Titel
EEG study on the differences between lean and obese individuals during
regulation of food desire

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"In order to succeed, we must first believe that we can."

Nikos Kazantzakis

Abstract

Saurabh KUMAR

Obesity as an epidemic is a major contributor to ill-health, disability and mortality worldwide and therefore intervention is of utmost importance. Brain regions involved in the reappraisal of tasty but unhealthy foods are of special interest for the development of new therapeutic interventions for obesity. Using electroencephalogram (EEG), we visually presented food items to obese and lean individuals, while they admitted or reappraised their desire for food. During admitting the desire for low and high calorie food, obese as well as lean individuals showed higher activity in the left dorsolateral prefrontal cortex (DLPFC), whereas the right frontal operculum was involved in the reappraisal of the same food, suggesting interplay between executive control and gustatory regions. In lean participants, we found an interaction between calorie content and admit/reappraise condition in bilateral anterior insular cortices, suggesting that the anterior insula, assumed to primarily host gustatory processes, also underpins higher cognitive processes involved in food choices, such as evaluating the foods' calorie content for its reappraisal. We also questioned how eating to satiety affects food reappraisal abilities and corresponding neuronal activity in the left DLPFC and right frontal operculum in lean and obese women. When hungry, lean women self-rated the ability to reappraise visually presented food as more difficult than allowing desire for the same food. Obese hungry women instead rated their ability to reappraise food as equally well as allowing the desire, probably suggesting hunger-related impaired self-reflection of food reappraisal abilities. In obese women frontal operculum was involved in the reappraisal of foods and surprisingly also in admitting the desire for the same food suggesting that right frontal operculum in the obese female brain underpins evaluation processes involved in regulation of food desire after eating to satiety. Therefore, the frontal operculum may in future serve as a target for non-invasive brain stimulation or neurofeedback studies that aim at modulating eating behavior in obese women towards better food reappraisal abilities.

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List of Abbreviations

BMI	Body Mass Index
WHO	World Health Organization
DLPFC	Dorso Lateral Pre Frontal Cortex
MRI	Magnetic Resonance Imaging
fMRI	functional Magnetic Resonance Imaging
TMS	Transcranial Magnetic Simulation
EEG	Electro Encephalo Gram
EP	Evoked Potential
ERP	Event Related Potential
EOG	Electro Oculo Gram
BSS	Blind Source Seperation
TDA	Time Domain Approach
FDA	Frequency Domain Approach
TEEG	True Electro Encephalo Gram
MEEG	Measured Electro Encephalo Gram
VEOG	Vertical Electro Oculo Gram
HEOG	Horizontal Electro Oculo Gram
ICA	Independent Component Analysis
TDSEP	Temporal Decorrelation Source sEPeration
SOBI	Second Order Blind Identification
SCADS	Statistical Control of Artifacts in DenSe EEG
IPA	Isolated Problem Approach
ISA	Isolated Skull Approach
BEM	Boundary Element Method
MSP	Multiple Sparse Priors
BCI	Brain Computer Interface
BBCI	Berlin Brain Computer Interface<
mV	milli Volts
microV	micro Volts
Hz	Hertz

Chapter 1

Introduction

The human race since its existence had to struggle constantly to overcome the scarcity of food. Survival of the fittest dictated that individuals who stored energy in the most efficient way would survive the inevitable fast and famine that would follow times of plenty (Spencer, 1864). With the beginning of the industrialization this struggle became manageable as there were advances made in technology, agriculture, communications and trade (Fogel and Costa, 1997) which enabled easy access to nutritional food. The rapid development in these fields lead to year 2000 where the first time in the human history the number of adults with excess weights surpassed the number of adults who were underweight (Gardner and Halweil, 2000) making the problem of obesity pronounced. There are three aspects of obesity that presently make it a public health burden : its the seriousness, the prevalence and the resistance to change (Bray, 1969; Van Itallie, 1979; Simopoulos and Van Itallie, 1984; Brownell, 1982). Along with the medical implications (Sobal and Stunkard, 1989; Van Itallie, 1979; Simopoulos and Van Itallie, 1984; Hubert et al., 1983) the socio-psychological risks are also evident and more prominent for the obese individuals (Brownell, 1982; Wadden and Stunkard, 1985).

Much effort has been put in dealing with this ever growing problem of obesity. The current weight-loss programs consist of dieting (Soeliman and Azadbakht, 2014), physical activity (Jakicic and Davis, 2011), combination of both (Amorim Adegboye and Linne, 2013) or the energy intake program (Rolls, Ello-Martin, and Tohill, 2004; Rolls, Drewnowski, and Ledikwe, 2005). The reviews of these programs have repeatedly indicated that most of the interventions

have limited effects or failed, and introduced no change in the dietary behavior (Summerbell et al., 2005; Ammerman et al., 2002; Contento et al., 1995). New strategies combining physical activity and psychological motivation have also been tried (Looney and Raynor, 2013; Ausburn et al., 2014). The majority of the participants do not sustain the weight loss and gain weight immediately after the program has ended. The general lack of success can be attributed to incorrect theoretical knowledge of the mechanisms involved through which the dietary behavior can be modified (Shaikh et al., 2008; Michie et al., 2008). Therefore it is needed to shed light on the underlying mechanisms and to develop innovative strategies against obesity.

Though food intake and body weight are under homeostatic regulation, when highly palatable food is available, the ability to resist the urge to eat hinges on self-control. Exercising self-control involves the modulation of dorsolateral prefrontal cortex (DLPFC) (Hare, Camerer, and Rangel, 2009). The DLPFC is associated with a variety of executive functions in the human brain like decision making, attentional control, inhibitory control, working memory, and cognitive flexibility, as well as reasoning, problem solving, and planning (Funahashi, 2001; Stuss and Benson, 1984; Luria, 1969). Recent studies have also shown that the high cognitive control activates the DLPFC (Fehr and Krajbich, 2013; Gupta and Tranel, 2012; Arnsten and Jin, 2014). It is also shown that the DLFPC has neuronal connections to virtually all sensory and motor systems as well as subcortical structures (Miller and Cohen, 2001).

There has been a recent study using functional magnetic resonance imaging (fMRI) to identify the brain regions on the reappraisal of food (Hollmann et al., 2012). FMRI bears limitations regarding the temporal resolution (Kim and Ugurbil, 1997; Amaro and Barker, 2006) despite high spatial resolution (Menon and Kim, 1999). One of the first techniques to study human brain function non-invasively was electroencephalography (EEG). Over the years, EEG has proven to be the most widely used brain research technique in numerous experiments owing to its advantages like very high temporal resolution, its simplicity of implementation, its portability among others and despite its limited spatial resolution it is a viable tool to identify the neuronal responses. In the experiments of this thesis we used EEG

to identify brain sites underpinning the reappraisal and the admission of food desire in obese as well as in lean individuals. We expect to find differences in neuronal responses for these two different executive demands in the DLPFC.

High calorie food seems to have an identical affect on the brain as drug usage. The brain's reward system is dopaminergically controlled (Volkow et al., 2013). Like drug abusers, obese individuals seem to have an attenuated dopamine reward for high calorie food and increased craving for food (Stice et al., 2008). The consumption of excess high calorie food is like drug abuse that triggers amplified dopamine responses as well as the down regulation of the dopamine receptor availability (Wang et al., 2001). This suggests that obese individuals have a lower dopamine response to the same high calorie food as compared to lean prompting them to overeat. Hence it is of utmost importance to understand the mechanisms of the admission and the reappraisal of food desire. Brain sites involved in the executive control of food desire may serve as targets for non-invasive brain stimulation or neurofeedback training aiming to improve cognitive control over food craving.

We study the effects of high calorie food versus low calorie food to study interaction effects between allowing and reappraising food desire in obese as compared to lean individuals. In the first study of the project we used visual stimulus in the form of food pictures presented to the participants. While in the second study of this project the participants were also subjected to real food consumption in the form of a buffet in addition to the food pictures. We hypothesized that when hungry, the admission of food desire is an easier task which reverses when the participants are sated, i.e. the reappraisal of the food desire become easier when sated. We also hypothesized that eating to satiety is associated with decreased activation in brain regions underpinning the admission of food desire; While brain region underpinning the reappraisal of food desire present elevated neuronal activation.

Chapter 2

Theoretical Background

2.1 Obesity

Obesity is an epidemic and is a result of industrialization (James et al., 2001). It spreads not only in the developed countries but also in the fast developing countries like China, India and many others. From a relatively minor health burden of a very few affluent societies, it has slowly developed into a world-wide problem (Roman et al., 2014). Interestingly only the high-income countries which would presently mean Europe, North America and Australasia have come forward and publicized it but the developing and new emerging economies suffer from it nevertheless (Molarius et al., 2000; Monteiro et al., 2004). The more recent increase in obesity population in low and middle income countries is noticeable (Finucane et al., 2011; Ng et al., 2014). The increase can be mainly attributed to the easy availability of high calorie food that has been linked to the increasing rates of obesity (Spence et al., 2009; Pereira et al., 2005; Rosenheck, 2008). The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group analyzed data from 199 countries and territories and 9.1 million adults with respect to the prevalence of overweight and obesity between 1980 and 2008 (Finucane et al., 2011). During that 28-year period, the prevalence of obesity nearly doubled worldwide. Obesity according to the body mass index (BMI) can be classified into three broader categories of underweight, normal-weight and over-weight. To understand obesity one should extend the broader categories into the classification of obesity provided by the world health organization (WHO) (Seidell and Halberstadt, 2015) (see figure 2.1). In 2008, about 1.5 billion adults were

estimated to have a body mass index (BMI) of 25 or more (about 34%). Of these, 500 million were considered obese (about 10% men and 14% women). More recently, the analyses for the Global Burden of Disease Study 2013 (Ng et al., 2014) further documented that worldwide, the proportion of adults with a BMI of 25 or greater increased between 1980 and 2013 from about 29% to 37% in men and from about 30% to 38% in women. It is not a surprise that the increase in worldwide obesity has come to show that it has major impact on the quality of life and impairs health (Taylor et al., 2013; Visscher and Seidell, 2001). It has major impact on the cardiovascular disease, cancer, osteoarthritis, type 2 diabetes hence more effect on the morbidity then on mortality. The Global Burden of Disease Study and the WHO have recently documented that obesity is indeed a major contributor to ill-health, disability and mortality in many regions of the world (Lim et al., 2012; WHO, 2009).

Classification	BMI	Associated health risks
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0 or higher	
Preobese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderately increased
Obese class II	35.0–39.9	Severely increased
Obese class III	40 or higher	Very severely increased

FIGURE 2.1: The classification of obesity into different groups dependent on the BMI and the severity of associated health risks attached to it. (Source: World Health Organization: Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. WHO Technical Report Series, No 894. Geneva, World Health Organization, 2000)

For the study purpose of this thesis work and related publications the category of obese class I, obese class II and obese class III are regarded as a single group referred as 'Obese'. (refer figure 2.1).

2.1.1   Fighting obesity

Excess body weight is related to many health risks like type 2 diabetes, cardiovascular diseases, hypertension and many others (Fogel, 1986). Hence successful treatment strategies become essential. The people who are already obese require a lot of care and management

considering the health and the social implications. The environmental factors like sociocultural and economic factors and the physical environment also influence obesity (Seidell and Halberstadt, 2015; Huang et al., 2009; Swinburn et al., 2011; Glass and McAtee, 2006) (see figure 2.2). Dietary restraint (a measure of the extent to which conscious control is exerted on food intake) provides an effective measure against obesity. Restrained eaters, as compared with unrestrained eaters, avoid increases in energy intake and weight gain (Westerterp-Plantenga et al., 1998). This suggests that careful control of food intake can prevent weight gain. To build on this idea we use the help of EEG to study the restraint behavior of obese and lean individuals towards food pictures. We hypothozised the DLPFC as a key player in these processes since the DLPFC is widely regarded as an executive regions underpinning decision making (Funahashi, 2001; Stuss and Benson, 1984; Luria, 1969). We look for the differences between the obese and lean and take this knowledge as a base for future intervention studies (non-invasive brain stimulation, neurofeedback).
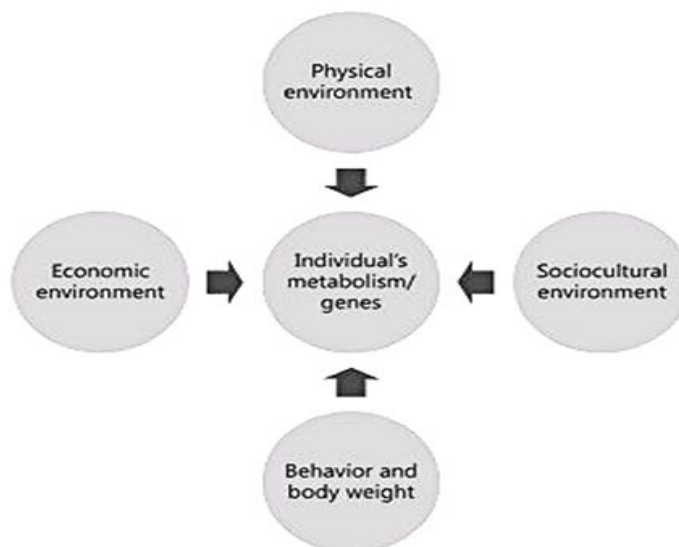
FIGURE 2.2: Obesity is affected by individual's physical, social and economic environment and also through one's behavior. (Source: (Seidell and Halberstadt, 2015))

Based on this work an intervention study has been conducted using transcranial direct current stimulation (tDCS). In a large series of previous studies tDCS was shown to modulate cognitive functions

in healthy individuals (Brunoni et al., 2012; Antal et al., 2004; Paulus, 2011; Fregni et al., 2005; Iyer et al., 2005; Nitsche et al., 2012) and can be applied safely for upto thirty minutes (Hummel et al., 2005; Iyer et al., 2005; Nitsche et al., 2012) (For more insight into tDCS effects on brain sites identified in the studies of this thesis please refer to the outlook section 4.2). The other method to modulate local neuronal responses identifed by EEG is neurofeedback. It is an operant conditioning technique providing neuronal feedback in real-time, which in combination with mental strategies, may improve associated behaviour in all-day life. Self regulation of brain activity facilitated by EEG neurofeedback has proven to be effective in intervention studies of epilepsy (Sterman and Friar, 1972; Sterman, Macdonald, and Stone, 1974), attention deficit hyperactivity disorder (ADHD) (Shouse and Lubar, 1979; Rossiter and La Vaque, 1995; Lubar et al., 1995; Linden, Habib, and Radojevic, 1996) and also in the treatment of substance abuse (Peniston and Kulkosky, 1989). An alternative non-invasive brain stimulation technique is transcranial magnetic simulation (TMS) that can temporarily excite or inhibit neuronal responses in the brain with higher spatial resolution as compared to tDCS (Hallett, 2000; George, Lisanby, and Sackeim, 1999). Its effects can last beyond the simulation period and hence can be used as potential therapy as suggested by studies on depression (Pascual-Leone et al., 1996).

2.2 Electroencephalogram (EEG)

The literal translation of Electroencephalogram (EEG) is 'Electro - *electrical'*, 'encephalo - *brain'*, 'gram - *picture'* hence an ***electrical brain picture***. It is close to that as it measures the electrical activity in the brain and can be presented in a picture form. The discovery of EEG was initially started by experiments on rabbits, monkeys and dogs (Swartz, 1998) which is in line with the other noteworthy experiments. Since then the recording of electrical activity in the human brain was started by Hans Berger (Berger, 1935), a German neurologist. He used his normal radio equipment as an amplifier for measuring the brain's electrical activity that he measured from the scalp. He was the first to show that brain's activity can be measured

even from the scalp without opening it. Theses responses can also be recorded paper making them visually accessible and measurable. It was a breakthrough as he also announced that electrical activity assessed over the brain changes according to different physiological or pathological states like during sleep, lack of oxygen, anesthesia, and diseases like epilepsy (Collura, 1993; Haas, 2003). This was the starting point which has led to many advancements in scientific and clinic EEG methodology (Borck, 2005; Gloor, 1994).

2.2.1 Neuronal basics

EEG basically records the summation of excitatory and inhibitory post synaptic potentials. To understand it in more detail one has to look to a single neuron (see figure 2.3).
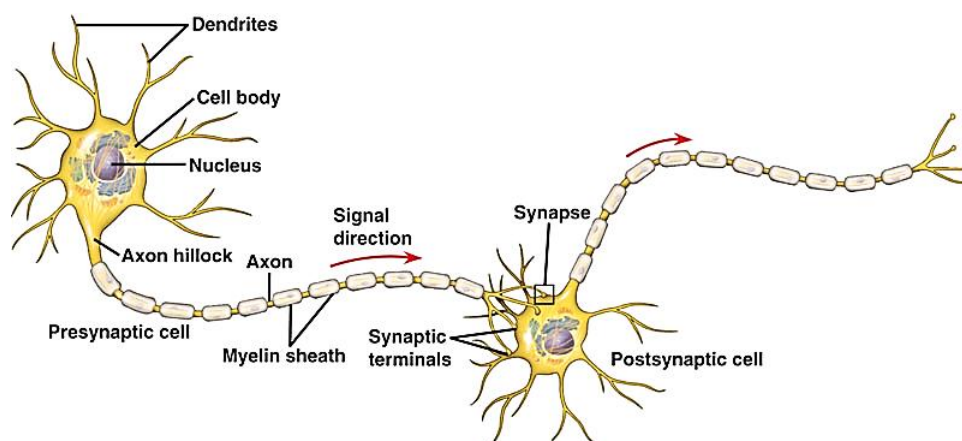
FIGURE 2.3: Shown is a single neuron consisting all the major parts that contribute to the signal transmission broadly. The signal is transmitted from the dendrites to the cell membrane in the cell. The axon hillock is the threshold decider which when overwhelmed passes the signal through the axon to the synaptic terminals. Where this is taken over by another cell and the process is repeated. (Source: Humanity+ magazine - Neuroscience – and the Future of Humanity – Interview with Ken Hayworth)

Neurons communicate with each other with passing an electrical potential. This is basically a culmination of the movement of positively and negatively charged ions that are flowing though channels in neuron membranes in the direction that is governed by the membrane

potential (H.L. Attwood, W.A., 1989). Electrical current is transmitted from the dendrites to the cell membrane where they meet at the axon hillock, here the summation of all the charges from the dendrites is concentrated at the axon hillock, which has the important decision to make whether or not the signal should be passed on to the axon terminals. The axon hillock is the point where the summation of the excitatory post synaptic potentials and the inhibitory post synaptic potentials meet. If the summation of these potentials reaches a certain threshold then the current passes. Neuron has a resting membrane potential of about -70 mV, voltage gated sodium channels will open when the membrane potential becomes more positive or depolarizes. When this occurs, the sodium rushes into the cells transmitting the depolarization down the axon, this occurrence is called an action potential. Along with the sodium $'Na+'$, potassium $'K+'$, calcium $'Ca+'$ and the chlorine $'Cl-'$ ions also play a part (H.L. Attwood, W.A., 1989).

However, a single electrical event (action potential) is not big enough to be detected by EEG. The action potentials can also cancel each other out so there would be no detection. Luckily there are pyramidal neurons that are present in the most superficial layers of the brain and are spatially aligned and thus their activity is synchronous to each other which produces a larger signal that can be measured superficially from the scalp (for a structural representation of the pyramid cell, please refer to figure 2.4). Axons from the neighboring neurons synapse with the pyramidal neurons. Chemically gated ion channels on the post synaptic membrane open in response to increased concentration of neuro transmitters that bind to the protein. However when the depolarization begins at one end of the neuron the other end re-polarizes back to -70mv thus creating a dipole in the neuron and conducting the current. It is important to remember that regardless to whether an action potential is reached or not all post synaptic potentials will contribute to the EEG signal. Every post synaptic potential causes the charge inside the neuron to change and the charge outside the neuron to change in opposition. The summation of dipoles created by hundreds and thousands of neurons is what is detected by the EEG.
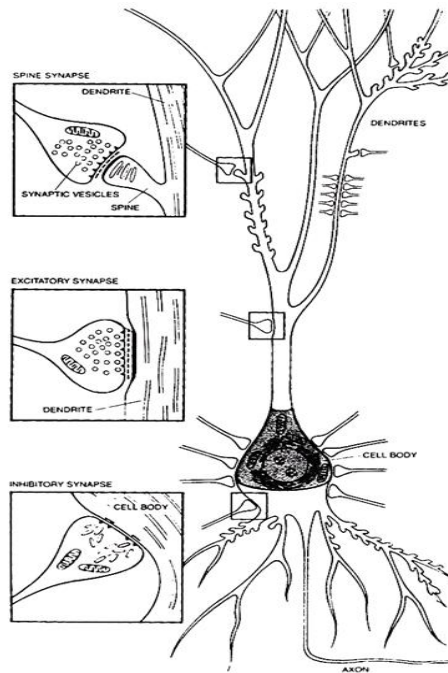
FIGURE 2.4: Shown here is a pyramid cell that is present in the most superficial layers of the human scalp and is spatially aligned. They have many synaptic connections with other neurons that communicate with it as seen in the figure. When a synchronous activation of a number pyramid cells happen there is a noticeable action potential which can be measured by the EEG electrodes placed on the scalp. (Source: jkroger lab (The Mind and Brain Laboratory. Department of Psychology. New Mexico State University. James K. Kroger, Ph.D. Neural Mechanisms of Reasoning))

2.2.2 EEG measurement methodology

There are a number of steps in order to measure a good EEG signal at the scalp which is then digitized for further processing. The electrodes placed on the scalp measure the electrical signals relative to the designated reference electrode amongst them, also one electrode performs the role of the ground electrode. There are designated places on the human scalp where the electrodes are placed based on the distance measured from the inion and the nasion points (see figure 2.5). The 'nasion' is the intersection of the frontal bone and two nasal bones of the human skull. Its manifestation on the visible surface of the face is a distinctly depressed area directly between the eyes, just superior to the bridge of the nose. The 'inion' is a small protuberance on the external surface of the back of the skull near

the neck (both are represented in figure 2.5). These electrodes have a letter and a number attached to them for the quick identification of its approximate position. The alphabetical abbreviations of the electrode identifies the area or the lobe of the brain on which it is located, and the proceeding number identifies the brain hemisphere (odd numbers on the left brain hemisphere and even numbers on the right brain hemisphere, for center 'z' is used) and the distance from the center of the scalp (higher the number, greater the distance from the center of the head). For example *'F - Frontal'*, *'C - Central'*, *'T - Temporal'*, *'O - Occipital'* and *'P - Parietal'*. The attachment of the electrodes to the scalp in the traditional way is an extensive process that involves lot of measurement of the scalp surface to guarantee an exact location. For example a set of 32 electrodes would take over an hour to be attached. This is not very practical when there are lot of measurements to be made with different participants . To overcome this problem there are EEG caps that have fixed opening for the attachment of the electrodes into the correct location. The electrodes are attached to the adapters that are present in the specified openings and act as a housing place. This also gives flexibility as the user is able to desire which adapters are to be used for electrode connections depending upon the requirement. There are also varying amount of cap sizes that are available in order to fit any head shape and size and all are designed with the international '10-20' and '10-10' electrode placement standards (see figure 2.5). These standards were developed too ensure standardized reproducibility so that a participant studies could be compared over time to each other. The '10' and '20' refers to the actual distances between adjacent electrodes that are either 10% or 20% of the total front–back or right–left distance of the skull. There are three anatomically defined main measures, **(i) nasion to inion via 'Cz' (center of the scalp) = 100%** - uses percentage of this to place 'FPz', 'Cz', 'Pz', **(ii) left ear channel opening to right ear channel opening via 'Cz' = 100%** - uses percentage of this to place '$T7$', '$C3$', 'Cz', '$C4$', '$T8$' and **(iii) nasion to inion via ear channel opening = 100%** - uses percentage of this to place '$FP1/2$', '$F7/8$', '$T7/8$', '$P7/8$', '$O1/2$'. All the other electrodes are places using the same logic (see figure 2.5). For this thesis work a cap with 64 electrodes was used from the Easycap company using the '10-10' standard, we also used an extra electrode below the left eye to deal

with the eye artifacts which we discuss in section 2.3. The cap makes the process of electrode placement much simpler and faster. There is always some impedance between the electrodes and the skin surface usually due to dead skin cells, daily cosmetic products and even hair which acts as a barrier in the effective electrical conductance. To get around this problem we use a conductive gel placed between the electrodes and the skin surface to reduce this impedance.
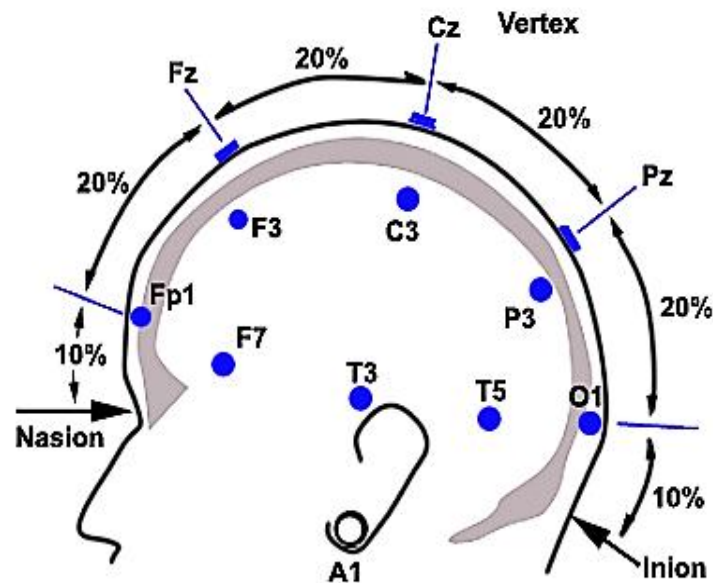
FIGURE 2.5: Shown is a human head form with the scalp layer with the reference points *'nasion'* and *'inion'*. These points help design the placement of the other electrodes on the scalp. Here is an example of the international 10-20 system where the percentage of the distance from the nasion and the inion is used for the electrode positioning. (Source: The McGill Physiology Virtual Lab - Biomedical Signals Acquisition - Recording the EEG - Electrode positioning (10/20 system))

The recorded EEG signals need amplification in order to be used by the analog to digital converter (A/D converter) and the display unit. The amplifiers need to do a selective amplification of the physiological signal and reject the superimposed noise and other interfering signals. Amplifiers also work as circuit breakers providing protection for the participant and the equipment. The amplifier gain is the ratio of the output signal to the input signal. In EEG this ratio has

to be of an order of $100 - 100000$ for adequate voltage level. Along with the amplification the amplifier need to also maintain a high signal to noise ratio. In order to decrease other electrical noise coming from the the input side a differential amplifier is used that uses the technique of common mode rejection to clean the signal. This is basically the rejection of the common signal components obtained from different channels. The reasoning being that if the signal is coming from two different channels then it is ought to be different but with the similar electrical noise. Moreover the EEG recordings are done in a shielded cabin which forms a Faraday cage. This is done in order to avoid as much as possible the influence of the external noise sources. If possible all the equipment inside the cabin is used that can run on a direct current source. This avoids interference with the alternating brain activity. Computers are used as the recording devices and hence they require an A/D converter. The channels of the analog signal are repeatedly sampled at fixed time intervals (sampling interval) and each sample is converted into a digital form, which is then saved. The sampling rate required should be atleast double of the highest frequency component of interest based on the Nyquist criteria. Highpass filters are also used in the complete arrangement to remove low frequency noise sources like breathing. Before performing the final measurements we tested the whole EEG system and also before the start of the study a pilot experiment was done.

2.2.3 Forward solution

Forward solution is a process of simulating the brain and the head model in general. It is a combination of the model and the internal connections defined by the lead-field matrix (refer section 2.2.3) contributing to the electrical activity on the scalp (see figure 2.6). Its realism is very important for the localization of the neuronal source activity (Akalin Acar and Makeig, 2013; Montes-Restrepo et al., 2014). It is dependent on the requirement of the particular task and capability as to how complex one wants to create this brain model. Various parameters need to be considered as the idea of modeling the human brain is very enticing. For instance one needs to decide the size of the brain and the different layers it may consist. The different layers

may have their own permeability relating to the magnetic and electric potentials that are generated during the neuronal activity. For this thesis work including the two publications we used the boundary element method (BEM) for the generation of the brain model which included more than eight thousand dipoles inside the brain and the brain itself was layered into the inner cortical brain, the skull and the scalp. The different layers of the brain model have their different conductivities. The BEM model assumes homogeneous and isotropic conductivity through the volume of each tissue shell (e.g., brain, skull, scalp) but not across the boundaries of these shells.
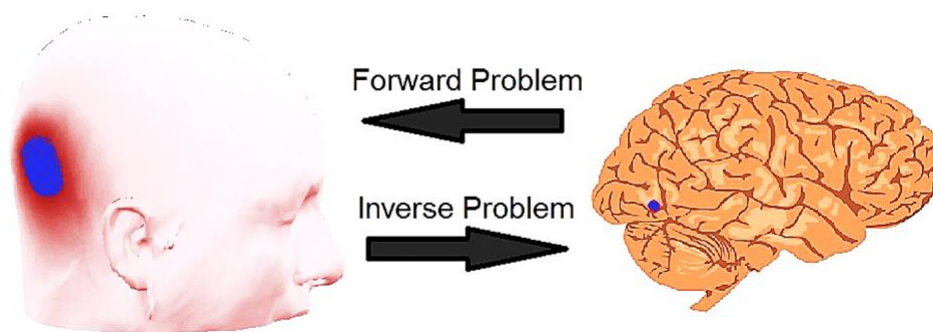
FIGURE 2.6: Visual representation of the forward and inverse problem. Figure shows the blue spot at some location on the brain and the task is to simulate this spot onto the scalp digitally. A successful completion of this task is the forward solution. Alternatively to find the correct location of that activation in the brain from the scalp is the successful completion of the inverse solution. (Source: Neuroelectromagnetic Source Imaging of Brain Dynamics - Rey R. Ramírez, David Wipf, Sylvain Baillet)

Boundary element method (BEM)

The forward model in simple mathematical terms can be expressed as the product of the primary currents by the vector lead-field (see 2.2.3) (J, 1983; Brody, Terry, and Ideker, 1973). The BEM method can be explained by the method of weighted residuals (Mosher, Leahy, and Lewis, 1999). It is a numerical technique for calculating the surface potentials which are a result of the current sources (dipoles) inside the brain model. It relies on separating the regions of different conductivities inside its model. In its basics the model consists of three surfaces namely brain-skull interface, skull-scalp interface and

the outer surface, and the regions between these interfaces are de-
faulted to having homogeneous and isotropic conductivities. Each
interface has its own boundary elements and at every point in the
entire volume a potential can be defined (Geselowitz, 1967; Barnard,
Duck, and Lynn, 1967; Sarvas, 1987). Each interface is digitized in
triangles as seen in figure 2.7. The center of each triangle has a po-
tential and the entire interface can be defined over the surface by the
summation of all the triangle potentials keeping its distance and ori-
entation. In general the exact calculation is not possible and therefore
an approximation is expected.
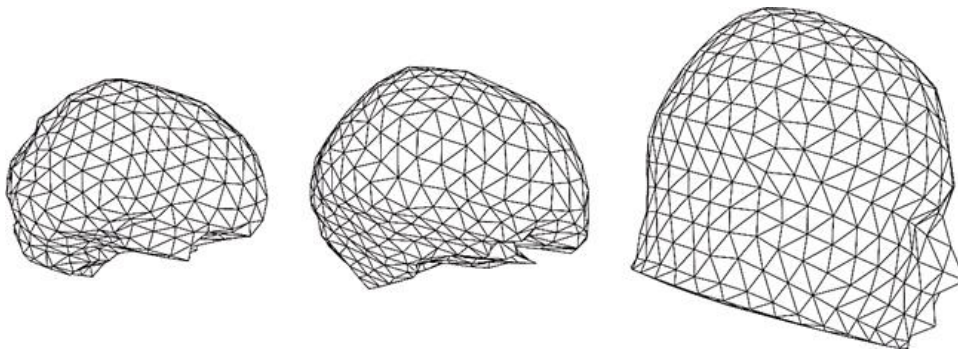
FIGURE 2.7: Example mesh of the human head used
in BEM. Triangulated surfaces of the brain, skull and
scalp compartment used in BEM. The surfaces indi-
cate the different interfaces of the human head: air-
scalp, scalp-skull and skull-brain. (Source: Review on
solving the forward problem in EEG source analysis
- Hans HallezEmail author, Bart VanrumsteEmail au-
thor, Roberta Grech, Joseph Muscat, Wim De Clercq,
Anneleen Vergult, Yves D'Asseler, Kenneth P Camil-
leri, Simon G Fabri, Sabine Van Huffel and Ignace
Lemahieu)

The calculation is quite an extensive one and computationally very
exhausting. There exists three kinds of approaches for it called the
'solutions for the solid angle' (Barnard, Duck, and Lynn, 1967; Barnard
et al., 1967; Meus et al., 1989). Typically the skull conductivity is
lower than the the brain and scalp layers. There can be issues with
the differences in the conductivities of the three layers since the dif-
ferences are quite large. To avoid the amplification of the numerical
errors in the calculation the technique of isolated problem approach
(IPA) also sometimes referred to as the isolated skull approach (ISA)
is applied (Hämäläinen and Sarvas, 1989; Fuchs et al., 1998; Gençer
and Akalin-Acar, 2005). The BEM method benefits from the increased

number of triangles and nodes and is relatively simple. In figure 2.8 we see the exact BEM model that was used for this research project.
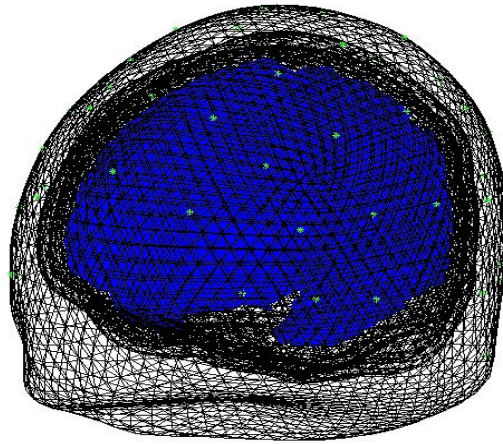
FIGURE 2.8: The BEM model that consists of different layers including the brain (coloured blue here) and the scalp used in this research project. The green '∗' represent the location of the electrodes placed on the scalp.

Lead-field matrix

Lead-field matrix is the matrix of coefficients that maps current sources to potential differences at the scalp. It can be considered as the missing puzzle piece that joins the sources in the brain to the recordings we make at the scalp through the EEG electrodes. Normally there are two ways the lead-field matrix can be generated. In the first way the sources are defined by three orthogonal dipoles, the lead-field will contain the number of columns equal to the number of sources times three for the three dipoles. The number of rows are dependent on the number of electrodes that are used for the measurement of the potentials at the scalp. The size of the this matrix is huge and has a very good resolution (see figure 2.9) but this is dependent on the requirement if one is ready to use such computational power in its calculation and solution. The other way of calculating the lead-field matrix is that instead of the the orthogonal dipoles, the nodes between the sources act as the columns of the matrix and the rows are as in the previous case dependent on the electrodes at the scalp. When the lead-field matrix is created in this way the size of the matrix is greatly reduced but on the flip side the calculations run faster.

This has a lower resolution therefore should only be used where the accuracy of the sources is not the most important criteria. For this thesis work and the two publications the first method was used aiming for the better resolution as the locations of the sources inside the brain played an important part in the study.
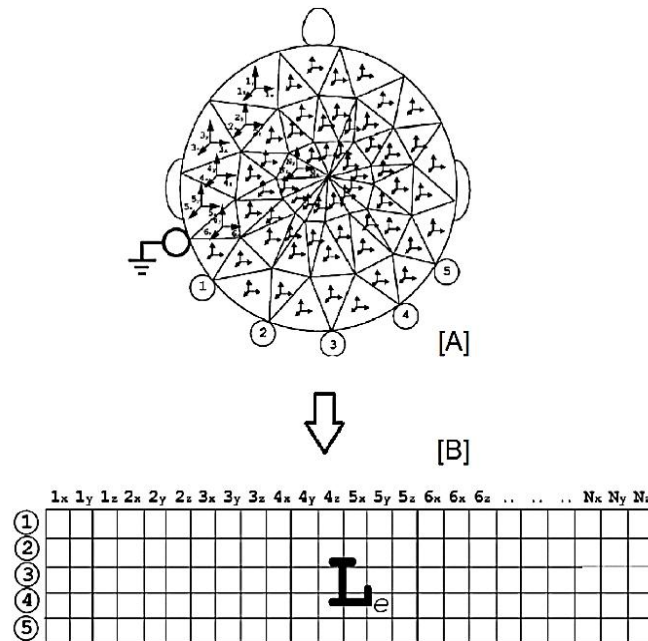
FIGURE 2.9: [A] Visual representation of the sources in the brain with the three orthogonal dipoles. They show the three dimensions x,y and z. The numbers shown in circles are the positions of the electrodes. [B] shows the structure of the leadfield matrix based on the representation of [A]. The number of rows are the number of electrodes and the number of columns are the number of dipoles multiplied by three for the three orthogonal dimensions. (Source: M. Muthuraman, Signal processing for medical applications - frequency domain analysis (Lecture 7), Uni-klinikum neurologie kiel, 2013-2014.)

2.2.4 Inverse solution

Inverse solution is the process of finding the sources in the simulated brain that is created by the forward model with the help of channels that we record on the brain scalp (see figure 2.6). It sounds simple enough but since the sources inside the brain outnumber the channels recorded on the scalp by a big margin, the problem becomes

ill-poised. Therefore, there is no unique solution to the inverse problem. We agree to the most likely solution and different methods of finding the inverse solution may produce slightly different results. The basis of choosing the inverse solution method depends on the particular case as different solutions have varying advantages and drawbacks. The inverse solution consists of solving the lead-field matrix (lead-field matrix described in section 2.2.3).

The raw EEG data recorded at the scalp is highly variable alternating time course. We can reconstruct the underlying neuronal activity with the assumption that the data comes from a group of discrete brain sources which in turn constitutes a group of neurons with synchronous fluctuations. There are generally two ways to solve this problem. The first way *'few sources way'* is to assume a small number of active sources and fit the measured data using a non-linear search method throughout the brain (Supek and Aine, 1993). The limitation of this way is that when the number of sources increase, the method does not work well. We usually are looking for an accurate representation which involves a very high number of sources in the brain. For this another way *'distributed way'* uses a large number of fixed dipoles that constitute the area of interest. It estimates their amplitudes (Dale and Sereno, 1993; Hämäläinen and Ilmoniemi, 1994). The distributed way has the advantage of being linear with neuronal currents but the large number of unknowns make it an ill-posed problem and hence like any such problem one needs to make assumptions and include some prior information (Baillet, Mosher, and Leahy, 2001; Grech et al., 2008; Michel et al., 2004; Pascual-marqui, 1999). Despite the problem being ill-posed, the distributed solutions have received a boost because of its linearity and independence to the number of sources. It has become robust and also computationally viable. This thesis work uses the distributed way as its inverse solution.

Distributed way (distributed source activity reconstruction)

This inverse solution is a linear method based on the mapping of a fixed set of dipoles distributed in the brain to the set of signals / channels recorded on the scalp by the electrodes placed for this purpose (Dale and Sereno, 1993). The number of dipoles are far

greater than the number of sensors recording them at the scalp. This in turn means that it is not possible to find the inverse of the lead-field matrix easily. We need the help of the Bayesian assumptions to get around this problem. In Bayesian universe we can assume that the neuronal source activity is a zero mean gaussian process with some covariance (Auranen et al., 2005; Baillet and Garnero, 1997; Phillips, Leahy, and Mosher, 1997; Sato et al., 2004; Schmidt, George, and Wood, 1999; Trujillo-Barreto, Aubert-Vazquez, and Valdes-Sosa, 2004; Wipf and Nagarajan, 2009). It also tells us that the source estimates can be defined by the expected value of the posterior distribution (distribution of unobserved observations (prediction)) of the source activity. The source activity of the dipoles has a prior probability and the likelihood for the given activity gives us the probability of the data (Dale and Sereno, 1993).

In general the the expected value of the source activity can be obtained by a combination of the lead-field matrix with the recorded data and the related covariances, based on the Bayesian assumptions (Liu, Dale, and Belliveau, 2002; Lopez et al., 2014). This means that the main focus and the whole approach boils down to finding the appropriate sensor and source level covariances (Baillet and Garnero, 1997; Phillips, Leahy, and Mosher, 1997; Phillips et al., 2005).

In case where we are unaware of the noise covariance at the sensors, we assume the noise covariance to be unity (identity matrix), meaning the noise variance on all sensors is the same. This has been referred as as regularization parameter (Golub, Heath, and Wahba, 1979; Hansen, 2000) or a hyperparameter (Phillips, Rugg, and Friston, 2002). In many cases the sensor noise estimations are based on empty room recordings and not very accurate because there are other components to the noise that must be added (Henson et al., 2011), hence the unity covariance assumption is very common. Out of many variations of the distributed way the multiple spars priors method makes use of the limitations of the LORETA and the Minimum-norm method to give an accurate solution.

Multiple spars priors

There are multiple assumptions that can be used to come up with the prior source covariance matrix, the most common also being the simplest called the 'Minimum-norm'. It assumes that all source dipoles have approximately a same prior variance and no covariance (Hämäläinen and Ilmoniemi, 1994). Another popular assumption is used by the 'LORETA' which states that all sources vary smoothly over the space domain (Pascual-marqui, 1999). Although these are the very popular algorithms used around the world there is a bias associated with their usage. It states that all the superficial sources have a larger impact on the sensors then the deep sources. There are some other solutions available as many have tried to come around this very obvious bias like the method of column weighting (Fuchs et al., 1999; Hauk, 2004; Ioannides, Bolton, and Clarke, 1990; Lin et al., 2006) and the method of noise normalization (Dale et al., 2000; Pascual-Marqui, 2002). To make a smooth final solution one assumes that all the source dipoles are active at the same time which also helps to explain the source artifacts but this assumption makes the data more susceptible to external artifacts. There is another approach that comes around this problem called the beamforming approach which tries to remove the covariance (smoothness) from the solution (Hillebrand et al., 2005; Sekihara et al., 1999; Van Veen et al., 1997). This makes this solution very robust to external noise but it does perform poorly when there is a real covariance amongst the sources.

In the Bayesian universe the prior source covariance can be defined as the weighted sum of multiple prior components where each component is a prior source covariance matrix. The weights are called the hyperparameters for these components. It means that the large hyperparameter regions will have a larger variance. The choice of the selection of a particular model naturally depends on the choice of the prior components. Unlike the 'Minimum-norm' solution or the 'LORETA' solution, the multiple sparse priors (MSP) solution is based on a library of hundreds of covariance components, each corresponding to a different locally smooth focal region (or patch) of cortex (Lopez et al., 2014) and the size and the number of regions can be based on the the prior knowledge (López and Barnes, 2012). We have used the advantages of this solution in the localization of our

sources in both the studies of this research project .

2.2.5 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is an imaging technique that is extensively used for medical purposes in order to obtain high quality images of the insides of the human body and also the human brain. While localizing the source of the signals on the human head using an EEG, we need to visualize it for better understanding of the location and its implications, and for this purpose it is important to align the forward model of the human brain with the MRI scans (refer section: 2.2.3) . For the purpose of this thesis work and the related publications we have used a standard MRI that is an average of hundreds of scans that have been collected and is readily available for research purpose (see figure 2.10).
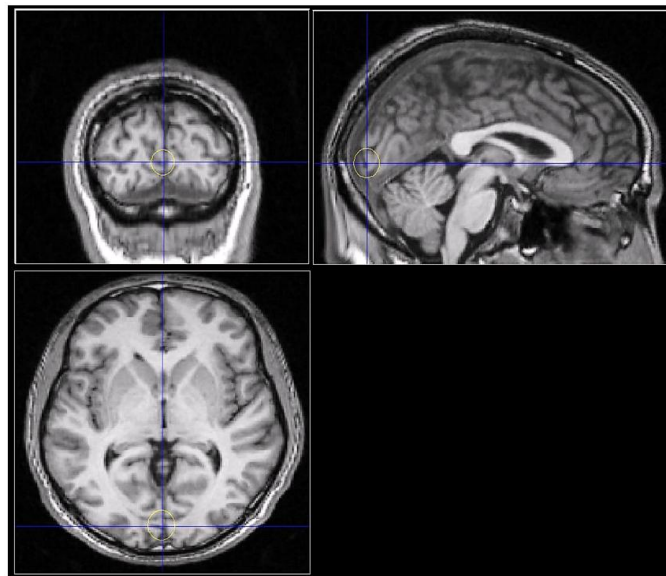
FIGURE 2.10: The figure shows a typical example of an MRI image. It has three views, the top left showing the $'coronal'$ view, the top right showing the $'sagittal'$ view and the bottom left showing the $'axial'$ view. The positioning of the blue cross-hair and the yellow circle around it shows the location of interest. (Source: Dipole Simulations with different phasic oscillatory signals - Saurabh Kumar - Kiel 2014 M.Sc. Thesis - Uni-Klinikum (Neurologie) Kiel Christian-Albrechts-University of Kiel Faculty of Engineering Digital Signal Processing and System Theory)

2.3 Artifact correction

In recent times there have been many new methods proposed for the correction of artifacts in the EEG recording in addition to the classical methods like the regression (Pham et al., 2011), ocular artifact correction (Croft and Barry, 2000b), filtering (Sweeney, Ward, and McLoone, 2012), blind source separation (BSS) (James and Hesse, 2005; Vigario and Oja, 2008). The new techniques are a combination of these methods in order to optimize the signal to noise ratio in post processing. It also points that the methods converge in terms of their performance and highly dependent on the requirement of a particular experiment or application.

Before one looks into the correction of the unwanted artifacts one has to understand the background activity of the EEG signals. EEG signal has a range of frequency from $0.01Hz$ to around $100Hz$ and the voltage varies from a few micro-volts to around 100μ. The amplitude has a larger range because of the artifacts not related to the signals received from the brain activity. There are some recordings at low frequencies like $0.01Hz$ which are not considered but in some cases useful in the brain computer interface (BCI) (Fatourechi et al., 2007). Most of the EEG activity is concentrated in the lower frequency spectrum (Daly et al., 2012). It is classified broadly into five different frequency bands: delta ($\sim$ 0.5-4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz) and gamma (> 30-< 100 Hz) (please also refer figure 2.11). Many EEG studies depend on these bands and the classification of normal or abnormal band activity depends on age and the mental state of the participant (Sanei and Chambers, 2007). Its been widely considered that prediction of the exact characteristics of the EEG signal in terms of amplitude, duration or morphology is not possible (Sörnmo and Laguna, 2014; Rèmond A Gasser, 1977) and hence it should be considered a stochastic signal even-though some of its characteristics are known (Daly et al., 2012). A specific kind of waveform in the EEG activity is called the evoked potential (EP) which is the part of deterministic signals, separated from the stochastic. It is deterministic in the sense that they are evoked and not spontaneous like the rhythms (figure 2.11). Event related potential (ERP) is also a name given to such waveforms which are generated in the brain. It is related to a specific stimulus and it time-locked (Sur and

Sinha, 2009). The amplitude of the ERP is small and not easily vi-
sualized by the human eye because of the background EEG activity
(Sanei and Chambers, 2007), therefore signal processing techniques
like averaging trials and others are required for its study.

Brainwave Type	Frequency range	Mental states and conditions
Delta	0.1Hz to 3Hz	Deep, dreamless sleep, non-REM sleep, unconscious
Theta	4Hz to 7Hz	Intuitive, creative, recall, fantasy, imaginary, dream
Alpha	8Hz to 12Hz	Relaxed, but not drowsy, tranquil, conscious
Low Beta	12Hz to 15Hz	Formerly SMR, relaxed yet focused, integrated
Midrange Beta	16Hz to 20Hz	Thinking, aware of self & surroundings
High Beta	21Hz to 30Hz	Alertness, agitation
Gamma	30Hz to 100Hz	Motor Functions, higher mental activity

FIGURE 2.11: This figure shows the brain waves clas-
sification and their frequency ranges. Shown also is
the particular mental states that the brain waves are
associated with.

Signal processing is also required to get rid of the artifacts that make
the EEG recording noisy, therefore in order to make the influence of
the artifacts on the EEG signal minimal it is required to know the
most common types that exist. Broadly they can be classified into
the physiological and the non-physiological (technical) (Sörnmo and
Laguna, 2014; Fish, 1999). Out of these the non-physiological ones
can be reduced by proper attachment of electrodes and setting up
the EEG recording arrangement in a controlled environment away
from the obvious sources of noise (Anderer et al., 1999). Our setup
of the experiments was well regulated and therefore we did not have
to deal with these types of artifacts. The physiological type is harder
to avoid because they are beyond control of the experimenter and
therefore there are lot of techniques and algorithms dedicated for the
reduction of such artifacts. We concentrated our efforts in getting rid
of such artifacts.

2.3.1   Ocular artifacts and correction

The electro-oculogram (EOG) is used to measure the activity pro-
duced by the eye movement, it is basically an electrode or a set of
electrodes attached near the eyes to measure the electrical signals
that can be used to correct for the eye blinks an the eye movements.
EOG is normally recorded with the EEG (Croft and Barry, 2000b),

although the EOG electrodes are dedicated for picking up the eye
artifacts the effects of the eye movements and the blinks extend fur-
ther onto other electrodes to be picked up by them also (Romero,
Mañanas, and Barbanoj, 2008; Fish, 1999). We used a single electrode
below the left eye of the participants to pick up eye movements. One
should be careful in placement of the EOG electrode in order to make
a better use of them and avoid the contamination of the EEG signal
in other electrodes. The eye blinks contaminates the EEG signal with
a more abrupt change in the amplitude and generally quite distin-
guishable than the eye movements (Croft and Barry, 2000b). It is
seen that of particular advantage to measure the EOG along with the
EEG for the cancellation of the ocular artifacts but one has to keep
in mind that as the EEG is contaminated by the signals picked in
EOG, the EOG is also contaminated by the EEG (Gratton, 1998; Wall-
strom et al., 2004; Romero, Mañanas, and Barbanoj, 2008). For the
eye blinks we used the difference of the EOG electrode with the elec-
trode that is placed on the top of the left eye as these electrodes are at
the most appropriate locations to pick up these abrupt changes in the
amplitude. We also used the summation of the electrodes above the
two eye as the reference for the eye movements (Parra et al., 2005).

Regression technique

A common technique that is widely used seems to be a old one which
has the basics in the use of the 'least-squares' regression function (PM
Quilter, 1977; Croft and Barry, 2000b). The regression function cal-
culates the proportion of one variable that is explained by the other
hence the estimate of the EOG that is present in the EEG. A time
domain approach (TDA) is used that compares the voltage from the
EOG channel with the EEG channel voltage at each time instance ir-
respective of the frequency. It can be used for a single channel EOG
but also can be extended into a double channel (VEOG, HEOG) and
also into a multiple channel calculation as per the requirement and
the application. We took the VEOG and HEOG channels as the com-
bination of the EOG, FP1 an FP2 electrodes (Parra et al., 2005). The
next step after using a technique is to check for its validation, and for
the EEG artifact correction it is not straight forward.

Validation and usage

There are many ways in order to correct for the artifacts but there is
no one efficient or correct way to check for its validation. The main
reason is that there is no actual way of measuring EEG without con-
tamination from the artifacts. One way to say if the correction is
good, is to check if the correlation between the EOG and the EEG is
very low as one would expect and assume that there is no correla-
tion between the EOG and the corrected EEG (Verleger, Gasser, and
Mocks, 1982). This may not be a very good way to decide because of
the obvious flaw that there actually exists a correlation between EEG
and the EOG. This is due to the fact that EEG and the EOG channels
pick up the brain activity intended for them individually (Gratton,
1998). Another way of validating the correction procedure is to check
if the uncontaminated EEG is similar to the corrected EEG (Gratton,
Coles, and Donchin, 1983). The flaw with this technique is that there
is no uncontaminated EEG and hence the uncontaminated EEG that
can be used is basically the EEG which does not have the specific ar-
tifact that we are correcting for. Because of the limitations of the val-
idation, one has to revert back to the face validity (Verleger, Gasser,
and Mocks, 1982) which means one has to rely on the experience of
the experimenter and also on discussions with other researchers. We
therefore used the tested technique (least mean square fitting proce-
dure (Parra et al., 2005)) and checked for the performance comparing
with the other techniques.

There have been discussions whether the eye blinks and the eye move-
ments should be dealt differently and separately. There have been
studies that say that the eye blinks and the eye movement voltages
propagates differently (Corby and Kopell, 1972; Gratton, Coles, and
Donchin, 1983; Lins et al., 1993; Overton and Shagass, 1969) and
some studies therefore say that these artifacts should be corrected
separately (Gratton, 1998). The counter argument is that the correct
methods need to be implemented effectively in order to deal with
the two types of eye artifacts regardless of the type of artifact (Croft
and Barry, 1998b). It has also been shown that when the sources of
interference are removed from the EOG and the EEG then the differ-
ences between the blinks and the movements are also non-existent
(Croft and Barry, 1998a; Croft and Barry, 2000a; Brunia et al., 1989;

Kamiya and Francisco, 1973). Therefore eye blinks and eye movements should be handled together if an appropriate interference removing is implemented. Another way to argue about the eye artifacts correction is through the argument that different movements in the eye are a result of a combination of frequencies (Whitton, Lue, and Moldofsky, 1978) and therefore the correction of these artifacts should be done on different frequencies using the frequency domain approach (FDA) (Gasser, Sroka, and Möcks, 1985; Gasser, Ziegler, and Gattaz, 1992; Woestenburg, Verbaten, and Slangen, 1983). However there is no study that puts the FDA at a higher advantage than the time domain approach that we have used in this research project and some studies have shown that the TDA and the FDA produce similar results hence there is no point in disregarding the time based artifact correction of the eye artifacts (Brunia et al., 1989; Kenemans et al., 1991; Berg-Lenssen, Gisbergen, and Jervis, 1994).

2.4 Other considerations

All the processing that was done on the EEG data (for the following two publications, refer section 3.1 and section 3.2) was done offline and hence we had time to look in each processing step and optimize the process for the participants where it could not be generalized. In order to work with the data we had to deal with the computation time and resolution issues and therefore we had to down-sample the data to one-fourth the recorded resolution. For our study we did not require any data that was over the frequency of $45Hz$ and hence our down sampling of the data to $250Hz$ did not have any impact and served us in saving a lot of out computation power. The filtering was done with the widely accepted and popular third order butterworth filter. The order of the filter was kept to three to avoid any unwanted noise that may creep in. The performance of the filter was also checked in the frequency domain using the frequency transformation method based on the Welch method. The decision to use the Welch method meant that no unwanted noise was introduced in the data due to this conversion. As much as the pre-processing of the recorded EEG data is concerned it must be mentioned that for correcting the ocular artifacts many methods were tested. The

method based on linear regression analysis was selected (Parra et al., 2005) (For more understanding please look in section 2.3). The method was tested and compared with other known popular methods like the independent component analysis (ICA) method (Zhou et al., 2005; Jung et al., 1998; Shen, Zhang, and Li, 2002), the temporal decorrelation source separation (TDSEP) method (Ziehe and Müller, 1998), the second order blind identification (SOBI) method (Delorme et al., 2007; Tang, Sutherland, and McKinney, 2005) and statistical control of artifacts in dense array EEG (SCADS) method (Junghöfer et al., 2000). For the purpose of this project it was decided that the method of regression by (Parra et al., 2005) provides sufficient correction of the artifacts and allows us to quickly and automatically remove them from the EEG recorded data. The implementation of regression method was taken from the Berlin Brain Computer Interface (BBCI) toolbox that is built to work in conjunction with MATLAB.

Chapter 3

Publications

3.1 Publication 1

Differences in Insula and Pre-/Frontal Responses during Reappraisal of Food in Lean and Obese Humans

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Brain regions involved in the reappraisal of tasty but unhealthy foods are of special interest for the development of new therapeutic interventions for obesity, such as non-invasive brain stimulation or neurofeedback. Here, we visually presented food items (i.e., high/low caloric) to obese and lean individuals during electroencephalogram (EEG) recordings, while they either admitted or regulated their food desire. During admitting the desire for low and high calorie foods, obese as well as lean individuals showed higher activity in the left dorsolateral prefrontal cortex (DLPFC), whereas the right frontal operculum was involved in the reappraisal of the same foods, suggesting interplay between executive control and gustatory regions. Only in lean participants, we found an interaction between calorie content and the regulate/admit conditions in bilateral anterior insular cortices, suggesting that the anterior insula, assumed to primarily host gustatory processes, also underpins higher cognitive processes involved in food choices, such as evaluating the foods' calorie content for its reappraisal.

Keywords: obesity, EEG, dorsolateral prefrontal cortex, frontal operculum, insular cortex, reappraisal of food

INTRODUCTION

Obesity is a major health burden and dramatically climbing incidence rates, especially in rapidly developing countries like China or India, lead to a demand on developing new therapeutic strategies (Roman et al., 2014). Currently available weight-loss programs consist either of dieting (Soeliman and Azadbakht, 2014), physical activity (Jakicic and Davis, 2011), or the combination of both (Amorim Adegboye and Linne, 2013), with mostly modest and also timely restricted effects on participants' body weight. The majority of participants start regaining weight directly after the program has ended. Based on these experiences, new therapeutic strategies started combining dieting and physical activity with regular psychological interventions to strengthen motivation and volition (Looney and Raynor, 2013; Ausburn et al., 2014). This combination seems specifically effective for stabilizing the program-associated weight-loss beyond the program's duration, but the influences on body weight and metabolism are *per se* small. Establishing new programs that, at the same time, produce profound weight loss and long-term body-weight stability seem generally difficult because the neuronal mechanisms driving and sustaining overeating are still not well understood.

Regular consumption of high-calorie foods affects the brain's reward system in comparable ways as addictive drugs (Volkow et al., 2013). If rats consume such foods over several weeks,

they react with compulsive eating habits that resemble drug craving behavior (Johnson and Kenny, 2010). One mechanism driving this addiction-like behavior is an altered dopaminergically mediated reward response to foods (Wang et al., 2001; Stice et al., 2008). Regular consumption of high-calorie foods regularly amplifies the dopaminergic response in regions underpinning habitual eating behavior such as the dorsal striatum, which over time is compensated by a reduction of the striatal dopamine receptor availability (Stice et al., 2008; Johnson and Kenny, 2010; Volkow et al., 2013). In rats, this reduced receptor availability leads to weakened dopaminergic responses to the same foods as before high-calorie diet, which, in turn, supports further overeating (Johnson and Kenny, 2010).

Wanting food is different from liking food, but both together are necessary for food-related reward responses (for a review see Berridge, 2009). Wanting food without liking it is merely a sham or partial reward, without the gustatory and olfactory pleasure. "Wanting" is still an important component of food reward, especially when combined with "liking". Food reward cannot happen without incentive salience, even if hedonic "liking" is present. Hedonic "liking" by itself is simply a triggered affective state. It is the process of incentive salience attribution that makes a specific associated food the object of desire. "Liking" and "wanting" are needed together for full food reward. Fortunately, both usually happen together in human life (Berridge, 2009).

Brain regions involved in the reappraisal of wanting and liking food are of special interest since the modulation of their functional implementation within brain circuitries commonly orchestrating eating behavior may represent a future target for brain-stimulation or neurofeedback training. Whether such interventions underpin, accelerate, or even initiate changes in body weight remains another area for future research.

On the search for neurofeedback targets, we recently used functional magnetic resonance imaging (fMRI) in a group of lean to overweight participants to identify brain regions involved in the reappraisal of food (Hollmann et al., 2012). As in the present study, participants were visually presented food items under two different conditions: Either they admitted the desire for the presented food by thinking, e.g., of its taste and flavor (i.e., admit condition), or they regulated their desire by thinking, e.g., that the food is unhealthy or its consumption is followed by weight gain (i.e., regulate condition). Comparing the regulate to the admit condition, we identified the dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA) and inferior frontal gyrus (IFG); regions that are well known to underpin top-down control of craving, inhibition of learned associations and prepotent responses. Furthermore, we observed increased activation in bilateral OFC, a key region of the brain's reward valuation system, as well as the anterior insula together with the frontal operculum and temporoparietal junction (TPJ) suggesting interoceptive awareness and self-reflection. These results suggest that reappraisal of food recruits the brain's valuation system in combination with prefrontal cognitive control areas associated with response inhibition (Hollmann et al., 2012).

FMRI is one method to assess neural underpinnings in the cortex. These neural responses can also be acquired in real-time

for neurofeedback training. Real-time fMRI for neurofeedback training, however, bears several limitations, such as the spatial (i.e., magnetic resonance imaging (MRI) environment), application-based (i.e., no self-application) and temporal (i.e., limited MRI scanning time, latency of the hemodynamic response) restrictions. Many fMRI-based neurofeedback attempts therefore failed in translating the training effect into every-day behavior. Electroencephalogram (EEG) instead offers real-time feedback capability, longer training and self-application, despite lower spatial brain resolution. In the present study, we therefore used EEG in combination with a study design adapted from our recent fMRI study (Hollmann et al., 2012), to identify neuronal responses involved in regulating the desire for food in obese as well as lean individuals. We hypothesized, that comparing EEG responses of the regulate and admit condition reveals neuronal activation in brain areas involved in executive control and active reappraisal, such as the DLPFC in the prefrontal cortex. Furthermore, we expected differences in the DLPFC's activity for lean as compared to obese participants, as well as for visually presented high as compared to low calorie foods.

MATERIALS AND METHODS

Participants

This study was approved by the local Ethics Committee of the Medical Faculty Leipzig and carried out according to the Declaration of Helsinki. All participants gave written informed consent prior to their participation. Forty-six right-handed participants took part in this study. Half of them were lean (Body mass index (BMI) >20 and <25 kg/m^2, mean = 23, SD = 1.4) and the other half obese (BMI > 30 kg/m^2, mean = 36.81, SD = 6.21). Participants were financially reimbursed for their participation. All participants were fasting for 5 h before the experiment and were tested around noon (12 am to 2 pm). As compared to shorter fasting periods, 5 h enhanced participants' attention for the visually presented food items as well as their effort in regulating their food desire (pilot data, not shown). Exclusion criteria were any present or past neurological or psychiatric diseases, as well as prescribed central acting drugs. Depression was assessed using the BDI-II questionnaire. A score of 29 or higher, indicating severe depression, was considered as an exclusion criterion. Five participants had to be excluded due to high BDI-II scores. One other subject had to be excluded due to technical problems in data recording. The remaining 40 subjects consisted of 20 males and 20 females. Each gender group consisted of 10 lean and 10 obese participants (see **Table 1**). Groups were matched for age (unpaired t-test $p > 0.5$). In addition, the BMI did not differ between males and females ($p > 0.1$), neither for the group of lean ($p > 0.3$), nor for obese participants ($p > 0.2$).

Visual Analog Scales (VAS)

By means of a quasi-continuous, digital VAS, we assessed six psychological states before and after the experiment. The processed levels for each VAS ranged from 0 on the left hand side (i.e., not at all) to 100 on the right hand side (i.e., fully true) and

the following questions were raised: "How tired are you?", "How hungry are you?", "How dry is your mouth?", "How stressed do you feel?", "How thirsty are you?", "How sated are you?" For pre-post comparisons, we used the paired *t*-test.

EEG Recording
EEG data was recorded with a 64-channel Brain Amp recorder (Brain Products, Gilching, Germany) with 1000 Hz temporal resolution. We applied 63 electrodes apart from the reference and the ground electrodes to participant's scalp arranged according to the international 10–10 system. One additional electrode was attached below the left eye to measure vertical eye movements (i.e., electro-occulogram or EOG).

Experimental Schedule
Participants were comfortably seated in front of a computer screen in a shielded EEG cabinet. First, we acquired 5 min of task-free resting-state EEG data to familiarize participants with the environment. These resting-state measurements were followed by the first session of task-based EEG recordings (20 min). Afterwards, we acquired another 5 min resting-state data. Participants were asked to relax during these 5 min. Finally, we recorded a second session of task-based EEG (see **Figure 1A**).

Task-Based EEG Recordings
During EEG recordings, we presented food pictures on the computer screen in front of the participant. Before the
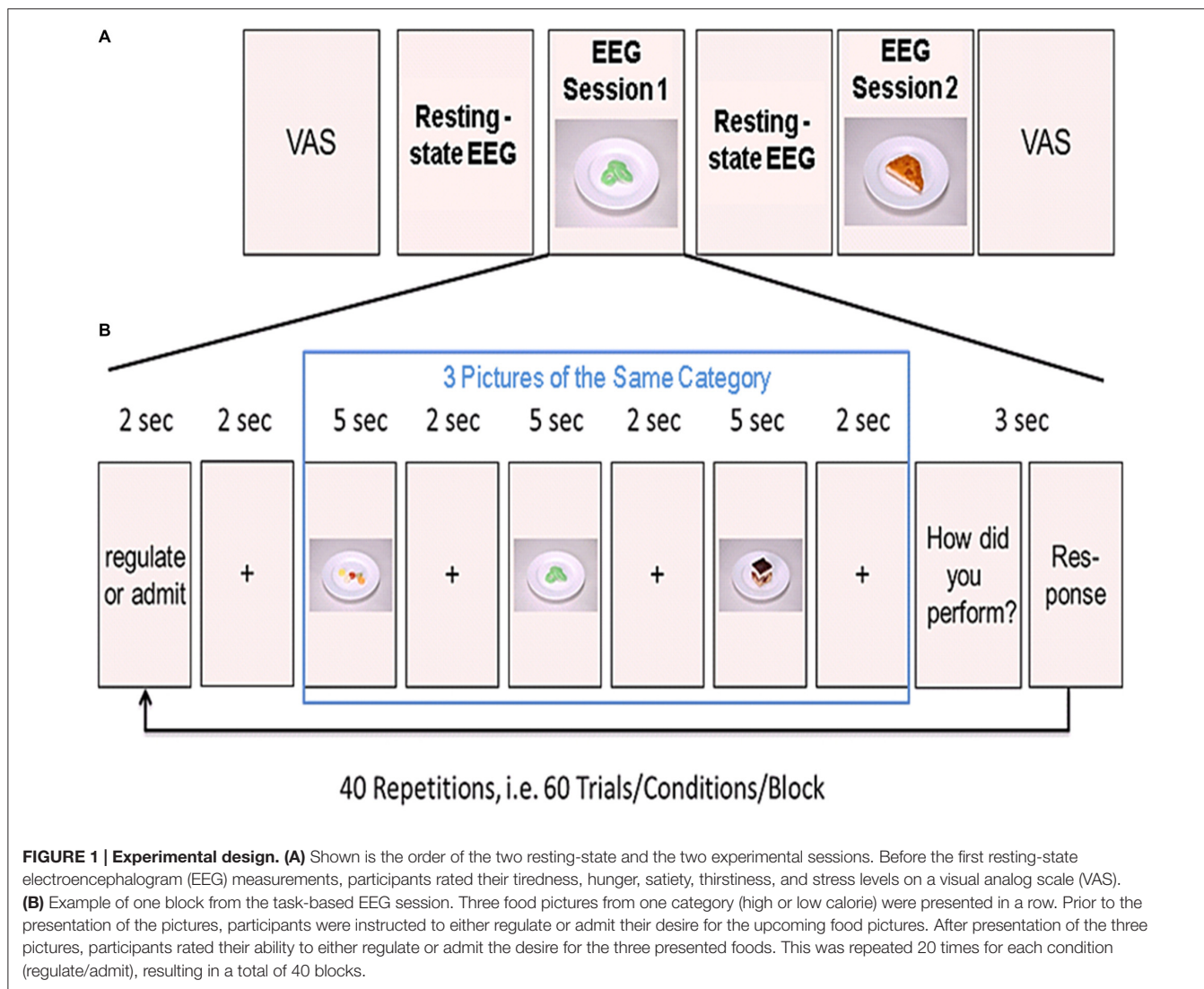
FIGURE 1 | Experimental design. (A) Shown is the order of the two resting-state and the two experimental sessions. Before the first resting-state electroencephalogram (EEG) measurements, participants rated their tiredness, hunger, satiety, thirstiness, and stress levels on a visual analog scale (VAS). (B) Example of one block from the task-based EEG session. Three food pictures from one category (high or low calorie) were presented in a row. Prior to the presentation of the pictures, participants were instructed to either regulate or admit their desire for the upcoming food pictures. After presentation of the three pictures, participants rated their ability to either regulate or admit the desire for the three presented foods. This was repeated 20 times for each condition (regulate/admit), resulting in a total of 40 blocks.

experiment, participants were instructed to either admit their desire for the presented food (ADMIT condition) or to regulate their desire (REGULATE condition) according to the instructions presented on the computer screen. The trials were grouped into blocks of three trials. At the beginning of each block, an instruction was shown. The instruction on the screen was either "ADMIT" or "REGULATE". The instruction was presented for 2 s followed by a crosshair for another 2 s. Afterwards, we presented the three food pictures. Each picture was presented for 5 s followed by a crosshair for 2 s (see **Figure 1B**). The order of blocks was pseudo-randomized across each session.

We used a 2-by-2 factorial design with the factors REGULATE/ADMIT-by-high/low calorie foods. Each calorie group consisted of an equal amount of sweet and savory foods. The comparison of sweet to savory (and *vice versa*) was of no interest and only implemented to better meet participants' food preferences and to keep the task interesting. Sixty food pictures were chosen from a pre-rated in-house repertoire of standardized food pictures with 60 pictures for each condition (Hollmann et al., 2012). In each of the 2 experimental sessions, we acquired 20 blocks (three food pictures per block) for both, the ADMIT and the REGULATE condition. To cancel out the influence of the presented foods, each food picture was presented twice, one time in the REGULATE, and the other time in the ADMIT condition in each session. After presenting the three food pictures, another screen with a 4-point Likert scale showed up for 3 s and participants rated their subjective impression on how well they regulated or admitted their desire for the three food items. The scale of these self-ratings were ranged from 1 (very bad) to 4 (very good).

After the experiment, we asked participants about the specific mental strategies they used to either regulate or admit their desire for the presented food items. The different strategies are summarized in **Table 2**.

Preprocessing of the EEG Data

Using the FieldTrip Software package (Donders Centre for Cognitive Neuroimaging, University Nijmegen, Netherlands) and the Berlin Brain Computer Interface (BBCI) toolbox (Berlin Institute of Technology, Germany), EEG data was first down-sampled to 250 Hz and band-pass filtered (3rd order Butterworth filter) between 0.05 and 45 Hz (BBCI toolbox). Then the data was re-referenced from the original reference of FCz to the common average reference (CAR; Bertrand et al., 1985; Pascual-Marqui and Lehamann, 1993). To correct for eye movement and facial muscles contractions we regressed out the sum of recordings from channels Fp1 and Fp2, indicating horizontal EOG, and the subtraction of channels Fp1 and EOG indicating vertical EOG, respectively, with a least mean-square fitting procedure (Parra et al., 2005). Since these channels acted as EOG channels, they were rejected from further analysis.

Thereafter, the EEG data was epoched into trials of 5 s length (i.e., presentation time for one food item) and baseline corrected using the mean value of the time course for the particular trial. The self-ratings across all epochs (i.e., same value for each picture within one block) were added as an interacting covariate.

TABLE 2 | Mental strategies the participants used in order to admit or regulate their desire of the foods.

ADMIT	Obese (N = 20, 28 indications)	Lean (N = 20, 27 indications)
Imagination of consuming	14	7
Combination with other food	6	9
Positive environment/atmosphere	3	1
Positive properties of the food	2	5
Appetite	0	3
Other/none specific strategy	3	2
REGULATE	**Obese (N = 20, 27 indications)**	**Lean (N = 20, 25 indications)**
Negative properties (rotten, etc.,)	12	11
Suppression of thinking about	8	2
Persuade oneself of being sated	1	8
Consequences for ones body	2	1
Other	4	3

Note that some participants used more than one strategy during the course of the experiment. That is why the N is higher than the actual number of participants.

The temporal window of interest was identified by a heuristic search, based on a signed point-biserial correlations that has been widely used in event-related potential (ERP) based brain-computer interfaces (BCIs) to select the most discriminative temporal windows between different experimental conditions (Blankertz et al., 2011). In particular, the sums of the absolute correlation coefficient values at the given time window were calculated and then the temporal window corresponding to the highest sum value was selected for the analyses. The time period between 1675 and 2055 ms after stimulus onset was selected for source localization.

Source Localization of the EEG Data

Source localization was done with the Statistical Parametric Mapping (SPM) Software package 12 (Wellcome Trust Centre for Neuroimaging at University College London, UK,[1]), running under MATLAB version 8.2 (The MathWorks, Ismaning, Germany). The forward model consists of the model of the brain itself, which was formed by the boundary element method (BEM) with the different layers of the brain tissue, the skull and the scalp. The co-registration was done by matching the electrode sensor locations on participant's scalp and the coordinate mapping from the scalp to the cortex. The standardized MRI was used with this cortical mesh model as implemented in SPM12. The inverse problem was solved by the multivariate source pre-localization (MSP) algorithm (Mattout et al., 2005).

On the group level we used the full factorial design as implemented in SPM 12 with the independent factor "obese/lean participants", and the dependent factors "high/low calorie foods" as well as "REGULATE/ADMIT". A family-wise error (FWE) corrected *p*-value of < 0.05 together with a minimum cluster size to 20 voxel indicated significance. We used *post hoc* paired (within-subject) and unpaired (between-subject) *t*-tests to decipher the structure of significance.

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[1]http://www.fil.ion.ucl.ac.uk/spm

Analyses of the Self-Ratings Assessed During the EEG Experiment

Besides the implementation of the trial-by-trial self-ratings as a covariate for the single participant EEG analyses, we also applied them to an ANOVA with the dependent factors "REGULATE/ADMIT", and "high/low calorie foods", as well as the independent factor "obese/lean participants" (same model as for the analyses of the EEG data). In case of significance, we applied *post hoc* paired (within-subject) and unpaired (between-subject) *t*-tests to investigate the structure of significance.
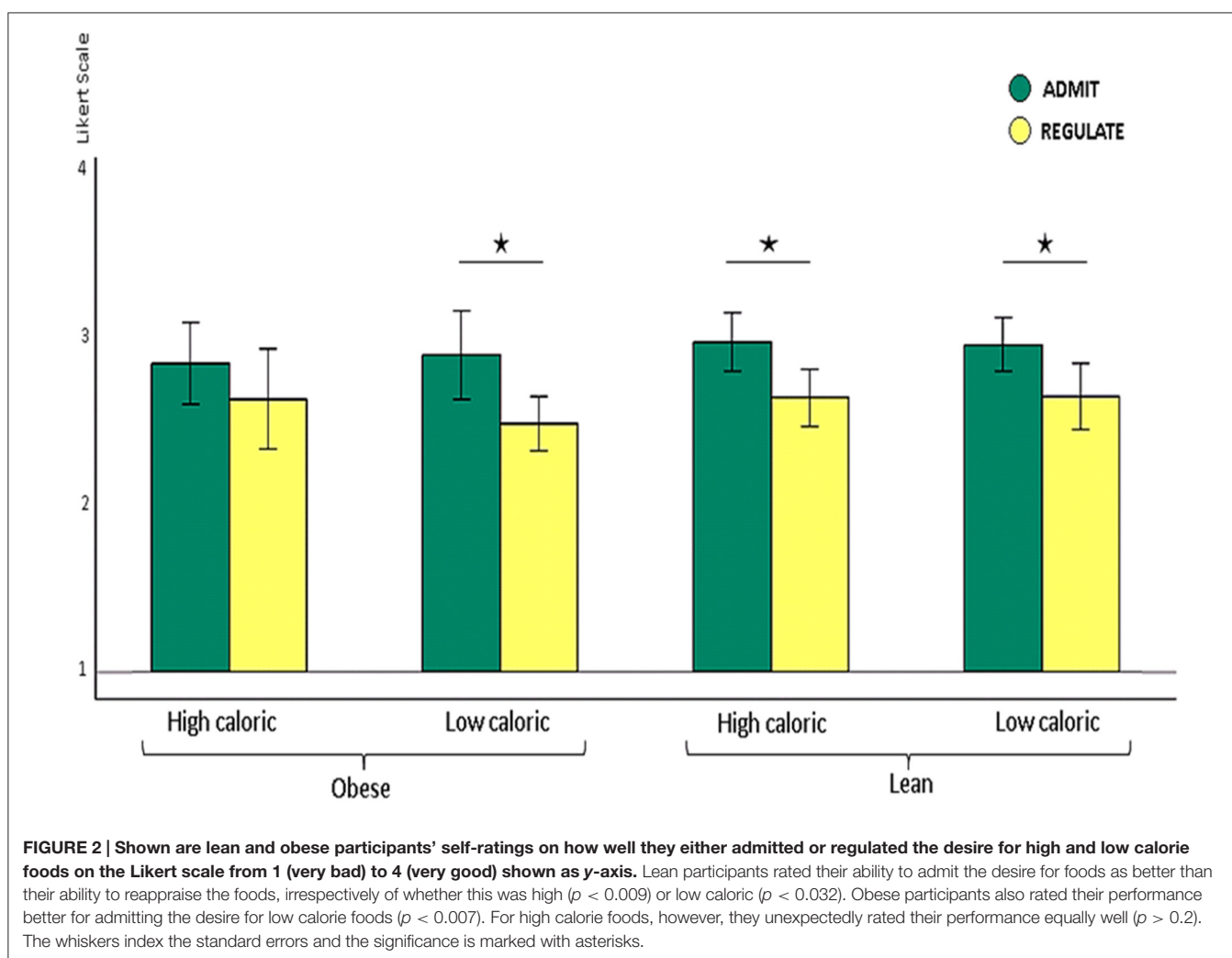
RESULTS

Visual Analog Scales

Comparing the post VAS to the pre VAS, we found significantly increased rating for tiredness (paired *t*-test $p < 0.001$), and hunger ($p < 0.001$), whereas the satiety ratings significantly decreased ($p < 0.035$).

Self-Ratings in the REGULATE/ADMIT Conditions

We found higher self-rating scores for the ADMIT as compared to the REGULATE condition for lean and obese participants together, across high and low calorie foods (ANOVA, $p < 0.0001$). *Post hoc* paired *t*-tests revealed that lean participants rated their performance better for admitting, relative to regulating their desire for food, irrespectively of whether this was high ($p < 0.001$) or low caloric ($p < 0.009$). Obese participants also rated their performance better for admitting, relative to regulating their desire for low calorie foods ($p < 0.007$). For high calorie foods, however, they unexpectedly rated their performance equally well ($p > 0.2$; **Figure 2**).

Task-Based EEG Findings

Comparing the ADMIT to the REGULATE condition (i.e., interaction between self-ratings and EEG activity) for both, lean and obese participants, we found a FWE-corrected activation ($p < 0.05$) in the left DLPFC (peak voxel: MNI coordinates (x, y, z): −42, 38, 20 mm, T = 5.55,

FIGURE 2 | Shown are lean and obese participants' self-ratings on how well they either admitted or regulated the desire for high and low calorie foods on the Likert scale from 1 (very bad) to 4 (very good) shown as y-axis. Lean participants rated their ability to admit the desire for foods as better than their ability to reappraise the foods, irrespectively of whether this was high ($p < 0.009$) or low caloric ($p < 0.032$). Obese participants also rated their performance better for admitting the desire for low calorie foods ($p < 0.007$). For high calorie foods, however, they unexpectedly rated their performance equally well ($p > 0.2$). The whiskers index the standard errors and the significance is marked with asterisks.
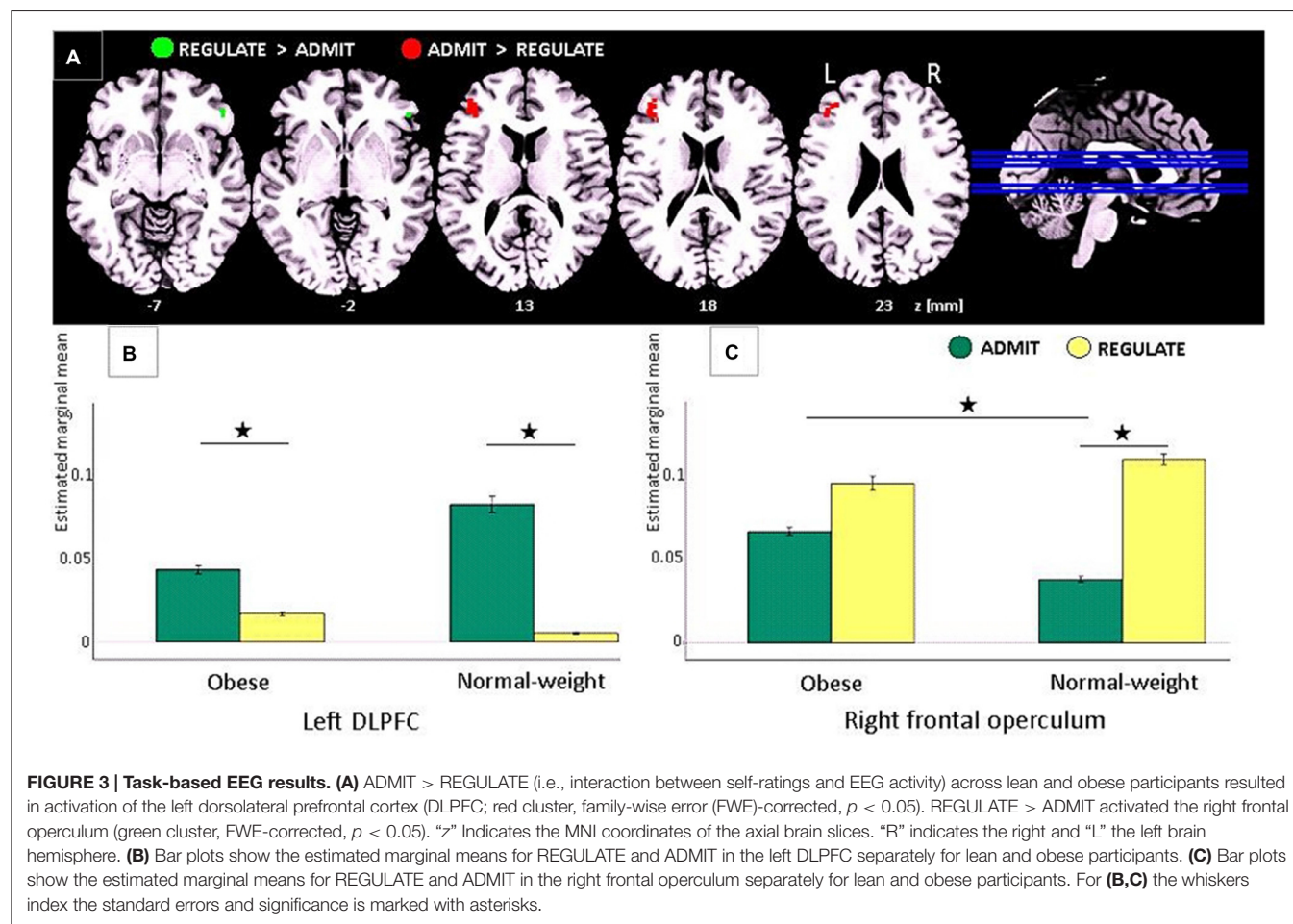
$p < 0.0005$; *post hoc* paired *t*-tests for lean $p < 0.005$ and for obese $p < 0.012$), whereas the inverse contrast (REGULATE > ADMIT), revealed an FWE-corrected activation in the right frontal operculum (peak voxel: MNI coordinates (*x*, *y*, *z*) 50, 34, −6 mm, $T = 5.28$, $p = 0.0123$; see **Figure 3A**). According to *post hoc* paired *t*-tests, the latter effect was driven solely by lean participants ($p < 0.001$; obese group $p > 0.137$; see **Figure 3C**). Comparing both study groups, we furthermore found higher activations in the ADMIT condition in obese as compared to lean participants ($p < 0.04$; **Figure 3B**).
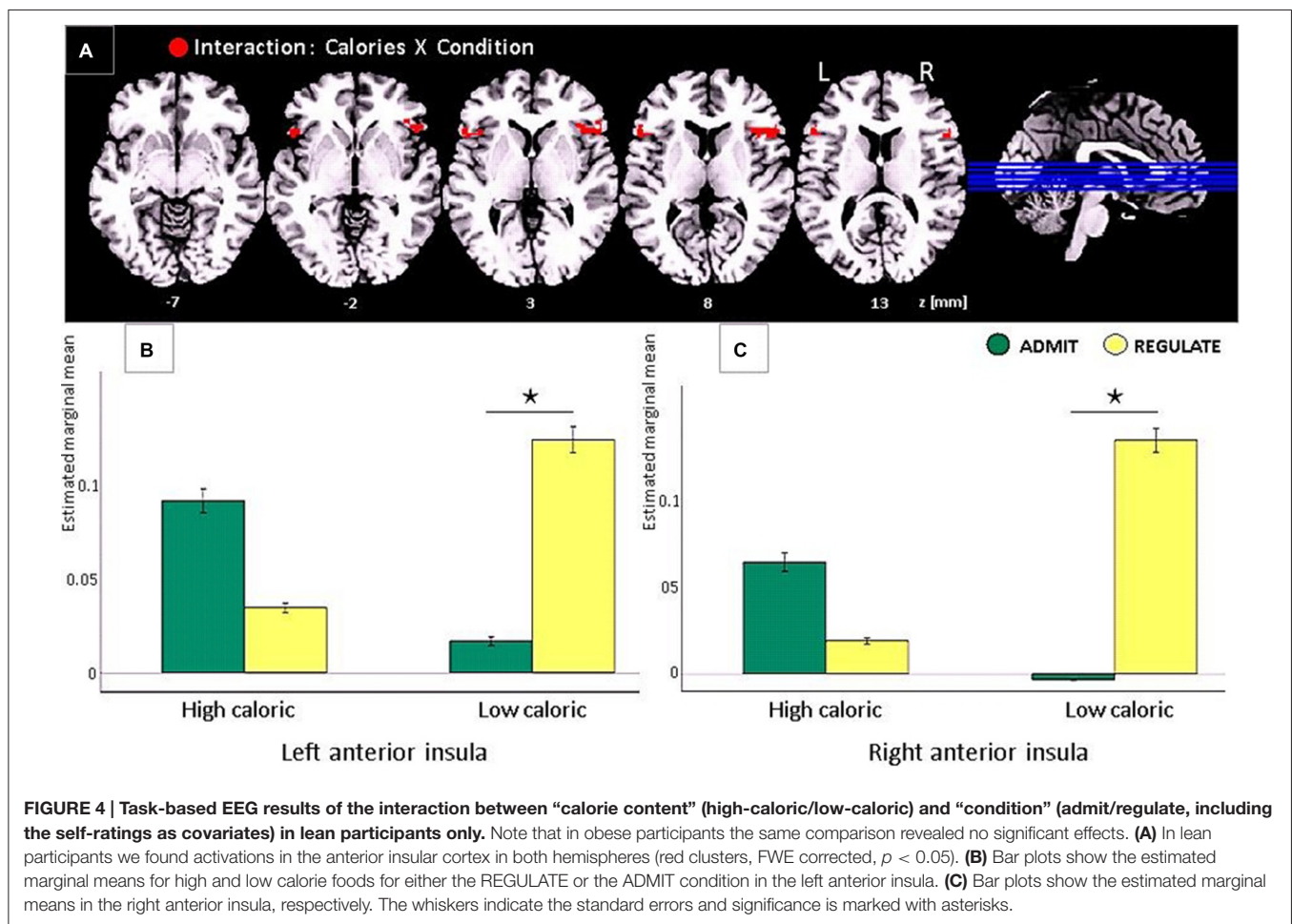
Only lean participants showed a significant interaction between "calorie content" (high-caloric/low-caloric) and "condition" (ADMIT/REGULATE), not in the DLPFC or the frontal operculum, but in the anterior insular cortex of both hemispheres (left: −50, 20, 8, $T = 6.45$, $p < 0.001$; right: 50, 22, 8, $T = 6.32$, $p < 0.0003$; **Figure 4A**). *Post hoc t*-tests revealed a significantly higher activity of the insula during the REGULATE as compared to the ADMIT condition in the left ($p < 0.01$) and right insular cortex ($p < 0.001$), but only for low calorie foods. For high calorie foods, we found the opposite pattern: higher activations during the ADMIT as compared to the REGULATE condition, although the difference between ADMIT and REGULATE did not

reach significance (left insula $p < 0.09$, right insula $p < 0.14$; **Figures 4B,C**).

DISCUSSION

In agreement with our a-priori hypotheses, we show that in obese as well as in lean individuals, the left DLPFC underpins the desire for foods, however, irrespectively of whether these were high or low caloric. We further hypothesized an interaction between participants' self-rated ability to reappraise foods and body weight in the DLPFC, which we could not confirm. Not the DLPFC, but the frontal operculum on the contralateral right hemisphere was involved in the self-rated ability to reappraise foods, again irrespectively of calorie content. During admitting the desire for low calorie foods (i.e., interaction between self-ratings and EEG activity), not the frontal or prefrontal cortex, but both hemispheres' anterior insular cortices responded with high activity for high calorie foods and low activity for low calorie foods. During the reappraisal of the same foods, the same areas showed the inverse pattern: low activity for high calorie foods and high activity for low calorie foods. Nonetheless, the difference between the admit and regulate condition reached significance only for low, and not for high calorie foods.

FIGURE 3 | Task-based EEG results. (A) ADMIT > REGULATE (i.e., interaction between self-ratings and EEG activity) across lean and obese participants resulted in activation of the left dorsolateral prefrontal cortex (DLPFC; red cluster, family-wise error (FWE)-corrected, $p < 0.05$). REGULATE > ADMIT activated the right frontal operculum (green cluster, FWE-corrected, $p < 0.05$). "z" Indicates the MNI coordinates of the axial brain slices. "R" indicates the right and "L" the left brain hemisphere. **(B)** Bar plots show the estimated marginal means for REGULATE and ADMIT in the left DLPFC separately for lean and obese participants. **(C)** Bar plots show the estimated marginal means for REGULATE and ADMIT in the right frontal operculum separately for lean and obese participants. For **(B,C)** the whiskers index the standard errors and significance is marked with asterisks.

FIGURE 4 | Task-based EEG results of the interaction between "calorie content" (high-caloric/low-caloric) and "condition" (admit/regulate, including the self-ratings as covariates) in lean participants only. Note that in obese participants the same comparison revealed no significant effects. **(A)** In lean participants we found activations in the anterior insular cortex in both hemispheres (red clusters, FWE corrected, $p < 0.05$). **(B)** Bar plots show the estimated marginal means for high and low calorie foods for either the REGULATE or the ADMIT condition in the left anterior insula. **(C)** Bar plots show the estimated marginal means in the right anterior insula, respectively. The whiskers indicate the standard errors and significance is marked with asterisks.

During EEG recordings, we visually presented food items out of two different categories (i.e., high/low caloric). Each picture was presented twice—one time, participants were instructed to regulate the desire for the presented foods, the other time, they had to allow the desire for the same foods. After picture presentation, participants rated their ability to either regulate or admit the desire for the presented foods on a 4-point Linkert-scale ranging from 1 (very bad) to 4 (very good). These self-ratings were implemented into the EEG data analyses as covariates to assess the related brain activity for either the admit or regulate condition. Participants were free in choosing the best strategy in order to either admit or regulate their food desire. After the experiment, we asked them which strategy they used. For regulating their desire, most participants reported of thinking that the presented foods were rotten. To allow the desire for the same foods they simply thought of its delicious taste during consumption. Comparing these two conditions, irrespectively of whether participants were obese or lean or whether the food was high or low caloric, we found a sub-region within the right frontal operculum involved in the regulation of the food desire. Its activity during admitting food desire was significantly higher in obese as compared to lean individuals possible indicating a stronger

gustatory response to the visually presented foods. In the DLPFC on the opposite hemisphere, we found a region involved in the desire for the same foods. During admitting food desire, its activity was enhanced by trend in lean as compared to obese participants probably suggesting a stronger executive control. Together, these findings address opposing effects in food choices to sub-regions within left prefrontal and right frontal cortex in both, lean and obese individuals.

Previous fMRI studies on central nervous taste processing showed, that taste stimuli applied either to the right or left side of the tongue predominantly activate ipsilateral brain regions as well as their connections, not only at the thalamus level, but also in higher-level gustatory cortices (Iannilli et al., 2012). We in the present study, however, found clearly lateralized effects for admitting or regulating food desire in the left DLPFC and right frontal operculum, respectively. In previous fMRI studies using almost the same experimental design as in the present study, we also found that regulating the desire for food activated the frontal operculum, however, not only in one but both brain hemispheres (Hollmann et al., 2012). This suggests that different study groups with different BMI ranges (lean to overweight in Hollmann et al., 2012 vs. lean and obese in the present study) induce

differentially lateralized brain effects related to the reappraisal of foods.

Only in lean individuals, we found an interaction between high and low calorie foods, in a region neighboring the frontal operculum, namely the anterior insular cortex. Regarding the insula's cognitive implementation, recent studies suggest that its activation relates to the sense of ownership and agency (Farrer et al., 2003), or the subjective awareness and affective processing of bodily signals (Craig, 2002, 2004). Especially the anterior insula is assumed to play a major role in viscerosensory (Oppenheimer et al., 1992) and interoceptive cognition (for a review see Craig, 2009), suggesting its involvement in higher-order perceptual processing of the body that is either related to a sense of ownership or to emotional experience. In the context of eating, the anterior insula, together with the neighboring frontal operculum, are described to host the primary gustatory cortex, which is assumed to primarily code taste (Rolls et al., 1988; Zatorre et al., 1992; Small et al., 1999). During eating, exteroceptive food-related sensory signals from taste and olfactory receptor cells activate the anterior insula together with the frontal operculum, where stimulus identity and intensity are merged into a stable representation, independent of the homeostatic or motivational state (Rolls et al., 1988; Zatorre et al., 1992; Small et al., 1999).

Our findings extend these functions, since in lean participants visually presented foods activated the anterior insular cortex, independently of signals from peripheral taste or olfactory receptor cells. This finding is well in line with previous studies in mice, showing that the insular cortex regulates food choices even in the absence of peripheral taste inputs (Oliveira-Maia et al., 2012). One possible interpretation of this finding is that the anterior insula in humans also contributes to the ability to imagery food and taste (as indexed by the self-ratings), with, however, different response profiles for high as compared to low calorie foods. Whether these calorie-related differences in neural responses primarily originate from the insular cortex or mirror top-down influences from other brain sources not captured by EEG remains an open question for future research. Food and taste evaluation and imagery, nonetheless, is an essential function for survival. Its implementation in the primary gustatory cortex may therefore represent an evolutionary well-preserved effect.

Lean and obese individuals together rated their ability to admit the desire for low-calorie foods as better than the ability to reappraise the desire for the same foods. These findings suggest that following the hedonic feelings of wanting and liking foods is easier than their reappraisal (Berridge, 2009). However, only in lean participants, self-ratings were well reflected by the activity obtained from the anterior insular cortices. For high-calorie foods, they showed an inverse insula response profile as for low calorie foods, which, however, did not reach significance. Obese participants unexpectedly rated their ability to reappraise high calorie foods as equally well as the ability to admit the desire

for the same foods. However, contrarily to lean participants, self-ratings in obese individuals were not reflected by neuronal responses neither by the insula's activity levels, nor by any other EEG sources throughout the brain. Although it is problematic to interpret such non-significant effects, since they still may become significant with increasing the sample size, they probably point to an association between obesity and an impaired self-reflection of the ability to reappraise foods in the insular cortex. However, in disagreement with our a-priori hypotheses, we found no differences between groups of obese and lean individuals: a lack of effect, which is possibly driven by the food pictures that we applied in the present study.

These pictures were chosen from a larger assembly that was validated in pilot experiments in only lean individuals (others than those who participated in the present study; data not published). The pictures chosen for the present study were those with the highest ratings in terms of esthetic and tastiness in the photographic presentation. Due to the validation in only lean individuals, the present set of food pictures may have been more sensitive to changes in lean ones, possibly explaining the lack of interaction effects in obese participants (admit/regulate-by-low/high calorie food) as well as the lack of differences between lean and obese participants.

In summary, we show distinct brain regions in obese and lean individuals involved in the evaluation of the food's calorie content and its reappraisal. The interplay between the left DLPFC and the right frontal operculum may in future serve as a target for non-invasive brain stimulation or neurofeedback studies that aim at modulating eating behavior towards better reappraisal capacities for foods. The involvement of the anterior insular in lean subjects suggests that the insula, so far assumed to host primary gustatory processes, also plays a role in processes underpinning higher cognitive functions involved in food choices.

AUTHOR CONTRIBUTIONS

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3.2 Publication 2

Satiety-induced enhanced neuronal activity in the frontal operculum relates to the desire for food in the obese female brain

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Author contribution statement

Conception and design of study: SK, JM, BP
acquisition of data: FG, CB
analysis and/or interpretation of data: SK, HJH, FG, CB, JM, BP
Drafting the manuscript: SK, BP
revising the manuscript critically for important intellectual content: SK, HJH, FG, CB, JM, BP
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Keywords

Obesity, EEG, Frontal operculum, reappraisal of food, Hunger, satiety

Abstract

Word count: 297

Identifying brain regions involved in the reappraisal of tasty but unhealthy foods is important for the development of cognitive interventions for obesity, such as non-invasive brain stimulation or neurofeedback. In a recent EEG study, we showed that allowing the desire for low and high calorie food in hungry obese as well as lean women and men related to enhanced activity in the left dorsolateral prefrontal cortex (DLPFC), whereas the right frontal operculum, suggested to host gustatory processes, was involved in the reappraisal of the same food. These findings suggest an interplay between executive control (DLPFC) and gustatory regions (frontal operculum) for opposing cognitive influences on the desire for food. In the present EEG study, we questioned how eating to satiety affects cognitive influences on the desire for food and corresponding neuronal activity in the left DLPFC and right frontal operculum in lean and obese women. When hungry, lean women self-rated the ability to reappraise visually presented food as more difficult than allowing the desire for the same food. Obese women instead, rated their ability to reappraise food as equally well as allowing the desire, suggesting hungriness-related problems in self-reflection of food reappraisal abilities. Comparing the EEG data of the sated to the hungry state, we found that the frontal operculum was involved in the reappraisal of food, but surprisingly also in admitting the desire for the same foods - an effect which we expected to find in the left DLPFC. This suggests that the right frontal operculum in the obese female brain underpins or at least reflects both opposing cognitive influences on the desire for food after eating to satiety. In the future, these findings may help to find potential brain targets for non-invasive brain stimulation or neurofeedback studies that aim at modulating the desire for food.

Funding statement

Ethics statements

(Authors are required to state the ethical considerations of their study in the manuscript, including for cases where the study was exempt from ethical approval procedures)

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This study was carried out in accordance with the recommendations of 'name of guidelines, name of committee'. The protocol was approved by the 'name of committee'.

If the study was exempt from one or more of the above requirements, please provide a statement with the reason for the exemption(s).
Ensure that your statement is phrased in a complete way, with clear and concise sentences.

Participants were financially reimbursed for their participation. The study was approved by the local ethics committee of the University Clinic Leipzig and conducted in line with the declaration of Helsinki.
Participants were informed of the full procedure of the EEG study.

Satiety-induced enhanced neuronal activity in the frontal operculum relates to the desire for food in the obese female brain

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1 Abstract

Identifying brain regions involved in the reappraisal of tasty but unhealthy foods is important for the development of cognitive interventions for obesity, such as non-invasive brain stimulation or neurofeedback. In a recent EEG study, we showed that allowing the desire for low and high calorie food in hungry obese as well as lean women and men related to enhanced activity in the left dorsolateral prefrontal cortex (DLPFC), whereas the right frontal operculum, suggested to host gustatory processes, was involved in the reappraisal of the same food. These findings suggest an interplay between executive control (DLPFC) and gustatory regions (frontal operculum) for opposing cognitive influences on the desire for food. In the present EEG study, we questioned how eating to satiety affects cognitive influences on the desire for food and corresponding neuronal activity in the left DLPFC and right frontal operculum in lean and obese women. When hungry, lean women self-rated the ability to reappraise visually presented food as more difficult than allowing the desire for the same food. Obese women instead, rated their ability to reappraise food as equally well as allowing the desire, suggesting hungriness-related problems in self-reflection of food reappraisal abilities. Comparing the EEG data of the sated to the hungry state, we found that the frontal operculum was involved in the reappraisal of food, but surprisingly also in admitting the desire for the same foods - an effect which we expected to find in the left DLPFC. This suggests that the right frontal operculum in the obese female brain underpins or at least reflects both opposing cognitive influences on the desire for food after eating to satiety. In the future, these findings may help to find potential brain targets for non-invasive brain stimulation or neurofeedback studies that aim at modulating the desire for food.

2 Introduction

Obesity is a worldwide health burden of industrialization (James et al. 2001). Especially in rapidly developing countries, the quickly expanding access to high calorie foods causes dramatically increasing rates of obesity and its comorbidities (Spence et al. 2009; Pereira et al. 2005; Rosenheck 2008). Despite these alarming facts, therapeutic options remain sparse. Most modern weight loss programs combine calorie restriction and physical activity with behavioral or cognitive therapy, with, however, limited influences on body weight and long-term weight stability (Soeliman and Azadbakht 2014; Jakicic and Davis 2011; Amorim Adegboye and Linne 2013; Ausburn et al. 2014; Looney and Raynor 2013). The central problem in developing effective therapies is that central nervous mechanisms guiding everyday food choices, especially those underpinning overeating, are not well understood.

High-caloric foods seem to affect the brain's reward responses like drugs of abuse (Volkow et al. 2013). Like drug-dependent persons, obese individuals present increased craving as well as attenuated reward responses to high-calorie food, probably supporting compensatory overeating (Wang et al. 2001; Stice et al. 2008; Johnson and Kenny 2010). Breaking this vicious circle demands the understanding of the brain's top-down influences on food craving, such as those involved in reappraisal of food.

In recent studies, we investigated hungriness-related functional brain processes related to the desire for food in lean and obese men and women (Hollmann et al. 2012; Kumar et al. 2016). We visually presented food items (i.e., high/low caloric) while acquiring neural or neuronal brain activity with, either functional magnetic resonance imaging (fMRI) (Hollmann et al. 2012) or electroencephalography (EEG) (Kumar et al. 2016), respectively. In both studies, food items were presented under two opposing conditions; once , participants were instructed to admit the desire for the presented food, by thinking, e.g. of its delicious smell or taste; the other time they were instructed to reappraise the food, e.g. by thinking that it might be poisoned, spoiled or lead to weight gain. Participants were free to choose the best strategy in order to admit or regulate their desire. During the task, they additionally rated their ability on how well they admitted or regulated their food desire from trial to trial.

Comparing fMRI responses in lean to obese women and men of the "REGULATE" to the "ADMIT" condition, revealed the dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA) and inferior frontal gyrus (IFG) (Hollmann et al. 2012); regions that are well known to underpin top-down control of craving, inhibition of learned associations and prepotent responses (Sharp et al. 2010; Swick, Ashley, and Turken 2008). Furthermore, we observed increased activation in bilateral orbitofrontal cortex (OFC), a key region of the brain's reward valuation system, as well as the anterior insular cortex and temporoparietal junction (TPJ) suggesting interoceptive awareness and self-reflection (Zald 2009; Kringelbach 2005; Kahnt et al. 2010; Kennerley et al. 2009; Peters and Büchel 2010). These results suggest that the

85 reappraisal of food recruits the brain's valuation system in combination with prefrontal cognitive
86 control areas associated with response inhibition (Hollmann et al. 2012).

87 With EEG, we found that allowing the desire for low and high calorie food in obese as well as
88 lean women and men was related to enhanced activity in the left DLPFC, whereas the right
89 frontal operculum, assumed to host gustatory processes (Rolls et al. 1988; Zatorre et al. 1992;
90 Small et al. 1999), was involved in the reappraisal of the same food (Kumar et al. 2016). These
91 findings suggest an interplay between executive control (DLPFC) and gustatory regions (frontal
92 operculum) for opposing cognitive influences on the desire for food. Only in lean participants,
93 did we find an interaction between calorie content of the visually presented food and the self-
94 rated ability to regulate/admit the desire for food in bilateral anterior insular cortices, suggesting
95 that the anterior insular cortex, assumed to primarily host gustatory processes (Rolls et al. 1988;
96 Zatorre et al. 1992; Small et al. 1999), also underpins higher cognitive processes involved in
97 food choices (Petit et al., 2016), such as evaluating the foods' calorie content for reappraisal.
98 Contrarily to lean women and men, obese individuals' self-ratings for regulate/admit were not
99 related to any brain responses, neither in the insular cortex's, nor by any other EEG sources
100 throughout the brain. Although it is generally problematic to interpret such non-significant
101 effects, as they may become more significant by increasing the sample size, they likely point to
102 an association between obesity and an impaired self-reflection of the ability to reappraise food in
103 the insular cortex (Kumar et al. 2016).

104 The present study is a follow-up study of our recent EEG study (Kumar et al. 2016). To impede
105 food reappraisal abilities, participants of the present and our previous two studies went five hours
106 without eating prior to the experiments (Hollmann et al. 2012; Kumar et al. 2016). In the present
107 study, we questioned how eating to satiety affects cognitive influences on the desire for food in
108 obese and lean women. To this end, women were tested twice: once before and once directly
109 after eating to satiety. As in our previous study (Kumar et al. 2016), we again used EEG to assess
110 neuronal brain responses related to the regulation of the desire for food.

111 We hypothesized that, when hungry, admitting the desire for food is easier than the reappraisal
112 of the same food (Kumar et al. 2016). After the buffet, we expected this effect to reverse, i.e.
113 reappraisal is easier, whereas admitting the desire for the same food is more difficult. Comparing
114 the EEG findings of the sated to the hungry state, we expected to find a decreased activity within
115 the left DLPFC in parallel to a decreased ability to admit the desire for food after eating to
116 satiety, whereas we expected to find an increased activity within right frontal operculum in
117 relation to strengthened reappraisal abilities. We hypothesized that all these effects were
118 significantly stronger in obese women as compared to lean.

3   Materials and methods

3.1   Participants

This study was approved by the local ethics committee of the medical faculty of the University of Leipzig and carried out according to the Declaration of Helsinki. Because of the known gender differences in brain morphology and function (Horstmann et al. 2011; Mueller et al. 2011; Melasch et al. 2016), we only invited women to participate in the present study. None of these women participated in our previous two studies (Hollmann et al. 2012; Kumar et al. 2016). All twenty right-handed women gave written informed consent prior to their participation. Before the experiments, we assessed each participant's age. We also measured participant's weight with a scale and height with a stadiometer to compute the body mass index (BMI, kg/m^2). Half of them were lean (BMI >20 and <25 kg/m^2, mean = 23.10, SD = 1.63) and the other half obese (BMI >30 kg/m^2, mean = 35.97, SD = 6.54). Age for lean (mean = 25.56, SD = 2.88) and obese women (mean = 26.75, SD = 2.81) were matched ($p > 0.759$ (parametric t-test)) (Table 1). All women were asked for any regular medication or contraceptives. Participants were financially reimbursed for their participation. All women were told to go five hours without eating prior to the experiment to enhance their sensitivity for visually presented food and to impede their reappraisal abilities (same design as in (Hollmann et al. 2012; Kumar et al. 2016)). All experiments were performed afternoon, between 1 to 2 p.m.

3.2   Visual Analog Scales (VAS)

VAS with scales ranging from 0 (i.e., lowest) on the left hand side to 100 (i.e., highest) on the right hand side were filled out before and after the first EEG session, before the second EEG session (i.e., after eating to satiety) as well as thereafter. We assessed six different VAS for each time point: degree of tiredness, hungriness, thirstiness, stress level, dryness of mouth, satiety. Participants were asked to make a cross between 0 and 100. The distance between 0 and the cross in cm was used for further analyses.

3.3   Buffet

The (cold) buffet was prepared during the first EEG experiment in a separate room, next to the EEG research facilities. All foods were weighted (in g) before and after the buffet with a standard kitchen scale to compute the consumed g per item. All items were presented identically for each participant in a palatable manner (cheese and meat pieces on plates, buns in a basket, fruit and vegetables cut, tomatoes in bite size). Every category (high/low calorie x sweet/salty) was represented by five food items. Additionally, we also offered snacks (pudding, peanuts, chocolate bars). We used the kcal/100g indications provided on the products' packages to translate consumed g into kcal. For fruit/vegetables we took the brand-specific kcal/100g

153 indications as provided by the Food database (fddb), accessible via
154 http://fddb.info/db/en/index.html.

3.4 EEG Recording

156 We used a 64-channel BrainAmp recorder (Brain Products, Gilching, Germany) with a temporal
157 resolution of 1000 Hz. The electrodes were placed on participant's scalp according to the 10-10
158 international system. Electrodes included the reference, ground, and the electrode below the left
159 eye as an electro-occulogram (EOG).

3.5 Experimental Schedule

161 We used a shielded cabin to exclude any electro-magnetic interference on EEG recordings as
162 well as distracting noises. Within the cabin, each participant was comfortably seated in front of a
163 computer screen. After we assessed VAS, we first acquired five minutes of task-free EEG
164 recordings before the food task started, to familiarize participants with the environment. The
165 food task thereafter was 20 min long. After the first EEG session, participants were offered a
166 buffet outside the cabin including all food categories that were included in the task. Participants
167 were instructed to eat to their preference and satiation. After the buffet, participants were again
168 placed in the EEG cabin while reassuring that the electrodes were in the correct spot with low
169 impedance. After the initial five min of task-free EEG recordings, a second EEG session started.
170 EEG electrodes were not removed from participant's scalp between the two EEG sessions.

3.6 Task-Based EEG Recordings

172 Each of the two EEG sessions included 40 blocks. Each block consisted of three food pictures
173 and was 28 seconds long. During the first two seconds of each block, an instruction screen
174 showed up, either showing "ADMIT" or "REGULATE", followed by three food items within
175 one block. Each food picture was presented for five seconds. The three pictures were separated
176 by the presentation of the crosshair for another two seconds. The three pictures within a given
177 block were from the same of four different food categories: high-calorie sweet, high-calorie
178 salty, low-calorie sweet or low-calorie salty. To this end, 60 food pictures were chosen from a
179 pre-rated standardized food picture database (see (Hollmann et al. 2012; Kumar et al. 2016)). We
180 used the same amount of high and low calorie pictures. Sweet and salty was equally distributed
181 across high and low calorie food. We included the latter conditions to meet each participant's
182 taste preferences (same as in (Kumar et al. 2016)). Within each of the two EEG sessions, a given
183 food picture was presented once in the "ADMIT" and once in the "REGULATE" condition,
184 cancelling out any influence of food preferences on the comparison of both conditions. For each
185 participant, we acquired 60 trials for the "ADMIT" and 60 trials for the "REGULATE" condition
186 within each EEG session. At the end of each block (i.e., presentation of three food pictures from

one category), and after another crosshair for two seconds appeared, a screen with a 4-point Likert scale was presented for three seconds. Participants rated how well they thought they either admitted or regulated the desire for the presented food items. The scale ranged from 1 (very bad) to 4 (very good). After participants rated their performance, the next block of three food items from another category started. The order of the food pictures within each block and the order of blocks was pseudo-randomized inter-individually (i.e., between participants) and intra-individually (i.e., between both EEG sessions) (Figure 1).

3.7   Pre-processing of the EEG Data

Pre- and post-EEG processing was done with MATLAB version 8.2 (The MathWorks, Ismaning, Germany). We down-sampled EEG data to 250 Hz using the Berlin Brain Computer Interface (BBCI) toolbox (https://github.com/bbci/bbci_public). The data was band-pass filtered between 0.05 and 45 Hz (3rd order Butterworth filter). To exclude any bias towards a particular reference electrode, we converted the data to a common average reference (CAR) (Bertrand, Perrin, and Pernier 1985; Pascual-Marqui and Lehamann 1993). To correct for vertical eye movements, we computed the difference between the EOG and the FP1 electrodes above the left eye. To correct for horizontal eye movements we computed the sum of the Fp1 and Fp2 electrodes above the two eyes. The resulting data was applied to a regression analysis to cancel out the corresponding variance from the EEG data using the least mean-fitting procedure (Parra et al. 2005) of the BBCI. The FieldTrip Software package (Donders Center for Cognitive Neuroimaging, University Nijmegen, Netherlands) was used for further pre-processing. The corrected EEG data was epoched into 5 seconds covering the presentation of each food picture and baseline corrected. For baseline correction, we applied the mean value of the given trial instead of the time prior to presentation to rule out any bias based on anticipation. To model the EEG data, we applied the self-ratings as an interacting trial-by-trial covariate. The temporal window for source analysis was selected between 1675 and 2055 ms, based on signed point-biserial correlations (Blankertz et al. 2011). In particular, sums of the absolute correlation coefficient values at a given time window were calculated and then the temporal window corresponding to the highest sum value was selected for further analyses.

3.8   Source Localization of the EEG Data

The Statistical Parametric Mapping (SPM) Software package 12 (Wellcome Trust Centre for Neuroimaging at University College London, UK, http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB version 8.2 was used for source localization. The boundary element method (BEM) was considered for the forward model consisting of the three cortical layers along with co-registration to the default model of electrode positions using the standard magnet resonance imaging (MRI) template as implemented in SPM. To overcome the inverse problem we applied the multivariate source pre-localization (MSP) algorithm (Mattout et al. 2005).

3.9 Second (group) level analysis of the EEG data

For second (group) level analysis, we applied the full factorial design (i.e., ANOVA) consisting of the between-subject factor "obese/lean participants" and the within-subject factors "pre-buffet/post-buffet", "REGULATE/ADMIT" as well as high/low calorie content. As in our former study (Kumar et al. 2016), self-ratings were inserted as interacting covariate. Following our a-priori hypotheses (see Introduction), we applied small volume correction. To this end we used a sphere of 10 mm centered on the Montreal Neurological Institute (MNI) co-ordinates (x, y, z, in mm) as derived from our latest EEG study (Kumar et al. 2016). For the right frontal operculum the coordinates were 50, 34, -06 (x, y, z, in mm); for the left DLPFC the coordinates were -42, 38, 20 (x, y, z). A voxel-wise family-wise error (FWE) corrected p-value of < 0.05 together with a minimum cluster size of 10 voxels indicated significance. In the post-hoc analysis, paired (within-subject) and unpaired (between-subject) t-tests were applied to decipher the structure of significance.

3.10 Analysis of self-ratings

We also applied self-ratings to the ANOVA (same design as for EEG data analysis). In case of significance post-hoc paired (within-subject) and unpaired (between-subjects) t-tests were applied.

3.11 Correlations between calorie consumption, EEG data, self-ratings and VAS

For each woman, we totaled the consumed calories from the buffet offered between both EEG sessions. Next, we applied Pearson's correlation analysis to assess a possible positive or negative relationship between calorie consumption and changes (i.e., post – pre) in EEG data, self-ratings and VAS.

4 RESULTS

4.1 VAS

Lean women were comparatively more tired than obese women after the first EEG session (i.e., before the buffet) as well as after the buffet (i.e., before the second EEG session) ($p < 0.045$ and $p < 0.0002$, respectively). Obese women instead, felt less stressed throughout the experiment than lean women (from first to fourth VAS: $p < 0.002$; $p < 0.0001$; $p < 0.014$; $p < 0.0002$). Lean women surprisingly felt less sated before the first EEG session (i.e., start of the experiment and after five hours without eating) ($p < 0.015$). Analyzing satiety, hungriness and thirstiness after the buffet (i.e. before the second EEG session) in the group of lean and obese women separately,

254 revealed an elevated level of satiety (lean: $p < 0.0001$; obese: $p < 0.0001$), whereas hungriness
255 (lean: $p < 0.0001$; obese: $p < 0.0001$) and thirstiness decreased (lean: $p < 0.0001$; obese: $p <$
256 0.031). There was also a trend of less dryness of the mouth but the t-test was inconclusive (lean:
257 $p > 0.062$; obese: $p > 0.087$). All women were taking contraceptives. Therefore, we could not
258 address any menstrual cycle-related influences in the present findings. None of the women took
259 other regular medication with central nervous (side-) effects.

4.2   Self-Ratings acquired during the first and second EEG session

261 According to our a-priori hypotheses (see Introduction), we found that for both, obese and lean
262 women, admitting the desire for food was easier during the EEG session prior to the buffet (i.e.,
263 five hours without eating) as compared to the EEG session after the buffet (i.e., after eating to
264 satiety) (obese: $p < 0.003$, lean: $p < 0.001$), whereas the reappraisal of food was easier after the
265 buffet, when sated (obese: $p < 0.032$, lean: $p < 0.006$). After the buffet, obese and lean women
266 rated their ability to reappraise food as better than admitting the desire for food (REGULATE >
267 ADMIT, obese: $p < 0.019$, lean: $p < 0.019$) (Figure 2A).

268 In line with our former study (Kumar et al. 2016), we found that before the buffet, when hungry,
269 lean women self-rated their ability to admit the desire for food as easier than reappraising food
270 (ADMIT > REGULATE, obese: $p > 0.525$, lean: $p < 0.001$), irrespective of calorie content (high
271 calorie $p<0.001$, low calorie $p<0.001$). Obese women resembled these findings, however only for
272 low calorie food ($p<0.0017$). For high calorie food they instead self-rated their ability in both
273 conditions and for both calorie groups as equally well ($p>0.03$) (Since only one-fourth of trials
274 were used for this analysis p value was set to 0.0125). An unexpected finding, which,
275 nevertheless, resembles previous observations (Kumar et al., 2016) (Figure 2B).

4.3   Task-Based EEG findings

277 Comparing the EEG data of both, lean and obese women, acquired after the buffet (i.e., after
278 eating to satiety) to the EEG data assessed prior to the buffet (i.e., five hours without eating)
279 revealed a significant FWE-corrected main effect represented by an increased activity in the right
280 frontal operculum ($p < 0.005$). Post-hoc paired t-test computed for the group of obese and lean
281 women separately, revealed that this post > pre effect was significant only in obese women (peak
282 voxel: MNI coordinates (x, y, z): 50, 36, 02 mm, T = 3.93, $p < 0.006$). Post-hoc t-tests in the
283 group of obese women surprisingly revealed significantly increased activity in the frontal
284 operculum, not only during the "REGULATE" condition (see Introduction for our a-priori
285 hypotheses), but in both, the "ADMIT" ($p < 0.045$) as well as the "REGULATE" condition ($p <$
286 0.027) (Figure 3). In lean women, we found no significant post > pre differences in activity
287 levels. Also the inverse contrast (i.e., pre > post) did not show the expected significant activity in
288 the left DLPFC, neither in the group of lean, nor in the group of obese women. Besides these two

289 regions identified in our former EEG study (i.e., right frontal operculum, left DLPFC, see
290 (Kumar et al. 2016) and our a-priori hypotheses in the Introduction), we found no other
291 significant increases or decreases in activity levels between the two EEG sessions and the two
292 conditions of interest throughout the entire brain. Furthermore, we could also not find any
293 significant interaction between lean/obese and high-caloric/low-caloric foods.

294 To assess whether present EEG findings replicate previous observations (Kumar et al., 2016), we
295 also analyzed EEG data acquired prior to the buffet (i.e., after five hours without eating).
296 Comparing the "REGULATE" to the "ADMIT" condition revealed enhanced activity in right
297 frontal operculum (peak voxel: (x, y, z): 48, 38, 02 mm, T = 3.64, p < 0.011). This finding
298 replicates previously reported effects (Kumar et al., 2016). Comparing the "ADMIT" to the
299 "REGULATE" condition, however, did not reveal the expected effect in left DLPFC (Kumar et
300 al., 2016). Since our previous study included women and men (Kumar et al., 2016) and the
301 present only women, we next split previous EEG data from left DLPFC into males and females.
302 We hypothesized that effects in the left DLPFC, as reported elsewhere (data from Kumar et al.,
303 2016), might account for men, but not women. Unpaired t-tests between women and men
304 however suggest that both genders contributed commonly to the effects in left DLPFC
305 ("ADMIT" condition: women 0.066, men 0.035, p > 0.21). The same accounted for right frontal
306 operculum that also showed no significant differences between women and men ("REGULATE"
307 condition: women 0.11, men 0.12, p > 0.82).

4.4   Calorie consumption from the buffet between the two EEG sessions

309 We surprisingly found no significant differences in the consumption of calories between lean and
310 obese women. We expected that obese women might consume more calories than the lean
311 women after going five hours without eating. Contrarily, we even found a vague trend that lean
312 women consumed more calories than obese (p > 0.108). We also found no differences in calorie
313 consumption between lean and obese women for the four different food categories (high caloric
314 sweet foods: p > 0.066, high caloric salty foods: p > 0.068, low caloric sweet foods: p > 0.196,
315 low caloric salty foods: p > 0.461). For both, lean and obese women, we found that they
316 consumed significantly more high calorie food than low calorie food (sweet: lean: p < 0.0001,
317 obese: p < 0.0001; salty: lean: p < 0.0001, obese: p < 0.0001). Both groups also showed a trend
318 for preferring salty over sweet food (lean: p > 0.197; obese: p > 0.139) (Figure 4). Pearson's
319 correlation analyses revealed a positive correlation between changes in hungriness ratings (VAS)
320 from before to after the buffet and calorie consumption, however, only in the group of obese
321 women (r = 0.69, p < 0.0266). This finding suggests that the more obese women ate, the more
322 their hungriness-ratings declined. We surprisingly found no such correlation in lean women (r = -
323 0.35, p > 0.1957). We also found no correlation between calorie consumption and the other VAS
324 (i.e., degree of tiredness, hungriness, thirstiness, stress level, dryness of the mouth, satiety) (p >
325 0.058). Furthermore, we found no correlation between calorie consumption and neuronal activity
326 in the frontal operculum in obese women (r = 0.17, p > 0.6431), as well as between calorie

consumption and self-ratings for admitting the desire for food (lean: r = 0.0056, p >0.9876, obese: r = 0.3342, p > 0.3453) or regulating the desire for food (lean: r = 0.2239, p > 0.5340, obese: r = 0.0842, p > 0.8171).

5 Discussion

The present study is a follow-up study investigating the influences of eating to satiety on the desire for food. In our former EEG study (Kumar et al. 2016), we used the same task design as in the present study to investigate brain responses in lean and obese women and men, involved in cognitive influences on the desire for food. To impede reappraisal of food, participants in both studies went five hours without eating prior to the experiments. In our former study (Kumar et al. 2016), we found that in hungry obese as well as lean women and men, admitting the desire for low and high calorie food related to higher activity in the left DLPFC, whereas the right frontal operculum, assumed to host gustatory processes (Rolls et al. 1988; Zatorre et al. 1992; Small et al. 1999), was involved in the reappraisal of the same foods.

In the present study, we questioned how eating to satiety affects reappraisal of food as well as corresponding neuronal responses. To this end, we enrolled a new group of lean and obese women in the same EEG task as in our former study (Kumar et al. 2016). All women underwent the task twice: once while hungry and the other time while sated. As in our previous study, participants went five hours without eating prior to the first EEG session. After this session, they were offered a buffet complied in accordance to the EEG food picture task. Obese as well as lean women, selected more high-calorie than low-calorie food from the buffet. Both groups, moreover, preferred salty over sweet food. Surprisingly, lean women showed a trend for consuming more calories as compared to obese women. This difference was well reflected by the VAS ratings, as lean women rated themselves being less sated before the first EEG experiment compared to obese women. Since all women were taking contraceptives, we were not able to consider menstrual cycle-related influences on the desire for food.

In contrast to the present findings, most studies in fact showed that overweight or obese individuals consume more calories (Batterham et al. 2003) and a greater proportion of unhealthy food (Medic et al. 2016), if a buffet is offered under lab conditions. Others studies, however, agree with our observation that obese and lean individuals consumed comparable amounts of calories under lab conditions (Druce et al. 2005). Besides a potential incompliance in food restriction, different study-related social-environmental factors, such as the gender and attractiveness of the instructor, as well as the choice and appearance of food items, may variably influence eating behavior, similar to obese women when feeling observed (Robinson et al. 2016).

In the present study, we found that when hungry (i.e., five hours without eating as in Kumar et al., 2016), lean women self-rated the ability to reappraise visually presented food as more

362   difficult than allowing the desire for the same food. Obese hungry women instead, rated their
363   ability to reappraise food as equally well as allowing the desire for food.

364   To test whether the present self-ratings replicate previous ones (Kumar et al. 2016), we
365   additionally split present self-ratings into low and high calorie food. Self-ratings only for low,
366   but not for high calorie food showed the expected effect with higher ratings for allowing the
367   desire for food when women were hungry (Kumar et al. 2016). In both studies, however, obese
368   women (and men, see Kumar et al. 2016), not lean, unexpectedly rated their ability to reappraise
369   high calorie food as equally well as the ability to admit the desire for the same food. These
370   findings most likely point to an association between obesity and an impaired self-reflection of
371   the ability to reappraise especially high-calorie food after five hours without eating.

372   Alternatively, obese women deliberately tried to show that they are capable of regulating their
373   food desire even when hungry, rendering social modeling as a potential influencing factor.
374   Cruwys et al., reviewed several studies published between 1974 and 2014 and found that social
375   modeling of eating seems at least to be partially mediated through behavioral mimicry, which
376   occurs without conscious awareness (Cruwys, Bevelander, and Hermans 2015). Since
377   participants in our study were alone at the buffet, there was no "ideal model" they may have
378   desired to affiliate with. This makes social modeling rather unlikely to account for the
379   unexpected low calorie intake in obese women. However, heightened awareness of observation
380   was more recently shown to cause obese females to reduce their calorie consumption during a
381   meal under lab conditions (Robinson et al. 2016). Since the room where we offered the buffet,
382   was right next to the EEG research facilities, our participants might have felt observed.

383   Alternatively, obese women simply might have not refrained from eating before the experiments
384   as required, since they also rated themselves being more sated as lean women before the first
385   EEG session. This would also explain the trend for lower calorie consumption from the buffet in
386   obese as compared to lean women. Future studies, should aim at controlling fasting periods in
387   both, lean and obese participants, especially when they are as long as in the present study (i.e.,
388   five hours). Nevertheless, only in obese women changes in hungriness ratings (VAS) from
389   before to after the buffet positively correlated with calorie consumption, suggesting that the more
390   obese women ate, the more their hungriness declined. We could not find such a relationship in
391   lean women, suggesting that obese women are probably more sensitive in reflecting their
392   hungriness with respect to calorie demand. However, this interpretation has to be considered
393   with caution since we could not find any supporting evidences in the literature (PubMed search).

394   In our former EEG study (Kumar et al., 2016), we showed that when admitting the desire for low
395   and high calorie foods, obese as well as lean individuals presented higher activity in the left
396   dorsolateral prefrontal cortex (DLPFC), whereas activity in the right frontal operculum related to
397   the reappraisal of the same foods. In the present study, after eating to satiety, we found enhanced
398   activity in the frontal operculum during reappraisal of food, but surprisingly also when admitting

399 the desire for food- an effect which we, based on our previous study (Kumar et al. 2016),
400 expected to find in the left DLPFC.

401 This contradictory finding, questions the comparability of both studies. That is why we
402 additionally analyzed the EEG data assessed prior to the buffet, which we acquired with the same
403 study design (particularly, five hours without eating prior to the experiment), the same task, and
404 the same EEG settings as in Kumar et al. (2016). When women reappraised food before the
405 buffet, we found significantly increased activity in the right frontal operculum – a finding that
406 resembles previous observations in women and men (Kumar et al., 2016). However, while
407 admitting the desire for the same foods, we unexpectedly found no effects in the left DLPFC,
408 which is against our a-prior hypotheses and former findings (Kumar et al., 2016). We next
409 revisited gender effects in our previous study (Kumar et al., 2016), and analyzed EEG recordings
410 from right frontal operculum and left DLPFC for women and men separately. Both regions, left
411 DLPFC and right frontal operculum, in both genders showed comparable activity levels during
412 admitting the desire for food, as well as their reappraisal, respectively.

413 In the present study, we revealed no significant effects in the left DLPFC in women, possibly due
414 to the halved sample size in the present (n=20) as compared to our previous study (n=40), and
415 also the halved trials that probably caused a power problem. In our former study (Kumar et al.,
416 2016), when women were hungry, activity levels in the frontal operculum were furthermore
417 higher than in the left DLPFC, possibly rendering the frontal operculum more sensitive to the
418 reappraisal of food than the DLFPC to admitting the desire for the same food. After eating to
419 satiety, the right frontal operculum, nevertheless, seems to contribute to or at least reflects
420 modulatory influences on both opposing cognitive influences modulating the desire for food.

421 To test in how far EEG results were influenced by the self-ratings that we included to the GLM
422 analyses as interacting covariate (see "3.9 Second (group) level analysis of the EEG data" for
423 further information), we reran all EEG first- and second level analyses excluding self-ratings.
424 Findings resembled effects reported in this paper (data not shown to avoid redundancy),
425 suggesting that self-evaluation of the ability to modulate the desire for food had rather minor
426 influences on frontal operculum's activity enhancements. These processes may alternatively be
427 embedded in other brain regions, possibly more deeply located in the brain (e.g., striatum or
428 posterior orbitofrontal cortex, (Hollmann et al. 2012)), and were therefore not captured by EEG.
429 In turn, frontal operculum in the obese brain may host more upstream processes not directly
430 related to self-evaluation, possibly reflecting elevated cognitive effort for the regulation of
431 opposing cognitive operations - the reappraisal of food and the desire for food.

432 In the context of eating, the frontal operculum, together with the neighboring anterior insular
433 cortex, are assumed to host the primary gustatory cortex – predominately involved in encoding
434 taste (Rolls et al. 1988; Zatorre et al. 1992; Small et al. 1999) but also higher cognitive
435 processing of gustatory sensations (Petit et al. 2016). While eating, exteroceptive sensory signals
436 arising from the food's taste and smell activate olfactory receptor cells that propagate associated

437 inputs to the frontal operculum together with the anterior insular cortex, where stimulus identity
438 and intensity are merged into a stable representation, independent of the homeostatic or
439 motivational state (Rolls et al. 1988; Zatorre et al. 1992; Small et al. 1999).

440 Regarding the insular cortex's functional non-gustatory implementation, recent studies suggest
441 its involvement in higher cognitive processes related to the sense of ownership and agency
442 (Farrer et al. 2003), or the subjective awareness and affective processing of bodily signals (a. D.
443 Craig and Craig 2002; A. D. Craig 2004). The anterior part of the insular cortex is specifically
444 assumed to play a major role in viscerosensory (Oppenheimer et al. 1992) and interoceptive
445 processing (for a review see ((Bud) Craig 2009). The frontal operculum, instead, has been
446 suggested as a key node in a network for exerting control over cognitive processes. It seems to
447 have a role in regulating the activity in relevant or irrelevant brain representations for response
448 selection (Higo et al. 2011), possibly also in the context of regulating the desire for food.

449 In our former EEG study (Kumar et al. 2016), we found that activity in the anterior insular cortex
450 was distinguished between high and low calorie foods. Whether these calorie-related differences
451 in neuronal responses primarily originate from the insular cortex or mirror top-down influences
452 from other brain sources not captured by EEG remains an open question. Nonetheless, these
453 findings suggest that the anterior insular cortex, so far assumed to host primary gustatory
454 processes, also plays a role in processes underpinning higher cognitive functions involved in
455 food imagery and food choices (Kumar et al. 2016). This finding is well in line with previous
456 studies in mice (Oliveira-Maia et al. 2012) and humans (Petit et al. 2016), showing that the
457 insular cortex regulates food choices even in the absence of peripheral taste inputs.

458 Our present findings suggest that it is not only the anterior insular cortex involved in such higher
459 cognitive processes, but also the neighbored frontal operculum. However, its cognitive
460 embedment seems different as compared to the anterior insular cortex. While the latter region
461 seems to encode calorie-related processes (Kumar et al. 2016), the former seems to relate to food
462 reappraisal in the obese brain after eating to satiety. Both regions' activity was however elicited
463 by visually presented foods, independent of signals from peripheral taste or olfactory receptor
464 cells, suggesting that the primary gustatory cortex, not only in mice (Oliveira-Maia et al. 2012),
465 but also in humans (Petit et al., 2016) contributes to the ability to imagine food and taste. Food
466 and taste evaluation, imagery and their influences on food choices are an essential function for
467 survival. Their implementation in the primary gustatory cortex may therefore represent a well-
468 preserved evolutionary effect (Kumar et al. 2016). Since we did not find any evidence for
469 differences between women and men when hungry, neither with respect to the function
470 assignment of the desire for food to brain regions at hand, nor to their activity levels, we
471 speculate that males may present comparable effects in the frontal operculum as women after
472 eating to satiety. However, unveiling the neural underpinnings of admitting or regulating food
473 desire in the male brain demands further studies.

In summary, we show that the right frontal operculum in obese women is involved in evaluation processes related to the regulation of the desire for food after eating to satiety. Therefore, it may in future serve as a target for non-invasive brain stimulation or neurofeedback studies that aim at modulating cognitive influences on the desire for food. The involvement of the frontal operculum and the anterior insular cortex in food-related higher cognitive processing suggests that the primary gustatory cortex also plays a role in higher cognitive processes related to food choices.

6 Acknowledgment

7   Figure legends and table

Figure 1. Experimental design. (A). Shown is the order of the two resting-state and the two experimental EEG sessions. Before and after each EEG sessions, lean and obese women rated their tiredness, hungriness, satiety, thirstiness, and stress levels on a visual analogue scale (VAS). The buffet was offered between the two EEG sessions. (B). Example of one block from the task-based EEG session. Three food pictures from one out of four categories (high or low calorie x sweet or salty) were presented in a row. Prior to the presentation of the pictures, participants were instructed to either regulate or admit the desire for the upcoming food pictures. After presentation of the three pictures, participants rated their ability to either regulate or admit the desire for the three presented foods. This was repeated 20 times for each condition (regulate/admit), resulting in a total of 40 blocks.

Figure 2. Shown are lean and obese women's self-ratings on how well they either admitted or regulated the desire for the visually presented foods on the Likert scale ranging from 1 (very bad) to 4 (very good) before and after the buffet. (A) Before the buffet, lean participants rated their ability to admit the desire for food as better than their ability to reappraise the same food ($p < 0.0001$). After eating to satiety, this effect reversed: the ability to reappraise food is easier as compared to allowing the desire for the same foods ($p < 0.019$). Also sated obese participants rated their ability to regulate the desire for food as better than allowing it ($p < 0.019$). The whiskers index the standard errors and significance is marked with asterisks. (B) Before the buffet, lean participants rated their ability to admit the desire for food as better than their ability to reappraise food, irrespectively of whether this was high ($p < 0.001$) or low caloric ($p < 0.001$). Obese women also rated their ability to admit the desire for low calorie foods as easier than to reappraise it ($p < 0.0017$). For high calorie foods, however, they unexpectedly rated their performance equally well ($p > 0.03$); an effect that is well in line with previous findings (Kumar et al., 2016) (Since only one-fourth of trials were used for this analysis p value was set to 0.0125). The whiskers index the standard errors and the significance is marked with asterisks.

Figure 3. Task-based EEG results comparing the pre-buffet EEG session to the post-buffet EEG session. (A) Only in obese women, did we find increased neuronal activity in the right frontal operculum after eating to satiety (red cluster, family-wise-error (FWE)-corrected, $p<0.006$). "z" indicates the MNI coordinates (mm) of the axial brain slices. "R" indicates the right and "L" the left brain hemisphere. (B) Bar plot shows the estimated marginal means for the "REGULATE" and the "ADMIT" condition in the right frontal operculum for obese women prior to the buffet and after the buffet. We found an increased activity in the frontal operculum after the buffet for both, the "REGULATE" ($p < 0.027$) and the "ADMIT" condition ($p < 0.045$). There was no

523 difference between REGULATE and ADMIT, neither prior to the buffet (p > 0.549), nor
524 thereafter (p > 0.164). The bars represent mean values and whiskers index standard errors.
525 Significance is marked with asterisks.

526

527 Figure 4. Calorie consumption in the buffet between the two EEG sessions. Obese as compared
528 to lean women did not show any significant differences in calorie consumption. Surprisingly,
529 lean women even showed a trend towards higher calorie consumption as compared to obese
530 women (p>0.108). We also found no differences between obese and lean women for the different
531 food categories (high calorie sweet food: p>0.066, high calorie salty food: p>0.068, low calorie
532 sweet food: p>0.196, low caloric salty food: p>0.461). Both lean and obese women showed a
533 tendency for preferring salty over sweet food (lean: p>0.197; obese: p>0.139). Both groups also
534 preferred high calorie over low calorie food (sweet foods: lean: p<0.0001, obese: p<0.0001; salty
535 foods: lean: p<0.0001, obese: p<0.0001). The bars represent the mean and whiskers index
536 standard errors. Significance is marked with asterisks.

537

538 Table 1: Mean and standard deviation for age and BMI of lean and obese women.

N/subgroup	Age range (mean) [years] +/- (standard deviation)	BMI range (mean) [kg/m^2] +/- (standard deviation)
10 lean females	22 - 30 (25.56) +/- (2.88)	20.06 - 24.91 (23.10) +/- (1.63)
10 obese females	21 - 34 (26.75) +/- (2.81)	30.49 - 47.88 (35.97) +/- (6.54)

539

540

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686

Figure 1.JPEG
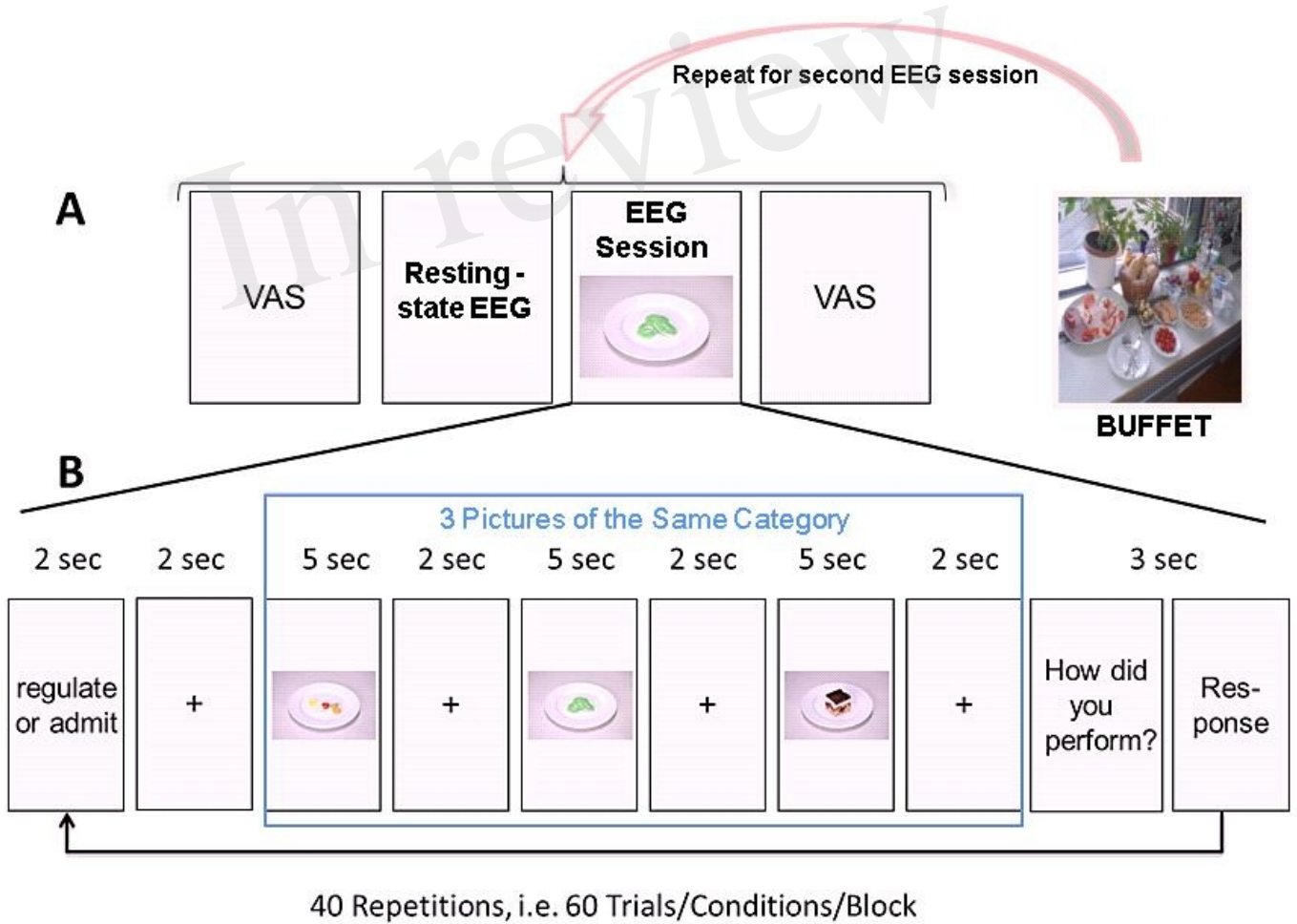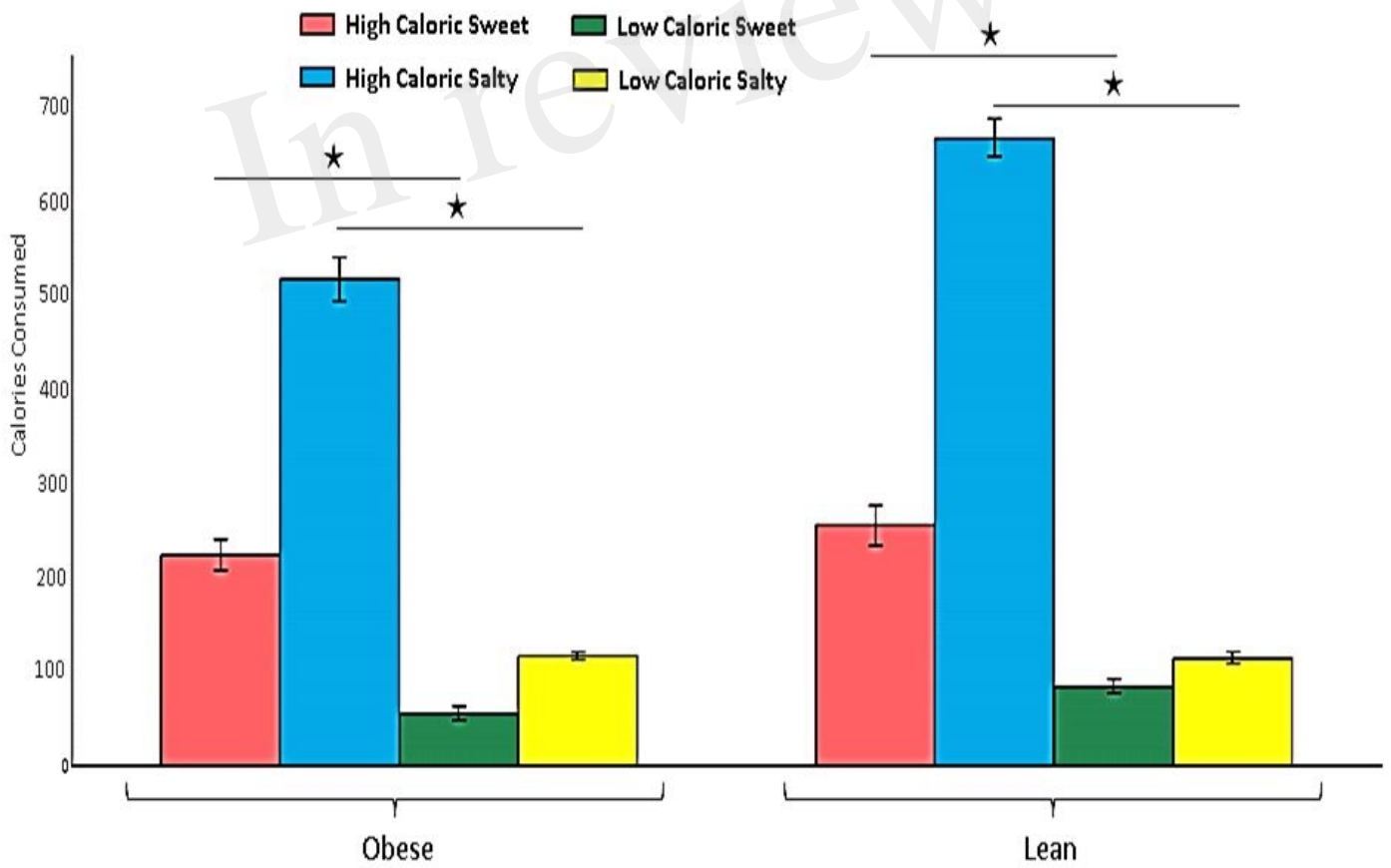
Figure 2.JPEG
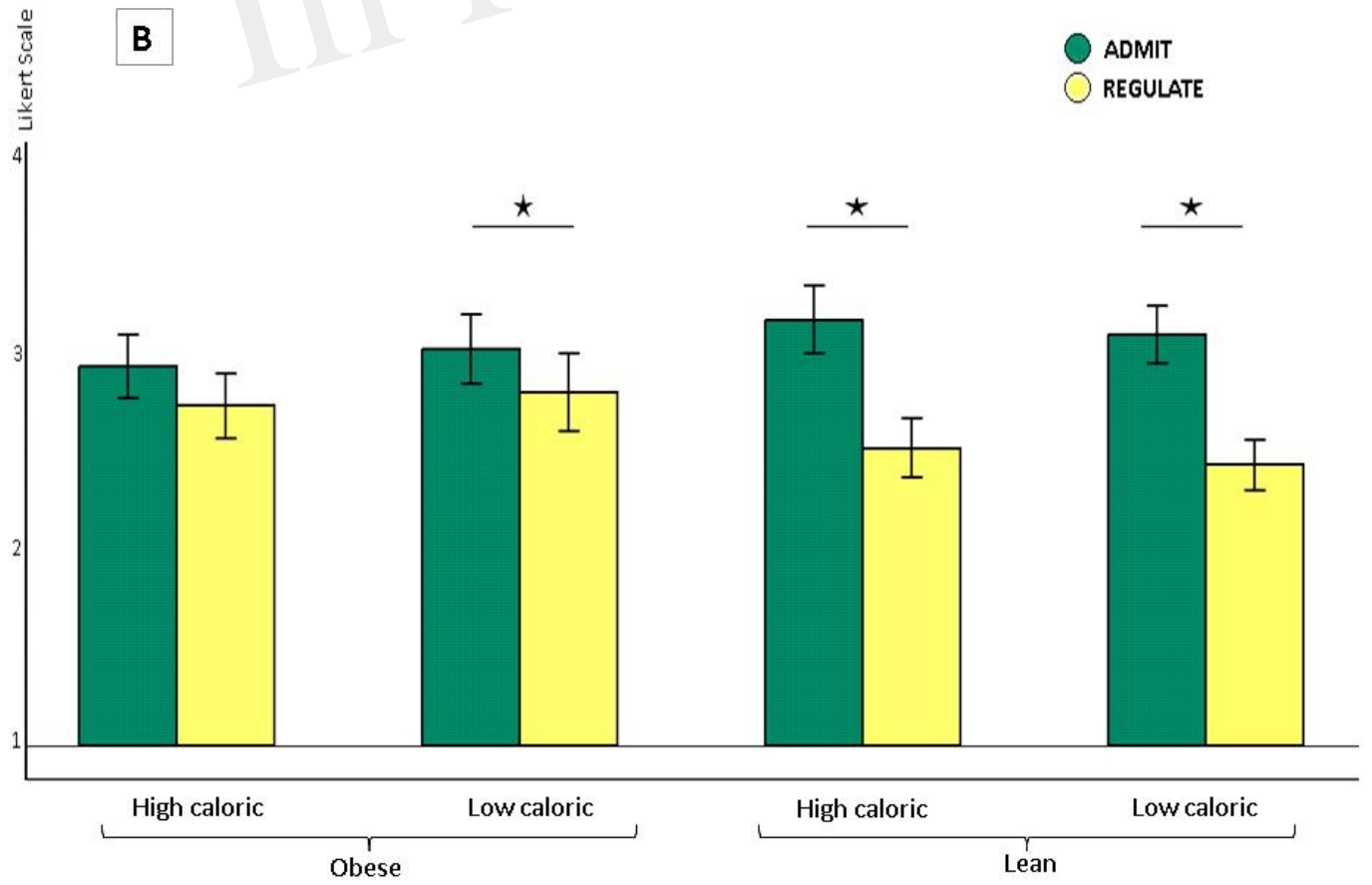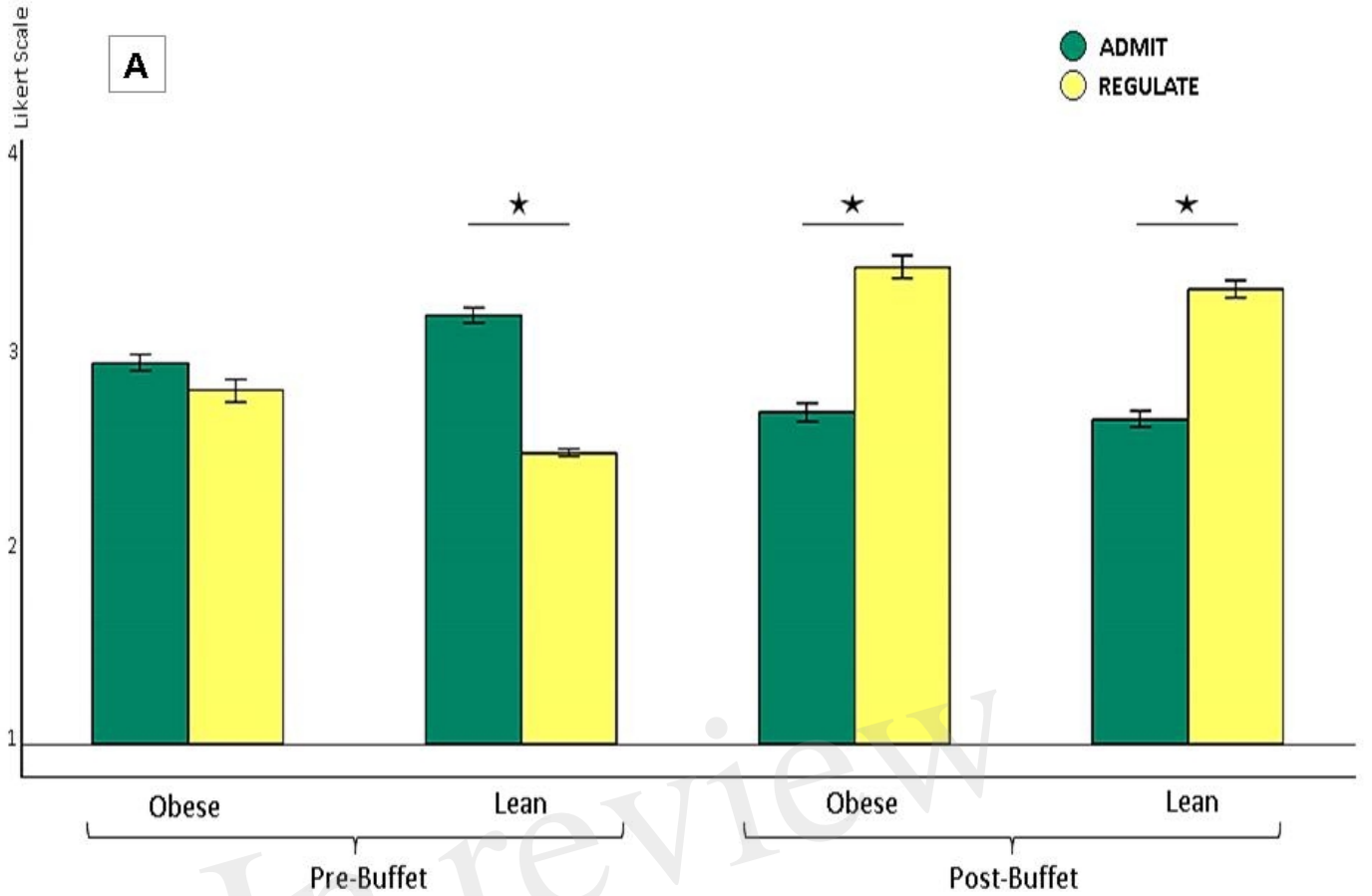
Figure 3.JPEG
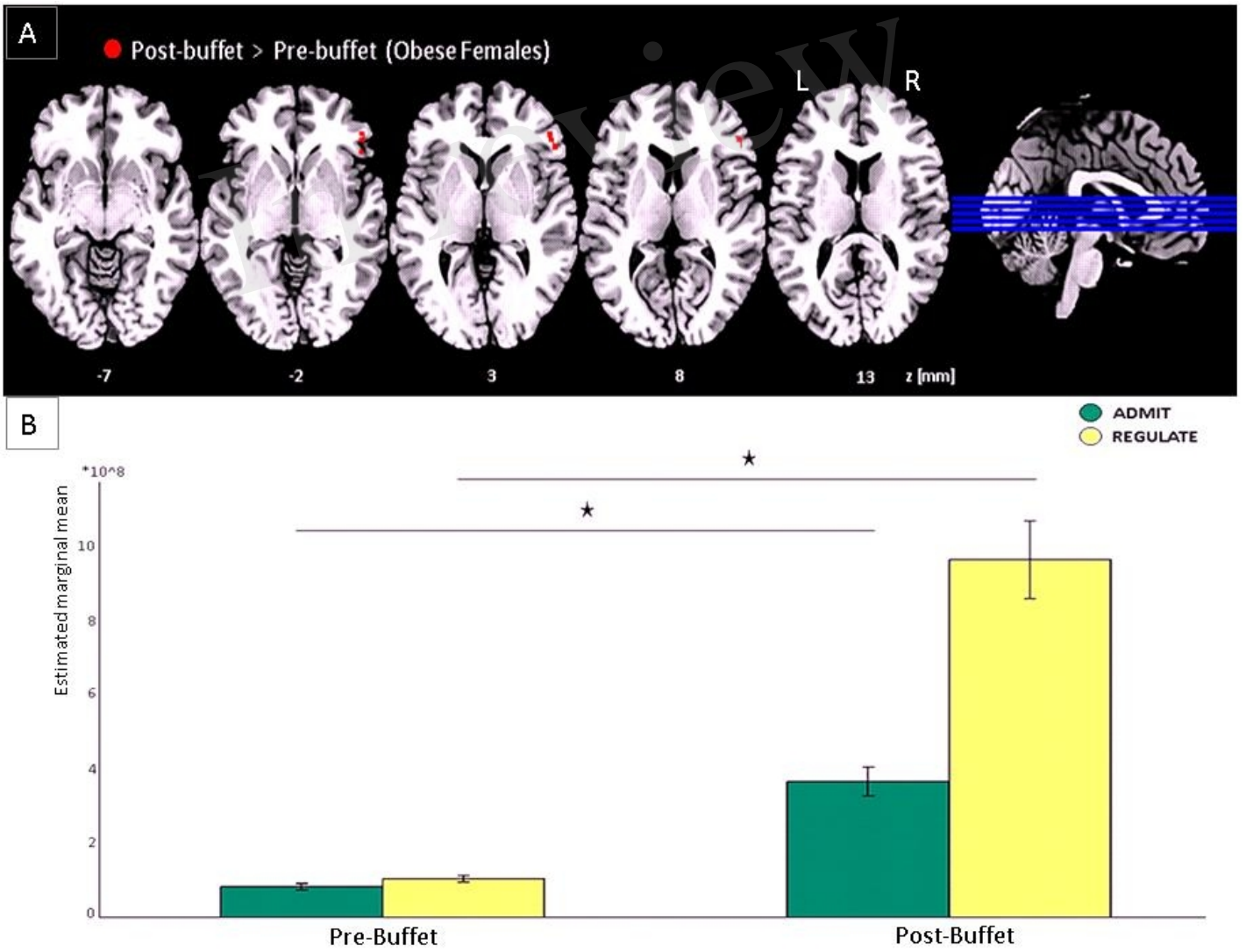
Figure 4.JPEG

Chapter 4

Discussion and outlook

4.1 Discussion

The experimental findings and the related understanding have been already discussed in the related publications attached in chapter 3. Here, I will be concentrating more on the general findings and general issues that have arisen through the course of this research project.

This thesis work is a combination of two studies and aims to add more knowledge in understanding the mechanisms of obesity. We hypothesized that participants irrespective of whether obese or lean will show activation in the DLPFC while admitting their food desire. We confirmed this hypothesis for the left DLPFC (see publication 1 in section 3.1). We also expected to find an activation in the DLPFC during the reappraisal of food desire. In contrast we saw activation in the contralateral right hemisphere, and more specifically in the right frontal operculum. The activation of both regions was independent of the food calorie content. In line with our expectation, we observed an interaction between the calorie content (high/low caloric food) and regulation of food desire (admit/reappraise food). We found this interaction in the anterior insular cortex of both hemispheres; not in the DLPFC. We moreover found this effect only for lean individuals. We saw that during admitting the food desire the bilateral anterior insular cortex responded with high activity for high calorie food and low activity for low calorie food. When the task was reversed, i.e. during the reappraisal of food, there was an inverse pattern: low activity for high calorie food and high activity for low calorie food.

In a recent fMRI study (Hollmann et al., 2012) (lean and overweight participants) which included a similar experimental procedure, it was found that the reappraisal of food desire activated bilateral frontal operculum. This is in line with our findings (in lean and obese participants together). Different BMI ranges seem associated to differentially lateralized brain mechanisms underpinning the reappraisal of food. The anterior insula is associated with a role in viscerosensory (Oppenheimer et al., 1992) and interoceptive perception (Craig, 2009). It has been shown that the anterior insula along with the frontal operculum form the primary gustatory cortex (Rolls et al., 1988; Zatorre et al., 1992; Small et al., 1999). In rats its shown that the insular cortex regulates food choices even in the absence of peripheral taste inputs (Oliveira-Maia et al., 2012). This could also suggest that the anterior insula in humans contributes to higher cognitive process such as the ability of food imagery and taste. The participants were asked to fast for at least five hours before the commencement of the study to increase cognitive demand to the food pictures. We found that both the obese and lean found it easier to admit their food desire than to regulate it. This could as well be because the hedonic feeling of wanting and liking food is easier to allow then its reappraisal. It is interesting to note that the obese rated their performance to reappraise food as equally good as to admit the food desire, while lean rated their performance better for admitting food desire as expected. This may suggest an impaired self-reflection of food reappraisal abilities in obese.

The second study was a continuation of the first and the primary difference was the structure of the experimental procedure. The study included a real buffet which was presented to the participants (only females) between two equally designed EEG sessions (see publication 2 in section 3.2). For the buffet the participants were told to eat to satiety and a questionnaire (Visual analog scale (VAS)) helped us to track levels of satedness and hungriness. Confirming our hypothesis we found that it was easier to allow food desire before the buffet and it was easier to reappraise the same food desire after being sated. Post-hoc tests revealed that obese women rated their performance regarding the reappraisal of food to be equally good as the admission of food desire. This is in accord with our findings from

the first study. In obese women we saw a positive correlation between the calorie consumption and the changes in their hunger ratings suggesting more sensitivity in reflecting hunger with respect to the calorie demand. We confirmed our hypothesis that after eating to satiety there is higher activation in the right frontal operculum indicating elevated reappraisal abilities. Contrary to our hypothesis we did not find any activation difference in the left DLPFC but instead in the right frontal operculum. This is surprising as the right frontal operculum was expected to be only involved during the reappraisal of food desire but not during the admission of food desire when sated. We confirmed the effects with and without the performance ratings as an interacting covariate. The elevated activation in the right frontal operculum in the obese may point to an elevated cognitive effort for regulating food desire when being sated.

4.1.1 Limitations

Looking at the number of participants over the two studies over the course of this research project we in general had a total of sixty participants and none of the participants were part of both the studies. In the first study there were forty participants that formed the cohort and were included in the analysis. They were divided into four groups (based on gender and BMI ranges) as a part of our study design which led to a relatively small number of participants for more specific results. A large number of participants could result in more robust insight. Observing gender differences in our preliminary results of the first study (Kumar et al., 2016) we saw that the obese female were more prominent to show significant results probably due to their known higher sensitivity towards food. We had a group of twenty female only participants in the second study which also involved a real buffet along with the visual picture presentation. The visual picture presentation was common in both the studies. We also made sure that in both the studies there was no overlap of any participant and hence no related bias can be expected. Another aspect of the EEG task was the total duration, as it was important to keep the task short and interesting offering a large variety of different food. This enabled the participants to be concentrated throughout the EEG

recording. Another limitation was the subjective assessment of mental strategies. Ideally we would want an efficient control of participants' strategies regarding the regulation of food desire. We could have suggested certain strategies, but we allowed each participant to decided on which strategy to use to support optimal performance. We also had no measure of the co-operative level of the participants regarding the fasting times before our experiments.

4.2 Outlook and further work

It has been shown during the course of this research project (the two studies included) that the left DLPFC region in obese and lean participants is involved in the admission of food desire. The right frontal operculum in obese women is associated with the regulation of food desire. It interacts with other regions of the brain like the anterior insular cortex (Kumar et al., 2016). Based on these findings we investigated the effect of tDCS over the left DLPFC and the right frontal operculum in obese women. We investigated tDCS effects on the active reappraisal of visually presented high/low calorie food and also their consumption. This study included the largest human obese sample size so far in the given context and is the first study conducted in a double-blinded, fully randomized, within-subject and placebo-controlled design. Most of the studies done so far were restricted to lean and overweight participants but our study included obese females only. Previous studies suggest that repetitive application of anodal prefrontal tDCS to the left DLPFC decreases calorie intake (Gluck et al., 2015) and reduces craving for food after anodal simulation applied to the right DLPFC (Ljubisavljevic et al., 2016). We instead used a single session tDCS of twenty minutes and our findings suggest that this single tDCS session is not effective to modulate reappraisal strategies as well as calorie intake in obese females. Our null findings are hard to interpret because the effects may become significant with a larger sample size or repetitive tDCS sessions. We however suggest that further investigation is required to identify a method that effectively modulates brain activity.

Other ways of non-invasive brain simulation (e.g., TMS) or neuro-feedback may target these regions (left DLPFC and right frontal operculum) . In an other study we are looking beyond the localized sources and searching for differences at the sensor level (in the ERP), mainly concentrating on the statistical significant difference between the obese/lean and between the admit/regulate condition. We want to classify these differences and use them specifically for neurofeed-back training. Our project hopefully offers basic knowledge for future interventional studies.

Chapter 5

Summary

5.1 English Summary

Obesity is a world epidemic resulting from unhealthy lifestyle choices and other socio-economic factors. It leads to lower quality of life and occurs together with many other major diseases like type 2 diabetes, cardiovascular diseases, hypertension and many others. It is of utmost importance to support research for its cure and prevention. Previous intervention studies mainly focused on dieting and exercising (Soeliman and Azadbakht, 2014; Jakicic and Davis, 2011; Amorim Adegboye and Linne, 2013), but it has been shown that as soon as the treatment is over participants started gaining weight (Summerbell et al., 2005; Ammerman et al., 2002; Contento et al., 1995). A recent fMRI study investigated brain mechanisms underpinning the admittance and reappraisal of food desire (Hollmann et al., 2012). Building on that knowledge, in this research project we used EEG due to its advantage of portability, simplicity and excellent temporal resolution. It located the brain regions that are involved in the decision making process that facilitates the consumption of presented food. The far reaching goal was to identify brain sites that serve as targets for future non-invasive brain stimulation or neurofeedback training.

This research project combines two related studies. In the first study we recruited forty participants - half obese, and half lean, based on their BMI. Both groups consisted of equally distributed males and females to better represent general population. All the participants were presented pictures of food on a computer screen and their task was to either admit their desire for the presented food or reappraise

the food. The participants were free to choose any strategy in their mind in order to do the task as efficiently as they could. We reported these strategies in the first publication (Kumar et al., 2016). While the participants were doing the task we recorded EEG. Participants were seated comfortably in an isolated room with no distractions but only the task to concentrate on. After each picture presentation participants were asked to rate their performance. We used these performance ratings for informing our analysis of the recorded EEG data. For the EEG analysis we simulated a human head using the standard BEM modeling. We identified and removed the artifacts that spoil the brain activity measurements such as eye blinks and body movements. For this various methods were compared including the ICA algorithm and the regression technique. Due to the speed of the regression technique and equal performance with the ICA algorithm we used the regression as the basis for the artifact correction which we used in both the studies of this project work. The head model created was incorporated with the standard MRI to better understand the obtained results regarding their origin within the brain. We also used the participants' performance as a covariate to inform EEG analyses by participants' confidence on given trials. In first study (publication 1 in section 3.1) we identified the left DLPFC involved in processes underpinning the admittance of the desire for food and the right frontal operculum in the reappraisal of the same food regardless whether the participants were obese or lean. We also found evidences that obese may have a impaired self-reflection when it comes to resisting visually presented foods.

Based on the results of the first study we were motivated to extend this even further. For the second study we enrolled twenty females out of which half were obese and half lean. We took only females for this study because during the analysis of the first study we found that females tend to be more sensitive towards food cues (Horstmann et al., 2011; Mueller et al., 2011; Melasch et al., 2016; Kumar et al., 2016). For the second study (publication 2 in section 3.2) we measured the participants once with the same task that was used in the first one. In the second study, participants were offered a real food buffet to assess calorie consumption. We also asseseed their psychological state (VAS ratings, please refer the publications in section 3.1 and section 3.2). Post buffet after eating to satiety, participants

were enrolled in the same food picture task as prior to the buffet. We aimed at investigating how eating to satiety affects food reappraisal abilities in lean and obese females and if there exists a difference between them. The EEG techniques used in this second study is comparable to the first one with the only difference that the second study involved two sessions divided by a buffet. In the second study we also found that the obese seem to have an impaired self-reflection of their abilities to reappraise food when hungry. EEG recordings revealed elevated activation in the right frontal operculum during the reappraisal of food: a replication of our findings in the first EEG study. We found a significant higher activation in the frontal operculum post buffet (sated state) comparing to the pre buffet (hungry state) for obese females during reappraisal of food desire. We saw a similar increase in the activation in the obese females in the same region while admitting the food desire. This came as a surprise because we expected to see this effect in the left DLPFC. The right frontal operculum in obese women is involved in evaluation processes underpinning the regulation of food desire after eating to satiety. We also indicated that the more obese women ate, the more their hunger declined, suggesting that obese women are probably more sensitive in reflecting hunger with respect to calorie demand.

This research project as a whole did add more knowledge to the understanding of the mechanisms underpinning the admittance and reappraisal of food in obese and lean individuals. The present findings add to the understanding of complex processes underpinning food choices in the obese brain. More research needs to be done but this project serves as a basis on which further interventions, such as non-invasive brain simulation or neurofeedback can be based.

5.2   German Summary

Adipositas ist eine weltweite Epidemie, die aus einem ungesunden Lebensstil und anderen sozio-ökonomischen Faktoren resultiert. Sie wirkt sich negativ auf die Lebensqualität aus und tritt häufig zusammen mit Erkankungen wie Typ 2 Diabetes, Bluthochdruck, kardiovaskulären und anderen Erkrankungen auf. Daher ist es von großer Wichtigkeit, Forschung zur Heilung und Prävention von Adipositas

zu fördern. Frühere Interventionsstudien fokussierten hauptsächlich auf Ernährung und körperliche Betätigung (Soeliman and Azadbakht, 2014; Jakicic and Davis, 2011; Amorim Adegboye and Linne, 2013). Die Effekte waren aber nur kurzfristig und die Teilnehmer nahmen nach Ende der Intervention wieder an Gewicht zu (Summerbell et al., 2005; Ammerman et al., 2002; Contento et al., 1995). Eine fMRI-Studie untersuchte die Gehirnprozesse, die dem Zulassen oder der Neubewertung des Verlangens nach Essen zugrunde liegen (Hollmann et al., 2012). Basierend auf den Erkenntnissen dieser Studie verwendete das vorliegende Forschungsprojekt die EEG-Methodik, um die Gehirnregionen zu lokalisieren, welche in den Entscheidungsprozess zur Nahrungsaufnahme bzw. -nichtaufnahme präsentierter Nahrung eingebunden sind. Das weitreichende Ziel dieser Studie war es, Gehirnregionen zu identifizieren, die als Target für zukünftige nicht-invasive Hirnstimulation oder Neurofeedback Training geeignet sind.

Dieses Forschungsprojekt kombiniert zwei zusammenhängende Studien. An der ersten Studie nahmen vierzig Personen teil, die aufgrund ihres BMIs zu einer der beiden Gruppen – adipös oder normalgewichtig – zugeordnet werden konnten. In beiden Gruppen war das Geschlechterverhältnis ausgeglichen, um die Allgemein - bevölkerung besser repräsentieren zu können. Allen TeilnehmerInnen wurden Bilder von verschiedenen Nahrungsmitteln auf einem Computerbildschirm präsentiert. Die Aufgabe der TeilnehmerInnen war es, ihr jeweiliges Verlangen anch den präsentierten Nahrungsmitteln zuzulassen beziehungsweise neuzubewerten. Daber waren die TeilnehmnerInnen frei darin eine geeignete mentale Stragetie zu wählen, um die Aufgabe so effektiv wie möglich zu bewältigen. Die gewählten Strategien berichten wir in der ersten Publikation (section 3.1). Während der Aufgabe wurden EEG-Aufzeichnungen gemacht. Während des Experiments saßen die TeilnehmerInnen in einem bequemen Stuhl in einem schall-isolierten Raum ohne Ablenkungen.

Nach der Präsentation jedes einzelnen Bildes wurden die Teilnehmer Innen gebeten Ihre Leistung zu bewerten. Wir verwendeten diese Bewertungen bei der späteren Auswertung der EEG Daten. Für die EEG Analyse simulierten wir einen menschlichen Kopf anhand von standard BEM modeling. Artifakte, wie z.B. Wimpernschlag oder

Körperbewegungen, wurden vor der Analyse identifiziert und eliminiert. Im Rahmen dessen verglichen wir verschiedene Methoden, wie ICA Algorithmus oder Regressionstechnik. Aufgrund der höheren Geschwindigkeit bei vergleichbarer Leistung, verwendeten wir die Regression als Basis für Artefaktkorrekturen in beiden Studien. Das Modell des Kopfes wurde in ein Standard MRI inkorporiert, um ein besseres Verständnis der erhaltenen Ergebnisse hinsichtlich ihres Ursprungs im Gehirn zu ermöglichen. Des Weiteren inkludierten wird die Leistungsbewertungen durch die TeilnehmerInnen als Kovariate in unserer EEG Analyse, um Informationen über die Selbsteinschätzung der Proband Innen in den jeweiligen Durchläufen einbeziehen zu können. In der ersten Studie (section 3.1) identifizierten wir den DLPFC als Region, die beim Zulassen des Verlangens nach Nahrung beteiligt ist, während das rechte frontale Operculum für die Neubewertung derselben Nahrung in adipösen wie normalgewichtigen Proband Innen involviert zu sein scheint. Des Weiteren fanden wir Hinweise darauf, dass adipöse Teilnehmer Innen eine beeinträchtigte Selbstreflexion hinsichtlich ihrer Fähigkeit visuell präsentierten Nahrungsmitteln zu wiederstehen aufweisen. Basierend auf den Resulaten der ersten Studie, waren wir motiviert eine zweite Studie zu entwickeln. In dieser nahmen zwanzig Frauen (10 adipös, 10 normalgewichtig) teil. Der Grund für die Aufnahme von ausschließlich Frauen in unsere Studie war ihre tendenziell höhere Sensitivität für Nahrungsreize im Vergleich zu männlichen Probanden in der ersten Studie (section 3.1). In der zweiten Studie (section 3.2) wurden die EEGs der Teilnehmerinnen aufgezeichnet, während sie dieselbe Aufgabe erfüllten, die in der ersten Studie beschrieben wurde. Danach wurde den Probandinnen ein Buffet angeboten, um die Kalorienzufuhr einzuschätzen. Darüberhinaus wurde der psychologische Status der Probandinnen abgefragt (section 3.1 und section 3.2). Nachdem die Teilnehmerinnen bis zur Sättigung gegessen hatten, durchliefen sie nochmals die Aufgabe mit den Abbildungen von Nahrungsmitteln wie vor dem Buffet.

Unser Ziel war es zu untersuchen, wie Nahrungsaufnahme bis zur Sättigung die Fähigkeit zur Neubewertung von Nahrungsmitteln in adipösen und normalgewichtigen Frauen beeinflusst und ob dabei Unterschiede zwischen den zwei Gruppen bestehen. Die EEG - Techniken der zweiten Studie sind vergleichbar mit denen der ersten Studie,

mit dem Unterschied, dass in der zweiten Studie zwei EEG - Aufzeichnungen durch ein Buffet voneinander getrennt waren. In Übereinstimmung mit den Ergebnissen der ersten Studie zeigten adipöse Probandinnen eine beeinträchtigte Selbsteinschätzung in ihrer Fähigkeit Nahrungsmittel neuzubewerten während sie hungrig waren. In der zweiten Studie konnten wir eine Aktivierung des rechten frontalen Operculums während der Neubewertungsaufgaben replizieren. Wir fanden außerdem eine signifikant höhere Aktivierung des frontalen Operculum in adipösen Teilnehmerinnen nach dem Buffet (im gesättigten Zustand) als vor dem Buffet (hungriger Zustand) während der Neubewertungsaufgabe. Wir beobachteten einen ähnlichen Aktivierungsanstieg in derselben Region in adipösen Proband innen während des Zulassens des Verlangens nach Nahrung. Dieses Ergebnis war überraschend, da wir diesen Effekt im linken DLPFC erwarteten. Das rechte frontale Operculum scheint in adipösen Frauen in den Evaluationsprozess, der mit der Regulation der Bedürfnisses zu Essen nach Sättigung zusammenhängt, eingebunden zu sein. Wir konnten auch zeigen, dass adipöse Teilnehmerinnen mit zunehmender Nahrungsaufnahme geringeren Hunger berichteten. Wir fanden außerdem, dass adipöse Frauen mit zunehmender Nahrungsaufnahme geringeren Hunger berichteten. Dies weißt darauf hin, dass adipöse Frauen möglicherweise sensitiver in der Einschätzung ihres Hungers im Zusammenhang mit ihrem Kalorienbedarf sind.

Dieses Forschungsprojekt hat zu einem besseren Verständnis der Mechanismen beigetragen, die beim Zulassen oder Neubewerten von Nahrungmitteln in adipösen und normalgewichtigen Individuen eine Rolle spielen. Die vorliegenden Ergebnisse helfen dabei, die komplexen Prozesse, die bei der Wahl von Nahrungsmitteln im adipösen Gehirn von Bedeutung sind, besser zu verstehen. Mehr Forschung ist nötig, um noch tiefere Einblicke in diese Prozesse zu bekommen. Dieses Projekt kann aber als Ausgangspunkt für zukünftige Interventionen mit Methoden wie z.B. nicht-invasiver Hirnstimulation oder Neurofeedback dienen.

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Bestätigung des wissenschaftlichen Beitrags durch die mitautoren

Confirmation of scientific work by coauthors

Conception and design of the studies: SK, JM, BP

Acquisition of data: FG, CB

Analysis and/or interpretation of data: SK, HJH, FG, CB, JM, BP

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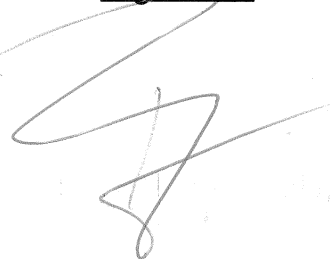
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Dr. Burkhard Pleger (BP)	2017-01-16	

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

....

Datum   Unterschrift

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"Make the change that you want to see in the world."

Experience

Max Planck Institute for Human Cognitive and Brain Sciences   *Leipzig, Germany*

RESEARCH ASSISTANT - (DOCTORAL WORK - PHD)   *Apr. 2014 - Exp. Feb. 2017*

- Working on project in order to develop a therapeutic treatment for obesity, and in turn progressing on my doctorate. The project revolves around the idea of finding the sources in the brain for a given task and then finding the differences in various groups of people and learn about the executive decision making capabilities of the human brain. The approach is through signal processing algorithms with the help of tools like MATLAB and various toolboxes. Its titled as 'EEG study on the differences between lean and obese individuals during regulation of food desire'.

University Clinic Kiel & Kiel University   *Kiel, Germany*

MASTER THESIS - STUDENT RESEARCHER (COMPUTATIONAL NEUROLOGY)   *Oct. 2013 - Mar. 2014*

- The project involved simulating a human brain in the very basic form and then inside simulating the different sources in the form of dipoles and then develop an algorithm in order to locate these sources. The basic idea is to develop a new method that is based on the phase differences of the different channel measurements that are obtained using an EEG. This research will help in the advancement of the very ill-posed problem of source localization of the human brain.

European Aeronautics Defence and Space Company - Eurocopter (presently AIRBUS Helicopters)   *Munich & Donauwörth, Germany*

INTERN, RESEARCHER (HEALTH USAGE MONITORING SYSTEMS (HUMS))   *Feb. 2013 - Aug. 2013*

- Health Usage Monitoring Systems (HUMS) During the flight of the Helicopter there is a lot of vibration inside the machine and the gearbox. The vibrations can eventually lead to wear and tear of the gears and shafts and hence failures that can result in accidents. Taking advantage of these vibrations it can be predicted in the future whether any part inside the gearbox will fail or not. I was responsible to simulate this gearbox and then also simulate the wear and tear due to the many flight hours and find out the effect that can have in the frequency and time domain, and to identify the better method to use, for this the method of 'Time Synchronous Averaging' was implemented, and this signal processing technique was to be studied with its different variants.

University Clinic Kiel   *Kiel, Germany*

STUDENT RESEARCHER (COMPUTATIONAL NEUROLOGY)   *Jul. 2012 - Jan. 2013*

- One way to do the source analysis from the EEG signal measurements is to use the Kalman Filtering and optimizations, the code is in the MATLAB and because of the importance of speed in this task, the requirement was to transfer the code on the GPU. So I was responsible to transfer the code on the GPU from Nvidia using the CUDA C. So the task is to set up the environment for the CUDA C and MATLAB to work in synchronization. Then to split the loops that are responsible to the long delay of the code into parallel and run them on the GPU.

European Aeronautics Defence and Space Company - Astrium (presently AIRBUS Defence and Space)   *Friedrichshafen, Germany*

INTERN, SOFTWARE DEVELOPER (SPACE TRANSPORTATION)   *Oct. 2011 - May. 2012*

- Project RUBY: The scientists are looking for answers regarding the formation of the bubble in micro gravity.There are thousands of images and they are not in order from the recent experiment of the project. Image processing is to be done on each image to order them and see for any missing ones.
- Project FOAM:There is a need by the food industry to study the formation and structure of foam in micro gravity and hence the ESA (European Space Agency) wants to do an experiment on the Columbus module in the ISS (International Space Station). For this the prototype was to be tested on the parabolic flight campaign to check its feasibility. I was responsible to create a software to operate the correlators and the cameras and also the motors in the experiment box. The article of this experiment can be found at this link : http://www.esa.int/Our_Activities/Human_Spaceflight/Space_for_dessert

Education

Technical Faculty (Christian Albrechts University)   *Kiel, Germany*

M.Sc. in Digital Communications   *Oct. 2010 - Mar. 2014*

- Main focus on digital signal processing and encryption

UVP College of Engineering and Technology (Ganpat University)   *Mehsana, India*

B.Tech. in Electronics And Communications Engineering   *Jul. 2006 - Jun. 2010*

- Main focus on the coding and the technological basics in the computer, electronics and the communications field

AJ International School (ISC Cambridge University)   *Bhavnagar, India*

High.school in Science Field   *Jul. 2002 - Jun. 2006*

- Main focus on Science and mathematics

Extracurricular Activity

- Presenting team member in Girls day (encouraging women into science) in 2015 at Max Plank Institute, Leipzig.
- IEEE member active since 2008
- AIESEC member (past) - largest student organization for internships and international experience

Honors & Awards

Gold medal, Macmillan exams for Mathematics (India region)   *Australia*

Gold medal, Macmillian exams for English (India region)   *Australia*

2nd Place, Technical college festival paper presentation   *India*

4th Place, National level debate competition   *India*

Publications

Differences in neuronal pre-frontal responses during reappraisal of food in lean and obese humans

Frontiers in Human Neuroscience

Publication

http://dx.doi.org/10.3389/fnhum.2016.00233

- Current research dealing with the obesity based on the EEG, signal processing based on food pictures

Satiety-induced enhanced neuronal activity in the frontal operculum relates to the desire for food in the obese female brain

Frontiers in Neuroenergetics and Brain Health

Publication   *In review*

- Current research dealing with the obesity based on the EEG, signal processing, extension of the previous knowledge with a real food buffet

Non-invasive prefrontal/frontal brain stimulation is not effective in modulating food reappraisal abilities or calorie consumption in obese females

Frontiers in Human Neuroscience

Publication   *Submitted February*

- Current research dealing tDCS and its effectiveness

Presentation

International Society of Applied Neurosciences (SAN) 2016 conference   *Corfu, Greece*

Presented in October 2016

http://dx.doi.org/10.3389/conf.fnhum.2016.220.00048

- Differences in neuronal pre-frontal responses during reappraisal of food in lean and obese humans

39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society   *Jeju Island, Korea*

July 11-15, 2017

- Establishing and validating a new source analysis method using phase

Skills & Expertise

Matlab,

C,

Labview,

CUDA - parallel programming,

Signal processing,

Image processing,

Data processing,

Statistics in research,   *End*

Publications

Title : Differences in neuronal pre-frontal responses during reappraisal of food in lean and obese humans
Journal : Frontiers in Human Neuroscience
http://dx.doi.org/10.3389/fnhum.2016.00233
• Current research dealing with the obesity based on the EEG, signal processing based on food pictures.

Title : Satiety-induced enhanced neuronal activity in the frontal operculum relates tothe desire for food in the obese female brain
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• Current research dealing with the obesity based on the EEG, signal processing, extension of the previous knowledge with a real food buffet.

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• Current research dealing tDCS and its effectiveness.

Presentations

Conference : International Society of Applied Neurosciences (SAN) 2016
conference Corfu, Greece
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