Pharmacological Functional MRI Technology: Potential for Use in Neurology

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Abstract

This review presents recent data on one of the most promising neuroimaging techniques, pharmacological functional magnetic resonance imaging (phFMRI). PhFMRI technologies are described as well as task-based approaches inducing neuronal activation in the areas of interest when evaluating the effects of neuroactive agents. We reviewed the potential use of phFMRI in various neurological disorders such as cerebrovascular disease and epilepsy, as well as in the management of metabolic disorders, cognitive impairment, pain syndrome, etc. Limitations of phFMRI and possible ways to address them in designing and conducting studies are presented. The potential uses of phFMRI for the objective assessment of the targeted effects of pharmacological agents are suggested.

Keywords: *pharmacological magnetic resonance imaging; functional magnetic resonance imaging; targeted effects; paradigm; personalized medicine*

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Технология фармакологической функциональной МРТ: потенциал использования в неврологии

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Аннотация

В обзоре представлены современные данные об одной из перспективных нейровизуализационных методик – фармакологической функциональной магнитно-резонансной томографии (фарм-фМРТ). Описаны технологии проведения фарм-фМРТ, варианты применения парадигмы в качестве триггера нейрональной активации зон интереса при изучении эффектов нейроактивных препаратов. Рассмотрены потенциальные возможности применения фарм-фМРТ при различных неврологических состояниях, таких как цереброваскулярные заболевания, эпилепсия, а также в отношении коррекции метаболических расстройств, когнитивных нарушений, болевого синдрома и др. Представлены ограничения применения фарм-фМРТ, возможные пути их преодоления при планировании и проведении исследований. Предложены перспективы применения фарм-фМРТ, которые позволят дать объективную оценку таргетного воздействия фармакологических агентов.

Ключевые слова: *фармакологическая магнитно-резонансная томография; функциональная магнитно-резонансная томография; таргетное воздействие; парадигма; персонифицированная медицина*

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Introduction

Due to the challenges of developing and evaluating agents that affect the central nervous system (CNS), techniques and approaches are needed to make a translational leap from preclinical models to predicting clinical effects in patients [1]. *In vitro* and *in vivo* laboratory studies characterize various pharmacological properties of study molecules, but efficacy data from such studies (especially for neuroactive agents) should be interpreted with particular caution in the context of the human population. There is currently no generally accepted reference for determining the effect of agents on the CNS, whether they are neuroprotective, antidepressant, antipsychotic, etc. [2]. Neuropharmacological functional magnetic resonance imaging (FMRI) of the brain may be one of the most promising techniques.

FMRI technologies using relative cerebral blood flow (rCBF), blood oxygen level dependent (BOLD) signal [4] or T1-weighted cerebral blood flow quantification [5] have revolutionized brain mapping [6]. All of these approaches are based on the interplay between neuronal activity, metabolism, and hemodynamics, parameters that are sensitive to changes in MR signal intensity. Although all of these techniques can be considered functional, the term "FMRI" traditionally refers to the assessment of the BOLD signal.

FMRI typically uses a specific paradigm (e.g., visual stimulation, finger movements, cognitive tasks, etc.) as a trigger for neural activation in the areas of interest (so-called task-based fMRI). However, a similar effect can be achieved using various types of pharmacological agents, both as a direct stimulant and as a mediator that modulates the brain response to another paradigm (e.g., cognitive). In 1997, Y.C. Chen et al. called this type of FMRI "pharmacological MRI" (phMRI) [7]. In mouse experiments, they evaluated the regional selectivity of dopamine ligands (although a conceptually similar approach was implemented by others at least since 1993 [8, 9]).

In early-phase clinical trials, FMRI techniques can demonstrate the functional effects of a pharmacological agent on the CNS in those regions of the brain that are etiologically and/or pathogenetically relevant to the biochemical mechanisms [10]. It should be noted that, technically, we are not talking about markers of target action (e.g., visualization of the agent binding to a corresponding site), but rather about indirect evidence of the effect between the fMRI response and the biological plausibility of the agent's action. Dose-dependent associations identified by FMRI may be valuable in planning further stages of research or clinical implementation of the agent [11].

In later-phase clinical trials, phFMRI findings will be likely used to demonstrate normalization of disease-related MR signal changes (e.g., activation/deactivation of specific brain regions in response to a paradigm or changes in functional connectivity). This may be potentially considered a more objective assessment of the change in CNS impairment.

PhFMRI can also be used to determine the cerebral targets of investigated pharmacological compounds, to clarify expected/unexpected mechanisms of action, to identify dose-dependent responses, and to provide valid markers of therapeutic response (including for clinical trials) [12]. Since the development of phFMRI, a rather wide range of neuroactive molecules has been studied in experimental and/or clinical models, both chemical compounds (nicotine, amphetamine, etc.) and therapeutic agents (neuropeptides, cholinergic, serotonergic and glutamatergic agents, cannabinoids, opioids, etc.) [14].

Several criteria should be met for phFMRI to be used as a relevant diagnostic and research tool (including in pharmaceutical development):

1) PhFMRI data should be reproducible and should change with the effects of a pharmacological agent.
2) Quantitative phFMRI characteristics (based on equipment) should be standardized.
3) Prior to study initiation, the specific features of phFMRI performance and analysis should be determined.
4) For further research, selected fMRI techniques should be available in multiple centers (e.g., type of pulse sequences, voxel sizes, slice thickness, temporal resolution, deflection angle, and selected paradigms should be similar for all MR examinations).
5) An MRI technician should be engaged in the FMRI process (e.g., in case of excessive head movement, a repeat scan should be performed).
6) Quality control should be performed at all stages (DICOM[1] verification of protocol compliance, artifact identification, etc.).

[1]DICOM (Digital Imaging and Communications in Medicine) is a medical industry standard for the creation, storage, transmission, and visualization of digital medical images and documents of examined patients.

The ability of pharmaceutical agents to induce short- and long-term changes in the FMRI signal is one of the most important reasons for the phFMRI investigation. Multiple studies published suggest that FMRI findings may be sensitive to both short- (i.e., after the first dose) and long-term (chronic, after multiple dosing) pharmacotherapy. For example, several studies show that the FMRI response of the amygdala increases when patients with depression are exposed to photographs of faces with negative emotions, while the use of clinically effective doses of antidepressants normalizes this response [15, 16]. Other groups of agents thought to produce changes in phFMRI signals include analgesics, antipsychotics, calcium channel blockers, cyclooxygenase-2 inhibitors, and immunotherapy.

Many targets for neuroactive molecules have been identified in previous experimental studies (e.g., positron emission tomography). The cumulative effect of phFMRI per examination can be classified as specific (i.e., directly related to receptor activation) and general or non-specific (related to side effects that may affect the FMRI signal intensity).

PhFMRI can identify single points of agent application. Similar patterns of FMRI activation can be observed when agents with the same indication (e.g., pain) but radically different mechanisms of action (e.g., non-steroidal anti-inflammatory agents, opioid analgesics, etc.) are used. In addition, the functional status (i.e., FMRI characteristics) of certain brain structures may serve as predictors of therapeutic response, as has been shown for pregabalin in the insula and inferior parietal lobule [17].

Technology from a current perspective

The echo-planar gradient echo sequenceis the most commonly used technique to obtain the BOLD signal. This sequence is sensitive to local magnetic field inhomogeneities, such as those caused by paramagnetic substances such as deoxyhemoglobin, in the presence of which the signal is attenuated [5]. When excitation occurs in a particular region of the brain, a local increase in blood flow to that area is observed, leading to increased oxyhemoglobin levels and decreased deoxyhemoglobin levels. As a result, a change (increase) in the signal is observed and recorded using the sequence described. Therefore, FMRI records the distribution of neuronal activity, which is indirectly assessed by the change in the signal as a function of the blood oxygenation level in the cerebral vessels. In each voxel, signal oscillations during the scanning time are recorded and then evaluated using various statistical tools with the subsequent possibility of data group presentation as well as between group and within group analysis (Fig. 1).

Signal oscillations occur not only during task performance (task-based FMRI), but also spontaneously at resting state. Due to internal neuronal activity, such oscillations are recorded during resting-state FMRI [18], i.e., when a patient is scanned without being presented with stimuli of any modality. When BOLD signal oscillations are similar and correlate between gray matter regions, there is a high probability that these regions are functionally related. Based on this claim, several resting-state brain networks have been described using different methods of mathematical analysis. This technique has some advantages over paradigm-based FMRI, including the ability to perform an examination even when a patient is unable to understand or perform a task, and the elimination of the need to use multiple devices to present stimuli, thus reducing labor and cost. However, processing such data is more complex and error-prone due to multiple physiological noises.

For phFMRI, both techniques are used [19, 20]. Administration of a pharmaceutical agent or other substrate that has the potential to alter functional brain activity may affect the BOLD signal at both the vascular and neuronal levels, impeding interpretation of the results. The signal changes associated with the substance administration are insignificant. This justifies studying its effects in the context of paradigm-based FMRI signal changes and comparing stimulus-related activation areas in subjects receiving a substance with activation areas and those not receiving a substance or receiving a placebo. In addition to being a simpler technique, resting-state FMRI has the advantage of evaluating the effect of the administered substance at the network level, even far from the expected area of maximum concentration of substance receptors or the expected area of activation/deactivation [10].

However, for a valid phFMRI, some pharmacokinetic and pharmacodynamic aspects of the administered substances should be considered, such as time to maximum blood concentration, half-life, and cumulative effect, in order to perform the examination when the maximum substance effect on the human body is achieved. In addition, the administration of other substances that may interact with the study substance or may alter the functional activity of the brain should be considered [14]. These data are used to calculate the time of examination after the study substance administration and the time of examination after the course of therapy.

PhFMRI in different areas of neurology

Cerebrovascular diseases

The available data on the use of phFMRI in cerebrovascular disorders are limited and mainly relate to chronic cerebrovascular diseases and neuroprotective agents. One of the pilot studies in this area was conducted by the Research Center of Neurology. For example, in a 2010 study, course treatment using an agent with a reported neuroprotective effect was associated with the expansion of existing activation areas and/or the development of new activation areas, primarily in the parietal occipital region, which was accompanied by improved performance in basic cognitive tests [21]. In contrast, a year later, a study of a neuropeptide showed a reduction in activation areas (especially in the temporal and frontal lobes) in response to an original cognitive paradigm developed at the Research Center of Neurology [22]. An indirect phFMRI comparison of several potential neuroprotective agents suggested the main targeted mechanisms of action and phFMRI patterns, such as cerebroactivating effect, improved microcirculation, reduced brain energy expenditure, and neurometabolic effect [23].

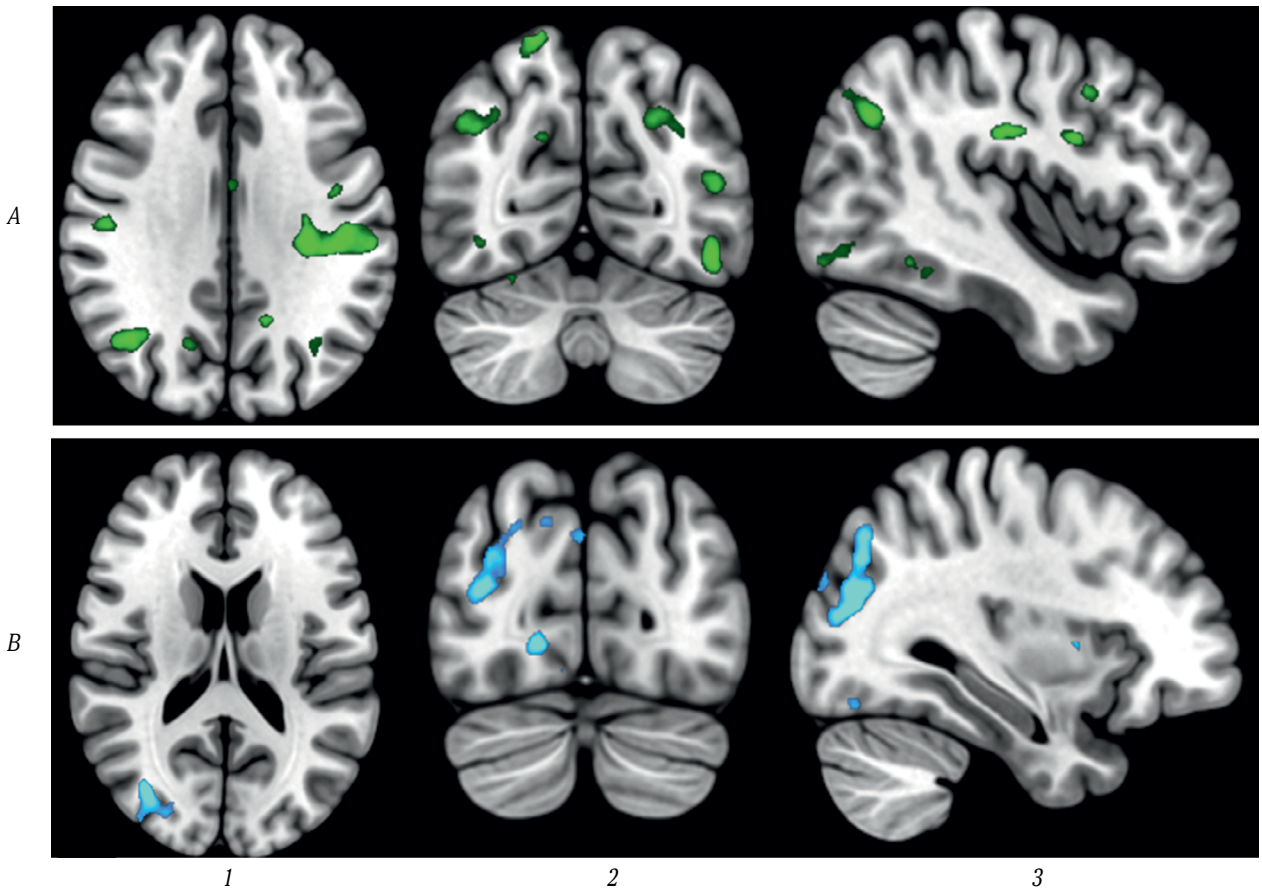


Fig. 1. Results of within groupcomparison of brain activation during a cognitive paradigm before and after treatment.
A – patients who received vascular and metabolic therapy for 10 days demonstrated a decrease in activation in the supramarginal and angular gyri and in the visual cortex; *B* – patients who received placebo demonstrated a decrease in activation only in the visual cortex.
1 – axial view; *2* – coronal view; *3* – sagittal view.

The phFMRI results for a domestic neuroprotective agent were intriguing; the treatment was followed by a decrease in the areas responsible for performing a cognitive task (in the supramarginal and angular gyri) and improved executive cerebral functions associated with processing language information (enhanced connection between the left dorsolateral prefrontal cortex and the superior temporal gyrus). Clinically, these neuroimaging changes were manifested by an increase in functional activity and optimization of executive functions, which is an important pathogenetic effect in patients with cerebrovascular diseases [24].

Pain syndromes

Some studies evaluated the analgesic properties of opioid agents on the activity of brain structures [25, 26]. The opioid analgesic nalbuphine increased BOLD signal intensity in 60 brain regions and decreased it in 9 regions, including the middle frontal cortex, inferior orbitofrontal cortex, postcentral parietal cortex, superior temporal pole, and cerebellum. However, after naloxone administration, the pattern of altered activation changed significantly: BOLD signal intensity increased in only 14 areas and decreased in 3 areas. Low doses of naloxone significantly blocked nalbuphine activity in the superior medial and middle frontal cortex, postcentral parietal cortex, occipital cortex (Rolandic fissure), caudate nucleus, pons (principal sensory nucleus of the trigeminal nerve), and cerebellum.

Currently, antidepressants and anticonvulsants play a special role in pain management, demonstrating their multimodal capabilities in the control of chronic pain syndromes. A.E. Edes et al. evaluated the effects of intravenous citalopram/placebo on the activity of the anterior cingulate cortex as a major structure involved in descending modulation and the emotional aspect of pain in 27 healthy volunteers and 6 patients with migraine without aura [27]. A significant difference in the temporal pattern of activation of the anterior cingulate cortex was found between healthy controls and patients with migraine without aura in response to even small increases in serotonin levels induced by citalopram.

Epilepsy

Research on the use of phFMRI in epilepsy is quite extensive. Considering the diversity of available antiepileptic agents

and the heterogeneity of epileptic syndromes in terms of the neural networks involved, FMRI-based biomarkers should be developed for early assessment of treatment efficacy and potential side effects [10]. For example, phFMRI showed that the use of a higher dose of valproic acid in patients with juvenile myoclonic epilepsy was associated with attenuation of abnormal coactivation of motor cortex with cognitive networks in a working memory study [28]. The use of another antiepileptic agent, levetiracetam, in patients with temporal lobe epilepsy was associated with restoration of the normal activation pattern, according to phFMRI findings [29]: for example, an increase in deactivation in response to a cognitive paradigm was observed in the affected temporal lobe during the treatment with the agent, and a dose-dependent effect was confirmed.

Studies with topiramate demonstrate the potential role of phFMRI in clarifying the cerebral mechanisms of adverse effects of neuropharmacological agents. During the use of topiramate (both in patients with epilepsy and migraine and in healthy volunteers), phFMRI with its multiple capabilities identified a pattern of reduced activation in language-dependent areas of the brain (inferior and middle frontal gyri, superior temporal gyrus of the dominant hemisphere) [30–32], as well as the absence of deactivation of paradigm-independent areas, including the default mode network [33, 34].

Cerebral metabolic health

The concept of cerebrometabolic health encompasses a wide range of syndemic neurological and metabolic disorders and suggests that it is relevant to evaluate the effects of different agents to address specific symptoms [35].

Currently, several modalities are available to investigate eating behavior, with neurocognitive testing using various questionnaires being the most important modality. FMRI allows real-time assessment of changes in activation of brain structures in response to different stimuli (e.g., a visual food paradigm). The main areas evaluated in obese patients are called the reward system and include the prefrontal cortex, insula, cingulate gyrus, and limbic system. A simple and reproducible visual FMRI paradigm was developed by the Research Center of Neurology to assess the system of eating behavior control [36], which was subsequently used in studies involving phFMRI patterns. For example, sibutramine (a centrally acting drug for the treatment of obesity, with the mechanism of action based on selective inhibition of serotonin and norepinephrine reuptake) was shown to produce a different pattern of signal changes in response to a eating paradigm in obese patients compared to healthy volunteers. The most significant changes in functional activity were found in the occipital lobes, insula, and middle and superior frontal gyri. It should be noted that before the initiation of pharmacotherapy, patients with obesity showed excessive activity in the occipital lobes compared to the control group (healthy volunteers), which indirectly indicates a more significant emotional response to the demonstration of high-calorie food in people with overweight [37].

The study by O.M. Farr et al. in 20 patients with type 2 diabetes showed the effect of liraglutide (a human long-lasting GLP-1 analogue) on the activation of brain areas (dorsolateral prefrontal cortex, midbrain, thalamic region) in response to food stimuli [38]. H. Cheng et al. demonstrated multimodal effects of liraglutide on cognitive function with increased activation in the hippocampal region, expanding the use of this class of agents in patients with type 2 diabetes and obesity [39].

The focus on the effects of various nutrients on the brain and human behavior has increased significantly in recent decades. Sugar and artificial sweeteners are widely used in modern nutrition science. Brain FMRI can evaluate these mechanisms with assessing neural activity over time in response to nutrient consumption. Glucose is known to activate reward systems in the brain (such as the dopamine system) associated with pleasure and motivation. Understanding how fast-digesting carbohydrates, such as sucrose, activate different areas of the brain in healthy people may provide clues to the mechanisms of overeating and addiction.

Sweeteners (aspartame, sucralose, stevia, erythritol) are offered as healthier alternatives to sucrose and fructose. However, their effects on brain activity and human behavior remain debatable. Some studies suggest that artificial sweeteners may not activate reward systems like carbohydrates, which could affect satiety and subsequent food consumption. In obesity, FMRI is used to assess functional neuronal activity involved in the regulation of energy exchange and metabolism. The Research Center of Neurology obtained pilot FMRI data comparing the effects of sucrose and an artificial sweetener, showing differences in activation in the supplementary motor area and dorsolateral prefrontal cortex in healthy volunteers (Fig. 2).

Cognitive disorders

PhFMRI may be a promising modality for identifying targets for the treatment of cognitive impairment. The differential effect of cholinergic therapy (galantamine) is convincingly demonstrated depending on the target patient cohort, such as mild cognitive impairment (activation of the posterior cingulate gyrus, left inferior parietal and anterior temporal lobes) or Alzheimer's disease (bilateral hippocampal activation) [40]. Such changes in response to cholinergic load may reflect a baseline difference in the functional status of the cholinergic system between two groups, which is consistent with clinical studies. In addition, differences in activation patterns were found after single and chronic administration of agents, highlighting the need for evaluating phFMRI as a dynamic modality.

Key areas for using phFMRI in neurology include:
- study of classical neuroprotectants in patients with cerebrovascular disease;
- study of antidepressants in neurological patients (post-stroke depression, chronic pain, neurodegeneration, etc.);
- resting-state assessment in patients with epilepsy depending on pharmacokinetics/pharmacodynamics of antiepileptic agents;
- management of acute/chronic pain;
- evaluation of FMRI correlates of neuroplasticity in post-stroke patients;

- cholinergic therapy in patients with cognitive disorders (vascular dementia, Alzheimer's disease, Parkinson's disease, etc.);
- dopaminergic therapy in patients with Parkinson's disease;
- patients with multiple sclerosis on pulse corticosteroid therapy.

Technological challenges of phFMRI and potential solutions

PhFMRI is a complex modality that requires a high level of logistical effort, as well as caution and a balanced approach to interpretation of the results.

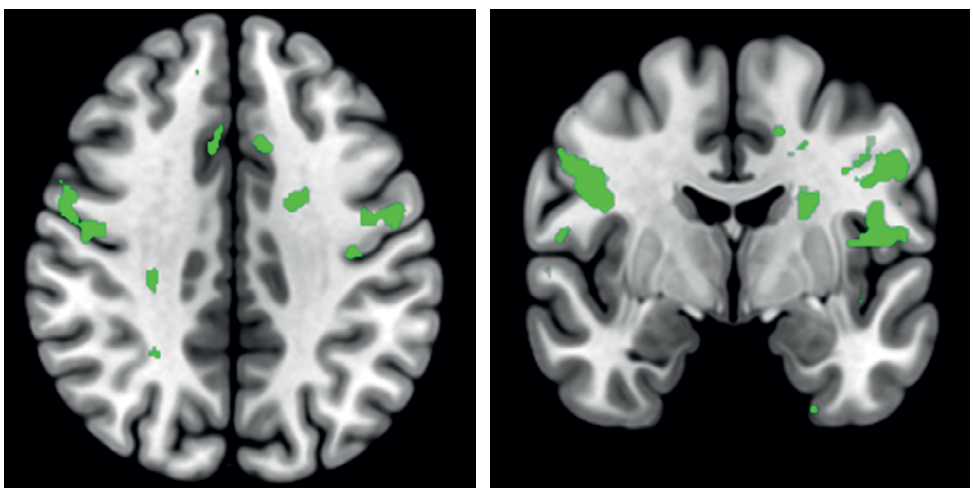
Some of the existing limitations of phFMRI are listed below:
- lack of an optimal set of settings for obtaining and processing MR images;
- limitations of generalized linear model as a basic approach to statistical analysis of FMRI data;
- lack of standardized paradigms for specific research tasks;
- inadequacy of current phFMRI data presentation standards for proper evaluation and interpretation;
- bias in conducting and publishing FMRI validation (repeated) studies;
- challenges in selecting and assessing potential covariates;
- the use of the BOLD signal as a surrogate indicator depending on the baseline level of neurovascular coupling, and its modulation by pharmacological agents is often difficult to predict;
- for most studies, small and highly heterogeneous sample size;
- high inter- and intra-individual variability of the FMRI signal [14, 41].

Understanding limitations and above-described characteristics of phFMRI may allow for (at least partial) modification of the methodology to obtain reproducible and meaningful results. For example, the selection of neuroactive molecules for an experiment should be based on clinical feasibility as well as pharmacokinetics/pharmacodynamics and target interaction. Time of onset and duration of the expected effect should also be considered to properly design the experiment. Since changes in the BOLD signal during FMRI may be attributed to systemic effects (heart rate, blood saturation level, etc.), it is recommended to include these routine parameters in the statistical analysis [42]. Normalization of baseline differences in cerebrovascular reactivity between patients and in the context of placebo/active agent use is recommended to overcome the limitations of the BOLD signal assessment method. This task requires assessment of the baseline level of cerebral perfusion (using arterial spin labeling) [43] and measurement of the cerebral metabolic rate of oxygen consumption [44].

When using different phFMRI paradigms, it is important to perform separate (several days/weeks apart) scans with placebo [45]. In addition, the study of pharmacological agents with predominantly subjective effects (e.g., sedative or energizing effects, mood modulation, etc.) should be supplemented with psychometric tests at pre-specified time intervals during and/or between scans (in case of suspected long-term effects) [46]. In some cases, resting-state FMRI should be used instead of or in addition to phFMRI, as resting-state FMRI can assess functional connectivity and identify potentially more stable markers of treatment response [47].

Conclusion

Brain phFMRI, as one of the multiple angio-neuroimaging subtypes, has significant potential for neuroscience research. With the proper study design, this modality is suitable for objective *in vivo* assessment of the target effect of a pharmacological agent. This is critical for several reasons:
1) Personalization of prescribed treatment (e.g., in the case of antiepileptic therapy adjustment).
2) Validation and/or discovery of new mechanisms of action of neuroactive agents (especially neuroprotectants).



A *B*

Fig. 2. Within group comparison of brain activation in healthy subjects during visualization of a food paradigm (images of foods that look tasty and foods that do not look tasty) after intake of sugar and a sweetener. Brain slices show areas of different activation. After sugar intake, higher activation was observed in the supplementary motor and dorsolateral prefrontal cortex bilaterally.
A – axial view; *B* – coronal view.

3) Reduced time to develop new agents due to direct visualization of the presence/absence of cerebral effects.
4) Clarification of the origin of adverse effects of neuroactive drugs.
5) Expansion of basic science tools and the ability to investigate specific receptors.

Collaboration between advanced phFMRI laboratories and the pharmaceutical industry can provide a competitive advantage for domestic research and developementand accelerate clinical implementation of experimental neuroscience findings. However, the modality has many limitations that require both the search for a solution and direct investigation of the issue.

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