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The brain's role in human obesity

Introduction

Obesity stands for extreme overweight, which is indicated by an amount of body fat that exceeds the normal range. According to the World Health Organisation (WHO), humans with a body mass index (BMI) over 30 kg/m^2 are defined as obese. Obesity may cause and promote the development of, e.g. cardiovascular diseases, high blood pressure, diabetes mellitus type 2 and, moreover, it increases the odds ratio of various forms of cancer or dementia. In a representative study from 2008–2011 they found out that almost 1/4 of all adult Germans are obese (male 23.3%, female 23.9%). A positive energy balance is the main cause for obesity, i.e. more energy is consumed than is expended, e.g. by physical exercise. However, the cause for the increase in obesity rates in industrialized cultures cannot be traced back exclusively to the changed environment which offers an excessive supply of high-energy food and does not necessarily promote physical activity. Individual differences in the development of body weight should not be underestimated. Thus, the interaction between individual behaviour and environmental changes might be a reason for obesity. In this context, it is important to investigate the role of our brain since it controls our behaviour. Do the brains of obese and lean people react differently to food stimuli in the environment? Do they interpret hunger differently? Are there main differences in brain regions that are responsible for the inhibitory control of behaviour?

Latest neuroscientific research focuses more and more on the exact role of our brain in the development and maintenance of obesity. In Leipzig, a group of neurobiologists, psychologists, medical and computer scientists are investigating this topic together as part of the Integrated Research and Treatment Center AdipositasDiseases (IFB AdipositasErkrankungen) in cooperation with the Department of Neurology at the Max Planck Institute for Cognitive and Brain Sciences (http://www.ifb-adipositas.de, http://www.sfb-1052.de). Amongst others, non-invasive neuroimaging methods such as magnetic resonance imaging (MRI) are used in order to observe human brain structure and function.

Homeostatic and hedonic system

The central nervous regulation of energy balance, i.e. the sum of consumed and expended energy, is a complex interplay of various factors. Basically, two main systems can be described in the brain, which are interdependent: the homeostatic system is regulated by the hormone level rather unconsciously. Hormones which are produced e.g. in the digestive organs or the fat tissue send information via the hypothalamus to the brain and, hence, modulate its activity in different regions and networks in order to start or respectively end ingestion. The hormone leptin for instance is able to directly modify the activity of the reward system in our brain.

In the hedonic system food intake is controlled mostly by evaluating the sensory attributes of food or the consequences of its consumption. Both systems are evolutionary old systems and are not exclusive to humans. Considerable parts of the brain react to food, its sensory qualities, for example appearance, taste and odour, or even its associated stimuli (**Fig. 1**, [4]). Thereby, different brain regions adopt varied functions (**Tab. 1**): the sensory cortices such as the visual cortex in the occipital lobe, the gustatory one in the frontal operculum or the olfactory cortex in the posterior orbitofrontal cortex code modality-specific sensory characteristics. Whereas the orbitofrontal cortex mostly assumes the cross-modality subjective evaluation of food stimuli, the anterior insular cortex incorporates interoceptive signals with a subjective value of a stimulus and, thus, generates motivation. The reward system in the basal ganglia (nucleus accumbens, striatum) indicates the subjective reward value of the expected or actually consumed food. The amygdala presumably serves as saliency marker, which provides not only affective attributes to a certain stimulus but also manages the interconnection between eating behaviour and emotional conditions.

Eating is essential for every organism; as a matter of fact, it is often even more important than reproduction. Consequently, complex and extraordinarily effective mechanisms developed on the level of the brain to ensure sufficient energy intake. They ascertain that high-energy nutrition is preferred and, moreover, perceived as pleasant. From an evolutionary point of view, excessive food intake

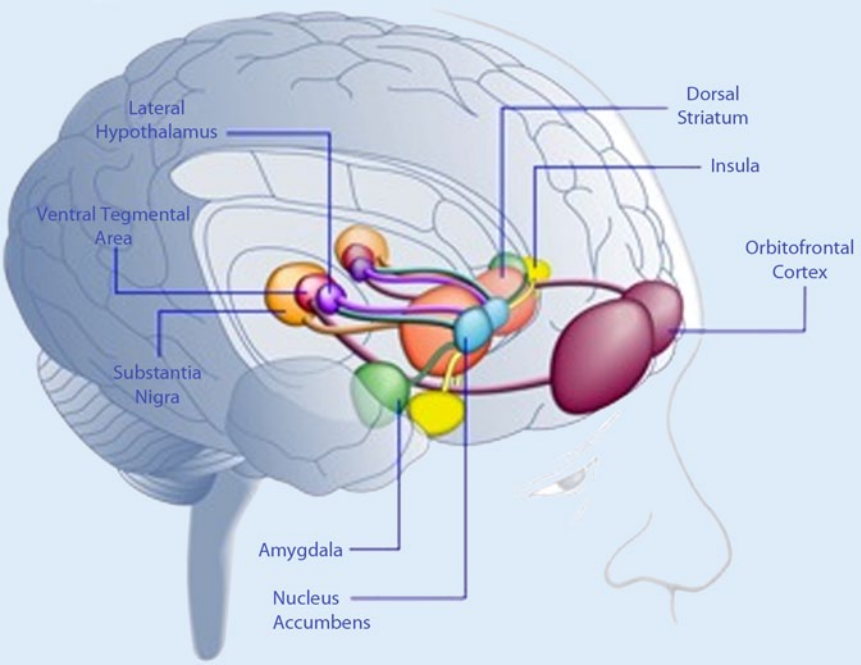

Fig. 1 ▲ Areas of the Human Brain Activated in Response to Palatable Food or Food-Associated Cues [4]. The orbitofrontal cortex and amygdala are thought to encode information related to the reward value of food. The insula processes information related to the taste of food and its hedonic valuation. The nucleus accumbens and dorsal striatum, which receive dopaminergic input from the ventral tegmental area and substantia nigra, regulate the motivational and incentive properties of food. The lateral hypothalamus may regulate rewarding responses to palatable food and drive food-seeking behaviours. These brain structures act in a concerted manner to regulate learning about the hedonic properties of food, shifting attention and effort toward obtaining food rewards and regulating the incentive value of environmental stimuli that predict availability of food rewards. For the sake of clarity, not all interconnections between these structures are shown. (Modified with kind permission from [4])

appears unperilous and is therefore not strictly regulated.

Function of food as natural reinforcer

Since food intake is of essential significance for the organism, a natural reinforcement system has developed in favour of consuming physiologically valuable food. We identify the taste of sugary or fatty food with high caloric density as agreeable and the reward system of our brain sends corresponding signals. Hence, the connection between the sensory and associative characteristics of the food product and expected reward will be intensified. This functionality is probably mediated largely by the neurotransmitter dopamine, which is as relevant in both subcortical and cortical structures.

For some people, in fact, this system risks an undesirable side effect: intensification proves to be too strong in some cases and addiction-like behaviour may follow. Analogous to addiction research, it is assumed that obese persons develop an insufficient reward response while consuming food, which they compensate by eating more. This hypothesis was tested and confirmed by several studies using functional magnetic resonance imaging (fMRI). Here, scientists provided evidence that the striatum, i.e. the reward system, of subjects with a higher BMI responded less to a palatable milk shake. This effect seems to be a consequence rather than the cause for obesity. By means of fMRI response in the striatum, an increase of weight could be predicted after 1 year: the lesser the response in the dorsal striatum, the more weight the subjects gained [9]. However, a correlation between risk and response in the reward system could not be discovered in a study population of subjects with a higher risk of obesity due to parental obesity.

Neuroscientific results

MRI provides different measures with which brain structure and function can be investigated. T1-weighted images are the basis for volumetric measurements such as voxel-based morphometry (VBM, a voxel is a three-dimensional pixel) where volume and density of the brain can be quantified and analysed for each compartment separately (grey matter, white matter, intracranial volume).

Some cross-sectional studies revealed that obese subjects consistently show less volume of the total brain in comparison to lean or overweight subjects. Additionally, white matter volume of obese compared to overweight subjects was decreased. In contrast to women, men were observed to show a negative correlation between BMI and the ratio of grey matter to the total intracranial volume.

Studies that investigated the relation of local structures of grey matter and obesity by means of VBM have not yet produced consistent results. This might originate in the vast variance of the age spectrum on the one hand and the varying percentage of women and men within the populations under study on the other.

Compared to lean participants, obese subjects displayed a significantly reduced density of grey matter in brain regions that play an important role in the regulation and perception of taste (gyrus postcentralis, frontal operculum), supporting the control of habitual behaviour (striatum, more precisely putamen) and the cognitive control of inhibitory behaviour (DLPFC). Another study revealed that a general atrophy of the frontal cortex, the anterior cingulum, the hippocampus as well as the thalamus could be observed in obese participants in comparison to lean subjects.

In recent years, several studies provided evidence that the gender of subjects is an important factor when investigating the relation between the brain and obesity. A Japanese study could not prove a reliable association between brain structure and obesity in women. Yet for male subjects, local grey matter volume of both hippocampi and the precuneus—regions that are responsible for encoding and retrieving memories—correlated negatively with the BMI. On the contrary, the vol-

ume of the inferior frontal gyri, the thalamus and the caudate nucleus interact positively with the BMI. The subjects were between 12 and 81 years old. Comorbidities of obesity such as diabetes type II occur more often the older the subjects are. Therefore, we investigated younger adults and their obesity-dependent changes of brain structure [2]. As measures of correlation for obesity we used BMI on the one hand and the level of leptin on the other. Leptin is a hormone that is secreted proportionally to the amount of body fat and, hence, is suitable as a good measure of fat percentage in body weight. In both genders structural changes were observed to be proportional to obesity markers in brain regions which code the individual value of food [nucleus accumbens, orbitofrontal cortex (OFC)] and in the hypothalamus that controls the energy balance of the body (**Fig. 2**, top). Both results might explain an eating behaviour where hedonically motivated food consumption exceeds the homeostatic benefit. However, the causal relation between these neuroscientific results and eating behaviour is still not clarified. In female subjects, we found in addition complementary obesity-dependent changes of the brain structure in the dorsal striatum (**Fig. 2**, bottom) and in the dorsolateral prefrontal cortex (DLPFC). These areas mediate habitual behaviour (striatum) on the one hand and goal-directed behaviour (DLPFC) on the other.

The relevance of these changes in the brain structure was proven by other studies lately: one study showed that a reduced volume in the dlPFC was associated with an increase in weight within 1 year. Another study gave evidence that people who were on a diet just then displayed a higher activity in these brain regions when they made decisions about the consumption of food [1]. This could mean that a reduced volume of brain regions which are involved in inhibitory cognitive control correlate with a perspective increase in weight.

Diffusion tensor imaging (DTI) measures the diffusivity of water molecules in brain tissues. It has proven extremely beneficial in observing the architecture and integrity of the brain's white matter. Due to the fact that cell membranes and the myelin sheath of the neurons form a natural barrier, the diffusivity orthogonal to the direction of the fibres (radial diffusivity) is lower than that along the fibres (axial diffusivity). The fractional anisotropy (FA) serves as an index which quantifies the imbalance between the different diffusivities and is a sensitive marker for changes in the microstructure of white matter.

In two independent cohorts, a similar negative correlation between BMI and diffusion parameters in the corpus callosum and particularly in the area of the splenium was observed [6, 8] which argues for a stable effect. Again, the gender of the subjects played a crucial role: one study showed that the effect on women was much larger than in men. In addition, there seems to be an interaction between the effects of obesity and aging processes on the microstructure of white matter: aging processes reinforce the observed obesity-dependent effects further.

A possible connection between the integrity of brain structure and obesity-typical metabolic disorders was suggested lately: adolescents with metabolic syndrome had smaller hippocampi, smaller total brain sizes and reduced microstructural integrity in the major fibre tracts of white matter, dependent on the severity of their syndrome. Voxel-based correlations between the participants' cholesterol profiles and the FA of their brains resulted in a negative dependence in both frontal cortices. That could mean that the results of the aforementioned studies might also be attributed to an abnormal cholesterol profile. The concentration of fibrinogen, an inflammatory marker, is normally increased in overweight and obese subjects in comparison to lean subjects with the same age and gender distribution. In correlating this with the volume of the grey matter, a negative relation between fibrinogen and the orbitofrontal cortex became apparent. In the same group of participants, a positive association between the concentration of fibrinogen and the diffusivity of grey matter of the amygdala and the parietal lobe was observed. These data support the interpretation that the neuroanatomical results may originate partly in obesity-related inflammation or metabolic abnormalities.

Abstract

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Abstract

The most common cause for obesity is a positive energy balance, i.e. more energy is being consumed than is expended. The rise in obesity rates cannot be explained on the basis of our obesogenic environment alone, because large interindividual differences in weight status exist between people. Therefore, the cause is most probably to be found in an interaction between individual behaviour and our changed environment. This warrants the investigation of the brain's role in the development and maintenance of obesity that indeed has become a growing field in the neurosciences. This article will give an overview about the findings in neuroimaging associated with human obesity. Further, this article will elucidate the relationship between common genetic variation, eating behaviour and brain structure in the context of obesity. Finally, important open questions in the field will be summarised.

Keywords

Obesity · Brain structure · Functional connectivity · Genetics · Reinforcement

The functional connectivity between several compartments of the brain is based on the relationship of their signal change across time. A set of regions that exhibit similar signal changes is defined as a functional network. Without external stimulation it is specified as a resting state network (RSN). The functional connectivity presumably reflects the coordination of activity of several neuronal subpopulations achieving a complex computation as an interconnected network. Differences in this measure have been observed between lean and obese subjects.

Functional connectivity of brain regions involved in the processing of food and reward stimuli were found to be sensitive to the peripheral hormone insulin: In the orbitofrontal cortex and the striatum the functional connectivity was negatively associated with the sensitivity for insulin [5]. This could indicate that hormonal signals are able to reduce food intake by directly modifying the intrinsic activity of the brain.

Tab. 1 Brain regions and their role in food perception and eating behaviour

Name	Brain region	System	Function in the context of eating
Amygdala	Mesiotemporal lobe	Limbic system	Behavioural salience, stress responses
Hippocampus			Memory, learning
Dorsolateral prefrontal cortex (DLPFC)	Frontal lobe		Goal-directed behavior
Frontal operculum			Primary gustatory cortex
Insula			Interoception, homeostasis, integration of sensory signals across modalities
Orbitofrontal cortex (OFC)			Valuation, secondary gustatory cortex
Ventromedial prefrontal cortex			Valuation
Fusiform gyrus	Occipital lobe		Visual association cortex
Hypothalamus	Diencephalon		Integration of homeostatic information from the body
Thalamus			Major sensory gateway
Nucleus accumbens (NAcc)	Ventral striatum	Basal ganglia (BG)	Reward prediction, conditioning
Nucleus caudatus	Dorsal striatum		Feedback processing
Putamen			Mediation of habitual behaviour
Substantia nigra (SN)	Midbrain		Control of BG circuit, dopamine supply
Ventral tegmental area (VTA)			Responds to novel stimuli, unexpected rewards, and reward predictive sensory cues
Posterior cingulate cortex (PCC)	Parietal lobe		Episodic memory

In comparison to women of normal weight, obese women show a reduced modulation of activity in the orbitofrontal cortex and in the reward system by the amygdala during the presentation of food pictures. In addition, modulation of activity in the reward system through the orbitofrontal cortex was increased. The reduced influence of the amygdala could lead to a suboptimal modulation of the affective aspects of food. Furthermore, obese subjects show increased functional connectivity between the putamen and the saliency network as well as between the nucleus caudatus and both the amygdala and the insula.

Taken together, the described differences between normal- and overweight subjects in brain structure and in the interaction between brain regions which are involved in the processing of affects, the computation of the motivational value of stimuli, memory formation an inhibitory control of behaviour, could contribute to an overconsumption of food with high hedonic value. Furthermore, metabolic alterations, which are associated with obesity, seem to facilitate adverse alterations of the brain.

Since most of the described studies are cross-sectional, the important question of cause and effect remains open. Currently, longitudinal studies are performed in several places including samples from the normal population or special groups of patients (e.g. patients undergoing bariatric surgery, i.e. weight loss surgery) in order to examine alterations leading to the development of obesity and which alterations could be reversed by a massive loss of excess weight.

Most studies investigating functional brain responses to e.g. food stimuli were performed in exclusively female populations. Thus, it is still difficult to generalize these findings on the interplay of obesity and brain responses to both genders.

Genetic influence on obesity and eating behaviour

The so-called "thrifty genes hypothesis" postulates that our present gene pool evolved by a positive selection of the ability to store energy resources for periods of scanty supply. Individuals that could superiorly store energy benefited from a better chance of survival and, thus, succeeded with passing on their genes. Nowadays, there is an oversupply of high-caloric food in many parts of the world. Furthermore, in general energy expenditure declines more and more in everyday life. This could automatically lead to obesity in modern times. During the last 50 years, society and environment rapidly changed in many regions of the world; far too rapid for our gene pool to adjust to this new situation.

According to the latest state of the art, body weight is passed on from one generation to the next in 40–70% of the cases. In addition to genetic causes, cultural and social factors play an important role in the development of body weight, i.e. it is always influenced by the interplay of genes and environmental conditions. During the last 10 years there has been substantial progress in the understanding of genetic underpinnings of obesity, made possible by technical innovation. Today, 9 genes are known in which mutations cause overeating and obesity. Although these mutations have a strong influence on body weight, they occur only rarely (5–10% in obese subjects) and can thus only account for a small fraction of all cases of obesity.

On the other hand, many common genetic variations with a small individual impact on body weight are known. Most of them are single nucleotide polymorphisms (SNPs) that consist of variations of single nucleotides in the DNA. Genome wide association studies (GWAS) are used to identify SNPs that have an influence on phenotypes such as obesity. It is believed that a large set of SNPs determines collectively how a property develops, as is the case for body height. However, all known obesity-related SNPs explain together as little as 2–4% of variance in body weight.

Interestingly, most of the known obesity-associated SNPs influence energy intake or the perception of hunger and satiety and have a direct link to brain function; some even influence the brain's development [7, 10]. This implies a predominant genetic effect on eating behaviour (i.e. what, when and how much is eaten). Despite the small influence of individual SNPs on body weight we could demon-

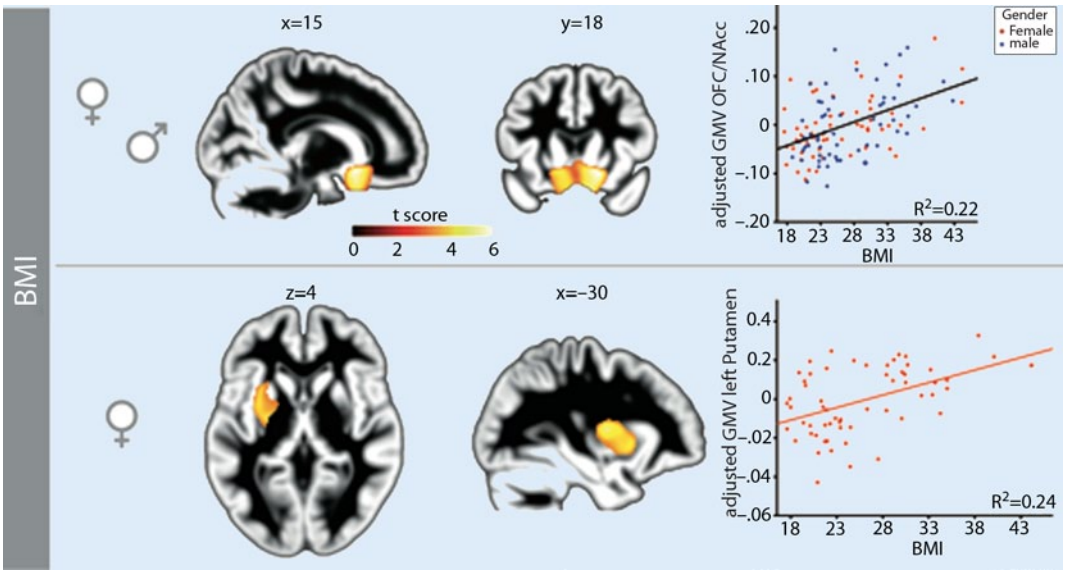

Fig. 2 ◀ The association of obesity with profound, gender-dependent structural alterations within brain regions involved in reward processing and homeostatic control. The volume of posterior medial orbitofrontal cortex (*OFC*), nucleus accumbens (*NAcc*), and hypothalamus increases significantly with BMI (*top*, warm colours; scatterplot) in both genders. For women, an additional positive association between *grey* matter volume and BMI can be observed in the left putamen (*bottom*: warm colours and scatterplot). (Adapted from [2])

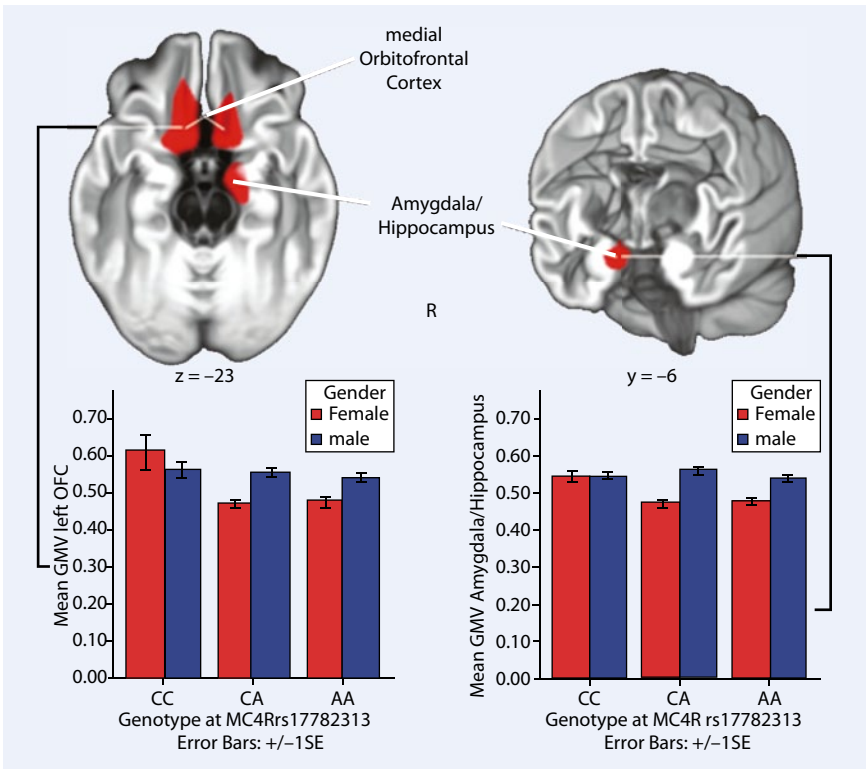

Fig. 3 ▲ Sex-specific association between common genetic variation near MC4R and the brain's *grey* matter volume (*GMV*). Genetic variation near MC4R has been shown to be associated with obesity. Here, we show sex-specific effects of genotype on GMV in the *right* amygdala/hippocampus and bilateral medial orbitofrontal cortex, adjusted for participant's BMI, age, global *grey* and *white* matter volume. Female homozygous carriers of the obesity risk allele (*CC*) had higher values than heterozygous subjects (*AC*) or non-carriers (*AA*). No significant difference was found for men. (Adapted from [3])

strate consistent differences in eating behaviour and brain structure dependent on genotype in an obesity-associated SNP [3].

Female carriers of an obesity-associated SNP near the gene for a melanocortin receptor (MC4R) showed disinhibited eating which was paralleled by structural changes in the amygdala, orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex when compared to non-carriers of the risk allele (**Fig. 3**). This genetic variation had no such influence in men. Whether these differences are causal for differences in body weight warrants further investigation. For some of these SNPs a modulating effect of physical exercise has been shown: The genetic influence on body weight could be alleviated by physical exercise. This indicates a genetic predisposition that does not necessarily lead to obesity but can be influenced substantially by lifestyle and environment. In addition, societal factors such as quality of life and equality of income also influence obesity rates.

Genetic factors most probably determine whether an individual is located at the lower or upper border of the normal weight distribution. But obesity can be explained rarely on the basis of genetics alone. Therefore, the common shift of the weight distribution to higher values of BMI is most probably the result of our modern society.

Conclusion

Obesity depends mostly on altered eating behaviour. Evolution did not generate a central nervous mechanism to prevent exaggerated energy intake. A broad body of studies have demonstrated complex differences in brain structure and intrinsic information processing between lean and obese subjects. Whether these differences are causal or consequential to obesity remains to be elucidated. In addition, obesity-associated ge-

netic variation influences brain structure and function. The specificity and reversibility of the observed differences remain open questions that have to be answered in the near future to offer suitable therapy strategies.

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Compliance with ethical guidelines

Conflict of interest. A. Horstmann and A. Villringer state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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