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Research review

Transcranial magnetic stimulation of medial prefrontal cortex modulates implicit attitudes towards food

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ABSTRACT

The medial prefrontal cortex (mPFC) is known to be associated with food representation and monitoring of eating behaviour, but the neural mechanisms underlying attitudes towards food are still unclear. Transcranial magnetic stimulation (TMS) was used in combination with the implicit association test (IAT) to investigate the causal role of mPFC in controlling implicit food evaluation in healthy volunteers. Participants performed an IAT on tasty and tasteless food to test TMS interaction with food evaluation. Moreover, IATs assessing self-related concepts and attitude towards flowers and insects were carried out to control whether TMS could also affect self-representation or, more in general, the cognitive mechanisms required by the IAT. TMS was applied over mPFC; the left parietal cortex (lPA) was also stimulated as control site. Results revealed that mPFC-TMS selectively affected IAT on food, increasing implicit preference for tasty than tasteless food, only in a subgroup of participants who did not show extreme explicit evaluation for tasty and tasteless food. This demonstrates that mPFC has a critical causal role in monitoring food preference and highlights the relevance of considering individual differences in studying food representation and neural mechanisms associated with eating behaviour.

Contents

Introduction

Food consumption is a daily activity essential for life, but in modern society food has become less a question of survival and more a matter of social interaction in which different factors influence personal feelings and behaviour in eating. In this context weight-related diseases and eating disorders are growing problems for health and a field of great interest for researchers and clinicians (Fairburn & Harrison, 2003; Treasure, Claudino, & Zucker, 2010). Taking into account biological factors related with food consumption and linked with the risk to develop eating disorders, recent neuroimaging studies have investigated which brain regions are involved in food representation and which are the neural mechanisms underlying motivations and attitudes towards food. The visual presentation of food images typically produces activation in cortical and subcortical regions including the amygdala, hippocampus, insula, anterior cingulate cortex, orbitofrontal cortex, medial and dorsolateral prefrontal cortex (Frank et al., 2010; Killgore et al., 2003; LaBar et al.,

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2001; van der Laan, de Ridder, Viergever, & Smeets, 2011). These areas seem to be involved in food-related activity because of their role in processing biologically relevant stimuli and part of a brain network recruited during the evaluation of the reward value of the stimuli and monitoring behaviour (Tang et al., 2012). In particular, different variables modulated the activity in the orbitofrontal and prefrontal cortex, namely, hunger or satiety (Führer, Zysset, & Stumvoll, 2008), the calorie content of the food (Killgore et al., 2003) and the request to actively control the desire for food (Hollmann et al., 2012), consistent with the hypothesis that these areas are crucial for reward anticipation and behavioural control. Interestingly, prefrontal regions showed also different food-related activity depending on individual differences in reward drive, emotional eating style and cognitive restraint of eating (Beaver et al., 2006; Blechert, Goltsche, Herbert, & Wilhelm, 2013; Hollmann et al., 2012); finally, the activation of the prefrontal cortex differed when healthy volunteers were compared to participants with eating disorders such as obesity or anorexia (Martin et al., 2010; Uher et al., 2004). These results have led researchers to consider the prefrontal cortex as part of a neural circuit contributing to the pathophysiology of eating disorders (Kaye, Wagner, Fudge, & Paulus, 2011) and therefore an interesting candidate as cortical target for studies aiming at exploring the modulatory effects of non-invasive brain stimulation techniques on food-related behaviour (McClelland, Bozhilova, Campbell, & Schmidt, 2013). Indeed, medial and dorsolateral prefrontal cortices have been selected as target sites in studies with transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) showing that stimulation sessions reduced food craving in healthy participants (Fregni et al., 2008; Goldman et al., 2011; Uher et al., 2005) and pathological feelings and behaviour in participants with eating disorders (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012; Van den Eynde et al., 2010; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013). However, the mechanisms underlying the behavioural outcome and how stimulation of specific target areas could modulate attitudes towards food are still poorly understood.

One relevant issue to consider is that these studies used self-report and explicit measures which can be vulnerable to social desirability and motivation to adhere to social norms, whereas it has been shown that taste preference and attitudes towards food are a kind of automatic evaluation related to implicit affect towards different types of food, which could vary in groups with different dietary restraints and can also be seen as contradictory with respect to actual eating behaviour of these people in daily life (Papies, Stroebe, & Aarts, 2009; Roefs & Jansen, 2002; Spring & Bulik, 2014). Moreover, Hofmann, Rauch, and Gawronski (2007) showed that the behaviour of candy consumption in an experimental setting depended on automatic evaluation of candies and participants' dietary standards with a significant modulatory effect of self-regulation resources manipulated with an emotion suppression task, a result that highlighted how explicit and implicit attitudes are both relevant to determine food-related behaviour but with different impact depending on personal resources of cognitive control.

The implicit association test (IAT; Greenwald, McGhee, & Schwartz, 1998) is one of the most used tools to measure implicit attitudes. It consists in a double categorization task of two opposite categories associated with two opposite valence attributes. Participants are asked to sort a set of stimuli pressing two response buttons; stimuli belonging to opposite categories (e.g. palatable/unpalatable foods) and valence attributes (e.g. positive/negative words) are first presented separately, then categories and attributes are associated in pairs which can be congruent (e.g. palatable foods – positive words) or incongruent (e.g. unpalatable food – positive words) relative to the dominant thoughts for each specific category. The IAT assumes that a stronger association between categories and attributes causes increased difficulty in categorizing stimuli in the incongruent condition; therefore, differences in accuracy and reaction times between congruent and incongruent conditions are considered an index of the automatic evaluation of the categories. Applied to preference for food IAT has been used to investigate valence for food as a function of deprivation and attitudes towards high-fat and low-fat food in normal weight and obese participants (Roefs & Jansen, 2002; Seibt, Ha, & Deutsch, 2007); moreover, Richetin, Perugini, Prestwich, and O'Gorman (2007) showed that with a large sample of participants IAT predicted behavioural preference for fruit or snacks.

In the present study we combined IAT and TMS in order to investigate the causal role of medial prefrontal cortex (mPFC) in controlling implicit attitudes for tasty and tasteless food. As mentioned above, mPFC showed abnormal responses to images of food in patients with eating disorders and obesity as compared to healthy participants (Martin et al., 2010; Uher et al., 2004); in addition, a case report of Downar et al. (2012) showed remission of symptoms in a bulimic patient following a treatment with rTMS on mPFC. In our study TMS was applied while participants performed an IAT with tasty and tasteless food associated with positive and negative valence words, with the aim to clarify the neural mechanisms responsible for implicit food representation in a healthy population. A different IAT assessing positive and negative valence towards self and others was also included in the experiment in the light of previous neuroimaging findings showing that cortical midline structures, including the mPFC, are involved in explicit and implicit self-related concepts (Moran, Heatherton, & Kelley, 2009) and psychological studies which highlighted a relation between eating behaviour and self-esteem (Bevelander, Anschütz, Creemers, Kleinjan, & Engels, 2013; Vohs et al., 2001). The analysis of the TMS effect on different IAT performances would allow clarification whether the mPFC, for which we expected a causal role in food evaluation, is causally involved also in implicit self-esteem. Finally, in order to check the site specificity of mPFC stimulation and to control whether the IAT-TMS interaction did not depend on a general effect of TMS on IAT cognitive mechanisms, the experimental design included stimulation of the left parietal cortex (lPA) as control site and a third IAT on valence for insects and flowers as control task.

Methods

Participants

Thirty-six (15 males, 21 females, mean age = 23.25 years, s.d. = 2.88, mean years of education = 14.5, s.d. = 1.75) healthy volunteers participated in the experiment, which took place in the TMS laboratory of the University of Milano-Bicocca with the approval of the local Ethic Committee. All participants were right-handed, had normal or corrected to normal vision, no clinical history of neurological or psychiatric disorders, including eating disorders, or other specific contraindications to TMS. Written informed consent was obtained prior to participation.

Procedure

The IAT (Greenwald et al., 1998) was used to measure implicit attitudes towards tasty and high-fat food versus tasteless and low-fat food (IAT-food), self versus others related concepts (IAT-self), flowers versus insects (IAT-flowers). For each IAT six words for every category of interest, six words with positive valence and six words with negative valence were selected as stimuli. The positive and negative words were the same across the three IATs. Foods and positive/negative valence words were selected throughout a pilot rating submitted to 40 subjects (20 males, 20 females, mean age = 27.2 years, s.d. = 5.3, mean educational level = 15.8 years, s.d. = 2.4) who did not take part in the TMS experiment. From two lists of 45 foods and 45 positive/negative valence words rated on a six-point Likert scale (very tasteless – very tasty food, very negative – very positive word), the six foods with the highest and the lowest score on the tasty scale and the six words with the highest and lowest score on the valence scale were selected.

Self-related and others-related words, flowers and insects were the Italian translation of stimuli used in previous studies (Greenwald & Farnham, 2000; Greenwald et al., 1998). T-tests showed that words belonging to opposite categories and positive and negative valence words did not differ in frequency as assessed by the COLFIS database (http://www.istc.cnr.it/grouppage/colfisEng) and in number of letters (all $p > .05$). See Appendix for the complete list of words.

Before the experiment participants received the list of words presented in the three IATs and were asked to rate on a six-point Likert scale how much tasty they consider the food, the positive-negative valence of the words used as attributes and to categorize flowers, insects, self-related and others-related words. The IATs were presented on a computer screen using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Each form of IAT included seven blocks. In the IAT-food, block 1 asked to classify tasty (left key) and tasteless (right key) food. In block 2, participants classified positive (left key) and negative (right key) words. In blocks 3 and 4 foods and attributes were presented together and participants were asked to press the left key for tasty food and positive words and the right key for tasteless food and negative words (congruent condition). In block 5 keys for food classification were reversed, namely, the left key for tasteless food and the right key for tasty food. Finally, in blocks 6 and 7 participants were asked to press the left key for tasteless food and positive words and the right key for tasty food and negative words (incongruent condition). The same blocks schema was used for the IAT-self and IAT-flowers (see Table 1) considering the combinations self-positive and flowers-positive as the congruent condition, respectively. For half of the participants the position of blocks 1, 3 and 4 were switched with those of blocks 5, 6 and 7, respectively; namely, the incongruent condition was presented first (Greenwald, Nosek, & Banaji, 2003). Participants responded pressing the z (left key) and x (right key) buttons of the computer keyboard with two fingers of the left hand and they were instructed to respond as quickly and as accurately as possible. The left hand was chosen to avoid any possible interaction of the TMS with motor responses since the left mPFC was a stimulation site (Cattaneo, Mattavelli, Platania, & Papagno, 2011). Each IAT was repeated three times in a no-TMS condition and with TMS applied over the mPFC or the lPA. The order of IATs and TMS conditions was counterbalanced across the subjects.

After the experiment participants were asked to complete some questionnaires to evaluate the presence of depressive symptoms (Beck Depression Inventory, BDI-II, Beck, Steer, Ball, & Ranieri, 1996), impulsiveness (Barrat Impulsiveness Scale, BIS-11, Patton, Stanford, & Barratt, 1995), eating disorders (Eating Disorder Inventory, EDI-3, Garner, 2004), dysmorphic appearance concerns (Italian Body Image Concern Inventory, I-BICI, Luca, Giannini, Gori, & Littleton, 2011) and general psychological problems (Symptom Checklist, SCL-90-R, Derogatis, 1994; Prunas, Sarno, Preti, Madeddu, & Perugini, 2012).

TMS stimulation

TMS was delivered with an Eximia TMS stimulator (Nexstim, Helsinki, Finland) using a focal bi-pulse, figure of eight 70-mm coil. Two pulses with a gap of 143 ms (7 Hz) were delivered at the fixed intensity of 60% of the maximum stimulator output at target onset in blocks 3, 4, 6 and 7 of the IATs (Cattaneo et al., 2011). On the basis of previous studies we used a type of stimulation known to interfere with the activity of the target regions (Cattaneo et al., 2011; Crescentini, Aglioti, Fabbro, & Urgesi, 2014); moreover, as in several previous studies (Campana, Cowey, & Walsh, 2002; Cohen Kadosh, Muggleton, Silvanto, & Walsh, 2010; Pitcher, Garrido, Walsh, & Duchaine, 2008; Pitcher, Walsh, Yovel, & Duchaine, 2007), a fixed TMS intensity was applied to all participants in the light of consistent evidence that the susceptibility to TMS depends on the specific stimulated cortical region (Robertson, Théoret, & Pascual-Leone, 2003). The TMS targets were identified in each subject using a Navigated Brain Stimulation (NBS) system (Nexstim, Helsinki, Finland) that uses infrared-based frameless stereotaxy to map the position of the coil and the subject's head within the reference space of a standard model of MRI space. The NBS system uses a set of digitalized skull landmarks (nasion, inion, right and left preauricular points) and eight scalp points to fit subjects' head with an average MRI brain and create a 3D model. A maximum matching error of 6 mm was considered as acceptable. Moreover, the NBS system allows an online control of the coil position and orientation to maintain the coil stability during stimulation.

The mPFC was our site of interest and its location was selected on the basis of a previous study (Downar et al., 2012) using the MNI coordinate $x = -1$, $y = 26$, $z = 50$. The lPA was selected as control site being in the same hemisphere of the site of interest, but far enough from frontal or temporal areas, which could be involved in cognitive processing required in IATs execution. The MNI coordinates $x = -34$, $y = -74$, $z = 50$ were considered as target. Each IAT was also completed without TMS as baseline condition. A masking noise reproducing the time-varying frequency components of the TMS 'click' was continuously played into earplugs worn by participants during the experimental sessions to avoid possible influence of the repetitive sound of the TMS on IAT reaction times.

Results

Explicit rating

Participants classified correctly insects, flowers, self-related and others-related words. Mean rating was 5.05 (s.d. = 0.76) for tasty food, 2.3 (s.d. = 0.69) for tasteless food, 5.57 (s.d. = 0.44) for positive words and 1.18 (s.d. = 0.26) for negative words. For the correct execution of the IATs participants were expected to consider foods and valence words as belonging to different categories, therefore we also calculated the differences "tasty minus tasteless food" and "positive minus negative words" to check how extreme were the ratings for foods and valence words. The mean differential score for valence words was 4.39 (s.d. = 0.62) confirming that participants actually considered valence stimuli as positive or negative. The mean differential score for foods was instead more heterogeneous with a mean value of 2.75 (s.d. = 1.05), showing that not all participants classified foods as belonging to two opposite categories. To take into account possible relations between

Table 1
Sequence of trial blocks in the IATs. In half of participants the position of blocks 1, 3 and 4 were switched with those of blocks 5, 6 and 7.

Block	Number of trials	IAT-food		IAT-self		IAT-flowers	
		Left-key	Right-key	Left-key	Right-key	Left-key	Right-key
1	24	Tasty	Tasteless	Self	Others	Flowers	Insects
2	24	Positive	Negative	Positive	Negative	Positive	Negative
3	16	Tasty positive	Tasteless negative	Self positive	Others negative	Flowers positive	Insects negative
4	32	Tasty positive	Tasteless negative	Self positive	Others negative	Flowers positive	Insects negative
5	24	Tasteless	Tasty	Others	Self	Insects	Flowers
6	16	Tasteless positive	Tasty negative	Others positive	Self negative	Insects positive	Flowers negative
7	32	Tasteless positive	Tasty negative	Others positive	Self negative	Insects positive	Flowers negative

individual differences in explicit food preferences and IAT performances, we used a mean split method to divide participants into two groups, and then group was considered as a factor of interest in the IAT analyses. Seventeen participants with differential score for foods above the mean value of 2.75 were classified as extreme food evaluators (EF; 7 males, 10 females, differential score for food: range 2.83–4.67, mean = 3.67, s.d. = 0.56), whereas nineteen participants with differential score below 2.75 were classified as non extreme food evaluators (NEF; 8 males, 11 females, differential score for food: range 0.67–2.67, mean = 1.93, s.d. = 0.6).

Independent t-tests confirmed that EF and NEF participants rated in a significantly different way tasty [$t(34) = 4.68$, $p < .001$] and tasteless food [$t(34) = -4.15$, $p < .001$], as they did with positive valence words [$t(34) = 2.85$, $p = .007$], rated as significantly less positive by the NEF group.

Questionnaires

Participants did not show any values above threshold for general psychopathology (mean SCL-90R Global Severity Index = 0.73, s.d. = 0.41), for eating disorders symptoms (mean EDI3 Eating Disorders Risk Composite = 25.69, s.d = 24.55), for impulsiveness (mean BIS-11 global score = 61.36, s.d = 7.03), for body image altered representations (mean I-BICI global score = 44.27, s.d. = 16.89) and for depression symptoms (mean BDI-II global score = 7.44, s.d. = 6.34).

We also compared NEF and EF groups in psychiatric symptomatology; independent t-tests showed that there were no significant differences (GSI, $t(34) = 0.384$, $p = .703$; EDRC, $t(34) = -.514$ $p = .611$; BIS-11, $t(34) = -0.859$, $p = .40$; I-BICI, $t(34) = -1.261$, $p = .216$; BDI, $t(34) = 1.182$, $p = .25$). Thus, results confirmed that participants did not show any psychiatric distress and especially the two subgroups (NEF and EF) were homogeneous for the evaluated clinical dimensions.

IAT results

Analyses on IAT effects were performed computing the D score as an index of strength in the automatic associations according to the improved algorithm by Greenwald et al. (2003). Four participants (3 males, 1 females) were excluded from the following analyses because their accuracy rate was below 3 s.d. in at least three IATs out of the nine repetitions of the task (three different IATs in three TMS conditions). One more female participant was excluded because of EDI-3 score above threshold for pathological eating disorder. Hence, analyses were carried out on 31 participants, 16 included in the EF group (6 males, 10 females) and 15 in the NEF group (6 males, 9 females). To test the effect of TMS on the three different IATs, D scores were entered as dependent variable in a mixed-model ANOVA with IAT (IAT-food, IAT-self, IAT-flowers) and TMS (no-TMS, mPFC, lPA) as within factors and Group (EF, NEF) as between factor. Results revealed a significant main effect of IAT [$F(2,58) = 14.12$, $p < .001$] and a significant three-way interaction IAT × TMS × Group [$F(4,116) = 2.62$, $p = .038$]. Other main effects or interactions were not significant ($p > .05$). Bonferroni's corrected post hoc tests showed that the main effect of IAT was due to higher D scores in IAT-food than IAT-self ($p < .001$) and IAT-flowers ($p < .001$). Post hoc tests for the three-way significant interaction showed that only in the NEF group TMS on mPFC selectively interfered with the IAT-food performances increasing D scores ($p = .035$). All the other post hoc tests comparing IATs performances in the three TMS conditions in each group of participants were not significant ($p > .05$) (see Fig. 1).

This D score modulation could depend on TMS selectively affecting accuracy or response latencies (RTs) in congruent or incongruent trials of the IAT-food (Cattaneo et al., 2011; Crescentini et al., 2014). To further investigate this issue, accuracy rate and RTs for correct responses in the NEF group were separately analyzed in the three TMS conditions of the IAT-food by means of repeated measures ANOVAs with factors TMS and Block (congruent, incongruent). The analysis on accuracy showed significant main effects of TMS [$F(2,28) = 4.3$, $p = .023$] and Block [$F(1,14) = 22.76$, $p < .001$], with participants less accurate when TMS was applied over mPFC as compared with no-TMS condition ($p = .036$) and overall more accurate in congruent trials, whereas the interaction TMS × Block was not significant [$F(2,28) = 1.74$, $p = .19$]. Analyses on RTs revealed a significant main effect of Block [$F(1,14) = 61.87$, $p < .001$], with participants faster in congruent trials, and a significant interaction TMS × Block [$F(2,28) = 4.45$, $p = .02$]; the main effect of TMS was not significant [$F(2,28) = 1.88$, $p = .17$]. Post hoc comparisons showed that mPFC-TMS selectively increased RTs of incongruent trials as compared with no-TMS condition ($p = .003$), whereas RTs in lPA-TMS condition were not significantly different from no-TMS condition, nor were significant comparisons for congruent trials ($p > .05$) (see Fig. 2).

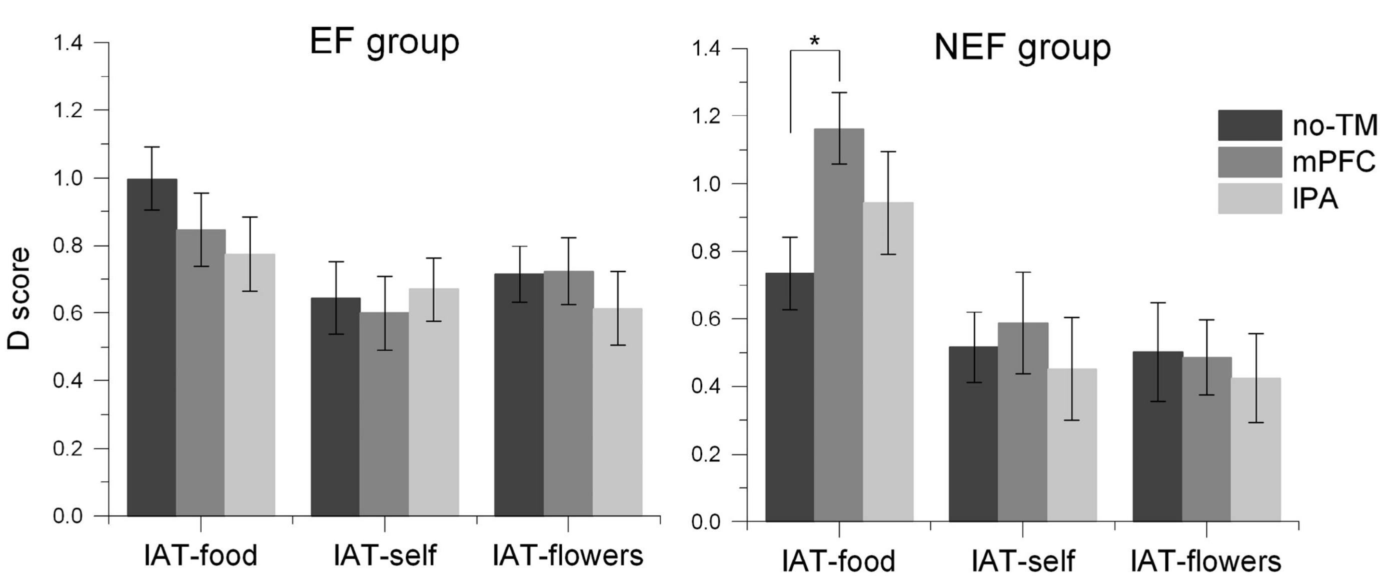

Fig. 1. Mean D score measuring the IAT effects for EF and NEF groups in the three TMS conditions. Error bars represent standard error of the means. Asterisk indicates a significant effect ($p < .05$).

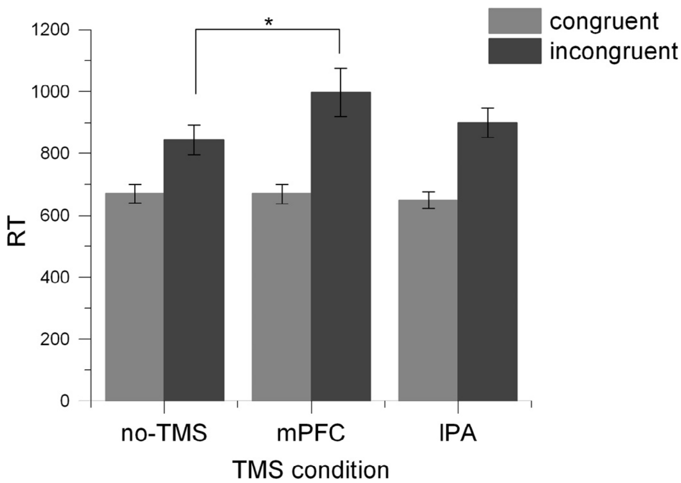

Fig. 2. Mean RTs for correct responses in congruent and incongruent trials for the NEF group in the IAT-food during the three TMS conditions. Error bars represent standard error of the means. Asterisk indicates a significant effect ($p < .05$).

Discussion

The present study aimed at investigating the causal role of mPFC in implicit evaluation of tasty and tasteless food. TMS was used to interfere with activity in the mPFC and lPA while participants performed three different IATs assessing attitudes towards food, self- and others-related concepts, flowers and insects. Results showed that individual differences in explicit food preference modulated the effect of mPFC-TMS on IAT-food performances. Indeed, stimulation applied on mPFC increased the IAT-food effect, namely the implicit association of tasty food with positive attributes and tasteless food with negative attributes, but only in a subgroup of participants, who did not declare extreme preference in terms of palatability in the explicit rating of food stimuli (NEF group). Crucially, the effect proved to be specific for site of stimulation and task, since none of the IATs was affected by stimulation of the control site, and TMS on mPFC did not interfere with other types of IAT, such as IAT-self and IAT-flowers.

Previous neuroimaging studies showed a significant correlation between personality differences and frontal response to pictures of food (Beaver et al., 2006) and highlighted a greater mPFC response to food stimuli in obese than normal weight participants tested in pre-meal condition with correlation between self-report state of hunger and mPFC activity (Martin et al., 2010), suggesting a role of the mPFC in food motivation and individual differences in neural mechanisms involved in food processing. Moreover, as already cited, Downar et al. (2012) reported remission of bulimic symptoms in a patient treated with rTMS sessions on mPFC, showing that the enhancement of mPFC activity increased the ability to control the dysfunctional eating behaviour. Our results are in line with those findings. Participants in the NEF group could be considered as more controlled in their attitudes towards food since they did not assert explicit preference for tasty versus tasteless food. In this group TMS interfered with activity of mPFC reducing the monitoring role of this area and thus increasing the IAT effect. Indeed, analyses on congruent and incongruent trials of the IAT-food revealed that TMS selectively increased RTs for incongruent trials, which are those requiring more cognitive control. The type of stimulation used in our study is known to transiently interfere with the activity of the targeted regions (Walsh & Pascual-Leone, 2003), differently from the rTMS treatment applied by Downar et al. (2012) to enhance the activity of the same region (Hallett, 2007; Thut & Pascual-Leone, 2010). Therefore, both results are in the same direction: interference with mPFC reduced control on IAT-food performance and, on the contrary, enhanced activity of mPFC increased control on eating behaviour. One question concerns why TMS interfered with the activity of mPFC in the NEF group, but not in the EF group. Participants in the EF group appeared to be already less controlled in their explicit and implicit attitudes towards food, as shown by more extreme evaluations in food rating and greater D score in the IAT-food, thus the disinhibitory effect of mPFC-TMS could be less evident. At a neural level this can be explained with the state-dependent effects of TMS; indeed, it has been demonstrated that the interaction of TMS with a cognitive task depends on the activation state of neurons in the targeted area (Silvanto & Pascual-Leone, 2008). As mentioned above, individual differences affect the activity of the mPFC in response to food stimuli (Beaver et al., 2006); NEF and EF participants, because of the different control exerted during the task, could have a different state of cortical activation when TMS was applied over mPFC during the IAT-food; this produced the different behavioural outcome.

The IAT on flowers and insects was included as a control task to verify whether the TMS effects on the IAT-food were due to a general interference with the cognitive mechanisms involved in the task. Our results confirmed that stimulation of mPFC selectively affected attitudes towards food, being the control task not affected by TMS. Concerning the IAT-self we had no specific a priori hypothesis, since there is evidence of relations between eating disorders and self-esteem (Bevelander et al., 2013; Vohs et al., 2001) and the dorsal portion of mPFC has a relevant role in evaluation and decision about self-relevant concepts, as reported in neuroimaging studies (Schmitz & Johnson, 2007). In our experiment mPFC-TMS did not affect IAT assessing self-esteem. This result could be due to differences in the type of task and material used in previous studies, mostly explicit and implicit measures on personality traits, social opinions or affective stimuli (Moran et al., 2009; Schmitz & Johnson, 2006, 2007), and the IAT assessing self-esteem that we used in the present study. Besides this, a remarkable methodological issue concerns the fact that previous neuroimaging studies highlighted a network of regions activated by self-referential processing, but fMRI does not allow to conclude about the causal role of the responsive areas, differently from the TMS method in which a significant effect on behaviour demonstrates that the targeted area is causally related to task performance. Thus, it could be that mPFC is part of a network involved in processing self-relevant stimuli, but its causal role is more specific to food representation.

Previous studies have demonstrated that the IAT is a sensitive tool to discriminate healthy participants on drive for thinness (Ahern, Bennett, & Hetherington, 2008) or emotional eating (Bongers, Jansen, Houben, & Roefs, 2013), but only few studies have measured implicit attitudes in eating disorder psychopathology with the IAT, so far. Using the IAT, Cockerham et al., 2009 found significant differences in self-esteem between patients with bulimia nervosa or binge eating disorders and healthy controls and Rudolph and Hilbert (2014) showed good correlations between a self-discrimination IAT and body mass index, experiences of weight stigma and depressive symptoms in binge eating disorders and obesity. These studies supported the feasibility of the IAT to measure different constructs in clinical eating disorders and to improve understanding of predictive and explanatory aspects of the psychopathology (Vartanian, Polivy, & Herman, 2004). In the light of our results on individual differences in response to TMS during the IAT, it would be of interest for the future research to combine IAT and TMS treatment in clinical populations.

In summary, the present study supports the involvement of mPFC in food representation and adds evidence to the specific causal role of this area in monitoring implicit attitudes towards tasty and tasteless food, showing that individual differences are a critical aspect in studying neural mechanisms associated with food preference.

Appendix

List of words used in the IATs; English translation are in brackets.

IAT-food		IAT-self		IAT-flowers		Attributes	
Tasty	Tasteless	Self	Others	Flowers	Insects	Positive	Negative
Pizza	Orzo *(barley)*	Io *(I)*	Tu *(you)*	Rosa *(rose)*	Ape *(bee)*	Amore *(love)*	Assassino *(killer)*
Lasagne *(lasagna)*	Merluzzo *(codfish)*	Me *(me)*	Egli *(he)*	Orchidea *(orchid)*	Mosca *(fly)*	Gioia *(joy)*	Cadavere *(cadaver)*
Tiramisù	Sedano *(celery)*	Noi *(we)*	Voi *(you)*	Violetta *(violet)*	Formica *(ant)*	Amico *(friend)*	Tortura *(torture)*
Cioccolato *(chocolate)*	Soia *(soy)*	Mio *(my)*	Tuo *(your)*	Garofano *(carnation)*	Ragno *(spider)*	Bacio *(kiss)*	Morte *(death)*
Patatine *(chips)*	Ravanello *(radish)*	Nostro *(ours)*	Loro *(they)*	Papavero *(poppy)*	Zanzara *(mosquito)*	Abbraccio *(hug)*	Agonia *(agony)*
Gelato *(ice-cream)*	Tofu	Miei *(mine)*	Lui *(he)*	Giglio *(lily)*	Grillo *(cricket)*	Pace *(peace)*	Omicidio *(murder)*

References

Ahern, A. L., Bennett, K. M., & Hetherington, M. M. (2008). Internalization of the ultra-thin ideal. Positive implicit associations with underweight fashion models are associated with drive for thinness in young women. *Eating Disorders*, *16*, 294–307.

Beaver, J. D., Lawrence, A. D., van Ditzhuijzen, J., Davis, M. H., Woods, A., & Calder, A. J. (2006). Individual differences in reward drive predict neural responses to images of food. *The Journal of Neuroscience*, *26*, 5160–5166.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck Depression Inventories-I and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*, 588–597.

Bevelander, K. E., Anschütz, D. J., Creemers, D. H. M., Kleinjan, M., & Engels, R. C. M. E. (2013). The role of explicit and implicit self-esteem in peer modeling of palatable food intake. A study on social media interaction among youngsters. *PlosOne*, *8*, e72481.

Blechert, J., Goltsche, J. E., Herbert, B. M., & Wilhelm, F. H. (2013). Eat your troubles away. Electrocortical and experiential correlates of food image processing are related to emotional eating style and emotional state. *Biological Psychology*, *96*, 94–101.

Bongers, P., Jansen, A., Houben, K., & Roefs, A. (2013). Happy eating. The single target implicit association test predicts overeating after positive emotions. *Eating Behaviors*, *14*, 348–355.

Campana, G., Cowey, A., & Walsh, V. (2002). Priming of motion direction and area V5/MT. A test of perceptual memory. *Cerebral Cortex*, *12*, 663–669.

Cattaneo, Z., Mattavelli, G., Platania, E., & Papagno, C. (2011). The role of the prefrontal cortex in controlling gender-stereotypical associations. A TMS investigation. *Neuroimage*, *56*, 1839–1846.

Cockerham, E., Stopa, L., Bell, L., & Gregg, A. (2009). Implicit self-esteem in bulimia nervosa. *Journal of Behavior Therapy and Experimental Psychiatry*, *40*, 265–273.

Cohen Kadosh, R., Muggleton, N., Silvanto, J., & Walsh, V. (2010). Double dissociation of format-dependent and number-specific neurons in human parietal cortex. *Cerebral Cortex*, *20*, 2166–2171.

Crescentini, C., Aglioti, S. M., Fabbro, F., & Urgesi, C. (2014). Virtual lesions of the inferior parietal cortex induce fast changes of implicit religiousness/spirituality. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *54*, 1–15.

Derogatis, L. R. (1994). *Symptom Checklist-90-R. Administration, scoring, and procedures manual (3rd ed.)*. Minneapolis, MN: National Computer Systems.

Downar, J., Sankar, A., Giacobbe, P., Woodside, B., & Colton, P. (2012). Unanticipated rapid remission of refractory bulimia nervosa, during high-dose repetitive Transcranial Magnetic Stimulation of the dorsomedial prefrontal cortex. A case report. *Frontiers in Psychiatry*, *3*, 1–5.

Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. *Lancet*, *361*, 407–416.

Frank, S., Laharnar, N., Kullmann, S., Veit, R., Canova, C., Hegner, Y. L., et al. (2010). Processing of food pictures. Influence of hunger, gender and calorie content. *Brain Research*, *1350*, 159–166.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A. M., Nitsche, M. A., et al. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite*, *51*, 34–41.

Führer, D., Zysset, S., & Stumvoll, M. (2008). Brain activity in hunger and satiety. An exploratory visually stimulated fMRI study. *Obesity*, *16*, 945–950.

Garner, D. M. (2004). *The eating disorder inventory-3. Professional manual*. Odessa, FL: Psychological Assessment Resources, Inc.

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K., et al. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite*, *56*, 741–746.

Greenwald, A. G., & Farnham, S. D. (2000). Using the implicit association test to measure self-esteem and self-concept. *Journal of Personality and Social Psychology*, *79*, 1022–1038.

Greenwald, A. G., McGhee, D. E., & Schwartz, J. L. K. (1998). Measuring individual differences in implicit cognition. The Implicit Association Test. *Journal of Personality and Social Psychology*, *74*, 115–139.

Greenwald, A. G., Nosek, B. A., & Banaji, M. R. (2003). Understanding and using the implicit association test. I. An improved scoring algorithm. *Journal of Personality and Social Psychology*, *85*, 197–216.

Hallett, M. (2007). Transcranial magnetic stimulation. A primer. *Neuron*, *55*, 187–199.

Hofmann, W., Rauch, W., & Gawronski, B. (2007). And deplete us not into temptation. Automatic attitudes, dietary restraint, and self-regulatory resources as determinants of eating behavior. *Journal of Experimental Social Psychology*, *43*, 497–504.

Hollmann, M., Hellrung, L., Pleger, B., Schlögl, H., Kabisch, S., Stumvoll, M., et al. (2012). Neural correlates of the volitional regulation of the desire for food. *International Journal of Obesity*, *36*, 648–655.

Kaye, W. H., Wagner, A., Fudge, J. L., & Paulus, M. (2011). Neurocircuity of eating disorders. *Current Topics in Behavioral Neuroscience*, *6*, 37–57.

Killgore, W. D. S., Young, A. D., Femia, L., Bogorodzki, P., Rogowska, J., & Yurgelun-Todd, D. (2003). Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage*, *19*, 1381–1394.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., Kim, Y. H., Nobre, A. C., & Mesulam, M. M. (2001). Hunger selectively modulates corticolimbic activation to food stimuli in humans. *Behavioural Neuroscience*, *115*, 493–500.

Luca, M., Giannini, M., Gori, A., & Littleton, H. (2011). Measuring dysmorphic concern in Italy. Psychometric properties of the Italian Body Image Concern Inventory (I-BICI). *Body Image*, *8*, 301–305.

Martin, L. E., Holsen, L. M., Chambers, R. J., Bruce, A. S., Brooks, W. M., Zarcone, J. R., et al. (2010). Neural mechanisms associated with food motivation in obese and healthy weight adults. *Obesity*, *18*, 254–260.

McClelland, J., Bozhilova, N., Campbell, I., & Schmidt, U. (2013). A systematic review of the effects of neuromodulation on eating and body weight. Evidence from human and animal studies. *European Eating Disorders Review*, *21*, 436–455.

Moran, J. M., Heatherton, T. F., & Kelley, W. M. (2009). Modulation of cortical midline structures by implicit and explicit self-relevance evaluation. *Social Neuroscience*, *4*, 197–211.

Papies, E. K., Stroebe, W., & Aarts, H. (2009). Who likes it more? Restrained eaters' implicit attitudes towards food. *Appetite*, *53*, 279–287.

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*, 768–774.

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *Journal of Neuroscience*, *28*, 3929–3933.

Pitcher, D., Walsh, V., Yovel, G., & Duchaine, B. C. (2007). TMS evidence for the involvement of the right occipital face area in early face processing. *Current Biology*, *17*, 1568–1573.

Prunas, A., Sarno, I., Preti, E., Madeddu, F., & Perugini, M. (2012). Psychometric properties of the Italian version of the SCL-90-R. A study on a large community sample. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *27*(8), 591–597.

Richetin, J., Perugini, M., Prestwich, A., & O'Gorman, R. (2007). The IAT as a predictor of food choice. The case of fruits versus snacks. *International Journal of Psychology*, *42*, 166–173.

Robertson, E. M., Théoret, H., & Pascual-Leone, A. (2003). Studies in cognition. The problems solved and created by transcranial magnetic stimulation. *Journal of Cognitive Neuroscience*, *15*, 948–960.

Roefs, A., & Jansen, A. (2002). Implicit and explicit attitudes toward high-fat foods in obesity. *Journal of Abnormal Psychology*, *111*, 517–521.

Rudolph, A., & Hilbert, A. (2014). A novel measure to assess self-discrimination in binge-eating disorder and obesity. *International Journal of Obesity*, 1–3.

Schmitz, T. W., & Johnson, S. C. (2006). Self-appraisal decisions evoke dissociated dorsal–ventral aMPFC networks. *Neuroimage*, *30*, 1050–1058.

Schmitz, T. W., & Johnson, S. C. (2007). Relevance to self. A brief review and framework of neural systems underlying appraisal. *Neuroscience and Biobehavioral Reviews*, *31*, 585–596.

Seibt, B., Ha, M., & Deutsch, R. (2007). Prepared to eat. How immediate affective and motivational responses to food cues are influenced by food deprivation. *European Journal of Social Psychology*, *37*, 359–379.

Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topography*, *21*, 1–10.

Spring, V. L., & Bulik, C. M. (2014). Implicit and explicit affect toward food and weight stimuli in anorexia nervosa. *Eating Behaviors*, *15*, 91–94.

Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. *Physiology and Behavior*, *106*, 317–324.

Thut, G., & Pascual-Leone, A. (2010). A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. *Brain Topography*, *22*, 219–232.

Treasure, J., Claudino, A. M., & Zucker, N. (2010). Eating disorders. *Lancet*, *375*, 583–593.

Uher, R., Murphy, T., Brammer, M. J., Dalgleish, T., Phillips, M. L., Virginia, W., et al. (2004). Medial prefrontal cortex activity associated with symptom provocation in eating disorders. *American Journal of Psychiatry*, *161*, 1238–1246.

Uher, R., Yoganathan, D., Mogg, A., Eranti, S. V., Treasure, J., Campbell, I. C., et al. (2005). Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. *Biological Psychiatry*, *58*, 840–842.

van der Laan, L. N., de Ridder, D. T. D., Viergever, M., & Smeets, P. M. (2011). The first taste is always with the eyes. A meta-analysis on the neural correlates of processing visual food cues. *Neuroimage*, *55*, 296–303.

Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W., et al. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry*, *67*, 793–795.

Van den Eynde, F., Guillaume, S., Broadbent, H., Campbell, I. C., & Schmidt, U. (2013). Repetitive transcranial magnetic stimulation in anorexia nervosa. A pilot study. *European Psychiatry*, *28*, 98–101.

Vartanian, L. R., Polivy, J., & Herman, C. P. (2004). Implicit cognitions and eating disorders. Their application in research and treatment. *Cognitive and Behavioral Practice*, *11*, 160–167.

Vohs, K. D., Voelz, Z. R., Pettit, J. W., Bardone, A. M., Katz, J., Abramson, L. Y., et al. (2001). Perfectionism, body dissatisfaction, and self-esteem: an interactive model of bulimic symptom development. *Journal of Social and Clinical Psychology*, *20*, 476–497.

Walsh, V., & Pascual-Leone, A. (2003). *Transcranial magnetic stimulation. A neurochronometrics of mind*. Cambridge, MA: MIT Press.