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Invited review

Pharmacological imaging as a tool to visualise dopaminergic neurotoxicity

A. Schrantee*, L. Reneman

Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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ABSTRACT

Dopamine abnormalities underlie a wide variety of psychopathologies, including ADHD and schizophrenia. A new imaging technique, pharmacological magnetic resonance imaging (phMRI), is a promising non-invasive technique to visualize the dopaminergic system in the brain. In this review we explore the clinical potential of phMRI in detecting dopamine dysfunction or neurotoxicity, assess its strengths and weaknesses and identify directions for future research. Preclinically, phMRI is able to detect severe dopaminergic abnormalities quite similar to conventional techniques such as PET and SPECT. phMRI benefits from its high spatial resolution and the possibility to visualize both local and downstream effects of dopaminergic neurotransmission. In addition, it allows for repeated measurements and assessments in vulnerable populations. The major challenge is the complex interpretation of phMRI results. Future studies in patients with dopaminergic abnormalities need to confirm the currently reviewed preclinical findings to validate the technique in a clinical setting. Eventually, based on the current review we expect that phMRI can be of use in a clinical setting involving vulnerable populations (such as children and adolescents) for diagnosis and monitoring treatment efficacy.

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1. Introduction

The dopaminergic (DA) neurotransmitter system is widely distributed throughout the brain and involved in a wide variety of CNS functions. The DA system is involved in functions such as for motivation, cognition, movement and reward. The involvement of the DA system has long been recognised in the pathophysiology of neuropsychiatric disorders, such as ADHD and schizophrenia. The current approach to studying these disorders is via targeting the DA system with pharmacological treatment. However, not much is known about the effect of these drugs and how they can alter dopaminergic functioning. For example, it has been shown that long-term use of DA drugs, such as methylphenidate, increases the risk of substance abuse in adults but not in adolescents (Wilens et al., 2003). However, the neurobiological underpinnings for this discrepancy are unknown. Therefore, it is important to investigate both the acute and chronic effects of these drugs on brain function.

At present, there is a rising awareness of the importance of brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in the field of psychopharmacology. PET has been successful in identifying receptor densities and levels of circulating enzymes as well as measuring neurotransmitter release after a pharmacological challenge. However, PET is not appropriate for repeated measurements and studies in patients, especially in the paediatric population, due to its invasiveness. As an alternative, a new technique combining fMRI with a pharmacological challenge (phMRI) shows promising results in assessing the integrity of various neurotransmitter systems. This technique is sensitive to changes in blood oxygenation as a result of neuronal activity in response to pharmacological challenges and therefore provides an index of neurotransmitter function. For this reason, as well as its non-invasive nature, it is a very promising method to measure DA imbalances in neuropsychiatric disorders.

This review aims to explore the clinical utility of phMRI in assessing the functional and dysfunctional dopaminergic system. To this end, we will give an overview of conventional neurochemical imaging modalities (PET and SPECT) in visualising DA neurotoxicity, and compare these to phMRI studies. PET/SPECT and phMRI will be compared by means of DA neurotoxicity models in animals and human drug abusers, as they provide good models to study disturbances to neurotransmitter systems in the brain. We will discuss the advantages and shortcomings of phMRI in

* Corresponding author. Department of Radiology, Room Z0-178, PO Box 22660, 1100DD Amsterdam, The Netherlands. Tel.: +31 205668324.
E-mail address: a.g.schrantee@amc.uva.nl (A. Schrantee).

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assessing DA dysfunction over conventional PET/SPECT studies. In addition, we will examine whether phMRI is ready to be used in the clinical setting and if not, what advances have to be made to achieve this goal.

2. Models of neurotoxicity

Animal models have been developed to study the intricate workings of the brain. Preclinical work has contributed tremendously to our understanding of neurotransmitter systems. Different types of animal models have been used to study the neurobiological underpinnings of neuropsychiatric disorders. Behavioural models have been used to evaluate the effect of treatment. Yet, this is not particularly informative for understanding about the neuronal basis of these disorders. Therefore, genetic models, in which genes have been modified, have been used in order to induce a certain disease state relevant to particular disorders. However, genes are often responsible for multiple neuronal processes and help to sculpt the brain in development. Interfering with these processes prevents modelling the natural development of neurotransmitter systems and may therefore mask several aspects of development that would otherwise have remained intact. Lesion models are the method of choice to investigate neurotransmitter systems and their development. By means of a physical or pharmacological lesion, neurotransmitter levels, its metabolites and receptors can be manipulated in a predictable fashion. This allows for careful assessment of dose–response relationships, interspecies differences and mechanisms of action. We have chosen the following neurotoxic lesion models because they were best represented in the molecular imaging literature and altogether give the best overview of DA neurotoxicity in both animals and humans. Neurotoxicity in this context refers to the potential of pharmacological agents to produce long-lasting changes in cell bodies and/or nerve terminals that cannot be attributed to an acute or neuroadaptive response to the drug (McCann and Ricaurte, 2004).

Several pharmacological compounds have been used to induce selective DA neurotoxicity and these are frequently used as models for clinical conditions characterized by DA cell loss, such as Parkinson's Disease (PD). In this review we will discuss 6-hydroxidopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), amphetamine (d-AMPH) and methamphetamine (METH). Unlike 6-OHDA, MPTP and d-AMPH, METH damages both the dopaminergic and serotonergic system. Other DA neurotoxins, such as Norsalsolinol and Rotenone will not be discussed, as they have not been extensively studied in this context.

6-OHDA lesions the nigrostriatal pathway and is used as an animal model of PD (Hantraye, 1998). Moreover, it has been shown to be a good model of DA neurotoxicity as its toxicity is selective for monoaminergic neurons. For specific DA neurotoxicity the noradrenaline inhibitor desipramine is often co-administered. 6-OHDA is thought to induce DA neurotoxicity through uptake by dopamine transporters and subsequently free radical formation causing neuronal damage. Although mostly used in rats, it is also a good model for other rodents and non-human primates (Gerlach and Riederer, 1996). This model is only available in an experimental setting and there have been no reports of this drug being (ab)used by humans.

MPTP is a neurotoxin that causes Parkinsonism in humans and is the main animal model for PD (Jakowec and Petzinger, 2004). It damages the DA nigrostriatal pathway and causes cell loss in the substantia nigra. It decreases concentrations of dopamine and its metabolites and reduces enzymatic activity. MPTP readily crosses the blood–brain barrier and is converted into MPP+, a toxic metabolite. MPP+ is taken up by the dopamine transporter (DAT) and subsequently inhibits mitochondrial complex I, depletes adenosine triphosphate (ATP) and consequently causes DA cell death. MPTP is not neurotoxic to the rat brain and has therefore mainly been used as a primate and mouse model of DA lesions. Although originally discovered as a substance misused by heroin addicts, it is no longer used in this way and therefore it is not a neurotoxic dopamine model in humans any more (Gerlach and Riederer, 1996).

Neurotoxic effects of d-AMPH and METH have been demonstrated by biochemical measures in many species, including rodents and primates (Davidson et al., 2001; Ricaurte et al., 1982, 2005). Histological analyses showed long lasting neurochemical deficits in DA nerve terminals after METH administration. This was accompanied by reductions in tyrosine hydroxylase (TH), DA and 3,4-dihydroxyphenylacetic acid (DOPAC). However, d-AMPH and METH administration are thought not to result in neuronal cell death (for review, see (Ricaurte et al., 1982)). METH differs from d-AMPH in that it exerts neurotoxic effects in both the DA and serotonin (5HT) system, although its effects are more pronounced for the DA system in most species (Gouzoulis-Mayfrank and Daumann, 2009). It causes degeneration of both DA and 5HT projections with cell bodies remaining undamaged (Brunswick et al., 1992). This is reflected by reduced DA and 5HT concentrations, reduced metabolite levels and decreased transporter density (Seiden and Sabol, 1996). Research has also shown neurotoxicity of d-AMPH and METH in humans. Both drugs are widely abused and therefore provide important models to study DA neurotoxicity in humans.

6-OHDA and MPTP are best studied in animals because of the extensive and obvious damage they induce in DA neurons, primarily by measuring DAT and D1/D2 receptor densities. However, the relatively mild damage caused by d-AMPH and METH might better reflect dopaminergic abnormalities as observed in neuropsychiatric disorders and are therefore important translational models. Furthermore, abuse of d-AMPH and METH is currently the only possible way to study DA neurotoxicity in humans.

3. Neurochemical imaging methods

The first methods to investigate DA neurotoxicity were conventional 'ex vivo' methods such as autoradiography and immunohistochemistry. These techniques have contributed significantly to the understanding of the DA system. Their strength lies in the high spatial resolution and they can be adapted to reflect neuronal activation, perfusion or metabolism. However, due to the invasive nature of these conventional techniques experimental animals can only be studied once, which does not render them useful for longitudinal designs. Other techniques such as microdialysis and cyclic voltammetry provide 'in vivo' measures of dopamine release and can be used in longitudinal studies, but they cannot be easily translated to human studies. In contrast, neuroimaging techniques such as PET, SPECT and especially MRI allow repeated or longitudinal measurements and can be used in vulnerable populations such as the elderly and paediatric population and patients. Indeed, these imaging techniques are already in use in clinical settings for accurate diagnostic purposes.

PET and SPECT both utilize pharmacologically or biochemically active compounds labelled with radionuclides to produce images of in vivo ligand distribution measured by an external detector. Thus, they can provide an index of number of transporters or extracellular levels of dopamine. PET isotopes have shorter half-lives than those used in SPECT. This results in better spatial and temporal resolution and therefore PET is more sensitive than SPECT. As a consequence, PET can be used for absolute quantification of tracer concentrations in the tissue. However, SPECT radiotracers are less costly and the equipment is more widely available. Nevertheless, both PET and SPECT have a relatively poor spatial resolution reducing the utility

to map subtle changes (Otte and Halsband, 2006). In addition, the binding potential of the available radioligands for the dopamine system is not potent enough to estimate receptor binding in all brain areas. Therefore, phMRI was put forward as an exciting new imaging modality because it is widely available, has a better spatial resolution and allows whole-brain visualisation of dopaminergic functioning. Most importantly, it can be used for longitudinal studies and is safe in vulnerable populations, such as children (Matthews et al., 2006).

MRI has widely been used to assess the brain's anatomical features (structural MRI) and its function (fMRI). fMRI utilises changes in magnetic properties of haemoglobin to investigate brain function (Jezzard et al., 2003). Increased activity of neurons induces a cascade of neurotransmitter and metabolite release, which is accompanied by an increase in local cerebral blood flow (CBF), volume (CBV) and oxygenation through a process called 'neurovascular coupling' (Logothetis and Pfeuffer, 2004). fMRI measures the blood oxygenation level dependent (BOLD) change in signal intensity over time. phMRI, like fMRI, measures changes in brain hemodynamics, but instead of a task to probe neuronal function the subject receives a pharmacological challenge. It offers the potential to study different hemodynamic processes using a contrast agent, BOLD or arterial spin labelling (ASL). CBV-phMRI utilises an exogenous intravascular contrast agent that sensitizes the images to relative CBV (rCBV). ASL-phMRI magnetically labels arterial blood water to provide an endogenous tracer for CBF measurements. In BOLD-phMRI the contrast is provided a difference in susceptibility between oxy- and deoxyhemoglobin. The change in brain hemodynamics induced by a neurochemical compound is thought to give an index of neurotransmitter function (Honey and Bullmore, 2004). Recent studies have demonstrated that MRI is sensitive to manipulations of the DA system. Signal changes have been observed in rats, monkeys and humans after administration of DA drugs such as d-AMPH and cocaine and the cocaine analogue CFT (Breiter et al., 1997; Chen et al., 1996, 1997; Honey et al., 2003), which correlate with extracellular concentrations of DA.

4. Imaging DA neurotoxicity

4.1. 6-ODHA

4.1.1. PET/SPECT

It has been shown that PET and SPECT studies can adequately detect nigrostriatal neurotoxicity resulting from 6-OHDA lesions. For example, using [^{123}I]-β-CIT SPECT, Scherfler et al. (2002) demonstrated reduced striatal binding (−59%) in 6-OHDA treated rats, which correlated positively with DA cell counts in the striatum. [^{123}I]-β-CIT is a radioligand for SPECT experiments that assesses DAT levels. Casteels et al. (2008) imaged DAT binding with the radiotracer [^{11}C]-FECT for PET studies. Rats received unilateral injections of 6-OHDA (24 μg) into the substantia nigra, which resulted in decreased binding levels in the caudate-putamen (−96%), nucleus accumbens (−89%) and substantia nigra (−75%) ipsilaterally. In mice, dose dependent reductions (2 or 4 μg) in DAT (−49 and −61%) were found, using the [^{11}C]-methylphenidate PET tracer, and this correlated with ex-vivo autoradiography (Fischer et al., 2011). Sun et al. (2010) evaluated both presynaptic and postsynaptic binding in two models, namely 6-OHDA injection (7 μg) into the striatum and medial forebrain bundle (MFB). Using the PET ligand [^{11}C]CFT they found reduced DAT levels in both models (−24 and −63% respectively). In contrast, using [^{11}C]-raclopride to assess postsynaptic D2 integrity, they found increases in D2 levels in the MFB model (+35%) but decreases in the striatal model (−18%). This suggests that different lesion sites might result in disparate dynamic pathophysiological processes. This is in agreement with a study reporting dose-dependent decreases in DAT (−92%) but increased D2 binding (+12%) in rats injected with 1 or 8 μg 6-OHDA into the medial forebrain bundle (Inaji et al., 2005).

Table 1
PET/SPECT and phMRI studies of the 6-OHDA neurotoxic model.

Article	Species	Neurotoxic model	PET/SPECT tracer	Brain areas	% Change	phMRI challenge	Brain areas	% Change
Scherfler et al. (2002)	Rat	8 μl in MFB	[^{123}I]β-CIT (DAT)	↓ Striatum, midbrain	−59			
Inaji et al. (2005)	Rat	1 or 8 μg in MFB	[^{11}C]PE2I (DAT)	↓ Striatum	−92			
			[^{11}C]raclopride (D2)	↑ striatum	+12			
Sossi et al. (2007)	Rat	8 μg in MFB	[^{11}C]DTBZ (DAT)	↓ Striatum	−83			
Casteels et al. (2008)	Rat	24 μg in SN	[^{18}F]FECT (DAT)	↓ Striatum	−96			
				↓ NAcc	−89			
				↓ SN	−75			
Sun et al. (2010)	Rat	7 μg in striatum	[^{11}C]CFT (DAT)	↓ Striatum	−24			
		7 μg in MFB	[^{11}C]raclopride (D2)	↓ Striatum	−18			
			[^{11}C]CFT (DAT)	↓ Striatum	−63			
			[^{11}C]raclopride (D2)	↑ Striatum	+35			
Fischer et al. (2011)	Mouse	2 μg in striatum	[^{11}C]MPH (DAT)	↓ Striatum	−49			
		4 μg in striatum			−61			
Chen et al. (1997)	Rat	8 μg in MFB	[^{11}C]CFT (DAT)	↓ Striatum	−42	AMPH (DAT)	↓ Striatum	−45
						CFT (DAT)	↓ Striatum	−48
Chen et al. (1999)	Rat	8 μg in MFB	[^{11}C]CFT (DAT)	↓ Striatum[a]	−40	AMPH (DAT)	↓ Striatum	−39
						CFT (DAT)	↓ Striatum	−42
Nguyen et al. (2000)	Rat	8 μg in SN	[^{11}C]CFT (DAT)	↓ Striatum	−75	AMPH (DAT)	↓Striatum	−64
			[^{11}C]raclopride (D2)	↑ Striatum	+22	Apomorphine (D1/D2)	↓Thalamus	N.A.
							↓Frontal cortex	N.A.
							↑ Striatum	+42
							↑Thalamus	N.A.
							↑Frontal cortex	N.A.
Björklund (2002)	Rat	24 μg in striatum	[^{11}C]CFT (DAT)	↓Striatum[b]	−75	AMPH (DAT)	↓ Striatum[c]	∼−100
							↓ Sensorimotor cortex	∼−100
Sánchez-Pernaute et al. (2007)[d]	Rat	8 μg in MFB with L-DOPA treatment				7-OHDPAT	↑ Striatum	+40
							↑ NAcc	

[a] Recovery after neural transplantation.
[b] Recovery after embryonic stem cell transplantation 75–90% of intact striatum.
[c] Recovery after embryonic stem cell transplantation similar to intact striatum and sensorimotor cortex.
[d] phMRI changes are observed only in the dyskinetic group.

Furthermore, another presynaptic marker, vesicular monoamine transporter (VMAT2), can be used to assess DA neurotoxicity. VMAT is a presynaptic intracellular protein that transports DA from the cytosol to synaptic vesicles and it is thought to reflect DA integrity. Its levels can be assessed using PET with the [^{11}C]-DTBZ tracer. Sossi et al. (2007) found reduced VMAT (−83%) levels in the rat striatum after 6-OHDA injection as measured by [^{11}C]-DTBZ-PET (Table 1).

4.1.2. phMRI

Chen et al. (1997) lesioned rats unilaterally with 6-OHDA and found a prominent loss of response to a d-AMPH and CFT challenge in the ipsilateral hemisphere compared to the contralateral hemisphere. The rCBV response (−45–48%) closely resembled the results from microdialysis and [^{11}C]CFT-PET (−42%) in the same animals and was not correlated with physiological parameters such as pCO_2, heart rate or blood pressure. The same model was employed to study both presynaptic and postsynaptic DA functioning by means of phMRI and PET (Nguyen et al., 2000). A contrast agent was injected in order to measure rCBV. D-AMPH administration increased rCBV in the striatum, thalamus and frontal cortex of the intact hemisphere, whereas the increase in hemodynamic response was much smaller in the lesioned hemisphere (64%). This was in line with [^{11}C]CFT-PET showing reduced DAT binding in the same animals in the striatum (−75%). Apomorphine (D1/D2 agonist), on the other hand, produced an increase in rCBV by 42% in the same areas in the lesioned hemisphere compared to the intact hemisphere, accompanied by an increased D2 binding as measured by [^{11}C]-raclopride PET (+22%). These results suggest a reduction of DAT combined with D1/D2 receptor supersensitivity. The fact that rCBV was larger in the lesioned hemisphere than in the intact hemisphere suggests an increase in excitatory postsynaptic activation and as such stronger D1 than D2 supersensitivity. One of the translational approaches that would have considerable potential for the clinic is evaluation of treatment methods by phMRI. For example Chen et al. (1999) induced a unilateral 6-OHDA lesion resulting in >95% denervation in the striatum. After an i.v. challenge of CFT or d-AMPH the BOLD response was increased in the intact hemisphere but

Table 2
PET/SPECT and phMRI studies of the MPTP neurotoxic model.

Article	Species	Neurotoxic model	PET/SPECT tracer	Brain areas	% Change	phMRI challenge	Brain areas	% Change
Hantraye et al. (1992)	Monkey	3 days of 3 × 0.7 mg/kg i.v.	[^{11}C]CFT (DAT)	↓ Caudate ↓ Putamen	−94 −93			
Pate et al. (1993)	Monkey	NA[a]	[^{18}F]F-DOPA (DA synthesis)	↓ Striatum	NA			
Brownell et al. (1998)	Monkey	0.6 mg/kg every 2 weeks until behavioural stability i.v.	[^{11}C]CFT (DAT)	↓ Caudate ↓ Putamen	−45 −70			
Eberling et al. (1999)	Monkey	2.5–4 mg intracarotid	[^{123}I]-β-CIT (DAT)	↓ Striatum	NA			
Doudet et al. (2002)	Monkey	2–2.5 mg/kg i.v. or 0.3–3.2 mg/kg intracarotid[b]	[^{11}C]raclopride (D2)	↑ Caudate; putamen	+27			
Saji et al., 2003	Marmosets	2.5 mg/kg i.v.	[^{123}I]-β-CIT (DAT)	↓ Striatum[c]	−70			
Andringa et al., 2005	Mouse	25 mg/kg i.p. 1 day 25 mg/kg i.p. 3 days 25 mg/kg i.p. 5 days	[^{123}I]FP-CIT (DAT)	↓ Striatum ↓ striatum ↓ striatum	−59 −82 −76			
Nagai et al. (2007)	Monkey	0.5 mg/kg/day i.m. until tremor	[^{11}C]PE21 (DAT) [β-^{11}C]DOPA (DA synthesis) [^{11}C]raclopride (D2)	↓ caudate ↓ Putamen ↓ Caudate ↓ Putamen No change	−85 −90 −66 −76			
Chen et al. (2008)	Monkey	0.1 mg/kg for two weeks, then 0.2 mg/kg for 7–8 months i.v.	[^{11}C]DTBZ (VMAT2) [^{11}C]raclopride (D2) [^{11}C]raclopride + AMPH (DA release)	↓ Caudate ↓ Putamen No change ↓ Striatum	−46 −35 −29			
Chen et al., 1996	Monkey	0.4 mg/kg intracarotid				Levodopa (DA precursor)	↓ Caudate; putamen	NA
Jenkins et al., 2004[d]	Monkey	0.3–0.5 mg/kg/week over 6 months i.v.	[^{11}C]CFT (DAT)	↓ Posterior putamen	−52	AMPH (DAT)	↓ Caudate ↓Putamen ↓ Cingulate cortex ↓ Insular cortex ↓NAcc ↓Precentral gyrus ↓pThal ↓ Red nucleus, ↓ VTA ↓ SN ↓ Dentate cerebellum	−91 −86 −49 −100 −37 −88 −51 −106 −100 −112 −109
Zhang et al., 2006	Monkey	2.4 mg intracarotid				AMPH (DAT) Apomorphine (D1/D2)	↓ Putamen, SN ↑ Putamen, SN	NA NA
Luan et al., 2008	Monkey	2.4 mg intracarotid				Apomorphine (D1/D2)	↑ Caudate; putamen[e]	NA
Sánchez-Pernaute et al. (2007)[f]	Monkey	0.3–0.5 mg/kg/week over 6 months i.v. with L-DOPA treatment	[^{11}C]CFT (DAT)	↓ posterior putamen	−55	7-OHDPAT	↑ Putamen	+20

[a] Full text article not available.
[b] Only in symptomatic parksonian monkeys.
[c] Recovery after deprenyl.
[d] Percentage change over −100 means reversed response: i.e. deactivation instead of activation.
[e] Recovery after GDNF.
[f] The PET studies are in both in the dyskinetic and non-dyskinetic group, phMRI changes only in the dyskinetic group.

significantly attenuated in the lesioned hemisphere (−39 to −42%). This was partially restored by transplantation of fetal cells. These results were correlated with [^{11}C]CFT PET imaging (−40%) and behavioural profiles. In a comparable model, female rats were injected stereotactically with 6-OHDA to induce a DA lesion and assessed with [^{11}C]CFT PET and phMRI (−75 and −100% respectively). Mouse embryonic stem cells were implanted into the rat striatum and DA function was evaluated again. rCBV changes after an intravenous d-AMPH challenge parallel [^{11}C]CFT PET and behavioural results indicating afunctional recovery of DA neurons in these lesioned rodents (Björklund et al., 2002). phMRI can also be used to assess side effects of treatment. Sánchez-Pernaute et al. (2007) induced 6-OHDA induced Parkinsonian symptoms in rats and treated some with L-dopa, which induced dyskinesias and compared their response to the D3 agonist 7-OHDPAT with the response of naïve rats. Naïve and Parkinsonian rats displayed a decreased CBV response whereas the L-DOPA-treated dyskinetic rats showed an increased CBV response. This could be explained through D3 receptor sensitisation which could in turn enhance D1 receptor signalling, resulting in an increased CBV response. The same experiment was repeated in non-human primates lesioned with MPTP and similar results were obtained (see Table 2).

4.1.3. Conclusion

PET and SPECT imaging studies have shown to be sensitive to detect changes to the dopaminergic system induced by a 6-OHDA lesion when compared to more conventional markers of dopaminergic toxicity in the above-mentioned animal studies. Radioligands assessing presynaptic DA function showed dose-dependent decreases in DAT and VMAT in the striatum of the rat brain and some studies reported additional deficits in the NAcc and SN. In addition, alterations in postsynaptic function were detected, but the direction of change is dependent on the injection site (MFB, SN or striatum). When compared to PET and SPECT, phMRI appears to be sensitive to detect changes in DA terminals to a similar extent. Both presynaptic and postsynaptic challenges with phMRI corroborate the results found in PET and SPECT imaging: dose dependent reductions in striatal brain activity are observed when targeting the DAT, whereas an increase is seen when targeting D1/D2 receptors. In the four studies in which direct comparisons were made between PET and phMRI, the extent of the changes were very similar between both techniques and did not differ by more than an average of 13%. However, with phMRI more activated brain areas were identified than were observed with PET/SPECT studies, which may be due to the chosen analysis method (ROI or voxel-by-voxel) and the reduced sensitivity of PET/SPECT in certain brain areas.

4.2. MPTP

4.2.1. PET and SPECT

Monkeys that were treated with low and high doses of MPTP exhibited reduced DAT binding. This was measured by the PET tracer [^{11}C]CFT, a selective radioligand for the DAT. A high dose of MPTP resulted in binding values diminished by 94% in the caudate nucleus and 93% in the putamen, whereas a low dose yielded decreases of 65% and 67% respectively. This was confirmed by immunohistochemical analyses of reduced tyrosine hydroxylase post-mortem (Hantraye et al., 1992). After chronic administration of MPTP, Brownell et al. (1998) performed [^{11}C]CFT PET scans in 5 cynomolgus monkeys and reported decreased DAT levels in the caudate and putamen (−45 and −70%). Scans were repeated and a faster decline was found for the putamen than the caudate nucleus. The assessment of dopamine terminal integrity can also be achieved with [^{18}F]F-DOPA PET, which reflects dopamine synthesis capacity. Pate et al. (1993) revealed decreased FDOPA binding values which correlated with histochemical and biochemical data. Nagai et al. (2007) replicated these findings with [β-^{11}C]DOPA (−66%). Chen et al. (2008) investigated receptor binding of the vesicular transporter VMAT with the [^{11}C]-DTBZ tracer in a monkey MPTP model and demonstrated VMAT reductions (−35 to −46%). This was detectable before symptomatic behaviour and is therefore promising as a biomarker of abnormal functioning in the presynaptic DA terminal. Reports on the postsynaptic changes as measured by [^{11}C]raclopride in MPTP treated monkeys are inconsistent. Chen et al. (2008) and Nagai et al. (2007) did not find any changes in D2 binding, whereas Doudet et al. (2002) observed an increase in D2 binding, but only in symptomatic subjects (+27%).

The DAT can also be studied with the SPECT tracer [^{123}I]β-CIT. Eberling et al. (1999) found that [^{123}I]β-CIT-SPECT was viable to assess the extent of nigrostriatal damage in MPTP-lesioned monkeys. [^{123}I]β-CIT-SPECT has also been used to test whether certain drugs could provide neuroprotection against DA lesions. For example, in MPTP-lesioned marmosets, pre-treatment with deprenyl resulted in similar accumulation of [^{123}I]β-CIT-SPECT in the striatum to control animals, compared to reduced accumulation (−70%) in animals that did not receive this pre-treatment (Saji et al., 2003). In an MPTP mouse model, Andringa et al. (2005) demonstrated that [^{123}I]FP-CIT-SPECT and immunocytochemistry results were highly comparable. A dose related effect was reported, where increasing number of treatment days resulted in more marked reductions (60–80%) in tracer binding. However, they conclude that although [^{123}I]FP-CIT-SPECT has shown promise in identifying the extent of the lesion in a moderate to severe damaged DA system, more studies are necessary to evaluate the value of this radioligand in detecting small DA lesions.

4.2.2. phMRI

Chen et al. (1996) injected MPTP into the right carotid artery of monkeys which subsequently developed Parkinsonian features. PhMRI revealed reduced signal intensity after a levodopa challenge in the caudate and putamen after MPTP administration compared to that at baseline. In another study, cynomolgus monkeys received MPTP lesions and were challenged with d-AMPH 2.5 mg/kg i.v. (Jenkins et al., 2004). A contrast agent was administered and d-AMPH increased rCBV in control monkeys, whereas MPTP-treated animals demonstrated marked loss of response to d-AMPH in dopamine-rich brain regions and even reversed responses; i.e. deactivation instead of activation (see Table 2). The rCBV loss in the SN was associated with DAT binding as measured by PET ($R = 0.71$) and behavioural indices ($R = 0.73$). Zhang et al. (2006) administered apomorphine and d-AMPH to MPTP-lesioned monkeys. This revealed an increased BOLD response after apomorphine administration in the putamen and SN of the affected hemisphere compared to the control hemisphere. The response to d-AMPH was the opposite, thus producing a decreased BOLD response in the affected hemisphere compared to the control hemisphere. d-AMPH evoked activation was correlated with the number of surviving neurons in the SN as detected by post-mortem examinations. This suggests phMRI could be a biomarker for the survival of DA neurons in the SN, which is of great relevance for research on Parkinson's disease for example. Interestingly, phMRI has also been used to monitor the effect of pharmacological therapy. Rhesus monkeys unilaterally injected with MPTP showed increased activation in the caudate and putamen after apomorphine administration. Subsequent chronic intraputamenal infusion of glial cell-line derived neurotrophic factor (GDNF) reversed the apomorphine increased activation observed after MPTP administration (Luan et al., 2008).

4.2.3. Conclusion

Similar to 6-OHDA, phMRI studies corroborate the results found in PET and SPECT imaging with several different drug challenges and demonstrated adequate sensitivity to detect MPTP lesions in non-human primates. Both PET/SPECT and phMRI studies report decreases in presynaptic indices of DA function, such as the DAT, VMAT and DA synthesis. In one study that directly compared phMRI with PET (Jenkins et al., 2004), a correlation was observed of $R = 0.71$ between both imaging techniques. phMRI was able to detect MPTP-induced changes in other brain areas than the striatum. Postsynaptically, the results for PET/SPECT were equivocal, only demonstrating D2 changes in symptomatic monkeys in one out of three studies. Results from phMRI studies revealed increased postsynaptic activity when apomorphine was administered, whereas with [11C]raclopride no changes or reductions in striatal D2 receptors were observed with PET. This discrepancy might be due to apomorphine being an unspecific DA-agonist, whereas raclopride is specific for the D2 receptor. Finally, as for PET/SPECT, phMRI was successful in the monitoring of treatment strategies in MPTP-lesioned animals.

4.3. d-AMPH and METH

4.3.1. PET/SPECT

4.3.1.1. d-AMPH. Ex vivo studies have demonstrated that repeated doses of d-AMPH damage striatal neurons in experimental animals, as indicated by reductions in DAT (Mintz et al., 1994; Ricaurte et al., 2005). Subsequently, these results were replicated using PET and SPECT. Melega et al. (1996) studied presynaptic dopamine integrity using [^{18}F]F-DOPA PET in vervet monkeys that were administered an increasing dose of d-AMPH over a 10 day period. They were scanned at 1–6 weeks post-treatment and showed a significant reduction in dopamine synthesis as reflected by a 70% reduced striatal F-DOPA uptake. This was parallelled by 95% reductions in DA concentrations and the HVA/DA ratio increased 3–10 fold as measured by biochemical analysis. However, follow-up scans at 5–6 months show relative increase of F-DOPA uptake (−47%) compared to acute effects, indicating partial recovery of dopamine synthesis. Similar results were obtained in monkeys receiving a different dose regimen (see Table 3) (Melega et al., 1997). Repeated d-AMPH administration in rats induced loss of [^{123}I]FP-CIT binding to DAT (Booij et al., 2006). Striatal binding was reduced by 17% compared to control rats.

d-AMPH-induced neuronal damage has also been studied in human drug users using [^{123}I]β-CIT-SPECT. Participants with an average lifetime use of 48 times (one dose approximately 0.4 mg/kg) display a 20% reduction in DAT binding levels compared to controls (Reneman et al., 2002), replicating previous observations in rats by the same group.

4.3.1.2. METH. Melega et al. (1997) compared METH to d-AMPH neurotoxicity in monkeys using [^{18}F]F-DOPA PET and found no differences between groups (both −65% reduction), indicating that METH also affects presynaptic dopamine integrity with partial reversibility over time.

The dopamine transporter has received much attention in METH research. One study in monkeys showed 75% reduction in [^{11}C]β-CFT binding after a neurotoxic METH regime (Melega et al., 1998). In another model in non-human primates mimicking human recreational use, baboons show reductions in striatal DAT revealing a dose–response relationship (−39 to −60%). These changes were highly correlated ($r = 0.77$) with in vitro [^{11}C]β-CFT changes as well as decreases in DA and DOPAC (Villemagne et al., 1998). Repeated measurements of the DAT with [^{11}C]β-CFT show partial recovery of binding levels after METH administration in non-human primates (Harvey et al., 2000; Melega et al., 2000). Immunoreactivity profiles also returned to control levels although some regional deficits remained. Furthermore, no evidence of loss of cell bodies in the ventral midbrain was found.

In humans, four groups have investigated DAT levels in METH users. For a detailed overview of these studies, see (Chang et al., 2007). In summary, all groups found decreased DAT binding in the striatum despite differences in radiotracers and subject characteristics (Johanson et al., 2006; McCann et al., 1998; Sekine et al., 2001, 2003; Volkow et al., 2001c). A longitudinal study found changes in DAT levels that recovered after prolonged abstinence (Volkow et al., 2001b). This was in concordance with a post-mortem study showing altered levels of DAT, TH and D2 receptors, but not DOPA decarboxylase and VMAT (Wilson et al., 1996). The latter two are also markers of presynaptic DA integrity and together these results suggest a reversible pattern of DA terminal alterations after METH abuse. Only two studies have investigated VMAT levels and they reported conflicting results. One study demonstrated a 10% decrease (Johanson et al., 2006), whereas the other showed an 11–22% increase in VMAT binding (Boileau et al., 2008). This discrepancy has been attributed to [^{11}C]-DTBZ not being a stable marker to measure this protein (Boileau et al., 2008).

In addition to presynaptic markers, Volkow et al. (2001a) investigated the effect of METH on D2 postsynaptic receptors using PET [^{11}C]raclopride. They demonstrated reduced binding (−10 to −16%) in METH users compared to controls, which seems paradoxical with reported chronic low striatal DA levels (Wilson et al., 1996). Furthermore, using [^{18}F]fallypride Lee et al. (2009) reported reduced striatal D2/D3 receptor availability (−8 to −16%), whereas the nucleus accumbens did not differ between groups. Wang et al. (2011b) discovered that in addition to reduced baseline D2 receptors (∼−11%), METH users also show lower DA increases after a MPH challenge compared to controls as measured with [^{11}C] raclopride, particularly in the caudate nucleus (−12%). Interestingly, a subgroup of the METH users in this study relapsed and this particular group showed no increase in DA release after the MPH challenge. This suggests that the response to a raclopride + MPH challenge could be used as a potential biomarker to predict relapse. With the availability of a more specific tracer, such as [^{11}C]PHNO, it is now possible to distinguish between D2 and D3 receptor uptake. METH users showed higher binding in the D3-rich SN (+46%), globus pallidus (+11%) and ventral pallidum (+4%), whereas binding was slightly decreased in D2-rich striatum (−4%).

4.3.2. phMRI

To our knowledge, only one study so far has investigated the amphetamine neurotoxicity with phMRI in humans. In an ASL-phMRI experiment MPH (35 mg) was administered orally to amphetamine users and controls (Schouw et al., 2013a). MPH administration induced a significant decrease in CBF in control subjects in the striatum, hippocampus, thalamus and prefrontal cortex (10–29%). In contrast, d-AMPH users only showed a slight CBF decrease in the hippocampus and displayed a blunted response in other brain regions studied, presumably reflecting d-AMPH induced changes in neurotransmitter function and thus also changes in hemodynamic function. DAT availability was also assessed using [^{123}I]FP-CIT and a trend towards lower DAT binding in amphetamine users was observed in the striatum. Yet, contrary to results in animal studies no correlation was found between DAT binding and CBF measures.

4.3.3. Conclusion d-AMPH/METH

The damage induced by d-AMPH and METH to dopaminergic neurons has been extensively studied with PET and SPECT in rodents and non-human primates. These studies consistently revealed decreased DA synthesis and decreased DAT levels. The effect of d-AMPH and METH on VMAT remains unclear, but it appears to reduce

Table 3
PET/SPECT and phMRI studies of the AMPH and METH neurotoxic model.

Article	Species	Drug	Neurotoxic model	Time postdrug	PET/SPECT tracer	Brain area	% Change
Melega et al. (1996)	Monkey	AMPH	4–18 mg/kg/day over a 10 day period	6 weeks 20–24 weeks	[^{18}F]F-DOPA (DA synthesis)	↓ Striatum	−70 −47
Melega et al. (1997)	Monkey	AMPH	2 × 2 mg/kg, i.m., 4 h apart	1 week 3–6 weeks	[^{18}F]F-DOPA (DA synthesis)	↓ Striatum	−65 −56
Booij et al. (2006)	Rat	AMPH	10 mg/kg twice daily, for 5 days	5 days	[^{123}I]FP-CIT (DAT)	↓ Striatum	−17
Melega et al. (1997)	Monkey	METH	2 × 2 mg/kg, i.m., 4 h apart	1 week	[^{18}F]F-DOPA (DA synthesis)	↓ Striatum	−65
Melega et al. (1998)	Monkey	METH	2 × 2 mg/kg, i.m., 4 h apart	1–2 weeks	[^{11}C]CFT (DAT)	↓ Striatum	−75
Villemagne et al. (1998)	Monkey	METH	0.5 mg/kg 4 × 2 h apart i.m. 1 mg/kg 4 × 2 h apart i.m. 2 mg/kg 4 × 2 h apart i.m.	2–3 weeks	[^{11}C]CFT (DAT)	↓ Striatum ↓ Striatum ↓ striatum	−39 −44 −60
Harvey et al. (2000)	Monkey	METH	2 × 2 mg/kg, 6 h apart	1 week 1.5 years	[^{11}C]CFT (DAT)	↓ Striatum ↓ Striatum	−80 −10

Article	Species	Drug	Exposure	Time postdrug(abstinence)	Tracer (PET/SPECT)	Brain area	% Change
Reneman et al. (2002)	Humans	AMPH	Mean = 4.4 years[b]	NA	[^{123}I]β-CIT (DAT)	↓ Striatum	−20
McCann et al. (1998)	Humans	METH	Mean = 6 years	3 years	[^{11}C]CFT (DAT)	↓ Caudate ↓ Putamen	−23 −25
Volkow et al. (2001c)		METH	At least 2 years	2 weeks-5 months	[^{11}C]raclopride (D2)	↓ Caudate ↓ Putamen	−16 −10
Volkow et al. (2001a,b)	Humans	METH	Mean = 11 years	5.9 months 9 months	[^{11}C]MPH (DAT) [^{11}C]MPH (DAT)	↓ Caudate ↓ Putamen ↑ Caudate[a] ↑ Putamen[a]	−28 −21 +19 +16
Sekine (2001, 2003)	Humans	METH	Range 1 month–15 years	7 days–1.5 years	[^{11}C]CFT (DAT)	↓ Caudate; putamen ↓ NAcc ↓ PFC ↓ OFC ↓ DLPFC ↓ Amygdala	−20 −30 −33.3 −39 −7 −42
Johanson et al. (2006)	Humans	METH	Mean = 10.3 years	At least 3 months	[^{11}C]CFT (DAT) [^{11}C]DTBZ (VMAT2)	↓ Striatum ↓ Striatum	−15 −10
Boileau et al. (2008)	Humans	METH	Mean = 5.1 years	1 week 7–21 weeks >21 weeks	[^{11}C]DTBZ (VMAT2)	↑ Caudate ↑ Putamen ↑ Ventral striatum ↑ Striatum ↑ Striatum ↑ Striatum	+22 +12 +11 +41 +15 +9
McCann et al. (2008)	Humans	METH	Mean = 7 years	28 months	[^{11}C]CFT (DAT)	↓ Left caudate ↓ Right caudate ↓ Left putamen ↓ Right putamen	−23 −22 −21 −13
Lee et al. (2009)		METH	Mean = 12.5 years	4–10 days	[^{18}F]fallypride (D2)	↓ Caudate ↓ Putamen ↓ NAcc	−16 −13 −8
Wang et al. (2011b)	Humans	METH	Mean = 13.1 years	~6 months	[^{11}C]raclopride (D2) [^{11}C]raclopride + AMPH challenge (DA release)	↓ Caudate ↓ Putamen ↓ Ventral striatum ↓ Caudate ↓ Putamen ↓ Ventral striatum	−11 −9 −12 −12 −3 −4
Boileau et al. (2012)	Humans	METH	Mean = 5.1 years	18.5 days	[^{11}C]PHNO (D2/D3)	↑ SN ↑ Global pallidus ↑ Ventral pallidum ↓ Dorsal striatum	+46 +9 +11 −4

Article	Species	Drug	Exposure	Time postdrug(abstinence)	phMRI challenge	Brain area	% Change
Schouw et al. (2013a,b)	Humans	AMPH	Mean = 13.9 years	1.1 months	Methylphenidate (DAT)	↓Hippocampus[c] ↓Striatum ↓Thalamus ↓ PFC ↓ ACC ↓ Cerebellum	−12 −8 −44 −7 −5 −31

[a] An increase compared to previous timepoint, not to controls.
[b] Compared ecstasy users with ecstasy + amphetamine users.
[c] Compared to controls, d-AMPH users show a blunted response, less decrease in CBF.

levels of D2 receptors while increasing D3 receptors. Similarly to ex vivo studies, no cell loss was observed, and only changes to the dopaminergic nerve terminals were found. Furthermore, abstinence resulted in recovery of DAT levels. Until now, only one study has evaluated phMRI in animals or humans with d-AMPH induced dopaminergic changes. A blunted CBF response to oral MPH was observed in d-AMPH users compared to controls. This is in line with primate and rodent studies with MPTP and 6-OHDA induced DA neurotoxicity which also report blunted hemodynamic responses. However, these studies differ in that MPTP and 6-OHDA lesions induce a stronger blunted hemodynamic response than d-AMPH pre-treatment does, which corroborates the idea that whereas MPTP

and 6-OHDA induces dopaminergic cell death, d-AMPH leaves the cell bodies intact. However, unlike some of the MPTP and 6-OHDA studies, in the human d-AMPH study CBF changes did not correlate with DAT availability, which raises the question of what changes in the dopamine system we are actually measuring. It could reflect DA receptor density or extracellular DA concentrations or a combination of these. Therefore, further research is needed to establish the neural correlates contributing to (ASL) phMRI signal changes.

4.4. Summary

This review of the literature demonstrates that phMRI is an adequate method to assess dopaminergic function and severe dysfunction in the preclinical setting. In animal models of 6-OHDA and MPTP neurotoxicity phMRI and PET/SPECT imaging provided very similar results. With respect to d-AMPH and METH models, only one phMRI study has been conducted. Therefore, additional research is needed to confirm whether phMRI can identify d-AMPH and/or METH induced DA dysfunction to the same extent as the PET/SPECT studies discussed above. This is important, because 6-OHDA and MPTP models induce severe loss of DA neurons and function, whereas d-AMPH and METH administration induces more variable and less extensive imbalances in the DA system. The latter model is therefore more relevant for the clinical setting. Validation of phMRI in assessing DA dysfunction in d-AMPH and/or METH users would be the ultimate step before this technique can be used in clinical practice, for instance in assessing DA dysfunction in neuropsychiatric disorders in vulnerable populations, such as children suffering from ADHD.

5. Pharmacological manipulation of the dopamine system

In order to optimally profit from pharmacological manipulation of the dopamine system it is important to decide which drug to use for phMRI. The functionality and efficiency of the DA system is dependent on a complex interplay between DA synthesis, DA release, basal and tonic levels of activation, number of (internalised) receptors and transporters, autoreceptors and rate-limiting enzymes. A combination of several ligands makes it possible to disentangle drug effects on these individual processes. A study by Chen et al. (2010) illustrates this wonderfully by using multiple DA challenges to characterise the differences in dopamine system between juvenile and adult rats in great detail. It is also important to consider variations in DA receptor distributions when interpreting phMRI results. For example, the NAcc is rich is D3 receptors, which have a much higher affinity for DA than postsynaptic D1 receptors (Sokoloff et al., 1992). D3 agonism induces a decrease in rCBV, whereas D1 agonism increases rCBV which has the implication that increasing DA efflux in the NAcc will show a net decrease of rCBV. Conversely, D1 receptors are more densely distributed in the striatum than D3 receptors. Furthermore, D2 autoreceptors play an important role in modulating “synaptic” dynamics and they have a much higher affinity for dopamine than D2 postsynaptic receptors (Chen et al., 2010). These factors need to be taken into account when designing the phMRI experiment. Besides the effect of dopamine on postsynaptic neurotransmission, it is also interesting to consider the effect of dopamine on the microvasculature. Choi et al. (2006) demonstrated that D1/D5 receptors are located directly on microvessels that induce vasodilatation. In contrast, D2/D3 receptors are not found on microvasculature, but can influence the hemodynamic coupling through astrocytic vasoconstriction. Therefore, the overall hemodynamic response is probably a mixture between vascular and neuronal effects of dopamine agonism.

In addition, it is important to realise that hemodynamic changes induced by a pharmacological challenge are highly dependent on the dose used. As Ren et al. (2009) showed, increasing doses of d-

Table 4
DA drugs that have been used in phMRI studies.

Drug	Primary target	Route	Dose	Method	Signal change	Article	Species
D-AMPH[a]	DAT block DA release	i.v.	0.5–3 mg/kg	CBV	Increase	Chen et al., 1997, 1999, 2005a,b, 2010; Jenkins et al., 2004; Mandeville et al., 2013; Ren et al., 2009; Zhang et al., 2006;	Rat, monkey
		i.v.	0.25 mg/kg	CBV	Decrease	Mandeville et al., 2013; Ren et al., 2009	Rat
		i.v.	0.3 mg/kg	CBF	Increase/decrease[b]	Schouw et al., 2013a	Human
		i.p.	3–4 mg/kg	CBV, BOLD	Increase	Choi et al., 2006; Nguyen et al., 2000; Williams et al., 2010	Rat
MPH[a]	DAT block	i.p.	4 mg/kg	BOLD	Increase/decrease[b]	Canese et al., 2009; Hewitt et al., 2005	Rat
		i.v.	2 mg/kg	CBV	Increase	Chen et al., 2010	Rat
		p.o.	0.5 mg/kg	CBF	Decrease	Schouw et al., 2013b	Human
CFT	DAT block	i.v.	0.6–0.75 mg/kg	CBV	Increase	Chen et al., 1997, 1999; Choi et al., 2006	Rat
Cocaine[a]	DAT block	i.v.	0.5–1 mg/kg	CBV, CBF	Increase	Ceolin et al., 2007; Marota et al., 2000; Schwarz et al., 2004	Rat
		i.v.	0.2–0.5 mg/kg	CBV	Decrease	Kaufman et al., 1998; Mandeville et al., 2011	Human, monkey
		i.p.	30 mg/kg	CBV	Decrease	Perles-Barbacaru et al., 2011, 2012	Mouse
Modafinil[a]	DA block	i.v.	10 mg/kg	CBV	Increase	Gozzi et al., 2011	Rat
Bupropion[a]	DA block	i.p.	15–30 mg/kg	BOLD	No change	Sekar et al., 2011	Rat
Apomorphine[a]	D2 agonist	i.v.	0.1 mg/kg	BOLD	Decrease	Zhang et al., 2000, 2006	Monkey
		i.p.	2 mg/kg	CBV	Decrease	Nguyen et al., 2000	Rat
Norpropyl apomorphine	D2 agonist	i.v.	2 mg/kg	CBV	Increase/decrease[b]	Choi et al., 2006	Rat
Bromocriptine[a]	D2 agonist	i.p.	10 mg/kg	BOLD	Decrease	Roberts et al., 2007	Rat
Quinpirole	D2/D3 agonist	i.v.	2 mg/kg	CBV	Decrease	Chen et al., 2005a, 2010; Choi et al., 2006	Rat
Eticlopride	D2/D3 agonist	i.v.	2 mg/kg	CBV	Decrease	Chen et al., 2005a	Rat
		i.p.	0.9 mg/kg	CBV	Increase/decrease[b]	Chen et al., 2005a	Rat
Quinelorane	D2/D3 agonist	i.v.	3–30 μg/kg	BOLD	Increase/decrease[b]	Ireland et al., 2005	Rat
7-OH-DPAT	D3 agonist	i.v.	0.25–1.3 mg/kg	CBV	Decrease	Choi et al., 2006, 2010; Sánchez-Pernaute 2007	Rat, monkey
SCH-23390	D1/D5 antagonist	i.v.	0.5 mg/kg	CBV	Decrease	Marota et al., 2000	Rat
SKF-77434	D1/D5 agonist	i.v.	10 mg/kg	CBV	Increase	Choi et al., 2006	Rat
Dihydrexidine	D1/D5 agonist	i.v.	3 mg/kg	CBV	Increase	Chen et al., 2010; Choi et al., 2006	Rat

[a] Indicate drugs that are either FDA or EMEA approved or have previously been used in human studies.
[b] Both increases and decreases are observed, but this is region dependent.

AMPH increased DA release as measured with microdialysis in a dose-dependent matter. phMRI experiments revealed increased rCBV at higher doses, but decreased rCBV at the lowest dose. This most likely reflects the balance between D2/3 and D1/D5 stimulation. Thus, a combination of different classes of ligands or a combination of ligands at optimal doses would best characterise changes to the dopamine system.

In Table 4 we have given an overview of different DA drugs used in phMRI studies so far. It illustrates the effects of different types of drugs in on hemodynamic parameters. Some drugs give an overall increase or decrease, whereas others show both increases and decreases, which is usually region dependent or time dependent as a consequence of DA receptor distributions and affinities. It will facilitate the reader to make a good selection, not only of the challenge and its dose, but we have also indicated which challenge drugs are registered by the Food and Drug Administration (FDA) or European Medicines Agency (EMEA) or previously used in human populations, and thus likely suitable for studies in human populations. Please note that rCBV makes use of intravascular contrast agents, or a blood pool agent, which have not yet been approved for clinical use.

6. Which MRI technique to use?

In addition to choosing the right pharmacological challenge it is important to decide which MRI technique to use. CBV-, BOLD- and ASL-phMRI all have its advantages and shortcomings and it depends on the goal of the study which one to use. Currently, CBV-phMRI is the most applied technique because of its excellent contrast-to-noise ratio due to increased sensitivity to hemodynamic changes, especially at lower field strengths (Mandeville, 2012). However, its most important drawback is that it uses intravascular contrast agents that have not yet been approved for clinical use. BOLD-phMRI is also often used because of its ease of acquisition. It has an excellent temporal and spatial resolution and is widely available. It is particularly suitable for phMRI studies using intravenous challenges, repeated injections of drug and saline as well as task phMRI. In addition, it enables us to study drug effects on resting state functional connectivity (Schwarz et al., 2007). However, BOLD-phMRI has several shortcomings, that make it less advantageous to use in longitudinal studies or studies that employ oral pharmacological challenges. First, the BOLD signal suffers from increases in noise at low frequencies, frequently referred to as 'signal drift'. In this respect, ASL is a more suitable method for repeated measurements. ASL is a technique that measures CBF by magnetically tagging blood as an endogenous tracer to monitor flow of the labelled blood into the target imaging slice (Wang et al., 2011a). As the tagged protons enter the tissue they reduce the MR signal intensity. The difference between labelled images and control images is used as a measure of changes in CBF. As a result of this pairwise subtraction, ASL does not suffer from low frequency drifts, therefore providing temporal stability of measurements. Despite its lower signal-to-noise ratio, ASL is a highly reproducible method within subjects. Also, compared to BOLD, some ASL pulse sequences are less sensitive to magnetic field inhomogeneities in brain regions such as the orbital frontal cortex. Furthermore, it is possible to correct for macrovascular effects and changes in flow velocity induced by large intracranial vessels. Secondly, BOLD is a measure that depends on several physiological variables including CBF, cerebral blood volume and oxygen consumption and has no absolute baseline. On the other hand, ASL is more specific in that it is a direct measure of neurotransmitter-induced changes in hemodynamic function, and several approaches exist that allow for quantification of the perfusion (Wang et al., 2011a).

7. Strengths and limitations of phMRI

PET/SPECT provide more homogenous results because they measure specific elements of the dopaminergic system, such as receptors, transporters and release. However, phMRI additionally shows downstream effects of dopaminergic activity on other pathways, thereby providing a more complete picture of what exactly is going on in the brain. phMRI also offers additional advantages that complement PET and SPECT techniques. First, it offers a much higher spatial resolution, allowing the visualisation of smaller brain regions. Using echo-planar images the time resolution of an MR image can be reduced to as little as 500 ms, therefore permitting tracking of time courses of fast-acting pharmacological compounds. Second, it allows for longitudinal studies and in contrast with PET or SPECT does not involve exposure to radiation. Therefore, one of the big advantages of MRI is that it can be used in vulnerable populations, such as children and older patients.

However, it is important to consider that phMRI is a novel technique that is still in its infancy and therefore suffers from several teething troubles that remain to be resolved in the future before it can be widely applied in the clinic. The interpretation of fMRI and its underlying neurobiological substrates remain subject to discussion. Research on neurovascular coupling has progressed over the past ten years and it appears that fMRI and phMRI are able to reliably assess synaptic activity indirectly through changes in the hemodynamic response function (Logothetis and Pfeuffer, 2004). Although increases in BOLD signal and other hemodynamic measures are relatively well understood, decreases in brain hemodynamics are still a topic of debate. The BOLD signal might reflect actual decreases in neuronal activity, but has also been attributed to increases in neuronal activity without a compensatory increase in CBF (Moraschi et al., 2012).

An additional problem arises specifically in phMRI because pharmacological compounds can affect vascular tone of the brain (Choi et al., 2006). However, Ceolin et al. (2007) demonstrated that vascular effects were not the main driving force behind the BOLD response to a cocaine challenge; in contrast, the phMRI response is largely attributed to tissue metabolism. Yet, it is possible that the acquired phMRI signal is a mix of changes in neuronal activation and vasculature. Furthermore, drugs may have systemic physiological effects, such as changes in blood pressure. Therefore, systemic parameters have to be monitored and can be included as covariates in the data analysis. Additionally, systemic effects on the phMRI response are expected to affect the brain globally and could in this way be distinguished from regional neuronal effects (Wang et al., 2011a). Another caveat exists when using phMRI to investigate disease states. Clinical conditions are known to lead to changes in cerebral microcirculation and thus changes in CBF. Therefore caution is warranted in the interpretation of such studies (Iadecola, 2004). Furthermore, even though a particular pharmacological compound might act on a specific receptor, its consequences may be more widespread and involve downstream projections. Because of the complex functional interplay between neurotransmitters, neuronal activity detected by phMRI will likely reflect neuronal activity in other transmitter systems as well.

8. phMRI in the clinic and future directions

Clinically, this technique could be of incredible importance as it is currently the only technique to assess brain neurotransmitter systems non-invasively in vivo in vulnerable populations. As reviewed above, dopaminergic abnormalities can be detected by phMRI in neurotoxic animal models. It is key to investigate further whether dopaminergic abnormalities can also be identified in psychiatric disorders. One study has used phMRI to validate an

animal model of ADHD in which rats were administered the dopamine reuptake inhibitor GBR12909 (30 mg/kg, i.p.) bi-daily for 4 days, which induced symptoms characteristic of ADHD, such as increased locomotor activity. This model was applied in a phMRI study with MPH as a challenge. The hemodynamic response was decreased in the caudate, frontal cortex, hippocampus and hypothalamus in treated rats versus controls (Hewitt et al., 2005). In addition, it has been shown that phMRI is able to track treatment response in animals. In one example, the effects of a potential new drug to treat schizophrenia were studied. Aripiprazole is a partial D2 agonist that reveals dose-dependent reductions in CBF in regions associated with the pathophysiology of schizophrenia. The next step would be to investigate the effect of the drug in an animal model of psychosis and compare it to existing antipsychotics (Nordquist et al., 2008). These examples illustrate the great potential of phMRI to contribute to drug discovery, by discovering new targets and comparing different treatment protocols. However, there is a lack of phMRI studies that investigate dopaminergic abnormalities in humans. Most of the available studies have used task-based phMRI, but in such experiments it is often difficult to tease apart the effect of the drug and the effect of the task and a possible interaction. Yet, they can be informative to highlight the clinical potential of phMRI and how this technique can be utilised to study drug effects. For example, some studies in PD patients have examined BOLD responses after administration of levodopa in response to a task (Farid et al., 2009; Martinu et al., 2012; Mattay et al., 2002). Although it seems that levodopa can normalise activation in corticostriatal loops to some extent, the spatial distribution and spread of activation remains incongruous with that of controls. This would be convergent with the idea that levodopa does not affect the cause of the disease, but artificially increases dopamine levels that are deficient due to the cell death in the SN.

It is crucial to fine-tune this relatively new technique to optimize it for use in the clinic. For example, ASL-phMRI studies in humans are pivotal in developing phMRI as a reliable technique for the clinic. For future research, it is crucial to disentangle hemodynamic processes underlying the phMRI signal to improve and standardise interpretation of data. phMRI is a powerful technique to evaluate the acute and long-term effect of treatment in human psychiatric populations. A better understanding of neurotransmitter changes in psychiatric disorders is imperative to drug discovery and to develop new treatment strategies. This makes phMRI a very valuable technique for translational research.

9. Conclusion

Dopamine abnormalities underlie a wide variety of psychopathologies, including ADHD and schizophrenia. The integrity of the DA system has traditionally been visualised by PET and SPECT imaging techniques. Recently, pharmacological MRI has been developed, which measures the hemodynamic response to a pharmacological challenge non-invasively. As this review demonstrates, phMRI is capable of measuring (relatively severe) dopaminergic abnormalities in animal models. Furthermore, this technique has the potential to monitor the effect of treatment on restoring neurotransmitter function. It offers a huge potential to non-invasively assess neurobiological mechanisms in disease states, it can aid in drug discovery and development, and it contributes significantly to a general understanding of the intricate working of the brain. Its strengths include its spatial resolution, its non-invasive nature and the multitude of clinical settings in which it can be applied. However, future research into the interpretation of the MRI signal changes is needed and also to show whether phMRI is also able to detect smaller changes in dopaminergic function. Despite phMRI studies in healthy volunteers showing similar results as with the conventional imaging tools PET and SPECT, phMRI is not yet a widely applied tool to study patients with dopaminergic abnormalities. Nevertheless, the literature reviewed above illustrates that with additional studies, phMRI could be widely applied in the clinical setting in the very near future.

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