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Neuropharmacological functional imaging

Introduction

The majority of neurons interact through the release of neurotransmitters that bind to specific receptors of downstream cells. Neurochemical communication is an essential element for the transmission of information between nerve cells and central to sensory, motor and cognitive processes. Changes in neurotransmitter systems are found in many neurological and psychiatric disorders and across the life span. In addition, individuals also differ in the availability of neurotransmitters due to genetic differences. Larger changes in neurotransmitter systems lead to declines in sensory, motor or cognitive performance. One example is the loss of cholinergic neurons and receptors in Alzheimer's disease, which is associated with cognitive deficits. Thus, a better understanding of the link between neurochemistry and behavior is of central interest for both basic research and clinical applications. The correlation between neurochemistry and behavior can be investigated using quite different methodological approaches in different species. In the following, pharmacological functional magnetic resonance imaging (fMRI) will be introduced as *one* of several approaches to systematically investigate the relationship of neurotransmission and cognition in the human brain. In the long run the combination of neuropharmacological approaches with functional neuroimaging can provide valuable contributions to the development of appropriate pharmacological treatments for neurological and psychiatric diseases.

Pharmacological fMRI

Methodological approach

The development of imaging techniques such as fMRI or positron emission tomography (PET) has enabled to investigate the mechanisms underlying cognitive functions in the human brain. fMRI makes use of the different magnetic properties of oxygenated and deoxygenated blood to measure neural activity. Since neuronal activity changes the ratio of oxygenated and deoxygenated blood, neural activation in MRI can be indirectly measured using the so-called BOLD (blood oxygen level dependent) contrast (see [5]). However, 'pharmacological fMRI', as the term might suggest, is not a method for its own, but combines a psychopharmacological approach with the measurement of brain activity by means of fMRI. Pharmacological fMRI is often used as general term to describe studies which administer a pharmaceutical agent before or during the performance of an fMRI study. Thereby, the drug will not necessarily be used to investigate the therapeutic efficacy of the substance, but with the goal to specifically manipulate neurochemical communication in the human brain. For example, the activity of the cholinergic neurotransmitter system can experimentally be reduced by the administration of drugs such as scopolamine, which blocks acetylcholine receptors, or can be increased by the administration of drugs such as physostigmine, which reduce the breakdown of acetylcholine (**Tab. 1**).

Most pharmacological fMRI studies investigate the effects of such experimentally induced and short-lasting manipulations in combination with cognitive, sensory or motor paradigms (see excursus). In other words, the participants of a study perform a task during the fMRI measurement. The drug, which was administered before the measurement, is already effective during the fMRI scan. By using this approach it is possible to investigate

Tab. 1 Commonly used substances for the experimental manipulation of the dopaminergic and cholinergic system in humans

Neurotransmitter system	Increase of activity		Decrease of activity	
	Substance	Mechanism	Substance	Mechanism
Dopamine	Amphetamines, methylphenidate	Increase of dopamine release	Sulpiride, haloperidol	Receptor antagonist (D2)
	l-Dopa	Dopamine precursor		
	Bromocriptine	Receptor agonist (D2)		
	Pergolide	Receptor agonist (D1/D2)		
Acetylcholine	Physostigmine, donepezil, rivastigmine	Cholinesterase-inhibitor	Scopolamine	Receptor antagonist (muscarinic)
	Nicotine	Receptor agonist (nicotinic)		

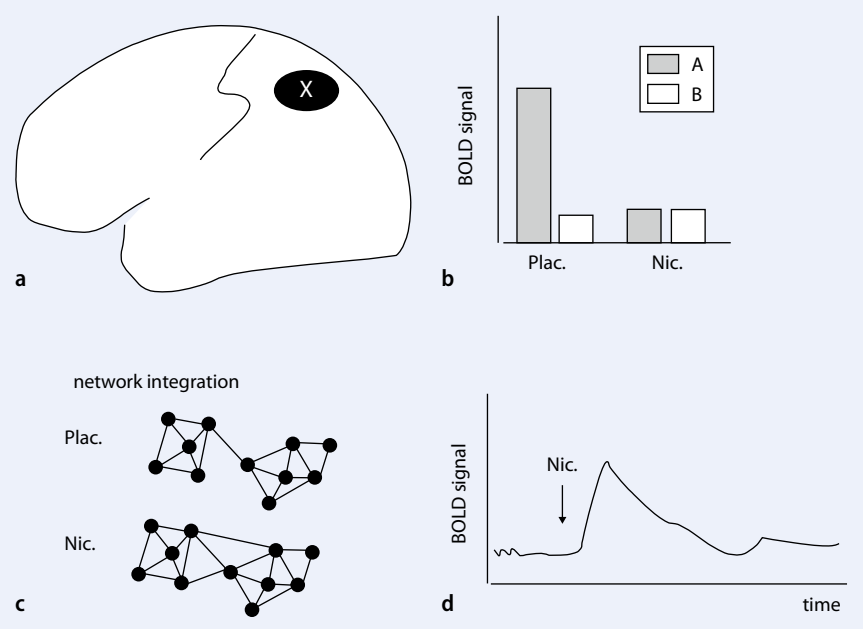

Fig. 1 ▲ Different pharmacological fMRI approaches. Drugs effects within cognitive paradigms describe a stimulus-specific modulation of brain activity. For example, the brain region X (**a**) might show a drug modulation (**b**): following drug administration the activation during stimulus *A* was reduced. Such a pattern was found in the parietal cortex during reorienting of attention; nicotine reduced the BOLD activation during invalid trails. **d** Within the pharmacokinetic approach, brain region X might show an increase in the BOLD MRI signal following drug administration similar to the curve that can be expected from the pharmacokinetic parameters. Such a pattern was found, for example, in the nucleus accumbens. **c** A simplified illustration describes how drugs can alter the organization of brain networks. The functional brain networks following nicotine administration show greater network integration

in which brain regions the drug changes task-specific brain activity. For example, it can be analyzed, in which regions of the brain a reduction of cholinergic neurotransmission (which, as mentioned above, induces memory deficits) affects brain activity. These brain regions need not necessarily correspond to those areas in which the drugs have a high receptor binding and can be very different depending on the task used. It is quite conceivable that one and the same drug affects BOLD activity within the motor cortex if subjects perform a motor task, but changes BOLD activity in the prefrontal cortex during a memory task.

In recent years a growing number of studies examining the effects of drugs on so-called resting state networks have been performed. Thereby, following the administration of a drug, subjects are investigated at rest inside the MRI scanner. The measured data are analyzed with methods which aim to identify brain networks that 'oscillate' in the same frequency, i.e. concurrently increase or decrease their BOLD signal. The investigated fluctuations are often seen at a low frequency range (<0.1 Hz) and are the result of joint information processing. An additional, less common approach analyzes changes in BOLD activity with pharmacokinetic parameters and investigates the direct neural effects of drugs instead of the modulation of task-specific brain activity or resting state networks. This approach allows scientists to obtain new insights into the drug's site of action as well as the specific dose–response relationships within a certain brain region [1].

Excursus: different approaches in pharmacological fMRI studies

In the following section, three pharmacological fMRI studies on the effects of nicotine are described to illustrate the different methodological approaches.

Method 1: drug effects in cognitive paradigms

Several studies support that the cholinergic agonist nicotine improves attention. In order to investigate how nicotine induces these attention enhancing effects, we analyzed the effects of the drug within an attention paradigm. As main question we investigated in which brain regions nicotine changes the BOLD activity during the reorienting of attention. To answer this question, subjects were administered either with nicotine or placebo before the investigation and afterwards performed a visual attention task within the MRI scanner. The task was a spatial cueing task in which a cue validly or invalidly predicted the position of the following target. By comparing the brain activity between these two stimuli it is possible to identify brain regions that are involved in the reorienting of attention. This 'reorienting-specific' brain activity was compared between nicotine and placebo. Our results revealed that nicotine, beside other brain regions, reduced brain activity within the parietal cortex during invalid trials ([22], **Fig. 1a, b**).

Method 2: drug effects on functional connectivity during resting state

In recent years, there have been an increasing number of studies within the field of functional imaging which do not investigate subjects during task performance, but during resting state. A short overview is given within the article of Greicius [9]. Several recent pharmacological fMRI studies used this technique to identify how drugs change correlated low frequency fluctuations in the BOLD signal between brain regions. Thereby an important aspect is the functional connectivity of these brain regions which can be analyzed with different methodological approaches. One of these methods is the graph analysis which describes brain networks as a collection of nodes that are connected by a complex network of edges. As a result, graph analyses provide statistical parameters that describe whether a network has a good or bad organization for information processing. Such an approach allows scientists to identify pharmacologically induced changes in

the organization of brain networks. Giessing et al. [8] aimed to investigate whether attention-enhancing effects of nicotine were associated with an altered efficiency of brain networks. Therefore, their subjects were administered either nicotine or placebo (as mentioned above) before the beginning of the experiment and afterwards were measured during several resting state periods within the MRI scanner. Functional connectivity was analyzed with a graph analytical approach. This approach revealed that the organization of the brain networks under nicotine changed so that information can be easily processed in parallel. Nicotine increased the network integration, that is, the network's components were more closely connected (**Fig. 1c**).

Method 3: effects of drugs assessed on the basis of the pharmacokinetic approach

Stein et al. [20] used fMRI to identify the binding sites of nicotine in the human brain. During the first part of their study subjects received a placebo that was intravenously administered during the fMRI scan. This was followed by three increasing doses of nicotine. During the MRI scan the brain activity was measured during the rise and fall of nicotine concentrations. In contrast to the aforementioned analyses, the approach described here used primarily pharmacokinetic parameters to analyze the data, such as the time of the maximum concentration of the drug. Thus, brain regions whose activation over time was consistent with pharmacokinetic data could be identified (**Fig. 1d**). One of these brain regions, for example, was the nucleus accumbens.

Advantages and disadvantages

Pharmacological fMRI is a valuable tool within the field of human psychopharmacology: for the first time it is possible to investigate the brain mechanisms of healthy subjects and patients that result from changes in neurotransmission during cognitive performance. This approach led to insights which outperform and go far beyond the results from classical approaches in psychopharmacology. For example, using classical psychopharmacology it is difficult to distinguish whether, following the administration of a drug, improvements in response times during an attention task result from a change in attention or a change in sensory or motor processing. Using fMRI, this can easily be differentiated in the human brain. Furthermore, fMRI approaches are also more sensitive to detect drug-induced changes in processing strategies which are not necessarily reflected in reaction times or performance accuracy.

In animal models the role of neurotransmitter systems can easily be investigated by intracerebral injections of a variety of specific agonists and antagonists or by optogenetics which allows specific receptors to be turned turn on and off. In contrast to these specific manipulations in animal research, the systematic and experimentally induced changes in humans are necessarily restricted to a limited number of approved drugs and seem to be rather unspecific. Nevertheless, using pharmacological fMRI studies in humans, it is possible to study research questions that otherwise can only be realized in animal experiments. Thus, pharmacological fMRI studies can make a valuable contribution to understanding the neurochemical modulation in the human brain. This is especially relevant for functions and diseases which, in an animal model, cannot be measured in their entire expression. Furthermore, usually fMRI measures the entire brain and thus provides data for whole brain network analyses. In recent years, network analyses were also used to identify endophenotypes for various diseases. In the long-term, a similar application could be developed for psychopharmacology.

The following will illustrate a few selected examples of pharmacological fMRI studies which document new findings and developments in the field over the last decade.

Neurotransmitters and cognition

In the last few years a number of functional imaging studies investigated the human brain to map cognitive functions. These maps suggest a "specialization" of different brain areas for specific cognitive functions. In a similar way and in addition to the correlation between higher brain functions and neuroanatomical locations, neuropsychopharmacology can be used to investigate the neurochemical basis of cognitive functions. However, what applies for the specialization of certain areas of the brain also holds for the neurotransmitter systems. There is no assignment of a single cognitive function to a single neurotransmitter system, but different neurotransmitter show specific, but quite overlapping profiles. Recent reviews of pharmacological fMRI studies in various neurotransmitter systems can be found in Thiel and Fink [21] and Honey and Bullmore [11]. Within this section only a few selected examples investigating the dopaminergic and cholinergic modulation of memory performance will be discussed.

Dopamine

In the dopaminergic neurotransmitter system three pathways can be distinguished. The nigrostriatal system originates in the substantia nigra and proj-

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Abstract
The marriage of psychopharmacology with functional neuroimaging enables the investigation of neurochemical modulation of cognitive functions in the human brain. From the point of basic neurocognitive research, pharmacological functional neuroimaging is hence a valuable completion of animal experiments. From the point of clinical neuroscience, pharmacological neuroimaging contributes to the understanding and development of pharmacological treatment approaches for patients with neurological and psychiatric disorders. The present paper provides an overview of the methodological approach and illustrates research findings and recent developments from pharmacological functional magnetic resonance imaging studies by means of selective examples from the dopaminergic and cholinergic neurotransmitter system.

Keywords
Psychopharmacology · Neuroimaging · Cognition · Acetylcholine · Dopamine

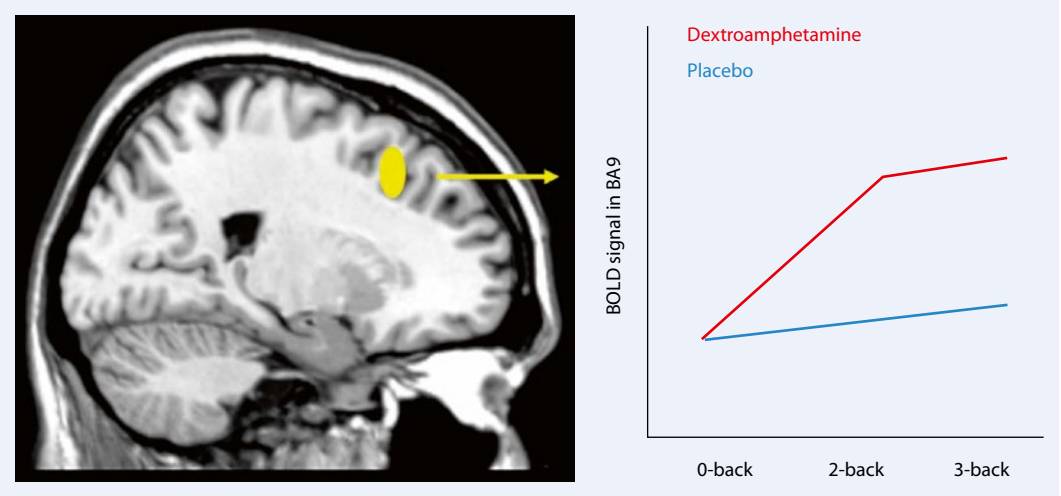

Fig. 2 ▲ Schematic and simplified illustration of the findings of Mattay et al. [15]. With rising working memory load, an increase in dopaminergic activity following the administration of dextroamphetamine in Brodmann area BA9 leads to an increase in prefrontal cortex activity. To gauge working memory the so-called n-back task was used, in which subjects have to specify, whether the currently presented stimulus is identical with the stimulus n trials before. The task becomes more difficult with an increasing number of trials between the current stimulus and the stimulus that should be remembered (thus, for example, in the 3-back condition)

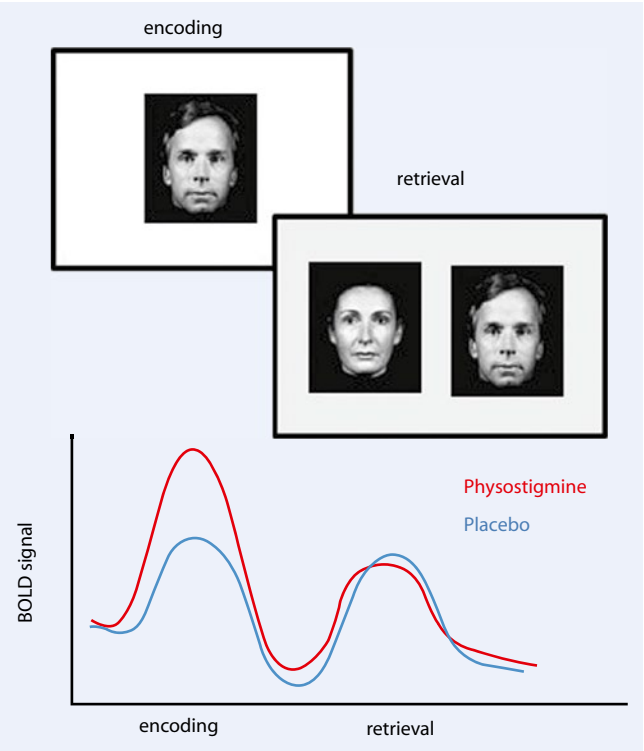

Fig. 3 ◀ Schematic and simplified illustration of the findings of Furey et al. [6]. Subjects were asked to remember a face. Shortly afterwards they had to decide which of two faces was presented previously. An increase in cholinergic activity by physostigmine during the encoding phase correlated with an increased BOLD signal in visual areas

ects to the dorsal neostriatum, whereas the mesolimbic system begins in the ventral tegmental area and ends in the ventral neostriatum. In the same region the third pathway originates, the mesocortical dopaminergic system, which sends projections to the frontal cortex, the cingulate and entorhinal areas. Dopaminergic receptors are divided into those of the D1 and D2 family.

Based on animal studies, which could specifically set neurochemical lesions in the prefrontal cortex, the mesocortical dopamine system was linked with working memory performance already in the late 1970s [2]. These results were further supported by later studies with electrophysiological manipulations. During the following years there was only little progress in human research; it could only be shown that dopaminergic agonists improve memory performance [14]. However, the localization of memory-dependent effects in the human prefrontal cortex, and thus a parallel to the experimental data found in previous animal studies could only be shown by a pharmacological fMRI approach. Mattay et al. [15] found that the pharmacological stimulation of dopaminergic neurotransmission with dextroamphetamine increased BOLD activity in the right prefrontal cortex, particularly with increasing working memory load (**Fig. 2**).

In the field of clinical neuroscience it could be shown by means of pharmacological fMRI that atypical antipsychotics, which achieve better results in the treatment of negative symptoms in schizophrenia and improve performance in cognitive tests, also increase prefrontal BOLD activity during a working memory task [12]. Especially in the area of psychiatric disorders, where animal models rarely cover the full range of behavior, methods that measure the neurophysiological effects of psychotropic drugs in the human brain are of particular importance. Also useful are pharmacological fMRI studies within the field of aging research

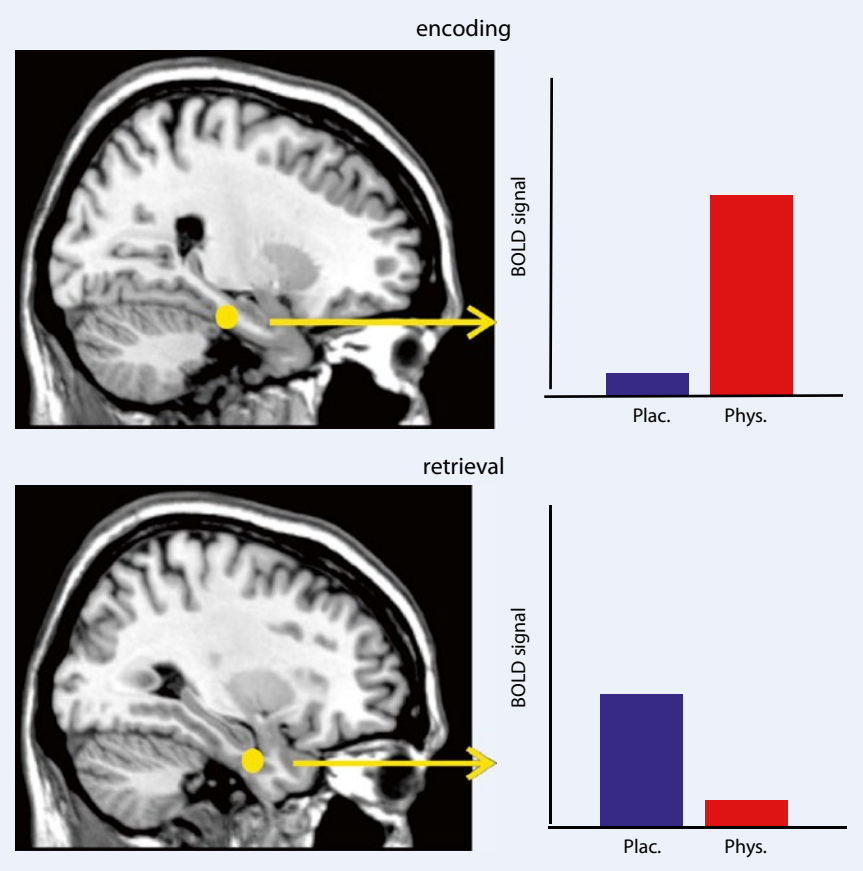

Fig. 4 ▲ Schematic and simplified illustration of the findings of Kukolja et al. [13]. Mediotemporal brain regions which showed increased activity under physostigmine during the presentation of objects within the encoding time period. These objects were later correctly remembered in the following source memory task. During retrieval these brain regions showed the opposite activation pattern

investigating the neurochemical mechanisms underlying the age-related changes in activation patterns in the human brain. For example, it could be shown that older subjects show more bilateral activations in several cognitive tasks and that this bilateral activation pattern can also be experimentally induced in younger subjects. This change was induced by a blockade of dopaminergic D1 receptors. The blockade resulted in a stronger bilateral frontal connectivity which was accompanied by a less pronounced drug effect on working memory [16]. This study shows that neuronal markers of aging may also be caused by a change in neurotransmission in young subjects. Since the increased 'bilaterality' correlated with less memory deficits on behavioral level, it can be assumed that bilateral activation patterns found in old age represent a compensatory mechanism.

Acetylcholine

There are two major cholinergic projection systems. One of them originates within the brainstem and projects to the thalamus and other subcortical areas; the other system originates in the basal forebrain and projects to the cortex and hippocampus. Cholinergic receptors are divided into nicotinic and muscarinic. The first pharmacological fMRI study which investigated the cholinergic system analyzed the effects of a cholinergic stimulation with the cholinesterase inhibitor physostigmine. The drug was intravenously administered to the test subjects; following drug administration test subjects performed a working memory task. In this working memory task, it was possible to analyze the BOLD activity in the different phases of memory (storage, maintenance, retrieval). On the behavioral level, cholinergic stimulation led to a slight, nonsignificant improvement in response times. The fMRI data showed that altered cholinergic neurotransmission especially increased activity in visual areas during the storage of information, whereas there were hardly any differences in recall ([6], ◘ **Fig. 3**). These findings illustrate the above-mentioned advantages of pharmacological fMRI. On the one hand pharmacological fMRI allows differentiation of drug effects on different components of cognitive performance and on the other hand it can also be more sensitive than behavioral data. Furthermore there are also several clinical pharmacological fMRI studies on the cholinergic system which demonstrate that clinically used cholinesterase inhibitors such as donepezil improve frontocortical BOLD activity in a working memory task in patients with mild cognitive impairment (MCI; [19]).

In animal experiments the cholinergic innervation of the hippocampus has been often associated with memory processes. A very influential model of Hasselmo, which is based on physiological data from animal experiments and modeling approaches, assumes that an increase in cholinergic activity promotes the storage of new stimuli, whereas the information retrieval benefits from low cholinergic activity [10]. In a pharmacological fMRI study, we demonstrated that cholinergic stimulation with physostigmine increased BOLD activity in the medial temporal lobe during the storage of stimuli, whereas physostigmine led to a decrease of activity in the medial temporal lobe during the following memory retrieval ([13], ◘ **Fig. 4**).

An additional research area, in which psychopharmacological approaches can provide deeper knowledge over and above classical animal research, are cognitive functions which, in their full expression, are specific for humans or measured differently in humans and animals. An example is prospective memory, which refers to the ability to remember an action to be performed in the future. Some classic psychopharmacological studies suggest that nicotine improves prospective memory [18]. Functional imaging studies have shown that the parietal and prefrontal cortex, particularly Brodmann's area BA10, are involved in prospective mem-

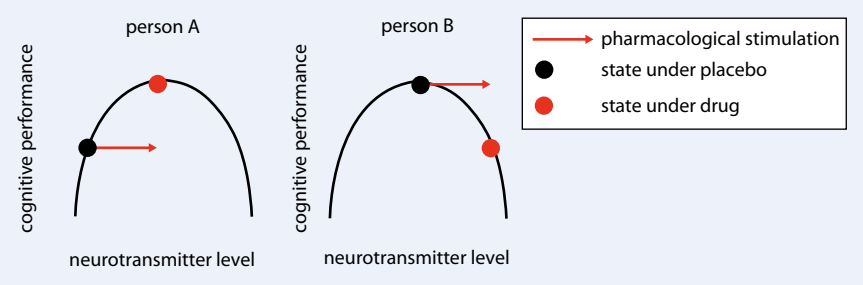

Fig. 5 ▲ A schematic illustration of the inverted U-shaped dose–response relationship. Firstly, the curve shows that both too low and too high neurotransmitter level lead to low cognitive performance. Furthermore, it is illustrated that two people—depending on their performance—can react differently to pharmacological stimulation. While person *A* shows an increase in performance, subject *B* shows a decrease in performance. The different performance at baseline can be related to, e.g. genetic differences in neurotransmitter levels

ory. To extend these findings, pharmacological fMRI was used to show that the nicotinic modulation is primarily due to a reduction in parietal activity. Furthermore, previous results found individual differences in behavior and on neuronal level that correlated with differences in genotype [4, 17].

Individual differences

Drug-induced changes of the dopaminergic or cholinergic system lead to behavioral effects which largely differ between subjects. In many studies only those subjects with initially low performance improved their memory following drug administration. This effect was explained by an inverted U-shaped dose–response relationship in which both too little or too much of dopamine or acetylcholine leads to cognitive decline (**Fig. 5**). This inverted U-shaped dose–response relationship can also explain individual differences of genetic-pharmacological neuroimaging studies, as already mentioned above for the cholinergic system. Similar effects were also found in subjects with genetically determined differences in the availability of dopamine (catechol-O-methyltransferase val158-met polymorphism) following dopaminergic stimulation. On the neural level these differences led to opposite frontocortical activations. An overview of the role of individual differences in the dopaminergic system was published by Cools and D' Esposito [3]. In our own studies, we could show that already the state of the brain prior to the drug administration accounts for at least a part of the behavioral pharmacological effects [7]. Our results suggest that future research should have a stronger focus on the role of such interindividual "brain states". In the long run brain activity measured with fMRI might be used as a diagnostic marker for the expected therapeutic effects of drugs.

Outlook

Although there are pharmacological imaging studies on various neurotransmitter systems for over 10 years, most studies have been limited to specific cognitive functions and neurotransmitter systems. Future research would profit from studies which compare the effects of one pharmacological intervention on various cognitive functions or to compare the effects of two pharmacological interventions on a single cognitive function. For example, memory-enhancing effects could be found following both cholinergic *and* dopaminergic stimulation (see above). Whether the underlying neural mechanisms are similar or different is largely unknown.

The methodological development in neuropharmacological functional imaging will follow the general trends in the field of neuroimaging. On the one hand these are characterized by a stronger focus on network analysis, on the other hand by a combination of fMRI with high temporal resolution methods such as electro- or magnetoencephalography (E/MEG). Network analyzes are useful in neuropharmacological imaging, since systemically administered drugs affect the state of the entire brain. In addition, drugs affect brain activity not only during the processing of stimuli, but also before and after task performance. This is why it is important to perform combined analyses which investigate drug effects during both during rest *and* the processing of cognitive tasks. For example, it is reasonable to assume that an increased efficiency of brain networks during rest is at least partly responsible for the procognitive effects of different drugs. A better understanding of these aspects would lead to a theory-based development of psychotropic drugs in future.

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Compliance with ethical guidelines

Conflict of interest. C. Thiel states that there are no conflicts of interest.

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