology, Goethe-University, Frankfurt am Main, Germany
[c] Department of Neurology, University Hospital Frankfurt am Main, Germany

ABSTRACT

In the later stages of addiction, automatized processes play a prominent role in guiding drug-seeking and drug-taking behavior. However, little is known about the neural correlates of automatized drug-taking skills and drug-related action knowledge in humans. We employed functional magnetic resonance imaging (fMRI) while smokers and non-smokers performed an orientation affordance task, where compatibility between the hand used for a behavioral response and the spatial orientation of a priming stimulus leads to shorter reaction times resulting from activation of the corresponding motor representations. While non-smokers exhibited this behavioral effect only for control objects, smokers showed the affordance effect for both control and smoking-related objects. Furthermore, smokers exhibited reduced fMRI activation for smoking-related as compared to control objects for compatible stimulus-response pairings in a sensorimotor brain network consisting of the right primary motor cortex, supplementary motor area, middle occipital gyrus, left fusiform gyrus and bilateral cingulate gyrus. In the incompatible condition, we found higher fMRI activation in smokers for smoking-related as compared to control objects in the right primary motor cortex, cingulate gyrus, and left fusiform gyrus. This suggests that the activation and performance of deeply embedded, automatized drug-taking schemata employ less brain resources. This might reduce the threshold for relapsing in individuals trying to abstain from smoking. In contrast, the interruption or modification of already triggered automatized action representations require increased neural resources.

1. Introduction

With around 6 million deaths per year worldwide related to smoking, nicotine addiction is one of the most significant public health burdens requiring the development of new treatment methods (World Health Organization, 2015). Recent findings highlight the compulsive aspect of addiction in the later phases of the disease controlled by deeply embedded habitual processes (Everitt and Robbins, 2005; Yalachkov et al., 2009, 2010). From a cognitive point of view, these processes have been described as “automatized action schemata”, which develop after extensive repetition of the same behavioral sequences (Tiffany, 1990). They can be triggered by drug-related cues and result in fast and efficient initiation and execution of drug-seeking and -taking behavior, while remaining largely independent of intentional processes. Eventually, automatic processes essentially impede the attempts to remain abstinent (Miller and Gold, 1994).

Automatized behaviors are executed more efficiently, with a higher speed and in an unconscious, uncontrollable manner (Moors, 2016). There is behavioral evidence indicating that cigarette smoking can become automatic after sufficient repetition and considerable experience (Baxter and Hinson, 2001; Field et al., 2006). It can be guided by automatic processes without volitional control (Baker et al., 2004; Piasecki et al., 2010). Extensive practice of the motor skills related to drug consumption (e.g. regular daily smoking) has been proposed to potentiate the progress and automatization of drug-related action schemata (Tiffany, 1990). This idea has been further developed into the concept of “motor cognition”, which suggests that sensorimotor brain regions not only control the basic aspects of movement (force, direction, amplitude) but can also shape and guide human behavior (Casartelli and Chiamulera, 2016). The further investigation of this concept has been envisioned as a possible “motor way” to close the gap between the basic neuroscience approach and clinical practice

* Corresponding author at: Department of Neurology, University Hospital Frankfurt, Schleusenweg 2-16, 60528 Frankfurt am Main, Germany.
E-mail address: Yalachkov@med.uni-frankfurt.de (Y. Yalachkov).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.nicl.2017.06.021
Received 3 March 2017; Received in revised form 24 May 2017; Accepted 16 June 2017
Available online 17 June 2017

(Casartelli and Chiamulera, 2016).

Studies on experience-based neural plasticity have suggested that repeated and frequent engagement in a specific activity changes the neural representation for that activity. Experience-related modulation of motor skills and their neural representations results typically in increased speed, precision and automaticity of behavior (Calvo-Merino et al., 2006; Grafton et al., 1992; Weisberg et al., 2007). Long-term training affects cerebellar activation and leads to neural reorganization of motor and sensory cortices in piano players (Jancke et al., 2000; Koeneke et al., 2004; Krings et al., 2000), experienced artists (Solso, 2006) and football players (Naito and Hirose, 2014). Those studies reported reduced activation in cortical motor regions for experts as compared to novices or neutral activities, possibly because of greater efficiency of neural processing gained through extended sensorimotor training. It has also been shown that extensive real-world sensorimotor experience with a specific object category leads to diminished activity in visual- and motor-related cortices when viewing these objects (Handy et al., 2006). This suggests that in terms of “neural efficiency”, specific sensorimotor experience is associated with optimized deployment of brain resources when the corresponding neural representations are activated.

Based on these findings, one could assume that drug-related automatized action schemata are associated with a diminished cue-triggered activation of the respective sensorimotor brain regions. However, this aspect has not been directly investigated yet. On the contrary, indirect evidence from studies, where patients view, hear, touch, smell or taste drug cues suggests that drug cues activate brain regions involved in reward, learning, memory, perception and action more strongly as compared to neutral cues or healthy subjects (Jasinska et al., 2014; Yalachkov et al., 2010, 2012). Functional brain imaging studies with a more ecologically valid approach, e.g. one measuring automatized motor actions, are still missing.

In the present study smokers and nonsmokers were scanned with functional magnetic resonance imaging (fMRI) while performing an orientation affordance task with images of smoking or control objects. This behavioral task is a well-established stimulus-response compatibility paradigm based on the idea that certain action-related properties of a stimulus can generate automatic response codes (Riggio et al., 2008; Symes et al., 2007; Tucker and Ellis, 1998; Vainio et al., 2007). A previous study from our laboratory employed this paradigm in the context of smoking and found increased behavioral responsiveness to smoking-related objects in smokers compared to non-smokers, suggesting that it is an appropriate instrument to investigate the automatic activation of motor representations in response to smoking paraphernalia and action-related tools (Yalachkov et al., 2009). While we found that the affordance effect for smoking paraphernalia in smokers measured outside the scanner is correlated with higher fMRI activation of sensorimotor brain regions triggered by passively viewed other smoking cues (Yalachkov et al., 2009), the neural correlates of the smoking-specific affordance effects have not yet been measured directly. Here we employed the affordance paradigm in the MR scanner and investigated whether conditions in which automatized action representations are triggered by smoking paraphernalia or neutral objects result in differential activation of sensorimotor brain regions in smokers as compared to non-smokers.

2. Materials and methods

2.1. Participants

Written informed consent was obtained from 37 adults. The study was approved by the ethics committee of Goethe University Medical School and was conducted in accordance with the Declaration of Helsinki. All participants were right-handed and had normal or corrected to normal vision. To minimize the acute effects of smoking while avoiding the emergence of distinct withdrawal symptoms, smokers were instructed to abstain from smoking for at least 2 h prior to the experiment. The individual levels of nicotine dependence, withdrawal and smoking urges were evaluated with the Fagerström Test for Nicotine Dependence (FTND; (Heatherton et al., 1991), the Wisconsin Smoking Withdrawal Scale (WSWS; (Welsch et al., 1999) and the Questionnaire on Smoking Urges (QSU; (Tiffany and Drobes, 1991). Non-smokers stated to have smoked fewer than 20 cigarettes during their life time. Breath carbon monoxide (CO) levels were determined upon participants' arrival and after the fMRI experiment. Participants were screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID I-II; (First et al., 1996) to exclude a current psychiatric disorder and substance abuse/dependence other than nicotine dependence.

2.2. Stimuli

Stimuli were pictures of smoking paraphernalia and everyday control objects (ashtrays with cigarettes as well as plates with a knife, fork or spoon placed on them). The graspable sides of the cigarettes and the cutlery pointed towards the left or right (45°) side of the viewer. The color and luminance of the photographs were normalized and we ensured that all images had the same size (340 × 340 px).

2.3. Design

The fMRI experiment was designed as a rapid event-related experiment and comprised four runs with 80 trials each. We used a design with two within-subject factors (“object category”: smoking objects vs. control objects; “compatibility” of hand and object orientation: compatible vs. incompatible) and one between-subject factor (“group”: smokers vs. non-smokers). Thus, the experiment had four different conditions (control compatible, control incompatible, smoke compatible, smoke incompatible), each of them consisting of 20 trials per run. Trials were presented in randomized order and separated from each other with jitter values between 2500 ms and 17,500 ms. Participants responded by pushing buttons on a response device with either their right or left index fingers. We ensured that both hands were positioned symmetrically. For the affordance task we applied a previously used paradigm (Yalachkov et al., 2009). Each trial began with a fixation cross visible for 1000 ms. Then, a randomly chosen stimulus was presented for 700 ms. After that, a white fixation cross appeared in the middle of the object for 150 ms and the cross changed its color from white to either purple or brown for 180 ms before changing its color back to white and staying on display for 1970 ms. Finally, the stimulus disappeared and the fixation cross was kept on the screen for 1000 ms, adding to 5000 ms in total. Participants were instructed to press the right button of the response box with their right index finger when the fixation cross changes its color to brown; and the left button with their left index finger when the fixation cross turned to purple. Participants were instructed to respond as fast as possible while maintaining accuracy. They viewed the screen through a mirror positioned on the head coil. The randomization order and the determination of jitter length values were obtained by using the Optseq2 software (http://surfer.nmr.mgh.harvard.edu/optseq) (Dale, 1999). The experiment was performed using PRESENTATION software (Version 18.0, www.neurobs.com).

2.4. MRI acquisition parameters

fMRI measurements were performed on a 3-T Siemens Magnetom Allegra scanner using a 4-channel phased array coil at the Brain Imaging Center in Frankfurt am Main. Participants underwent four functional runs and one anatomical scan. The blood oxygenation level dependent functional images were collected with a gradient recalled echo-planar imaging (GRE-EPI) sequence (repetition time (TR) 2500 ms; echo time (TE) 30 ms; field of view 192 mm; slice thickness 2.4 mm; gap thickness 0.792 mm, flip angle 90°, matrix size 64 × 64,

40 axial slices in descending order). 244 volumes were acquired per functional run. Images were acquired in an oblique orientation of 30° to the anterior commissure-posterior commissure (AC-PC) axis which reduced the signal dropouts in the ventral prefrontal cortex (Deichmann et al., 2003). For the anatomical scan, a magnetization-prepared rapid-acquisition gradient echo (T1MPRAGE) sequence with the following parameters was used: TR 2200 ms, TE 5.16 ms; flip angle 9°; matrix 256 × 256; and voxel size 1.0 × 1.0 × 1.0 mm^3. Each series started with a dummy block to avoid T1 saturation effects.

2.5. Analysis

2.5.1. Behavioral data

We excluded both trials with incorrect responses (2.1% of the total smokers' trials and 1.6% of the total non-smokers' trials; no significant group difference [*t*-test, $p = 0.5$, df = 30]) and unrealistic reaction times (< 150 ms or > 3000 ms; in total 2 trials) from further analysis.

The orientation affordance effect has been defined as a shorter reaction time when the spatial orientation of the object and the side of the responding hand are identical (Tucker and Ellis, 1998; Vainio et al., 2007). Trials were considered compatible if the orientation of the object and the responding hand were the same (e.g., left-oriented smoking object requiring left hand response) or incompatible if the orientation and the responding hand are different (e.g., right-oriented control object requiring left hand response). We calculated the median reaction times for compatible and incompatible conditions across both hands, generating four values per participant: control compatible (CC), control incompatible (CI), smoke compatible (SC), smoke incompatible (SI). Using median values of the reaction times allowed to minimize the effect of outlying reaction times without explicitly excluding any further trials from the analysis (Stanfield and Zwaan, 2001; Van Weelden et al., 2014; Zwaan et al., 2002).

We then calculated an "affordance index" (AI) separately for each object category to facilitate the search for specific interactions (see also Yalachkov et al., 2009):

$$AI_{Control} = \left[\frac{CI - CC}{CI + CC}\right] \times 100 \quad AI_{Smoke} = \left[\frac{SI - SC}{SI + SC}\right] \times 100$$

The affordance index indicates the size of the orientation affordance effect. Shorter reaction times for the compatible than for the respective category-specific incompatible conditions result in higher affordance indices.

We performed two repeated-measures ANOVAs. In the first one we searched for a general affordance effect and used the median of reaction times as a dependent variable, "object category" and "compatibility" as within-subject factors and "group" as between-subject factor. In the second ANOVA we used the affordance indices as dependent variable and "object category" as a within-subject factor as well as "group" as a between-subject factor in order to search for differential affordance effects depending on object category and group membership.

2.5.2. fMRI data

Data were analyzed using the Brain Voyager QX 2.8 software package (Brain Innovation). Preprocessing was performed with slice scan time correction with windowed sinc interpolation, three-dimensional motion correction with trilinear sinc interpolation and linear trend removal as well as temporal high pass filtering with a GLM-Fourier basis function. Functional and Talairach standardized anatomical data were combined in a voxel time course file and were spatially smoothed with an 8 mm full width at half maximum Gaussian filter. Volume-based statistical analyses were performed at the whole-brain level. First, we applied a general linear model (GLM) with deconvolution analysis with a special design matrix allowing to estimate the response function for each event type. The fMRI data analysis protocol comprised 4 different trial types (control compatible, control incompatible, smoking compatible, smoking incompatible). A set of eight shifted stick functions, each accounting for 2.5 s (i.e., equal to our TR), were defined per trial to cover the maximal length of a typical hemodynamic response (20 s) starting with the onset of each trial. Erroneous trials or trials affected by head motion of more than 1 mm were coded as dummy predictors. Thus, our model resulted in 40 predictors (5 trial types × 8 time points).

We calculated a whole-brain repeated measures random-effects (RFX) ANOVA with within-subject factors "object category" (smoking objects vs. control objects), "compatibility" (compatible vs. incompatible) and between-subject factor "group" (smokers vs. non-smokers) by using the β-values from the 4th predictor (the fourth from eight available time points, each of them with a duration of 2.5 s, corresponding to 1 TR). Time point zero is defined by the onset of the trial. Subjects were instructed with which hand they had to press the button approximately 2 s later. The mean reaction time accounts for approximately another 500 ms and the peak of the reaction-induced BOLD response is expected to be reached 4–6 s thereafter (Rosen et al., 1998), which means that the timing of the 4th predictor (7.5 s) would roughly correspond to the peak of the expected hemodynamic response function due to the motor reaction.

Whole-brain statistical maps were computed for the main effects, two-way interactions and three-way interaction. The three-way interaction "object category × compatibility × group" identified regions exhibiting differential fMRI activation across object category, compatibility and group. For illustrative purposes, i.e. to disentangle this complex interaction and to better understand the individual contributions of the single factors or two-way interactions to the significant three-way interaction, further analyses of these regions were performed with ROI-based RFX-GLMs. The estimated β-values from the ROIs resulting from the three-way interaction were used to compute two two-way ANOVAs for each ROI with the within-subject factors of "object category" and "compatibility" separately for smokers and non-smokers. For each significant two-way interaction from these additional ANOVAs, paired-samples post-hoc *t*-tests were calculated in order to further disentangle the factors contributing to the significance of the interaction. All statistical maps were corrected for multiple comparisons using the cluster-size thresholding plug-in provided by BrainVoyager QX based on the approach described by Forman et al. and Goebel et al. with 1000 iterations at a desired confidence level ($\alpha = 0.05$) (Forman et al., 1995; Goebel et al., 2006). Those maps were then projected onto anatomical data sets and averaged across all participants.

3. Results

3.1. Participants

Four smokers reported retrospectively that they had smoked less than 2 h prior to the experiment. The mean time since their last cigarette was 17.5 min (SD = 4.3) (compared to mean time > 120 min for the remaining smokers). Nicotine has been shown to increase the BOLD signal in motor and somatosensory cortices of rats even 10 min after administration (Bruijnzeel et al., 2014). In human subjects, peak nicotine level in serum is reached approximately 4 min after infusion and decreases over the course of time. However, even 30 min after administration it is still significantly elevated above baseline and has decreased by merely 50% from its peak value (Yamamoto et al., 2013). In the same study, Yamamoto et al. demonstrated that individual nicotine time courses of human subjects were associated with changes in BOLD signal in multiple brain regions, including the cingulate, cuneal and calcarine cortices and lingual gyri as well as temporal gyri (Yamamoto et al., 2013). Taking these findings into account, we excluded the four smokers who had not adhered to our initial inclusion criteria.

The remaining smokers ($n = 14$, mean age = 23.6 years, SD = 3.8 years, 9 men and 5 women) reported to have smoked at least

five cigarettes per day for at least one year (mean number of cigarettes per day = 16.5, SD = 6.3). Their mean FTND score was 5.4, SD = 1.9. Smokers' mean CO-pre level (9.8 ppm, SD = 5.4) was higher than non-smokers' mean CO-pre level (2 ppm, SD = 0.8) ($p < 0.001$, Student's *t*-test). After the fMRI experiment smokers' mean CO-post level (6.5 ppm, SD = 2.6) was higher than non-smokers' mean CO-post level (2.2 ppm, SD = 1) ($p < 0.001$, Student's *t*-test). One non-smoker was excluded because of high CO-pre levels (CO-pre = 13, CO-post = 11). Thus 18 non-smokers were included (mean age = 23.4 years, SD = 3 years, 7 men and 11 women).

3.2. Questionnaires

The mean scores for each questionnaire were averaged for smokers and non-smokers. For the WSWS, smokers' main score (40.4, SD = 15) before the fMRI measurement was higher than non-smokers' main score (27.6, SD = 8.5) ($p < 0.05$, Mann-Whitney *U* Test). For the QSU, smokers' main score (126.7, SD = 39) was higher than non-smokers' main score (30.6, SD = 7.7) ($p < 0.05$, Mann-Whitney *U* Test).

3.3. Behavioral results

The first repeated measures ANOVA (two within-subject factors: object category, compatibility; one between-subjects factor: group) revealed a significant effect of compatibility ($p = 0.01$) (Fig. 1A). Post-hoc comparison with Tukey's HSD ($p < 0.01$) showed that incompatible conditions required longer reaction times than compatible conditions reflecting the general affordance effect (Tucker and Ellis, 1998; Vainio et al., 2007). To better understand the affordance effect across groups and objects we computed an affordance index which indicated the amount of the affordance effect (see Yalachkov et al., 2009 and Materials and Methods). The ANOVA with the affordance index as a dependent variable revealed neither a main effect of object category or group nor an interaction of both factors (Fig. 1B). However, independent samples *t*-tests showed that when compared directly, smokers exhibited higher affordance indices than non-smokers for smoking ($p < 0.05$) but not for control objects ($p > 0.05$) (Fig. 1B).

3.4. fMRI results

We computed a three-way whole-brain RFX ANOVA with the factors "object category" (smoking vs. control), compatibility (compatible vs. incompatible) and "group" (smokers vs. nonsmokers). The regions that revealed significant activations for the main effects of "object category", "compatibility", and "group" as well as the two-way interactions of "object category × compatibility" and "object category × group" ($F \geq 7.57$, $p < 0.05$; corrected for multiple comparisons) are reported in Supplementary Tables S3–S7. No region showed a "compatibility × group" interaction after correction for multiple comparisons. The main interaction of interest, the three-way interaction "object category × compatibility × group" was significant in right primary motor cortex, right cingulate gyrus, right supplementary motor area, left cingulate gyrus, right middle occipital gyrus and left fusiform gyrus (Table 1, $F \geq 7.57$, $p < 0.05$; corrected for multiple comparisons). The two additional ANOVAs computed with the β values from the ROI-based RFX GLMs indicated differential BOLD activation patterns in smokers (Supplementary Table 1) and non-smokers (Supplementary Table 2) for compatible and incompatible conditions depending on object categories. For smokers, the BOLD response was higher for control than smoking objects for the compatible condition in right primary motor cortex (Fig. 2A) and in right cingulate gyrus (Fig. 2B). However, an inverse pattern was found in those regions for the incompatible condition with higher fMRI activations for smoking objects compared to control objects. Similarly, post hoc *t*-tests showed a higher fMRI signal in smokers for the control compatible as compared to smoke compatible condition in right supplementary motor area, left cingulate gyrus and right middle occipital gyrus and a higher fMRI activation for the smoke incompatible as compared to control incompatible condition in left fusiform gyrus (Fig. 2C–D). No such differences were found for non-smokers.

Table 1
Brain regions showing significant whole-brain RFX ANOVA interaction "stimulus category × compatibility × group" (df = 30, $p < 0.05$, corrected).

Brain region	Talairach coordinats			No. of voxels (1 mm^3)	*F* value
	x	y	z		
R primary motor cortex (BA 4)	37	−26	57	1463	9.39
R supplementary motor area (BA 6)	1	−29	55	1799	9.11
R cingulate gyrus (BA 24)	3	−9	41	970	9.97
R cingulate gyrus (BA 31)	14	−25	38	1143	9.51
R middle occipital gyrus (BA 19)	30	−78	22	1344	9.77
R middle occipital gyrus	37	−62	−2	3051	10.00
L cingulate gyrus (BA 23)	−7	−13	25	905	9.41
L fusiform gyrus (BA 19)	−36	−68	−13	993	9.69

4. Discussion

The results of our behavioral experiment demonstrated shorter reaction times for compatibility between responding hand and spatial orientation of the priming object (Fig. 1A), consistent with a general

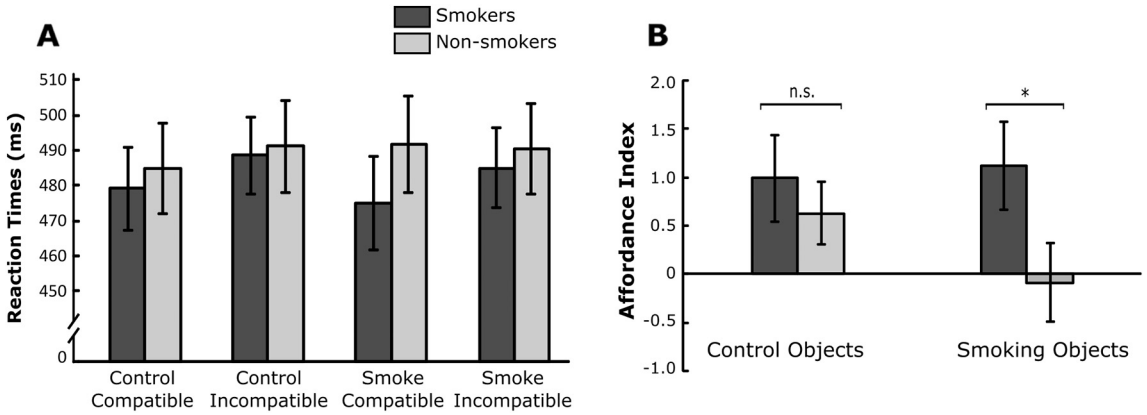

Fig. 1. A. Reaction times (means and SEs) of the two groups (smokers vs. non-smokers) for the two object categories (smoking objects vs. control objects) (main effect of compatibility $p = 0.01$) **B.** Affordance indices (means and SEs) of the two groups (smokers vs. non-smokers) for the two object categories (smoking objects vs. control objects). Error bars indicate SE from the mean; *$p < 0.05$., n.s. *t*-test not significant.

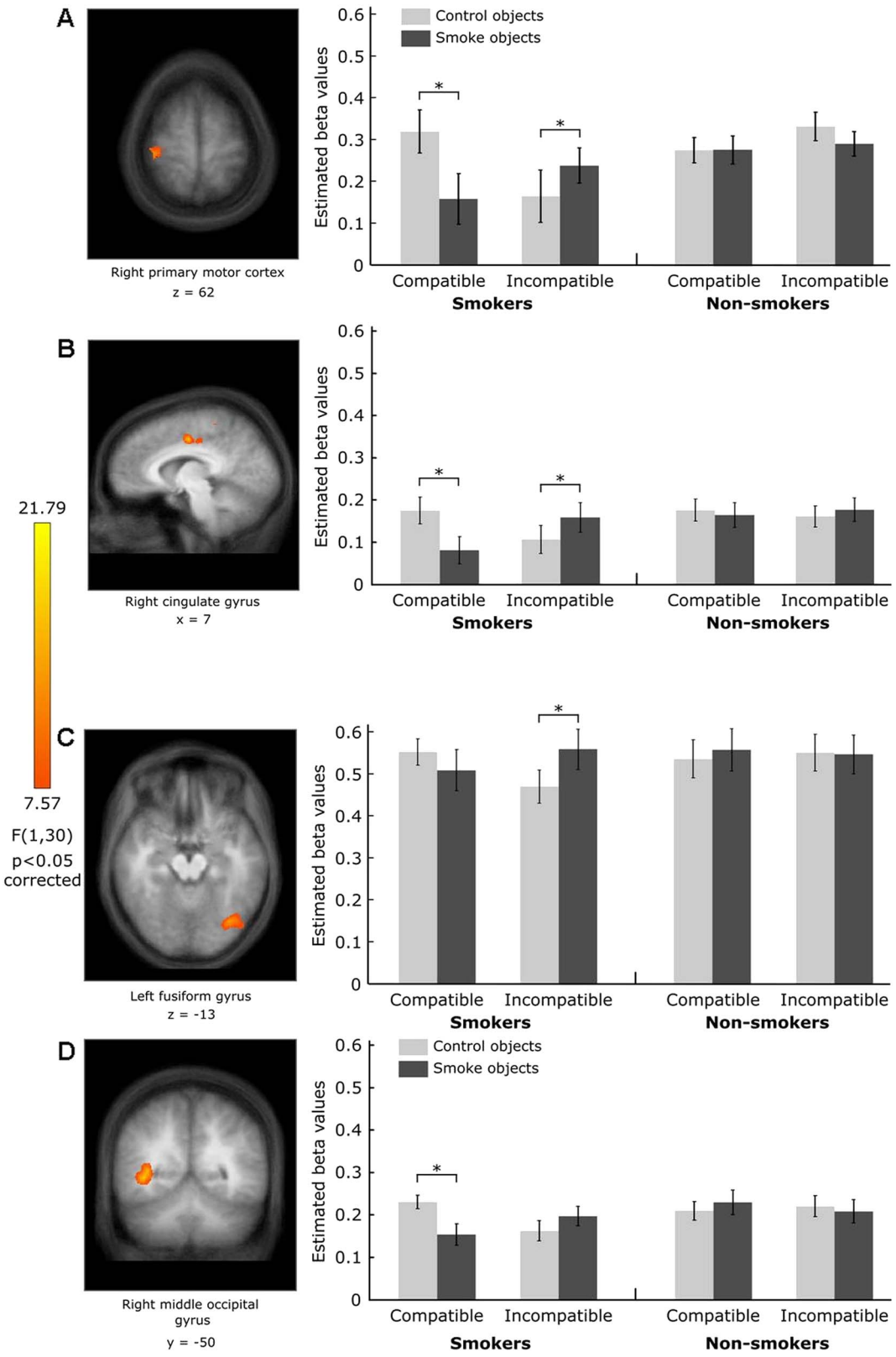

Fig. 2. A whole-brain RFX ANOVA interaction "object category × compatibility × group" revealed significant activations in several brain regions. ROI-based within subjects ANOVAs for smokers showed in right primary motor cortex (**A**) and right cingulate gyrus (**B**) higher fMRI activations for control objects in the compatible condition, whereas in the incompatible condition higher fMRI activations were observed for smoking objects. Similar activation patterns were revealed in left fusiform gyrus (**C**) and right middle occipital gyrus (**D**). The scale on the left side indicates minimum and maximum *F* values, the degrees of freedom, and the significance level for the interaction. Corrected for multiple comparisons using the cluster-size thresholding (1000 iterations, $\alpha = 0.05$). Error bars indicate SE from the mean; $^{*}p < 0.05$.

orientation affordance effect and indicating automatic activation of corresponding motor representations (Tucker and Ellis, 1998; Vainio et al., 2007). Furthermore, we replicated the behavioral results from our previous study, where we found that smoking paraphernalia induced affordance effects in smokers but not in non-smokers (Yalachkov et al., 2009). When directly comparing smokers and non-smokers, the affordance effect for control objects did not differ between the two groups, but was higher for smoking paraphernalia in smokers as compared to non-smokers (Fig. 1B). This effect seems to be mainly driven by the difference in non-smokers' affordance index for the two object categories: while it was positive for control objects (i.e. compatibility between hand and spatial orientation led to shorter reaction times), it was close to zero or negative for smoking paraphernalia, implying that the smoking-related cues were not able to activate any corresponding motor representations in non-smokers. This could be attributed to the fact that non-smokers possess only minor or no sensorimotor experience with smoking-associated objects.

Our analysis revealed reduced fMRI activation for compatible smoking as compared to compatible control objects in smokers but not in non-smokers in right primary motor cortex, supplementary motor area, middle occipital gyrus and bilateral cingulate gyrus (Fig. 2 and Supplementary Table 1). For the incompatible conditions we observed the opposite pattern: higher fMRI activation for smoking-related incompatible compared to control incompatible objects in right primary motor cortex, cingulate gyrus and left fusiform gyrus (Fig. 2). Motor areas like primary motor cortex and supplementary motor area have been consistently shown to be activated in response to motor tasks and action execution (Grafton et al., 1996; Grèzes and Decety, 2001). Furthermore, while primary motor cortex is activated during goal-directed actions and suggested to be involved in experience-related understanding of actions (Järveläinen et al., 2004), supplementary motor area is implicated in learning of sequential and visually guided motor movements (Grafton et al., 1992) and cingulate gyrus is activated in response to many motor-related tasks such as motor sequence learning (Jenkins et al., 1994), grasping and pointing (Grafton et al., 1996). Middle occipital gyrus, a brain region more deeply involved with perceptual processes, is crucial for processing known object manipulations, such as tool use (Brandi et al., 2014). Fusiform gyrus is involved in perception and recognition of complex visual stimuli and in the representation of category-specific information (Logothetis and Sheinberg, 1996; Ungerleider and Mishkin, 1982). Thus, performing the orientation affordance task with control objects and smoking paraphernalia activates a network of brain regions important for sensorimotor skills as well as preparation and execution of specific action sequences.

Diminished fMRI signals in sensorimotor brain regions have been observed after extensive object- and action-specific experience and have been explained by neural efficiency processing resulting in less neural resources being necessary for performing the respective activity (Handy et al., 2006; Jancke et al., 2000; Koeneke et al., 2004; Krings et al., 2000; Naito and Hirose, 2014; Solso, 2006). Similarly, smokers consume cigarettes on a regular basis and perform the act of smoking multiple times per day. Apart from the purely sensorimotor training effect which is built up by performing the same action sequence again and again, there are also significant pharmacological effects of drugs of abuse on procedural and motor skill learning as well as on neuroplasticity processes, as has been shown for cocaine (Ondracek et al., 2010; Willuhn and Steiner, 2006, 2009) and might be the case for nicotine (Batsikadze et al., 2015). Our results suggest that once established, smoking-specific automatized action schemata can be triggered by conditioned cues as shown by the activation of sensorimotor brain regions by smoking cues. Their performance requires less neural resources, indicated by the lower fMRI activation by smoking compatible as compared to control compatible objects in smokers, thus easily lowering the threshold for translating the cue-induced activation into an overt motor action. This mechanism is in accordance with the neural efficiency hypothesis which implies reduced brain activation after training on sensorimotor tasks (Bueichekú et al., 2016; Karim et al., 2016).

Interrupting or altering smoking results in increased reaction times (Baxter and Hinson, 2001), suggesting that changing the course of the automatized action requires the allocation of additional cognitive processing. Similarly, in our task the incompatible condition requires the use of the hand opposite to the response side afforded by the spatial orientation of the object. The resources necessary to modify and adjust the automatically afforded response are reflected in increased fMRI activation for the smoking as compared to control incompatible condition. Furthermore, Murphy et al. examined the role of perceptual load in action affordance and obtained faster responses for the compatible trials only in the low perceptual load condition (Murphy et al., 2012). In accordance with this observation, a recent study suggested that the affordance effect is reduced in high compared to low working memory conditions (Freeman et al., 2016). Thus, incompatible conditions might reflect also higher working perceptual or memory load, where more neural resources are necessary to modify the automatized action sequence.

There is a significant and interesting difference between our current results and the findings from our previous study where the affordance task was performed outside the scanner (Yalachkov et al., 2009). In this study the size of the affordance effect for smoking paraphernalia correlated positively with the fMRI activation of sensorimotor brain regions in smokers as measured in a separate fMRI experiment where smoking and control cues (pictures depicting people smoking or engaged in neutral activities) were presented. Thus, one could have expected that performing the affordance task inside the scanner would result in higher fMRI activation of action-related brain regions for the smoking compatible condition in smokers. While we obtained contrary results in our current experiment, we do not think that they necessarily contradict our previous findings. While in the previous fMRI experiment (Yalachkov et al., 2009) the subjects passively viewed smoking and control cues, participants in the current study actively performed the affordance task in the fMRI scanner. Viewing the cues passively might automatically activate the neural representations of the smoking-specific action as shown by higher fMRI activation of sensorimotor brain regions, possibly reflecting a greater readiness to trigger the action. In contrast, actually performing an automatized action would engage less neural resources than performing an untrained action.

A quantitative meta-analysis of multiple fMRI studies has shown that experts in a specific activity exhibit greater activation in the precentral gyrus as well as inferior frontal gyrus when compared to novices when the subjects were only observing the motor task (Yang, 2015). However, when actually performing the task, brain activation was stronger for experts only in the inferior parietal lobule, while novices demonstrated higher fMRI activation in both cerebellum and putamen (Yang, 2015). Even more interesting is a recent study in patients with obsessive compulsive disorder (OCD) who share some clinical signs as well as several pathophysiological mechanisms with addicted patients (Fineberg et al., 2010; Robbins and Clark, 2015). Here fMRI was recorded both during symptom exposure and avoidance responses (Banca et al., 2015). After being exposed to individually tailored symptom-evoking stimuli, OCD patients could decide to reject the stimuli, which modelled the behavioral avoidance response. During the decision phase in between exposure to the stimuli and the actual motor reaction, a bilateral hyperactivation of the putamen could be observed. However, this pattern reversed during the avoidance event and the putamen was deactivated in OCD patients. The results from studies with motor experts and OCD patients suggest that the activation of sensorimotor and habit-related brain regions depends on the phase of action (observation/stimulus exposure vs. performance/active avoidance) (Banca et al., 2015). While not completely identical with our experimental design and subject population, these findings are strongly supportive of the interpretation of our results from both our previous (Yalachkov

et al., 2009) and the current study.

One of the limitations of the current study is that the affordance task is obviously only an indirect approach to measure automatized smoking. Performing the whole act of smoking (opening the cigarette package, lighting up a cigarette, etc.) inside the fMRI scanner seems hardly feasible for technical reasons. Therefore, while we recognize that the affordance task allows us to investigate the automatized action sequence of smoking only partially, we believe that it is a reasonable and valid measure of smoking-related automatized action schemata.

A further limitation of the study is reflected by the fact that we did not provide any measures of relapse risk. This could be addressed in future studies where the activation of smoking-related automatized action schemata is measured and then correlated with abstinence rates in smokers trying to abstain from smoking.

In summary, we provide evidence that executing automatized smoking-related actions is reflected by reduced fMRI activity in sensorimotor brain regions of smokers, similarly to training effects observed in experts who perform or are involved in their firmly established activities. We believe that this experience-related modulation of neural representations in smokers should be further studied and tested as a marker for quantifying the risk for relapse in individuals trying to abstain from smoking. Furthermore, measuring the activation of these specific neural representations might be a valid instrument for supervising and predicting therapy success in treatment programs.

Funding and disclosure

This study has been supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), grant number YA 335/2-1. The authors declare no competing financial interests in relation to the work described.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.06.021.

References

Baker, T.B., Piper, M.E., McCarthy, D.E., Majeskie, M.R., Fiore, M.C., 2004. Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol. Rev. 111, 33–51.
Banca, P., Voon, V., Vestergaard, M.D., Philipiak, G., Pocinho, F., Relvas, J., et al., 2015. Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder. Brain 138, 798–811.
Batsikadze, G., Paulus, W., Grundey, J., Kuo, M.-F., Nitsche, M.A., 2015. Effect of the nicotinic α 4 β 2-receptor partial agonist Varenicline on non-invasive brain stimulation-induced neuroplasticity in the human motor cortex. Cereb. Cortex 25, 3249–3259.
Baxter, B.W., Hinson, R.E., 2001. Is smoking automatic? Demands of smoking behavior on attentional resources. J. Abnorm. Psychol. 110, 59–66.
Brandi, M.-L., Wohlschlager, A., Sorg, C., Hermsdorfer, J., 2014. The neural correlates of planning and executing actual tool use. J. Neurosci. 34, 13183–13194.
Bruijnzeel, A.W., Alexander, J.C., Perez, P.D., Bauzo-rodriguez, R., Hall, G., Klausner, R., et al., 2014. Acute nicotine administration increases BOLD fMRI signal in brain regions involved in reward signaling and compulsive drug intake in rats. Int. J. Neuropsychopharmacol. 1–13.
Bueichekú, E., Miró-Padilla, A., Palomar-García, M.Á., Ventura-Campos, N., Parcet, M.A., Barrós-Loscertales, A., et al., 2016. Reduced posterior parietal cortex activation after training on a visual search task. Neuroimage 204–213 Jul 15.
Calvo-Merino, B., Grèzes, J., Glaser, D.E., Passingham, R.E., Haggard, P., 2006. Seeing or doing? Influence of visual and motor familiarity in action observation. Curr. Biol. 16, 1905–1910.
Casartelli, L., Chiamulera, C., 2016. The motor way: clinical implications of understanding and shaping actions with the motor system in autism and drug addiction. Cogn. Affect. Behav. Neurosci. 16, 191–206.
Dale, A.M., 1999. Optimal experimental design for event-related fMRI. Hum. Brain Mapp. 114, 109–114.
Deichmann, R., Gottfried, J., Hutton, C., Turner, R., 2003. Optimized EPI for fMRI studies of the orbitofrontal cortex. NeuroImage 19, 430–441.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.
Field, M., Mogg, K., Bradley, B.P., 2006. Automaticity of smoking behaviour: the relationship between dual-task performance, daily cigarette intake and subjective nicotine effects. J. Psychopharmacol. 20, 799–805.
Fineberg, N.A., Potenza, M.N., Chamberlain, S.R., Berlin, H.A., Menzies, L., Bechara, A., et al., 2010. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacology 35, 591–604.
First, M., Spitzer, R., Gibbon, M., Williams, J., 1996. Structured CLINICAL Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Am Psychiatr Press.
Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. 33, 636–647.
Freeman, S.M., Itthipuripat, S., Aron, A.R., 2016. High Working Memory Load Increases Intracortical Inhibition in Primary Motor Cortex and Diminishes the Motor Affordance Effect. 36. pp. 5544–5555.
Goebel, R., Esposito, F., Formisano, E., 2006. Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. Hum. Brain Mapp. 27, 392–401.
Grafton, S.T., Mazziotta, C., Presty, S., Friston, K.J., Frackowiak, R.S.J., Phelps, M.E., 1992. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J. Neurosci. 12 (7), 2542–2548.
Grafton, S.T., Fagg, A.H., Woods, R.P., Arbib, M.A., 1996. Functional anatomy of pointing and grasping in humans. Cereb. Cortex 6, 226–237.
Grèzes, J., Decety, J., 2001. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum. Brain Mapp. 12, 1–19.
Handy, T.C., Tipper, C.M., Schaich, J., Grafton, S.T., Gazzaniga, M.S., 2006. Motor Experience with Graspable Objects Reduces Their Implicit Analysis in Visual- and Motor-Related Cortex. pp. 7.
Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.O., 1991. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br. J. Addict. 86, 1119–1127.
Jancke, L., Shah, N.J., Peters, M., 2000. Cortical activations in primary and secondary motor areas for complex bimanual movements in professional pianists. Cogn. Brain Res. 10, 177–183.
Järveläinen, J., Schürmann, M., Hari, R., 2004. Activation of the human primary motor cortex during observation of tool use. NeuroImage 23, 187–192.
Jasinska, A.J., Stein, E.A., Kaiser, J., Naumer, M.J., Yalachkov, Y., 2014. Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci. Biobehav. Rev. 38, 1–16.
Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S., Passingham, R.E., 1994. Motor sequence learning: a study with positron emission tomography. J. Neurosci. 14, 3775–3790.
Karim, H.T., Huppert, T.J., Erickson, K.I., Wollam, M.A., Sparto, P.J., Sejdić, E., et al., 2016. Motor sequence learning-induced neural efficiency in functional brain connectivity. Behav. Brain Res. 319, 87–95.
Koeneke, S., Lutz, K., Wustenberg, T., Jïncke, L., 2004. Long-term training affects cerebellar processing in skilled keyboard players. Neuroreport 15, 8–11.
Krings, T., Töpper, R., Foltys, H., Erberich, S., Sparing, R., Willmes, K., et al., 2000. Cortical activation patterns during complex motor tasks in piano players and control subjects. A functional magnetic resonance imaging study. Neurosci. Lett. 278, 189–193.
Logothetis, N.K., Sheinberg, D.L., 1996. Visual object recognition. Annu. Rev. Neurosci. 19, 577–621.
Miller, N.S., Gold, M.S., 1994. Dissociation of “conscious desire” (craving) from and relapse in alcohol and cocaine dependence. Ann. Clin. Psychiatry 6 (2), 99–106.
Moors, A., 2016. Automaticity: componential, causal, and mechanistic explanations. Annu. Rev. Psychol. 67, 263–287.
Murphy, S., van Velzen, J., de Fockert, J.W., 2012. The role of perceptual load in action affordance by ignored objects. Psychon. Bull. Rev. 19, 1122–1127.
Naito, E., Hirose, S., 2014. Efficient foot motor control by Neymar's brain. Front. Hum. Neurosci. 8, 1–7.
Ondracek, J.M., Willuhn, I., Steiner, H., West, A.R., 2010. Interactions between procedural learning and cocaine exposure alter spontaneous and cortically evoked spike activity in the dorsal striatum. Front. Neurosci. 4, 1–8.
Piasecki, T.M., Piper, M.E., Baker, T.B., 2010. Tobacco dependence: insights from investigations of self-reported smoking motives. Curr. Dir. Psychol. Sci. 19, 395–401.
Riggio, L., Iani, C., Gherri, E., Benatti, F., Rubichi, S., Nicoletti, R., 2008. The role of attention in the occurrence of the affordance effect. Acta Psychol. 127, 449–458.
Robbins, T.W., Clark, L., 2015. Behavioral addictions. Curr. Opin. Neurobiol. 30, 66–72.
Rosen, B., Buckner, R., Dale, A., 1998. Event-related functional MRI: past, present, and future. Proc. Natl. Acad. Sci. U. S. A. 95, 773–780.
Van Weelden, L., Schilperoord, J., Maes, A., 2014. Evidence for the role of shape in mental representations of similes. Cogn. Sci. 38, 303–321.
Solso, R.L., 2006. Brain activities in a skilled versus a novice artist: an fMRI study. Leonardo 34, 31–34.
Stanfield, R.A., Zwaan, R.A., 2001. The effect of implied orientation derived from verbal context on picture recognition. Psychol. Sci. 12, 153–156.
Symes, E., Ellis, R., Tucker, M., 2007. Visual object affordances: object orientation. Acta Psychol. 124, 238–255.
Tiffany, S.T., 1990. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol. Rev. 97, 147–168.
Tiffany, S.T., Drobes, D.J., 1991. The development and initial validation of a questionnaire on smoking urges. Br. J. Addict. 86, 1467–1476.
Tucker, M., Ellis, R., 1998. On the relations between seen objects and components of potential actions. J. Exp. Psychol. Hum. Percept. Perform. 24, 830–846.
Ungerleider, L., Mishkin, M., 1982. Two cortical visual systems. Anal. Vis. Behav.
Vainio, L., Ellis, R., Tucker, M., 2007. The role of visual attention in action priming. Q J

Exp Psychol (Hove) 60, 241–261.
Weisberg, J., Van Turennout, M., Martin, A., 2007. A neural system for learning about object function. Cereb. Cortex 17, 513–521.
Welsch, S., Smith, S., Wetter, D., Jorenby, D., Fiore, M., Baker, T., 1999. Development and validation of the Wisconsin smoking withdrawal scale. Exp. Clin. Psychopharmacol. 7, 354–361.
Willuhn, I., Steiner, H., 2006. Motor-skill learning-associated gene regulation in the striatum: effects of cocaine. Neuropsychopharmacology 31, 2669–2682.
Willuhn, I., Steiner, H., 2009. Skill-memory consolidation in the striatum: critical for late but not early long-term memory and stabilized by cocaine. Behav. Brain Res. 12, 103–107.
World Health Organization, 2015. WHO Report on the Global Tobacco Epidemic: the Empower Package. pp. 103.
Yalachkov, Y., Kaiser, J., Naumer, M.J., 2009. Brain regions related to tool use and action knowledge reflect nicotine dependence. J. Neurosci. 29, 4922–4929.
Yalachkov, Y., Kaiser, J., Naumer, M.J., 2010. Sensory and motor aspects of addiction. Behav. Brain Res. 207, 215–222.
Yalachkov, Y., Kaiser, J., Naumer, M.J., 2012. Functional neuroimaging studies in addiction: multisensory drug stimuli and neural cue reactivity. Neurosci. Biobehav. Rev. 36, 825–835.
Yamamoto, R.T., Rohan, M.L., Goletiani, N., Olson, D., Peltier, M., Renshaw, P.F., et al., 2013. Nicotine related brain activity: the influence of smoking history and blood nicotine levels, an exploratory study. Drug Alcohol Depend. 129, 137–144.
Yang, J., 2015. The influence of motor expertise on the brain activity of motor task performance: a meta-analysis of functional magnetic resonance imaging studies. Cogn. Affect. Behav. Neurosci. 15, 381–394.
Zwaan, R.A., Stanfield, R.A., Yaxley, R.H., 2002. Language comprehenders mentally represent the shapes of objects. Psychol. Sci. 13, 168–171.