



Theta-burst modulation of mid-ventrolateral prefrontal cortex affects salience coding in the human ventral tegmental area

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ABSTRACT

In the context of hedonic (over-)eating the ventral tegmental area (VTA) as a core part of the dopaminergic reward system plays a central role in coding incentive salience of high-caloric food. In the present study, we used functional magnetic resonance imaging (fMRI) to investigate whether transcranial magnetic theta-burst stimulation (TBS) over the right mid-ventrolateral prefrontal cortex (mid-VLPFC) can induce modulation of calorie-sensitive brain activation in the VTA. The prefrontal location for TBS had been predetermined by seed-based resting-state fMRI with a functionally defined portion of the VTA serving as seed region obtained from an independent second fMRI experiment. In a sample of 15 healthy male participants, modulation of calorie-sensitive VTA activation did not significantly differ between the two TBS protocols. Comparisons with baseline revealed that both TBS protocols significantly affected calorie-sensitive neural processing of the mid-VLPFC in a rather similar way. In the VTA significant modulation of calorie-sensitive activation was observed after continuous TBS, whereas the modulatory effect of intermittent TBS was less reliable but also associated with a decrease of activation for high-caloric food images. Neurostimulation of right mid-VLPFC is suggestive as a main entry point of downstream signal changes for high- and low-caloric food cues that could enforce a shift in valuating stimuli of initially different incentive salience.

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1. Introduction

There is a strong preference for high-caloric (HC) food in humans, and together with the over-supply of these foods in Western societies this preference has been related to the massive increase in obesity and associated illnesses (Hill, Wyatt, & Peters, 2012; Ng et al., 2014). Consequently, modern diet brings us into conflict between consumption of high-caloric food and its avoidance for reasons of health and longevity. This conflict is associated with the ability to exert control over superficially seductive options, a term previously introduced by Knoch et al. (2006), reflecting that these options are immediately rewarding but associated with a markedly increased risk for negative consequences in the long run. Dysfunction of this kind of control has not only been associated with overeating, but also with drug abuse, addiction, or other

symptoms suggestive of impairment in self-regulation (Knoch et al., 2006; Lieberman & Eisenberger, 2004; Starkstein & Robinson, 1997). If control over superficially seductive options could be enhanced, an increase of control over food intake could be achieved, which may help to prevent weight gain.

Neuropsychological lesion studies have shown that particularly right-sided frontal lesions are associated with impairment to inhibit response tendencies towards immediately rewarding but in the long run adverse consequences (Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Lieberman & Eisenberger, 2004; Starkstein & Robinson, 1997). Non-invasive brain stimulation studies, either with transcranial direct current stimulation (tDCS) or with transcranial magnetic stimulation (TMS) have also demonstrated that valuation of superficially seductive options can be changed in different contexts and with different stimuli, e.g., cigarettes (Amiaz, Levy, Vainiger, Grunhaus, & Zangen, 2009), palatable or high-caloric food (Camus et al., 2009), and drugs (Boggio et al., 2010; Mishra, Nizamie, Das, & Praharaj, 2010). In those studies (for review see Jansen et al., 2013), the dorsolateral prefrontal cortex (DLPFC) has most consistently been used as

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stimulation location. However, selection of either the left or the right DLPFC was much less consistent, and in cases where selection of the study-specific DLPFC location was reported, this selection was guided by either using the 10–20 system (e.g., F3 for active TMS, F4 for tDCS) or by the “5 cm rule” (DLPFC location determined as 5 cm anterior to the abductor pollicis brevis motor cortex region). Despite these inconsistencies a random effects analysis of 17 studies indicated a medium effect size favoring active non-invasive neurostimulation over sham stimulation in the reduction of food or drug craving, with no apparent difference between left and right DLPFC stimulation. While working under the hypothesis that modulating DLPFC activity may change control processes and possibly suppress mechanisms that drive the preference for high-caloric or palatable food, specific DLPFC-dependent processes mediating the observed behavioral effects have remained largely unknown (Val-Laillet et al., 2015).

Recently, however, Diana (2011) has hypothesized that DLPFC stimulation may affect neural processing in the ventral tegmental area (VTA), based on a previous report of changed firing patterns of dopaminergic neurons in the rat VTA upon electrophysiological stimulation of the prefrontal cortex (Gariano & Groves, 1988). That observation was replicated some years later (Karreman & Moghaddam, 1996; Taber, Das, & Fibiger, 1995), additionally showing that it is most likely a direct route from the PFC to the VTA that mediates this effect and that even the prefrontal cortex' regulation of dopamine release in the striatum is mediated by its influence on the VTA. Tracing studies (e.g., Carr & Sesack, 2000) in rats and in primates (Frankle, Laruelle, & Haber, 2006) have later shown that a broad region of the DLPFC projects monosynaptically to the VTA.

Against this background we therefore adopted a method as recently suggested by J. X. Wang et al. (2014; see also Fox, Halko, Eldaief, & Pascual-Leone, 2012) using functional connectivity from resting-state functional magnetic resonance imaging (fMRI) to identify prefrontal cortical regions strongly connected to the VTA, but also laterally enough to be reached by TMS. As we were interested in prefrontal regions exerting some kind of control over VTA signaling, we expected the correlation expressing the connectivity between the VTA seed region and the prefrontal cortical aspect to be negative during the resting state, because a negative coupling was seen more indicative of expressing mutual control compared to signal covariation in the same direction (i.e., positively correlated time course). This view is further supported by the finding that the degree of negative functional connectivity between prefrontal and limbic networks in the resting state predicts self-control (Lee & Telzer, 2016). Using this approach, we sought to overcome some of the previous methodological limitations with respect to the selection of the prefrontal hemisphere and determination of the individual localization of TMS application. Furthermore, our specific interest was to test directly whether prefrontal neurostimulation would indeed induce modulation of neural activation in the VTA in humans, thereby testing the putative mechanism as outlined above.

For neurostimulation we used two different modes of theta-burst stimulation (TBS), a specific repetitive TMS pattern (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The protocol was inspired by hippocampal in vitro studies in which theta-bursts were applied to evoke synaptic potentiation (Hess, Aizenman, & Donoghue, 1996; Larson & Lynch, 1986), and by in vivo recordings (Pistis, Porcu, Melis, Diana, & Gessa, 2001) showing that DLPFC neurons projecting to the VTA fire spontaneously in the theta frequency of around 4–6 Hz. Huang et al. (2005) established two modalities of TBS: intermittent TBS (iTBS) and continuous TBS (cTBS) which have been suggested to exert different effects in terms of neuronal excitability under the TMS coil. Recent studies have

reported that cTBS has the potential to reduce cortical excitability while there is an increased probability that iTBS enhances cortical excitability (Brownjohn, Reynolds, Matheson, Fox, & Shemmell, 2014; Brückner, Kiefer, & Kammer, 2013; Cárdenas-Morales, Grön, & Kammer, 2011; Di Lazzaro et al., 2011; Goldsworthy et al., 2016; Jelić, Milanović, & Filipović, 2015; Woźniak-Kwaśniewska, Szekely, Aussedat, Bougerol, & David, 2014). Given the prerequisite of anti-correlated resting-state activity between the TBS-targeted prefrontal region and the VTA, we expected cTBS to decrease prefrontal control activity, thereby enhancing VTA signaling, whereas iTBS should increase prefrontal control activity and therefore reduce VTA signaling.

In contrast to previous studies usually using self-report questionnaires and visual analogue scales to assess effects of DLPFC neurostimulation, in the present study we opted for blood oxygen level-dependent (BOLD) signaling obtained from fMRI during a food/non-food discrimination task with high- and low-caloric (LC) food stimuli as one of the dependent variables of interest. In previous studies (Ulrich, Endres, et al., 2016) this material has proved to elicit highly reliable activation differences in the VTA with greater activation for high- relative to low-caloric stimuli. For the present study we therefore conjectured that if theta-burst stimulation over the VTA-coupled aspect of the lateral prefrontal cortex would indeed affect the VTA, the different stimulating properties of cTBS and iTBS should induce opposite modulatory effects on VTA's signaling for high- and low-caloric stimuli, with both theta-burst protocols serving as mutual stimulation control condition.

2. Materials and methods

2.1. Participants

Participants were initially 20 healthy male students of medicine recruited from the local university, with a mean age of 24.9 years (standard deviation (SD): 3.2 years). The decision to recruit a males-only sample for the present study was motivated by previous observations that women's menstrual cycle is associated with hormonal alterations significantly affecting blood flow-dependent estimations of brain activation (e.g., Dietrich, et al., 2001; Hausmann, Becker, Gather, & Gunturkun, 2002) as used in BOLD fMRI (see also Discussion). Based on unstructured individual interviews food habits of our participants can be characterized as a Western-type diet. Vegetarians, vegans, or subjects with other accentuated food habits (e.g., low-carbohydrate diets) did not participate in the study. Overweight or obese participants were not explicitly excluded, causing variation of the body mass index (BMI) between 20.6 kg/m² and 32.9 kg/m² (mean: 23.9 kg/m², SD: 2.9 kg/m²). There were no self-reports of psychiatric/neurological disorders (including disordered eating behavior) or any other contraindications regarding the fMRI procedure. Written informed consent was obtained prior to the experiment. The study was approved by the local ethics committee at the University of Ulm, and it was in accordance with the Declaration of Helsinki.

While all of these 20 participants provided data at first visit, only 15 of them were willing to reappear for consecutive fMRI measurements investigating cTBS and iTBS effects about four months later. The mean age of this subsample was 24.8 years (SD: 3.7 years). Mean BMI was 23.7 kg/m² (SD: 3.0 kg/m²) and ranged between 20.6 kg/m² and 32.9 kg/m².

2.2. fMRI food/non-food discrimination task

All participants performed a discrimination task on visual high-caloric (e.g., burger, pizza, spare ribs) and low-caloric (e.g., apple,

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