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On the transmethylation hypothesis: stress, *N*,*N*-dimethyltryptamine, and positive symptoms of psychosis

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Abstract Past research suggests a relationship between stress and positive symptoms of psychosis. However, the biological substrate of this relationship remains unknown. According to the transmethylation hypothesis, schizophrenia could result from a biochemical disruption in the stress mechanism. This biochemical disruption would lead to the production of a substance that would account for the symptoms of psychosis. Moreover, some studies have tested endogenous *N*,*N*-dimethyltryptamine (DMT) in the context of the transmethylation hypothesis. Stress has been found to elevate DMT levels in rodents. Also, elevated DMT levels have been associated with positive features of psychosis in psychiatric patients. Additionally, healthy participants treated with exogenous DMT experience predominantly positive symptoms of psychosis. The present paper examines endogenous DMT as a possible biological mediator of the relationship between stress and positive symptoms of psychosis.

Keywords Dimethyltryptamine · Transmethylation hypothesis · Stress · Positive symptoms of psychosis · Schizophrenia · Biological markers

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Introduction

Myin-Germeys and van Os (2007) have proposed an affective pathway to psychosis. Particularly, they hypothesized that increased affective reactivity to stress (stress reactivity) could underlie the positive symptoms of psychosis. Also, they hypothesized that stress could account for the characteristic fluctuations in intensity that are commonly observed in positive symptoms. Indeed, an association between increased stress reactivity and positive—but not negative—symptoms of psychosis has been found in patients with schizophrenia (Lataster et al. 2013). Moreover, Myin-Germeys et al. (2005) have found an association between daily life stress and intensity of symptoms of psychosis in patients with schizophrenia in a state of remission. However, the biological mechanism underlying the relationship between stress and positive symptoms of psychosis remains unknown.

According to an early biological theory called the transmethylation hypothesis, schizophrenia could result from a biochemical disruption in the stress mechanism (Osmond and Smythies 1952). Osmond and Smythies (1952) noticed the clinical importance of anxiety and stress in schizophrenia. They also noticed that adrenaline, which becomes elevated in stress, bears a structural similarity to mescaline, a psychotomimetic substance. Therefore, they hypothesized that schizophrenia could result from a metabolic disorder of the adrenal glands. This metabolic disorder would methylate adrenaline into a substance structurally similar to mescaline and, in doing so, it would account for the clinical symptoms of schizophrenia. Since the introduction of the theory, a much more complex picture of neurobiochemical processes has been revealed through advances in cell and molecular biology. Thus, a simple increase or decrease of

a substance may not always explain what turns out to be dysfunction in highly complex and integrated processes, such as stress. Nonetheless, the transmethylation hypothesis, the methylation of known neurotransmitters to form hallucinogenic compounds in vivo, has continued to generate interest and further research. In this regard, researchers have also examined endogenous methylated indolealkylamines (MIAs) in the context of the transmethylation hypothesis. One of these endogenous MIAs is *N*,*N*-dimethyltryptamine (DMT).

DMT is an endogenous compound detected in the human cerebrospinal fluid (CSF), blood, and urine (Barker et al. 2012). It results from the *N*-methylation of tryptamine—which derives from dietary tryptophan—into *N*-methyltryptamine (NMT) and the *N*-methylation of NMT into DMT (Barker et al. 1981). These methylation processes are catalyzed by the indolethylamine-*N*-methyltransferase (INMT) enzyme (Barker et al. 1981). Moreover, DMT is catabolized by monoamine oxidase (MAO; Barker et al. 1981). Also, stress elevates DMT levels in rodent brain and adrenal gland (as cited in Barker et al. 1981) and elevated DMT levels have been associated with positive features of psychosis in psychiatric patients (Murray et al. 1979). Moreover, healthy participants treated with DMT experience predominantly positive symptoms of psychosis (Gouzoulis-Mayfrank et al. 2005). The aim of the present paper is to explore the possible role of DMT reactivity as a biological mediator of the relationship between stress and positive symptoms of psychosis in patients with schizophrenia.

Stress, DMT, and positive symptoms of psychosis

Stress and DMT

Osmond and Smythies (1952) hypothesized that schizophrenia could result from a metabolic disorder of the adrenal glands. Indeed, INMT is highly expressed in the adrenal glands of humans (Thompson et al. 1999). Moreover, adrenal tryptamine content increases in rats following stress (Harrison and Christian 1984). In addition, DMT is a substrate for the vesicle monoamine transporter 2 (VMAT2; Cozzi et al. 2009). Likewise, VMAT2 messenger ribonucleic acid (mRNA) expression has been found to be elevated in the chromaffin cells of the rat adrenal medulla following stress (Tillinger et al. 2010). Hence, it is hypothesized here that a stress-dependent increase in DMT levels—combined with a stress-dependent increase in DMT storage by the VMAT2—could lead to high levels of DMT being released as a response to stress. INMT is also expressed in primate nervous tissue (Cozzi et al. 2011). Moreover, brain levels of tryptophan (Curzon et al. 1972) and brain tryptamine content (Harrison and Christian 1984) increase following stress.

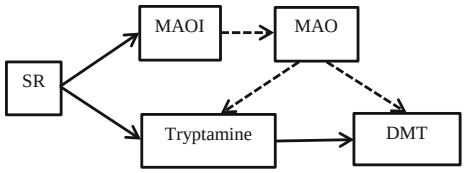

Fig. 1 Hypothetical relationship between stress reactivity and DMT metabolism. *Solid lines* represent positive relationships. *Dashed lines* represent negative relationships. *SR* stress reactivity, *MAOI* monoamine oxidase inhibitors, *MAO* monoamine oxidase, *DMT* *N*,*N*-dimethyltryptamine

Further support for an environmental or epigenetic, rather than a genetic, factor controlling DMT levels comes from a study measuring INMT activity. Wyatt et al. (1973) found significantly higher INMT levels in patients with schizophrenia compared to healthy controls. However, their monozygotic twin siblings who were discordant for the disorder did not differ from healthy controls (Wyatt et al. 1973). Hence, Wyatt et al. (1973) suggested that increased INMT activity in patients could be due to an environmental factor, such as stress. In addition to elevated levels of endogenous DMT as a response to stress, administration of exogenous DMT appears to affect biological mechanisms related to stress. In particular, exogenous DMT has been found to increase cortisol (Strassman and Qualls 1994) and striatal dopamine (Smith 1977). Increased cortisol and striatal dopamine have also been associated with both stress and psychosis (Collip et al. 2011; Mizrahi et al. 2012).

The aforementioned findings point towards a possible relationship between stress and DMT. Moreover, activity of MAO inhibitors (MAOIs) has been positively correlated with everyday stress in humans (Doyle et al. 1996). Consequently, a stress-dependent increase in MAOI activity could possibly decrease MAO activity. Indeed, Vitale et al. (2010) have reported a negative correlation between high DMT and low MAO in some patients with psychosis. Thus, it is hypothesized here that these observations made by Vitale et al. (2010) might have been due to stress (Fig. 1). Also, Vitale et al. (2010) reported that perceptual disturbances were associated with these markers. Therefore, it would be of interest to explore whether elevated DMT levels could underlie positive symptoms of psychosis in patients.

DMT and positive symptoms of psychosis

High levels of endogenous DMT have been correlated with delusions of persecution (Murray et al. 1979). Also,

Gouzoulis-Mayfrank et al. (2005) have observed paranoid ideation in healthy participants treated with exogenous DMT. Moreover, paranoid psychosis has been associated with high levels of DMT (Murray et al. 1979; Uebelhack et al. 1983), high levels of INMT (Strahilevitz et al. 1975), and low levels of MAO (Zureick and Meltzer 1988). In addition, Gouzoulis-Mayfrank et al. (2005) have suggested that exogenous DMT might be of value in modeling psychoses of the paranoid type. Also, Murray et al. (1979) found a correlation between DMT levels and the summary score "grandiose and religious delusions" of the Present State Examination (PSE) rating scale. Similarly, Warren et al. (2013) reported a case study describing a psychotic episode characterized by positive symptoms, including religious delusions, following a year of DMT abuse. However, the patient engaged in polydrug use and a causal role for DMT cannot be concluded.

Hallucinations (Murray et al. 1979; Spatz et al. 1993), and auditory hallucinations in particular (Murray et al. 1979), have also been correlated with high levels of DMT in psychiatric patients. Additionally, significantly low MAO activity has been found in patients with schizophrenia and auditory hallucinations compared to healthy controls and other patients with schizophrenia who did not hallucinate (Zureick and Meltzer 1988). However, exogenous DMT causes primarily visual hallucinations and only some auditory effects (Gouzoulis-Mayfrank et al. 2005). Nevertheless, one study of exogenous DMT reported visual hallucinations in healthy participants but not in patients with schizophrenia (Böszörményi and Szára 1958). In the same study, DMT exacerbated acoustic hallucinations in two patients with a history of intense acoustic hallucinations before the experiment. Therefore, DMT, particularly that which arises endogenously in reaction to stress or from discrete tissues, might exert different hallucinatory effects in patients with schizophrenia.

Murray et al. (1979) have also found a correlation between high DMT levels and the summary score "speech and behavior abnormalities" of the PSE rating scale. Also, Gouzoulis-Mayfrank et al. (2005) observed positive formal thought disorder (derailment or loose associations and distractibility) in all of their participants after a low dose of DMT. Furthermore, they observed prominent positive formal thought disorder in 4/9 patients after a high dose of DMT. Overall, the findings suggest a relationship between DMT and persecutory delusions, grandiose and religious delusions, auditory hallucinations, and disorganized thinking. Therefore, the evidence suggests that elevated DMT levels are associated with positive symptoms. Alternatively, DMT could merely be a metabolic consequence of positive symptoms. Positive symptoms could simply increase DMT levels by inducing stress. Moreover, increased DMT is not specific to patients with schizophrenia. Nevertheless, the evidence is important because exogenous DMT causes positive symptoms in healthy participants. The following section examines the possible ways in which DMT could cause such symptoms.

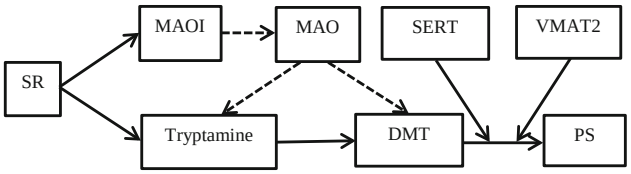

Fig. 2 Hypothesized role of neurotransmitter transporters in the relationship between DMT and positive symptoms. *Solid lines* represent positive relationships. *Dashed lines* represent negative relationships. *SR* stress reactivity, *MAOI* monoamine oxidase inhibitors, *MAO* monoamine oxidase, *DMT* *N*,*N*-dimethyltryptamine. *SERT* serotonin transporter density, *VMAT2* vesicular monoamine transporter 2 density, *PS* positive symptoms

Mechanism of action

Neurotransmitter transporters

Neurotransmitter transporters have been suggested as a possible mechanism that could allow endogenous DMT to act as a releasable neurotransmitter (Cozzi et al. 2009). Particularly, DMT is a substrate for the serotonin transporter (SERT), as well as the VMAT2 (Cozzi et al. 2009). This means that DMT could be transported into the cytosol by the SERT and stored into vesicles by the VMAT2 (Cozzi et al. 2009). Moreover, Vitale et al. (2011) have observed that radiolabeled DMT remains in the brain of rabbits for at least 1 week after injection. Therefore, they suggested that DMT might be stored by the SERT and the VMAT2 to be released as a neurotransmitter. Finally, secretion of DMT from nerve cells directly at receptor sites could perhaps lead to positive symptoms of psychosis (Cozzi et al. 2009).

Patients with schizophrenia have been found to have higher SERT (Govitrapong et al. 2002) and VMAT2 (Zucker et al. 2002) density compared to healthy controls. Hence, it is hypothesized here that increased density of these transporters could lead to more efficient storage and release of DMT in the central nervous system (CNS) of patients with schizophrenia. This would lead to increased levels of DMT being released at receptor sites (Fig. 2). Furthermore, a finding suggests that DMT can modulate SERT density. Callaway et al. (1994) have reported higher SERT density in chronic users of a DMT-containing drink (ayahuasca) compared to non-users. Especially in the case of ayahuasca, increased SERT density could possibly reflect an adaptation to counteract potentially harmful drug

effects. Moreover, it is hypothesized here that prolonged elevated levels of endogenous DMT might be responsible for the increase in SERT density found in some patients with schizophrenia. Consequently, increased DMT and decreased MAO activity, combined with increased SERT and VMAT2 density, could result in more efficient storage of DMT into vesicles.

Govitrapong et al. (2002) found that treatment with a variety of neuroleptics reduced the SERT density of patients to normal levels. This reduction in SERT sites was hypothesized to be involved in the clinical improvement of the patients. Also, reserpine—a VMAT2 inhibitor—has been used in the past as a treatment of positive symptoms of psychosis (Bøgesø and Bang-Andersen 2003). Reserpine's mechanism of action might reflect the nature of the processes that it suppresses. Particularly, reserpine blocks the VMAT2 transport of monoamines into vesicles (Bøgesø and Bang-Andersen 2003). Consequently, the monoamines are broken down by MAO (Bøgesø and Bang-Andersen 2003). However, reserpine has no selective target. Theoretically, dopamine, serotonin, and DMT could all deplete due to reserpine. Reserpine's mechanism of action indicates that VMAT2 activity is possibly related to positive symptoms of psychosis. Consequently, the monoamines that are transported by the VMAT2 could be involved in the pathogenesis of positive symptoms. Finally, assuming that endogenous DMT is stored by neurotransmitter transporters for synaptic release, it is important to examine the receptors that are possibly implicated in the effects of DMT.

Neurotransmitter receptors

Exogenous DMT acts at serotonin receptors (Deliganis et al. 1991; Smith et al. 1998). Much focus has been given to the 5-hydroxytryptamine 2 (5-HT_2) receptors. Smith et al. (1998) reported that the 5-hydroxytryptamine 2C (5-HT_{2C}) receptor, but not the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor, became desensitized after exposure to DMT. According to Smith et al. (1998), the fact that DMT desensitizes the 5-HT_{2C} receptor but does not produce tolerance to its psychological effects implies that the role of the 5-HT_{2C} receptor is not important for modulating the psychological effects of the substance. Additionally, many other hallucinogens act on the 5-HT_{2A} receptor (González-Maeso et al. 2007). Moreover, ketanserin, a 5-HT_{2A} antagonist and VMAT2 inhibitor, has been found to attenuate the positive symptoms caused by *O*-phosphoryl-4-hydroxy-*N*,*N*-dimethyltryptamine (4-PO-DMT; Carter et al. 2007). Also, atypical antipsychotic drugs with effect on the serotonin receptors are being developed for the treatment of schizophrenia (Meltzer et al. 2012). Although DMT is usually discussed as a serotonergic substance, research suggests that other receptors might also be involved in its effects.

A number of animal studies suggest that DMT regulates brain dopamine release (Haubrich and Wang 1977; Smith 1977; Waldmeier and Maître 1977). The findings of these studies might reflect an indirect action of DMT on the dopaminergic system. Particularly, Pehek et al. (2006) reported that stress induced an increase in cortical serotonin and dopamine levels. However, antagonism in the 5-HT_{2A} receptors attenuated the stress-induced dopamine release. This implies that the stress-induced dopamine release is under serotonergic control (Pehek et al. 2006). Hence, it is hypothesized here that DMT could possibly influence dopamine levels through serotonergic pathways and even underlie the increased stress-induced dopamine release observed in people with psychosis (Mizrahi et al. 2012). Interestingly, both serotonin and dopamine levels are increased by stress (Pehek et al. 2006), broken down by MAO, and transported by the VMAT2. Serotonin is also transported by the SERT. Hence, the evidence points towards an aberrant monoaminergic mechanism of stress in schizophrenia. However, the discussion of this hypothesis is beyond the scope of the present paper. DMT is the only one of these substances to experimentally cause positive symptoms in healthy participants.

Another site of action for DMT is the trace amine receptor 1 (TAR1; Bunzow et al. 2001). Based on the research that describes a calming effect for low doses of exogenous DMT (Strassman et al. 1994), Jacob and Presti (2005) hypothesized that low doses of exogenous DMT might mimic DMT's endogenous action. Thus, they hypothesized that DMT could have an anxiolytic role and that it could possibly exert neurotransmitter effects on the trace amine-associated receptors (TAARs). Instead, Wallach (2009) suggested that low dose administration of DMT probably exerts anxiolytic effects through serotonergic action. Therefore, Wallach (2009) hypothesized that DMT might indeed be a TAAR neurotransmitter, but without anxiolytic properties. He hypothesized that DMT could play a role in the regulation of sensory perception as a neurotransmitter and that when its regulatory role is altered, atypical states of consciousness occur.

The idea that DMT might act as an endogenous anxiolytic is of particular interest to the present paper. DMT could be released under stressful conditions to act as an anxiolytic (in low levels) or a dissociative (in higher levels) to protect the organism from intense stressful stimuli. This function of DMT would not be limited to people with schizophrenia, but could perhaps extend to healthy individuals undergoing severe stress. For instance, Siegel (1984) reviewed case studies of hostage victims. He found that people who had undergone isolation and life-threatening stress experienced visual hallucinations and

dissociation. Similarly, healthy participants treated with exogenous DMT frequently experience visual hallucinations and dissociation (Strassman et al. 1994). Increased DMT reactivity to everyday life stressors could perhaps underlie the positive symptoms of psychosis in a subgroup of schizophrenia patients with high stress reactivity.

A more recent finding is that DMT acts on the sigma-1 receptor (Fontanilla et al. 2009). Moreover, Fontanilla et al. (2009) found that DMT produces hypermobility in wild-type mice, but not in sigma-1 receptor knockout mice. Induction of hypermobility might imply a role of sigma-1 receptors in symptoms of psychosis. Moreover, Fontanilla et al. (2009) pointed out that DMT-induced hypermobility is inhibited by haloperidol in rodents (Jenner et al. 1978) and that haloperidol is also a sigma-1 receptor agonist (Matsumoto and Pouw 2000). Furthermore, hypermobility was not inhibited by dopamine or serotonin blockers (Jenner et al. 1978). However, it is not clear how these findings would translate in humans. The possibility of DMT-induced hallucinatory action in the sigma-1 receptor has been suggested by Su et al. (2009). Nevertheless, it is not yet clear whether DMT could exert psychological effects purely through the sigma-1 receptor.

Brain imaging

The resting state of acute DMT intoxication can be examined in relation to the neural substrates of acute psychosis. Riba et al. (2006) have examined the neural correlates of acute ayahuasca intoxication. Ayahuasca, however, contains more substances than DMT (Pomilio et al. 1999). Yet, this is a limitation as well as an advantage. Particularly, ayahuasca combines DMT with a MAOI (Pomilio et al. 1999). Because ayahuasca includes both of these substances, it has been suggested to be an appropriate model of the transmethylation hypothesis (Pomilio et al. 1999). Therefore, acute ayahuasca intoxication might provide a model for the neural mechanisms of psychosis. During acute ayahuasca intoxication, greater activity has been observed in the left amygdala, the bilateral (mostly right) anterior insula, and the right anterior cingulate cortex, among other areas (Riba et al. 2006).

Activity in the left amygdala has been correlated with positive symptoms of psychosis in patients with schizophrenia (Taylor et al. 2002). Recently, positive symptoms have also been correlated with the connection between the left amygdala and the nucleus accumbens (Bracht et al. 2014). In addition, Horga et al. (2014) observed atypically strong connections between the amygdala and auditory regions in the cortex and the thalamus in remitted patients with schizophrenia compared to healthy controls. Also, Horga et al. (2014) observed an exaggerated response of the left amygdala towards aversive stimuli resembling auditory verbal hallucinations (AVHs) in patients. Therefore, Horga et al. (2014) suggested that increased connectivity between the left amygdala and auditory regions might reflect atypical salience towards aversive stimuli. Activity in the bilateral anterior insula has also been involved in acute psychosis, particularly AVHs (Craig 2009; Sommer et al. 2008). Additionally, negative emotional content of AVHs was associated with right lateralization of activity (Sommer et al. 2008). Hence, the right anterior insula is also of interest in the concept of aberrant salience.

Myin-Germeys et al. (2005) have discussed the relationship between psychotic reactivity to daily life stress in the context of the neurobiological model of aberrant salience proposed by Kapur (2003). According to Kapur (2003), psychosis is characterized by aberrant assignment of salience to internal representations and external objects. Moreover, Palaniyappan and Liddle (2012) have suggested a distinction between the concept of motivational salience proposed by Kapur (2003) and the concept of proximal salience. Particularly, Palaniyappan and Liddle (2012) have suggested that proximal salience refers to the momentary, stimulus–response dimension of salience to internal and external stimuli. According to Palaniyappan et al. (2011), the anterior insula and the anterior cingulate comprise the network of proximal salience. Moreover, Palaniyappan et al. (2011) have presented evidence for the involvement of this network in schizophrenia. Consequently, aberrant proximal salience to internal and external stimuli might be involved in the effects caused by ayahuasca and in the positive symptoms of schizophrenia.

Conclusions and future prospects

To conclude, it is hypothesized that increased DMT reactivity as a response to stress could possibly underlie positive symptoms of psychosis in a subgroup of patients with schizophrenia. Additionally, peripherally and centrally produced DMT could be taken up by the SERT and the VMAT2 and stored in the CNS for synaptic release. Increased density of these transporters could lead to more efficient storage and release of DMT in the CNS. When released into the synapse, DMT could perhaps cause or exacerbate positive symptoms. Therefore, DMT could simply be involved in a monoaminergic mechanism of stress, and in doing so, it could produce positive symptoms of psychosis. Alternatively, patients with positive symptoms could experience more stress and this could result in increased DMT levels in these patients.

Some prospects for future studies arise out of these conclusions. Namely, the relationship between stress and DMT in humans should be examined to replicate animal

studies. Furthermore, past studies that measured DMT levels in patients with psychosis did not look for a relationship between stress, DMT and/or metabolite levels, and positive symptoms of psychosis. Therefore, examining DMT reactivity as a biological mediator of the relationship between stress and positive symptoms of psychosis in patients with schizophrenia could yield more detailed and complete results. There is also a need for the use of modern analytical, imaging and assessment instruments in the measurement of stress, stress reactivity, and positive symptoms. Finally, it would be of interest to explore the possibility that elevated density of the SERT and the VMAT2 could moderate the hypothesized relationship between DMT levels and positive symptoms of psychosis.

Conflict of interest The authors declare that they have no conflict of interest.

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