

## REVIEW

# Making Sense of: Sensitization in Schizophrenia

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## Abstract

Sensitization is defined as a process whereby repeated intermittent exposure to a given stimulus results in an enhanced response at subsequent exposures. Next to robust findings of an increased dopamine synthesis capacity in schizophrenia, empirical data and neuroimaging studies support the notion that the mesolimbic dopamine system of patients with schizophrenia is more reactive compared with healthy controls. These studies led to the conceptualization of schizophrenia as a state of endogenous sensitization, as stronger behavioral response and increased dopamine release after amphetamine administration or exposure to stress have been observed in patients with schizophrenia. These findings have also been integrated into the neurodevelopmental model of the disorder, which assumes that vulnerable neuronal circuits undergo progressive changes during puberty and young adulthood that lead to manifest psychosis. Rodent and human studies have made an attempt to identify the exact mechanisms of sensitization of the dopaminergic system and its association with psychosis. Doing so, several epigenetic and molecular alterations associated with dopamine release, neuroplasticity, and cellular energy metabolism have been discovered. Future research aims at targeting these key proteins associated with sensitization in schizophrenia to enhance the knowledge of the pathophysiology of the illness and pave the way for an improved treatment or even prevention of this severe psychiatric disorder.

**Keywords:** psychosis, positron emission tomography, amphetamine, dopamine, PHNO

## Significance Statement

Sensitization denotes a neuro-behavioral process where repeated exposure to a stimulus leads to a progressive enhancement in the response to this stimulus. The underlying neurobiological processes are essential for reinforcement learning in animals and humans. However, sensitization occurs also with many drugs of abuse. The neurotransmitter dopamine plays a key role in mediating the amplification of neuronal and behavioural responses to environmental stimuli and drugs of abuse. Amphetamines increase the release of dopamine in the brain, a mechanism that is essential for inducing addictive behaviour. However, release of dopamine also induces psychotic symptoms in patients with schizophrenia. Patients with schizophrenia are particularly sensitive to amphetamines even if they have never before consumed the drug. Thus, schizophrenia is believed to be associated with a state of 'natural sensitization' towards amphetamines. This review highlights the importance of understanding sensitization for better understanding and treating schizophrenia.

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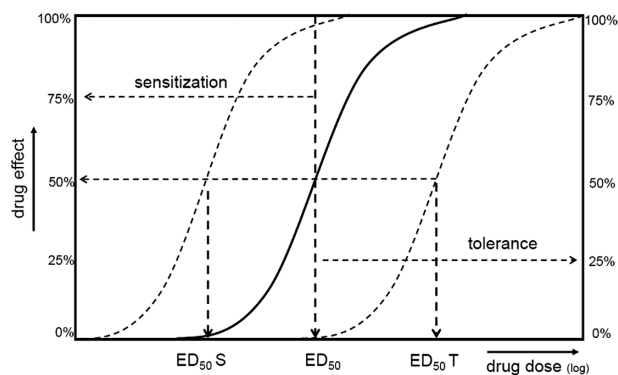
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## Introduction

### The Concept of Sensitization

Sensitization denotes a nonassociative learning process in which repeated exposure to a stimulus leads to a progressive amplification in the behavioral and neurochemical response. In a pharmacological context, sensitization is defined as an amplified response to a constant dose of a substance after repeated administration. Sensitization has been described for most drugs of abuse associated with addictive behavior, including amphetamines, cocaine, opiates, nicotine,  $\Delta^9$ -tetrahydrocannabinol, and alcohol. Sensitization is, so to say, the opposite of the more familiar concept of drug tolerance, the diminishing effect of a drug resulting from repeated administration. Sensitization is thus often referred to as reverse tolerance (see Figure 1). In animals, sensitization to cocaine or d-amphetamine typically presents as an increase in locomotor responses or stereotypies (Robinson and Becker, 1986). Humans sensitized with low-dose amphetamine report an increase in alertness, euphoria, or focus after amphetamine administration (Strakowski et al., 2001; Boileau et al., 2006).

A common mechanism of action of substances also serving as drugs of abuse is that they elicit a direct or indirect increase in brain extracellular dopamine levels immediately after drug administration. A release of dopamine is also a central element in the neurochemistry of behavioral learning (Keiflin and Janak, 2015), as dopamine release and specific patterns of activity in dopaminergic neurons are detected during conditioned (or Pavlovian) learning paradigms. In conditioned learning paradigms, a previously neutral environmental cue (the conditioned stimulus) is repeatedly presented in close temporal and spatial proximity to a primary or unconditioned stimulus such as food, sex, or an aversive pain stimulus. An animal's learning rate in conditioning paradigms can be influenced by manipulating brain dopamine transmission: Higher levels of extracellular dopamine are associated with an increased response to the conditioned stimulus (better "learning"), and lower levels are associated with a decreased conditioned response. The connection between dopamine release induced by drugs of abuse and conditioned (or "cue") learning is found across species using a broad variety of research methods, and it forms



**Figure 1.** Sensitization leads to an increase in drug effects. The dose of a drug producing half-maximal response (ED<sub>50</sub>) decreases with sensitization, so that a lower dose is needed to produce half-maximal drug effects (ED<sub>50</sub>S). Alternatively, the original ED<sub>50</sub> will cause larger effects in the sensitized state. The opposite is found in tolerance, where the efficiency of a drug decreases and a higher dose (ED<sub>50</sub>T) is now needed to produce half-maximal effects, or where the original ED<sub>50</sub> will now induce smaller effects.

something like the core of the dopamine theory of addiction. As outlined later in this manuscript, there is substantial evidence that sensitization to psychostimulants is associated with a progressive increase in the amount of dopamine released in response to a given dose of the drug. As reflected in the term "drug learning" sometimes used when referring to psychostimulant sensitization, release of brain dopamine is a neurochemical mechanism common to learning and sensitization to psychostimulant drugs.

### Amphetamines

Amphetamines constitute a group of chemically related synthetic derivatives of phenethylamine, a so-called trace amine that is naturally produced in catecholaminergic neurons by decarboxylation of the essential amino acid phenylalanine (Sitte and Freissmuth, 2015). Amphetamine itself is a synthetic compound first synthesized in 1887 (Edeleano, 1887) and is not known to occur naturally in any animals or plants. The main somatic effects of amphetamine include an increase in the activity of the sympathetic nervous system leading to mydriasis, bronchodilatation, and increased blood pressure and heart rate. The main psychophysiological effects are an increase in attention and vigilance, slight euphoria, increased drive, and an improvement in psychomotor speed and some cognitive domains related to attention and vigilance. However, amphetamine also increases errors in memory retrieval (Ballard et al., 2014). At higher doses, amphetamine induces stereotypies in animals and psychotic symptoms in humans.

The main sites of action of amphetamines are presynaptic monoamine-transmembrane transporters (the dopamine, norepinephrine, and serotonin reuptake transporters DAT, NET, and SERT) and the vesicular monoamine transporter 2 (VMAT2; Sulzer et al., 2005). The main physiological role of monoamine transporters is reuptake of monoamines into the presynaptic neuron immediately after they have been released into the synaptic cleft. Thereby, monoamine transporters regulate temporal and spatial spread of the monoamine signal. In contrast to pure transporter blockers such as cocaine or methylphenidate, amphetamines are also substrates of DAT, NET, and SERT and are thus transported in an ion gradient-dependent way into the neuron (Sitte and Freissmuth, 2015). There, amphetamines lead to neurotransmitter release from storage vesicles into the cytosol. Most importantly, however, amphetamines reverse the transport direction of monoamine transporters (Sitte and Freissmuth, 2015). By binding to the transporter from on the inside of the cell, amphetamines switch monoamine transporters from a reluctant to a willing state to perform outward transport and thus lead to a massive outflow of neurotransmitter into the synapse and surrounding extracellular space (Robertson et al., 2009).

Various amphetamines differ in their respective affinity to the 3 major monoamine transporters and have thus a distinct neuropharmacological profile. d-Amphetamine, the compound used in most animal and human studies, acts primarily at DAT and NET, and administration of d-amphetamine was shown to increase extracellular dopamine levels by several hundred percent over physiologic baseline levels (Zetterstrom et al., 1983; Laruelle et al., 1995; Breier et al., 1997).

## Sensitization in Schizophrenia

Schizophrenia is a disorder with heterogeneous clinical manifestations characterized by a large variety of so-called positive (hallucinations, delusions, thought disorder, and motor symptoms) and negative symptoms (poverty of speech, apathy, social withdrawal). The presence of pronounced positive symptoms is what marks an acute psychotic episode of the illness, and generally, positive symptoms respond better to antipsychotic treatment. Negative symptoms are frequently found also outside of acute psychotic episodes and present a major therapeutic challenge in the treatment of schizophrenia (APA, 2013). The good responsiveness of positive symptoms to antipsychotic dopamine  $D_{2/3}$  receptor-blocking drugs is one of the reasons why psychosis has been associated with a hyper-dopaminergic state. Several complex genetic and environmental factors (birth in the winter months, urban upbringing, parental age, and others) have been shown to increase the risk for schizophrenia (Collip et al., 2008; van Winkel et al., 2008). As of yet it is unknown how these risk factors are related to each other and in which way they increase the illness risk. However, according to current interpretations (Laruelle, 2000; Kapur, 2003; Collip et al., 2008; van Winkel et al., 2008; Howes and Kapur, 2009; van Os and Kapur, 2009) of the dopamine theory of schizophrenia (van Rossum, 1966), all known risk factors seem to converge in a common final pathway, a hyper-dopaminergic state that causes psychotic symptoms in schizophrenia.

While sensitization is a concept that has substantial face value for explaining many behavioral patterns observed in patients with substance use disorders, its relationship to the phenomenologically diverse schizophrenia syndrome is not as self-evident. However, first descriptions of newly emerging psychotic states related to amphetamine intake date back to the first half of the last century (Young and Scoville, 1938). Since then, a link between amphetamine intake and psychotic symptoms has been described in many studies, some of them using escalating doses of amphetamine for prospective induction of psychotic symptoms in healthy volunteers (Ellinwood et al., 1973). Low doses of amphetamine induce mild euphoria, sometimes an increased sense of purpose, subjects feel awakened and notice an increase in the ability to focus their attention. In a plastic description, N. Richtand (Richtand 2006) notes that with increasing dose and frequency of intake, “symptoms following repetitive stimulant drug use evolve gradually from intense curiosity, progressing to intense exploration of the environment, which may be displayed in repetitive stereotyped searching, sorting, and examining behaviors. This curious ‘suspiciousness’ of the environment later evolves into paranoia and psychotic thought.” Moreover, experimentally administered amphetamine induces hallucination and classical Schneiderian first rank symptoms in healthy subjects (Janowsky and Risch, 1979). In these studies, symptoms usually resolved within hours after discontinuation of stimulant intake. In addition to positive symptoms of schizophrenia, an analysis of subjects suffering from methamphetamine-induced psychosis (Srisurapanont et al., 2011) showed considerable frequency and severity of negative symptoms. In summary, amphetamine is able to induce a reversible clinical picture resembling psychosis in schizophrenia in many aspects. However, to do so, amphetamines need to be consumed repeatedly and at high doses. Although studies specifically designed to measure behavioral and neurochemical effects of sensitization in humans used low amphetamine doses only, there is no reason to assume that neurochemical mechanisms of sensitization to higher stimulant doses differ completely from those to lower doses. In fact, as further discussed below, neurochemical

findings in regular abusers of stimulants are in good agreement to what is found in prospectively sensitized animals.

Administering psychostimulants to patients with schizophrenia is one of the most frequently used challenge tests in psychiatric research. A classic 1987 review by Lieberman and colleagues (1987) lists 36 studies on the use of amphetamines or methylphenidate in patients with schizophrenia. Despite considerable heterogeneity of methods and design, the studies show that patients with schizophrenia exhibit greater responsiveness to psychostimulants than healthy subjects or patients with nonpsychotic illness. Generally, patients with full-blown psychosis showed larger changes in psychopathology upon psychostimulant administration, while patients with prominent negative symptoms showed no or little response. As described later in this review, today it is safe to say that hyper-responsiveness to stimulants in schizophrenia is due to an increased amount of dopamine released in response to the drug.

## Competition and Blocking Experiments in Schizophrenia

So-called competition, displacement, or blocking paradigms use a decrease in dopamine  $D_{2/3}$  receptor radioligand binding after administration of a dopamine-releasing agent such as d-amphetamine as a proxy for the amount of dopamine released into the extracellular space (Laruelle, 2000; Ginovart, 2005). The effects of amphetamine-induced dopamine release on  $D_{2/3}$  radioligand binding have also been repeatedly studied in patients with schizophrenia. Using [ $^{23}$ I]IBZM and single photon emission tomography, enhanced radioligand displacement in patients with schizophrenia and a positive correlation between displacement and the emergence or worsening of positive psychotic symptoms has been found (Laruelle et al., 1996). A study using [ $^{11}$ C]raclopride and positron emission tomography (PET) (Breier et al., 1997) confirmed the finding in patients with schizophrenia and showed a clear relationship between amphetamine-induced displacement and the amount of dopamine released into the extracellular space in a cohort of nonhuman primates undergoing PET and in vivo microdialysis. Further studies confirmed and extended the finding by adding a dopamine-depletion paradigm that also elicited larger changes in radioligand binding in psychotic patients (Abi-Dargham et al., 1998; Abi-Dargham et al., 2009).

## Presynaptic Dopamine Precursor Uptake and Storage in Schizophrenia

An increase in uptake and storage of the radiolabelled dopamine precursor [ $^{18}$ F]FDOPA into the striatum is a robust and well-replicated finding in patients with schizophrenia (Fusar-Poli and Meyer-Lindenberg, 2013). The uptake of [ $^{18}$ F]FDOPA shows a positive correlation with the severity of positive symptoms (Meyer-Lindenberg et al., 2002; McGowan et al., 2004; Kumakura and Cumming, 2009). This, together with evidence from the aforementioned competition studies where positive symptoms correlated with d-amphetamine-induced dopamine release, supports the close relationship between high dopamine levels and psychotic symptoms in schizophrenia. However, to our knowledge, there is no study directly relating increased uptake of [ $^{18}$ F]FDOPA to enhanced d-amphetamine-induced dopamine release in sensitization or schizophrenia. A recently described key finding is that increased [ $^{18}$ F]FDOPA uptake already occurs in prodromal stages of schizophrenia, where patients show no or almost no psychotic symptoms (Howes et al., 2009). This shows that dopamine overactivity predates the onset of full-blown psychosis and suggests that dopamine is causally involved in the pathogenesis of the illness.

In summary, several studies support a close link between the mechanism of action of psychostimulant drugs and psychotic symptoms in schizophrenia. The behavioral super-sensitivity of patients with schizophrenia towards substances increasing brain extracellular dopamine levels, together with an enhanced d-amphetamine-induced dopamine release suggest that schizophrenia is associated with a state of “natural sensitization” towards dopamine-releasing agents. We will further discuss below how the mechanisms of d-amphetamine sensitization might relate to the enhanced dopamine synthesis and storage capacity shown by [<sup>18</sup>F]FDOPA PET studies in schizophrenia.

## The Neuropharmacology of Sensitization

### Findings in Humans

On a neurochemical level, sensitization to amphetamines manifests as lasting hyper-responsiveness of mesencephalic dopaminergic pathways, paralleled by an increase in the amount of extracellular dopamine released from presynaptic terminals to a given dose of d-amphetamine in animals (Kalivas and Duffy, 1993; Wolf et al., 1993; Paulson and Robinson, 1995; Pierce and Kalivas, 1995; Robinson and Badiani, 1998; Robinson et al., 1998) and humans (Boileau et al., 2006; Booij et al., 2016). The literature reports only on a limited number of studies where humans were prospectively sensitized to stimulants (Strakowski et al., 2001; Farre et al., 2004; Boileau et al., 2006, 2016; O’Daly et al., 2011, 2014a, 2014b). An increase in d-amphetamine-induced reductions in striatal binding of the D<sub>2/3</sub> receptor radioligand [<sup>11</sup>C]raclopride after repeated administration of a constant dose of d-amphetamine shows a progressive increase in the amount of dopamine released into the extracellular space in the striatum of sensitized individuals (Boileau et al., 2006; Booij et al., 2016). This increase is paralleled by an enhancement in behavioral measures, for example the eye-blink rate, ratings of alertness, euphoria or focus, and by enhanced amphetamine-induced plasma cortisol secretion (Strakowski et al., 2001; Farre et al., 2004).

Interestingly, dopamine release after a single amphetamine or ethanol administration seems to be greater in males (Munro et al., 2006; Urban et al., 2010), while behavioral effects of sensitization in animals have been found to be stronger in females (Becker et al., 2001; Strakowski et al., 2001; Cope et al., 2010; Chen et al., 2014). Sex differences are frequently attributed to the action of gonadal steroid hormones either during an early organizational period or in adulthood (Gillies et al., 2014). Castration of male rats facilitated the behavioral sensitization produced by either repeated amphetamine treatment or repeated restraint stress. In contrast, ovariectomy in female rats was without effect (Camp and Robinson, 1988). Neurochemical effects of sensitization to amphetamines in humans have so far been studied in males only (Boileau et al., 2006). Since schizophrenia, substance use disorders, and many other dopamine-related psychiatric disorders show a robust sexual dimorphism, there is a clear need for studies filling the gaps in our knowledge on the effects of sex on sensitization and its neurochemistry in humans.

### Findings in Animals

Sensitization in research animals has been induced using several different protocols of repeated substance administration. The strength of sensitization is influenced by various factors, such as number and interval between treatments, dose, sex, age, and genetics (Post and Contel, 1983). Behavioral sensitization has been reported to occur in response to cocaine, amphetamine, morphine, ethanol, nicotine, and tetrahydrocannabinol (Joyce and Iversen, 1979; Robinson and Becker, 1986; Benwell and Balfour, 1992; Cunningham and Noble, 1992; Post et al., 1992;

Cadoni et al., 2001). An important finding of several studies is the occurrence of cross-sensitization of the behavioral response between drugs. Cross-sensitization has been shown for amphetamine to morphine (Vezina and Stewart, 1989), amphetamine to cocaine (Santos et al., 2009), ethanol to cocaine and vice versa (Itzhak and Martin, 1999), and Δ9-tetrahydrocannabinol to morphine (Cadoni et al., 2001).

### Molecular Mechanisms of Sensitization

As of yet, molecular mechanisms of sensitization of the dopamine system are only partially understood. Apparently, sensitization occurs in 2 stages, first by changes in VTA dopamine receptors, followed by a so-called expression phase, in which dopamine release is enhanced in the nucleus accumbens (Marinelli et al., 2003). Among others, a transient subsensitivity of dopamine autoreceptors in the ventral tegmental area has been suggested to play a role in the induction of sensitization (Wolf et al., 1993; Paulson and Robinson, 1995; Pierce and Kalivas, 1995; Calipari et al., 2015), as this change has been associated with increased basal activity of dopamine neurons (White and Wang, 1984; Henry et al., 1989). Long-lasting sensitization might also be accompanied by increases in the sensitivity of D<sub>1</sub> dopamine receptors in the nucleus accumbens (Henry and White, 1991). This is supported by findings of blunted locomotor sensitization in D<sub>1</sub>-deficient mice (El-Ghundi et al., 2010) and the prevention of pertussis toxin-induced sensitization by D<sub>1</sub> antagonists (Narayanan et al., 1996). For D<sub>2/3</sub> autoreceptors, animal work points to decreased intracellular signal transmission via intracellular G-proteins after repeated amphetamine transmission (Sharpe et al., 2015) and changes of regulatory proteins of intracellular G-proteins such as Rgs9 (regulator of G-protein signalling) (Maple et al., 2007). These changes may occur already after a single stimulant administration specifically in the ventral tegmental area (Arora et al., 2011; Padgett et al., 2012).

Other cellular mechanisms involved in sensitization include altered activation of VMAT2, as a recent publication discovered that argon blocks sensitization by its antagonistic properties at the VMAT2. Chen et al. (2014) on the other hand found an important role of AKT1, a protein directly downstream of dopamine D<sub>2/3</sub> receptors that interacts with beta-arrestin complex, a regulator of dopamine signalling cascades. Interestingly, male AKT1 knockout animals were less sensitive to methamphetamine-induced hyperlocomotion during methamphetamine challenge compared with wild-type controls and AKT1 knockout females (Chen et al., 2014). Another protein, the calmodulin kinase IIα (αCaMKII) is a transporter-interacting protein, which was found to regulate amphetamine-triggered reverse DAT transport. αCaMKII has been associated with development of sensitization, as mice depleted of this kinase showed blunted sensitization effects following repeated amphetamine exposure (Steinkellner et al., 2014). Furthermore, the authors speculate that subtle variations in the relative expression levels of DAT and of αCaMKII may contribute to inter-individual differences in the susceptibility to amphetamine addiction (Steinkellner et al., 2014).

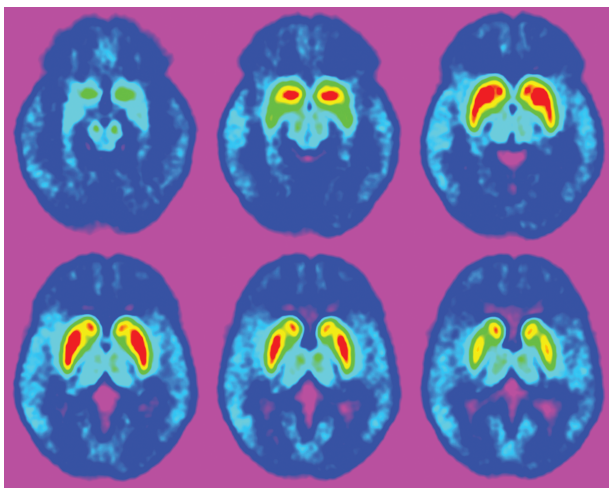
A recent proteomics study (Wearne et al., 2015) examined brain protein expression in rats sensitized to methamphetamine. Expression of proteins previously implicated in the pathophysiology of schizophrenia was significantly altered in the prefrontal cortex of sensitized rats. These proteins are involved in mitochondrial function, cellular architecture, cell signalling, and synaptic plasticity, which, in turn, are tightly related to stress mechanisms on a cellular level. In accordance, cell adhesion molecules assessed peripherally were found to be altered in patients with schizophrenia and correlated with prefrontal grey matter volume (Piras et al., 2015).

### The Role of Dopamine D<sub>2/3</sub> Receptors

Cocaine- or methamphetamine-dependent subjects can safely be assumed to be sensitized to the action of psychostimulant drugs. Studies using the dopamine D<sub>2/3</sub> receptor agonist PET radioligand [<sup>11</sup>C]-(+)-PHNO (Wilson et al., 2005) in humans addicted to cocaine or methamphetamine have consistently shown an increase in [<sup>11</sup>C]-(+)-PHNO binding in the substantia nigra/ventral tegmental area (Boileau et al., 2012; Matuskey et al., 2014; Payer et al., 2014). In these brain regions, the signal measured with [<sup>11</sup>C]-(+)-PHNO is predominantly due to binding to dopamine D<sub>3</sub> receptors (see Figure 2; Graff-Guerrero et al., 2010). An increase in dopamine D<sub>3</sub> receptor expression is also found in postmortem studies of cocaine addicted subjects (Staley and Mash, 1996; Segal et al., 1997). In view of these findings, dopamine D<sub>3</sub> receptor antagonists have been proposed as a possible treatment for stimulant addiction. This notion is supported by rodent studies administering D<sub>3</sub>-preferring agonists, such as pramipexole, which enhanced opioid-conditioned reinforcement (Bertz et al., 2015). Vice versa, D<sub>3</sub>-preferring antagonists inhibited related rewarding effects of cocaine- and drug-seeking behavior (Xi et al., 2006; Song et al., 2012; John et al., 2015; Galaj et al., 2016).

Still, this concept is somewhat at odds with a solid body of evidence showing that an increase in dopamine D<sub>3</sub> receptor signalling in the ventral tegmental area actually acts as a brake on dopamine release in the striatum and reduces psychostimulant-induced behaviors in rodents (Damsma et al., 1993; Ahlenius and Salmi, 1994; Pugsley et al., 1995; Caine et al., 1997; Richtand et al., 2001). A pilot study on the administration of the D<sub>3</sub>-preferring agonist pramipexole to patients with schizophrenia (Kasper et al., 1997) showed beneficial effects against negative and positive symptoms. Since positive symptoms in schizophrenia correlate directly with amphetamine-induced dopamine release in the striatum of patients with schizophrenia, D<sub>3</sub> agonism, although not directly shown in this or other studies so far, may have reduced striatal dopamine release in this collective.

There are various possible reasons for the discrepant findings. One is that most D<sub>2</sub> or D<sub>3</sub> receptor-preferring compounds are not entirely selective for either subtype. Therefore, it is hard to distinguish via which receptor behavioral or neurochemical effects are exerted, especially when opposing roles are suggested (Ellinwood et al., 2000). Another aspect is that D<sub>3</sub>-preferring compounds may



**Figure 2.** Adjacent transversal slices of a positron-emission tomography image using the dopamine D<sub>2/3</sub> receptor agonist radioligand [<sup>11</sup>C]-(+)-PHNO. Bright areas show binding to dopamine D<sub>2/3</sub> receptors in the human striatum and brainstem substantia nigra/ventral tegmental area.

act in a species-dependent way, and that their action may depend on the administration paradigm (cocaine self-administration vs conditioning/reinforcement) (Keck et al., 2015). Furthermore, studies suggest that individual D<sub>3</sub> availability and the resulting occupancy or alternative D<sub>3</sub> gene splicing might lead to differential effects when D<sub>3</sub> ligands bind (Richtand, 2006; Mugnaini et al., 2013; Kim et al., 2014; John et al., 2015). Interestingly, brain-derived neurotrophic factor might influence the expression of D<sub>3</sub> receptors and seems to be necessary for behavioral sensitization and co-occurring D<sub>3</sub> overexpression (Guillin et al., 2001).

Although it would be intuitive to state that sensitization leads to increased D<sub>3</sub> receptor expression and therefore that D<sub>3</sub> should be antagonized in order to prevent sensitization, increased expression of D<sub>3</sub> in its role as a regulator of DA release might be a compensatory mechanism in the development of sensitization, which, however, fails to fulfil its purpose.

In summary, the differential impact of dopamine D<sub>2</sub> autoreceptors and D<sub>3</sub> receptors in the substantia nigra/ventral tegmental area on induction and expression of sensitization appears insufficiently understood as of yet. An intriguing concept though is that sensitization to amphetamine, together with an increase in amphetamine-induced dopamine release into the striatum, are a consequence of tolerance in inhibitory systems induced by repeated exposure of brainstem dopamine receptors to high levels of dopamine itself (Richtand, 2006).

### Stress, Sensitization, and Neurodevelopment

Several studies on the relationship between stress and psychostimulants in rodents were able to show cross-sensitization between repeated stress and repeated exposure to amphetamine (Antelman et al., 1980; Kalivas et al., 1986; Hamamura and Fibiger, 1993; Febo and Pira, 2011; Booij et al., 2016). It is known that stress preferentially stimulates dopamine release in mesolimbic projection (Horger and Roth, 1996) and frontal areas (Lataster et al., 2011) and that glucocorticoids modulate the sensitivity of mesencephalic dopaminergic neurons to drugs of abuse (Sorg and Kalivas, 1991; Deroche et al., 1995). In good agreement with animal studies, it was shown that exposure to stress is able to induce recurrence of psychotic symptoms in remitted patients with methamphetamine-induced psychosis (Yui et al., 2002). Patients with schizophrenia exhibit distinct alterations in the hypothalamic-pituitary-adrenal axis (Borges et al., 2013), and an increase in dopamine release and behavioral reactivity in response to stress has been observed in healthy subjects sensitized to amphetamine, in patients with schizophrenia (Mizrahi et al., 2012; Lataster et al., 2013), and in subjects at high risk for psychosis (Soliman et al., 2008; Mizrahi et al., 2014).

Lieberman and colleagues (1997) have proposed a framework extending the classical stress vulnerability model of psychosis to integrate the neurodevelopmental model of schizophrenia with findings linking stress to altered dopamine signalling: in early development, neuronal circuits are being formed which then experience neuroplastic changes during early adolescence (Feinberg, 1982; Keshavan et al., 1994). There, stress-related activity of mesolimbic dopamine neurons sets the vulnerability for sensitization. Sensitization finally leads to excessive dopamine release and progressive development of psychosis (Laruelle, 2000; Seeman 2011). Importantly, the view of schizophrenia as a degenerative disease has been substituted by the view of a disorder in which deficits in regenerative capacity are present (Falkai et al., 2015). These deficits may include the previously mentioned alterations of cell architecture and metabolism, higher oxidative stress, and the consequent changes of synaptic

formations (Flatow et al., 2013; Wearne et al., 2015). In addition, as the prefrontal cortex is hypothesized to act as a brake on striatal dopamine release (Carlsson et al., 2001), a dysregulation of inhibitory feedback mechanisms involved in the regulation of ventral tegmental neuronal activity may result in a pathological potentiation of impulse-dependent phasic dopamine release. The association of frontal cortical thickness with amphetamine-induced dopamine release corroborates this notion (Casey et al., 2013). As of yet, the question is unresolved whether it is increased striatal dopamine transmission to cause altered activation of cortical networks (bottom-up) or whether insufficient frontal-cortical control of striatal neurons is leading to alterations in presynaptic dopamine release in psychosis (top-down).

### Sensitization in Cells

In an *in vitro* examination, rat pheochromocytoma cells (PC-12), which are capable of dopamine release upon pharmacological stimulation but possess no dopamine receptors, were sensitized successfully by intermittent treatment with amphetamine for 5 consecutive days followed by a >6-day, drug-free interval. Sensitization of PC12 cells was marked by significantly increased dopamine release upon amphetamine stimulation in sensitized when compared with nonsensitized cells. This was not accompanied by increase in [ $H^3$ ]-dopamine uptake (Kantor et al., 2002). Intermittent amphetamine treatment also led to increased neurite outgrowth in PC-12 cells after an interval of more than 3 drug-free days (Park et al., 2002). Increased dopamine release and neurite outgrowth were dependent on protein kinase C and MAP kinase *in vitro* (Park et al., 2003). The fact that it is possible to sensitize cells to amphetamine holds the promise that it may be possible to identify drug targets enabling to target alterations in dopamine release already in presynaptic neurons.

### What Can We Learn for Schizophrenia Research?

The observation of alterations in the dopaminergic system has led to the question how this effect might be related to clinical symptoms of schizophrenia. Notably, the dopaminergic changes are dependent on the illness phase (Laruelle et al., 1999), and the correlation of radioligand uptake and positive symptom severity (Meyer-Lindenberg et al., 2002; McGowan et al., 2004; Kumakura et al., 2007) suggests that the method does indeed capture a biologically meaningful signal closely connected to the pathogenesis of schizophrenia. There seems to be a differential effect of amphetamine on positive and negative symptoms of schizophrenia: positive symptoms and thought disorder intensify temporarily, while negative symptoms tend to improve. This suggests that, although positive and negative symptoms are likely to differ in their pathogenesis, dopamine plays a major role in both symptom groups. Patients in remission show comparably small responses to amphetamine (Lieberman et al., 1987), and amphetamine-induced dopamine release is larger during the acute phase of the illness (Laruelle, 2000). Although some authors consider the processes predisposing to psychosis in schizophrenia to be irreversible, especially those hypothesized to have a neurodevelopmental origin, and although the disorder has a progressive course in a considerable proportion of the patients, findings from imaging studies suggest that at least part of the dopamine-related pathogenetic alterations are reversible. In this context, antipsychotic medication has been proposed to contribute to the reversibility of sensitization by  $D_{2/3}$  blockade, although the exact mechanism is yet unknown. On the other hand, some observations suggest that chronic blockade of dopamine  $D_{2/3}$  receptors rather induces supersensitivity of postsynaptic receptor

systems, leading to increased vulnerability for relapse once antipsychotic medication is discontinued. However, the possibly life-long persistence of a predisposition of the dopamine system to sensitize supports the necessity of long-term proactive measures to prevent psychosis in many patients.

In sum, an increase in amphetamine-induced dopamine release is common to amphetamine-induced sensitization in animals and humans, and the natural sensitization of the dopamine system observed in patients with schizophrenia is associated with increased amphetamine-induced dopamine release as well. The exact mechanisms and the association with increased dopamine synthesis observed in schizophrenia and preceding phases of the illness have yet to be elucidated, and amphetamine-induced sensitization might provide a suitable model for this purpose. Nevertheless, sensitization of the dopamine system is probably only one small part of the bigger picture of neurobiological changes occurring in schizophrenia. Different molecular changes are under intense investigation and might shed light on the development of sensitization in schizophrenia. Antipsychotics might reverse sensitization and restore the flow of information from frontal areas to cortico-striatal-thalamo-cortical loops, thereby leading to symptom relief. As of yet, schizophrenia is a disorder often associated with nonresponse or partial response to treatment, leading to high disability. Sensitization to amphetamine is a narrowly defined pharmacological-behavioral construct. Its neurochemical signature can be readily studied in humans and animals. One day, translational research on amphetamine-sensitization will hopefully help to identify new molecular drug targets allowing for improved therapeutic strategies in schizophrenia.

### Sensitization

- Increased response after repeated exposure to a stable dose of a substance
- Cross-sensitization with stress described for most sensitizing substances
- Close relationship to dopamine-mediated learning (e.g. conditioned learning)
- Increased release of dopamine in response to a stable dose of amphetamine, cocaine, opiates, or methylphenidate
- Increased release of dopamine in sensitized animals and humans

### Sensitized dopamine response and psychiatric disorders

- Behavioral sensitization towards amphetamines and methylphenidate in schizophrenia
- Sensitization is believed to underlie habit-formation in addiction
- Blunted dopamine release in substance use disorders

### Dopaminergic changes in sensitization

- Increased presynaptic release of dopamine
- Increased quantal size
- Increase in markers of dopamine synthesis
- Increase in postsynaptic dopamine- $D_{2/3}$  function
- Sub-sensitivity of inhibitory auto-receptors
- Altered dopamine  $D_3$  receptor binding and function

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