The neurochemistry of hypnotic suggestion

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Abstract

A diverse array of studies has been devoted to understanding the neurochemical systems supporting responsiveness to hypnotic suggestions, with implications for experimental and clinical applications of hypnosis. However, this body of research has only rarely been integrated and critically evaluated and the prospects for the reliable pharmacological manipulation of hypnotic suggestibility remain poorly understood. Here we draw on pharmacological, genotyping, neuroimaging, and electrophysiological research to synthesize current knowledge regarding the potential role of multiple widely-studied neurochemicals in response to suggestion. Although we reveal multiple limitations with this body of evidence, we identify converging results implicating different neurochemical systems in response to hypnotic suggestion. We conclude by assessing the extent to which different results align or diverge and outline multiple avenues for future research. Elucidating the neurochemical systems underlying response to suggestion has the potential to significantly advance our understanding of suggestion.

Keywords: dopamine, GABA, glutamate, NMDA, oxytocin, serotonin

The Neurochemistry of Hypnotic Suggestion

A powerful yet poorly understood capacity of the human brain is its ability to modulate the contents of awareness. One of the more striking instances of this top-down regulation is exemplified in the phenomenon of *suggestion,* which can be understood as a communication for an involuntary response (Kirsch, 1999). Suggestion represents the hallmark feature of hypnosis and plays an integral role in a range of phenomena, most notably the placebo response (Wager & Atlas, 2015). Recent research has begun to converge around the proposal that the primary foci within this field should be the characteristics, correlates, and neurocognitive bases of (hypnotic) suggestion and suggestibility (Jensen et al., 2017).

Despite methodological and theoretical advances in in the cognitive neuroscience of hypnosis (Landry et al., 2017; Oakley & Halligan, 2013; Terhune et al., 2017), there has been relatively scant attention to the role of different neurochemicals in response to hypnotic suggestions. A wealth of studies has direct bearing on potential neurochemical mechanisms but to our knowledge they have not yet been systemically integrated and scrutinized. Here we aim to fill this conceptual gap in current research on the neuroscience of hypnotic suggestion. As a set of signposts for potential implications of neurochemical targets, we firstly introduce a lexicon of terms and highlight the value of hypnosis in various contexts. Next, we describe and evaluate research implicating specific neurochemicals in hypnotic responding. We subsequently attempt to integrate these results and highlight a range of methodological challenges with a view to outlining research questions that warrant further empirical attention.

Hypnosis and Hypnotic Suggestibility

Hypnosis is typically conceptualized as either a state of consciousness (Elkins et al., 2015) or as a set of procedures involving a hypnotic induction and suggestions for alterations in affect, cognition, and perception (Terhune, 2014). Variability in *hypnotic suggestibility*,

responsiveness to hypnotic suggestions as measured by standardized scales, represents the primary factor underlying various suggested and spontaneous hypnotic phenomena (for reviews, see Acunzo & Terhune, in press; Oakley et al., in press). Hypnotic suggestibility can be conceptualized as a manifestation of a broader psychological trait, *direct verbal suggestibility* (DVS; Oakley et al., in press, 2020), as highly suggestible individuals tend to still respond to verbal suggestions in the absence of an induction (Terhune & Cardeña, 2016).

Elucidating the characteristics and mechanisms of hypnosis and hypnotic suggestibility has direct implications for our understanding of a broad swath of cognitive phenomena including sense of agency, metacognition, the influence of priors on perception, and top-down regulation (Terhune et al., 2017). Hypnotic suggestion represents a powerful instrumental tool for studying these and other phenomena through the production and manipulation of hypnotic analogues (Oakley & Halligan, 2013), in particular as a method for producing temporary models of pathological symptoms (Deeley et al., 2013; Woody & Szechtman, 2011). Numerous researchers have highlighted links between hypnotic suggestibility and dissociative psychopathology (Oakley, 2012). In particular, it has been proposed that hypnotic suggestibility confers predisposition to dissociative disorders (Butler et al., 1996) and multiple lines of evidence indicate that these disorders are indeed characterized by elevated hypnotic suggestibility (Bell et al., 2011; Wieder et al., in press).

Understanding its neurochemical bases has further direct implications for clinical applications of hypnosis (Jensen et al., 2017). Numerous lines of evidence indicate that hypnotic suggestion is an effective component of treatment for psychological problems with both cognitive behavioural therapy (Kirsch et al., 1995) and psychoanalytic approaches (Baker & Nash, 2008). Establishing a positive link between neurochemicals, responsiveness to hypnotic suggestion and to DVS generally would raise the prospect that these compounds may be used to augment the effectiveness of interventions involving suggestion to counter the

presenting, suggestibility-related, clinical condition. A caveat is that the chemical intervention should be targeted to coincide with the intervention as prolonged elevation of suggestibility could in principle expose the already vulnerable individual to further pathological self-beliefs.

Neurochemicals implicated in hypnotic suggestion

In what follows, we review research pertaining to the ostensible link between individual neurochemicals and responsiveness to suggestion. This review is not intended to be exhaustive and we have omitted consideration of neurochemicals that have received only sparse attention, such as opioids (Goldstein & Hilgard, 1975), acetylcholine (Sternbach, 1982), and nitric oxide (Santarcangelo & Scattina, 2019). We focus on five neurochemicals that have been hypothesized to be implicated in hypnotic responding. Whenever possible, we draw on studies that have used different methods, including those that yield only indirect evidence as well as on research from domains germane to hypnosis and suggestion when relevant.

Dopamine

Dopamine is a monoamine neurotransmitter involved in the neuromodulation of a variety of systems and functions including motor control, spatial memory, motivation, reinforcement, reward and sleep. Dopamine signalling dysfunctions are involved in several pathologies, including schizophrenia and attention deficit/hyperactivity disorder (ADHD) (Klein et al., 2019).

Dopamine is the most studied neurochemical as a candidate for its involvement in (hypnotic) suggestibility. Executive functions such as cognitive control involve dopaminergic systems (T. Ott & Nieder, 2019) and parallels between attentional and suggestion processes have been repeatedly advanced (Raz, 2005). Neuroimaging studies of response to suggestion often observe an involvement of anterior cingulate cortex (ACC) (Landry et al., 2017), part of

the mesocortical dopamine system. Dopamine appears to also be involved in the placebo response (Wager & Atlas, 2015) which frequently involves direct verbal suggestions. A role for dopamine is also compatible with the hypothesised involvement of nitric oxide (NO) in suggestibility, as NO facilitates dopamine release (Santarcangelo & Scattina, 2019).

One of the earliest studies implicating dopamine in hypnosis (Spiegel & King, 1992) reported a positive correlation between homovanillic acid (a metabolite of dopamine) concentration in the cerebrospinal fluid and hypnotic suggestibility. To our knowledge, this effect has not yet been replicated nor have more direct imaging methods been employed to evaluate this link more systematically. Pharmacological evidence implicating dopamine in hypnotic suggestibility comes from a study of the impact of methylphenidate (MPH) treatment on hypnotic suggestibility in ADHD patients (Lotan et al., 2015). MPH inhibits the reuptake of dopamine by neurons in the central nervous system, which increases extracellular dopamine concentrations (Volkow et al., 2001). Lotan et al. found that MPH significantly increased hypnotic suggestibility, in particular among low suggestible patients.

Spontaneous eyeblink rate at rest has been repeatedly associated with striatal dopamine receptor availability (for a review, see Jongkees & Colzato, 2016; but see Dang et al., 2017), and multiple studies have utilized this measure to evaluate the potential involvement of dopamine in hypnotic responding. However, attempts to link baseline blink rates and trait (hypnotic) suggestibility, as well as changes in blink rate following an induction have yielded conflicting results (for a detailed review, see Cardeña et al. 2017).

The involvement of dopamine in suggestibility has also been studied using the indirect measure of pre-pulse inhibition (PPI), whose regulation involves the dopaminergic system (Swerdlow et al., 2016). PPI measures the inhibition of the startle reflex when the intense stimulus (pulse) generating the reflex is directly preceded by a milder stimulus (pre-pulse). At least four studies have investigated the link between PPI and suggestibility: three (Levin et al.,

2011; Lichtenberg et al., 2008; Storozheva et al., 2018) found an association between reduced inhibition and higher suggestibility, whereas one yielded results consistent with an opposite effect (De Pascalis & Russo, 2013).

A final line of evidence bearing on a role for dopamine in hypnosis comes from studies of the genetic polymorphisms underlying hypnotic suggestibility. A candidate gene is that coding for Catechol-O-methyl transferase (COMT), which is directly involved in prefrontal dopamine degradation, and whose $Val^{158}Met$ (rs4680) genetic variants degrade dopamine at different speeds (Lachman et al., 1996). Previous research suggests a link between this polymorphism and executive functions (Bilder et al., 2004), and placebo responding (Colloca et al., 2019). Studies of the link between this polymorphism and suggestibility have yielded conflicting results. Two studies (Lichtenberg et al., 2000, 2004) found effects differing according to gender. Raz and colleagues (2004) reported that val/met participants were the most highly suggestible whereas Szekely et al. (2010) reported an additive suggestibility effect of the val allele (see also Katonai et al., 2017). However, two studies (Rominger et al., 2014; Storozheva et al., 2018) observed that it was the met/met genotype that was characterized by the highest suggestibility. Finally, other studies failed to observe or report any links (Bryant et al., 2013; Presciuttini et al., 2014; see also U. Ott et al., 2005). Taken together, these results are equivocal and indicate that potential links between the COMT polymorphism and suggestibility are at best complex.

Preliminary biological, pharmacological, and behavioral (PPI) research suggest that elevated dopamine is associated with hypnotic suggestibility. Further work should aim to ground assessments of this association within predictive coding accounts of suggestion (Martin & Pacherie, 2019) as corresponding models of schizophrenia attribute an over-reliance on priors leading to symptoms to imbalances in dopamine (and glutamate) signalling (Corlett et al., 2016).

Glutamate

Glutamate is the primary excitatory neurochemical in the brain and is implicated in an array of neurophysiological processes and corresponding psychological functions including synaptic plasticity, memory, and cognitive control (Snyder & Gao, 2020). Abnormalities in the glutamate system, particularly hypofunction of the receptor subtype N-methyl-D-aspartate (NMDA; Emmanouil, 2020), have been proposed to contribute to psychosis (Corlett et al., 2011) and NMDA receptor antagonists elicit distortions in awareness that parallel schizophrenia symptoms (Krystal et al., 1998). Of direct relevance to hypnosis, NMDA signaling is hypothesized to play an integral role in the influence of priors on perception (Corlett et al., 2016).

Multiple studies have presented evidence implicating glutamate in hypnotic responding. Consistent data comes from research using NMDA receptor antagonists, such as nitrous oxide (N_2O) and ketamine, which are widely used for anaesthesia and analgesia (Emmanouil, 2020). Multiple early studies that lacked rigorous controls, and numerous clinical observations, suggest that N_2O augments suggestibility, that suggestion can be used to shape the response to N_2O, and that N_2O-induced dissociative states parallel the phenomenological effects of an induction (Dworkin et al., 1986; Parbrook, 1967). Inspired by these preliminary results, at least two controlled studies have shown that N_2O inhalation augments (non-) hypnotic suggestibility (Barber et al. 1979; Whalley & Brooks, 2009). Barber and colleagues (1979) reported that 20-40% N_2O inhalation was associated with greater hypnotic suggestibility than placebo (O_2) inhalation. A subsequent placebo-controlled study similarly found that 20% N_2O-inhalation was associated with greater non-hypnotic suggestibility (Whalley & Brooks, 2009). Interestingly, N_2O inhalation was also associated with increased imagery vividness that correlated with increases in suggestibility, which implies that suggestibility-augmentation is driven by greater imagery vividness or vice versa (see also

Terhune & Oakley, 2020). Importantly, participants were unable to distinguish drug conditions and the effects seemed to be independent of response expectancies.

Clinical trials similarly imply that ketamine also enhances suggestibility (e.g., Sklar et al., 1981). A recent study found that ketamine significantly enhanced hypnotic suggestibility in low, but not medium, suggestible participants despite significantly enhancing state dissociation in both (Patterson et al., 2018). This result complements the N_2O studies, as the two drugs have overlapping neuropharmacology (Jevtovic-Todorovic et al., 2001). These results broadly align with models conceptualizing hypnosis as a dissociative phenomenon as well as potential links between hypnotic suggestibility and schizotypy.

A finding that complements the foregoing results was reported in a recent magnetic resonance spectroscopy (MRS) study of ACC glx (an admixture of glutamate and glutamine) (DeSouza et al., 2020). This study found that glx concentrations negatively correlated with trait dissociative absorption, such that those high in absorption, who also tend to display high hypnotic suggestibility (Cardeña & Terhune, 2014; Tellegen & Atkinson, 1974), exhibited lower glx concentrations. This result implies that lower glutamate is a characteristic of those who are responsive to suggestions and thus is broadly congruent with the NMDA receptor antagonist studies. Independent research using transcranial magnetic stimulation has shown that highly suggestible participants display elevated motor cortex excitability (Spina et al., 2020), which suggests elevated motor cortex glutamate in this subgroup. Although this would seem to be inconsistent with the MRS results, glutamate concentrations in different anatomical regions do not correlate reliably (e.g., Terhune et al., 2015) and thus these may reflect independent effects that subserve disparate componential abilities (Barnier et al., in press). Aberrant glutamate has been proposed to relate to over-reliance on priors, potentially via dopamine-glutamate interactions (Corlett et al., 2016), and thus the current results have potential implications for predictive coding models of hypnosis (Martin & Pacherie, 2019).

GABA

Gamma-aminobutyric acid (GABA) is the dominant inhibitory neurochemical in the brain. The role of GABA extends beyond simple neuronal inhibition and includes regulation of synaptic integration, plasticity, and modulation of cortical network dynamics (Ende, 2015). GABA is involved in a variety of psychological functions including learning, memory and impulsivity and is aberrant in multiple psychiatric conditions (Reddy-Thootkur et al., 2020).

Multiple reports imply that elevated GABA produces increased suggestibility. However, these data come from studies that lacked placebo-controlled trials and robust measures of suggestibility and thus should be considered preliminary. Early research suggested that amobarbital, a $GABA_A$ receptor agonist, increases suggestibility (Eysenck & Rees, 1945). Recent research has highlighted how the abuse of benzodiazepines, which include a large number of sedative $GABA_A$ agonists, produces *automatism amnesia* where individuals will perform seemingly automatic behaviours and display elevated suggestibility often followed by anterograde amnesia (Goullé & Anger, 2004; Marc et al., 2000). Benzodiazepines have also been cited as increasing suggestibility in the context of narcotherapy in functional neurological disorder (Rosebush & Mazurek, 2011). Gamma hydroxybutyric acid, a $GABA_B$ agonist used in the treatment of narcolepsy and as an anesthetic agent, has similarly been reported to increase suggestibility (e.g., Bismuth et al., 1997). These encouraging, albeit preliminary, results point to a clear need to more rigorously assess the impact of GABA agonism on suggestibility, including an assessment of mediating factors in order to distinguish between competing interpretations of these results.

More robust evidence for a role of GABA in hypnotic suggestibility is provided by a recent study using MRS, which can be used to estimate extrasynaptic GABA tone (Ende, 2015). In alignment with the foregoing reports, hypnotic suggestibility was moderately positively associated with GABA concentrations in ACC (DeSouza et al., 2020), an

important node of the salience network that has occasionally been implicated in fMRI studies of hypnotic suggestion (Landry et al., 2017). Interpretation of this result is complicated by the broad mechanistic role that ACC is believed to play in a variety of cognitive functions, from conflict monitoring to adaptive control to agency (Darby et al., 2018; Mansouri et al., 2017). Moreover, no control voxel was included and thus the anatomical specificity of this effect is unclear. These results suggest a positive association between GABA levels and (hypnotic) suggestibility although the cognitive factors that mediate this association are as of yet unknown.

Oxytocin

Oxytocin functions both as a hormone and a neuromodulator and is produced by the hypothalamus and secreted by the pituitary gland. It has received considerable attention in a variety of domains as it regulates an array of social behaviors and stress responses (Jurek & Neumann, 2018). In particular, it appears to play a role in empathy, in-group preference, maternal behavior, and memory and salience of socially relevant cues (Shamay-Tsoory & Abu-Akel, 2016). The oxytocinergic system also appears involved in some impairments linked to social cognition, including attachment deficits as well as autism spectrum disorder (Heinrichs et al., 2009; LoParo & Waldman, 2015).

Owing to its involvement in social cognition and attachment, a role for oxytocin has been hypothesized to be important in facilitating treatment outcome in clinical applications of hypnosis (Zelinka et al., 2014). It is widely believed that the clinical efficacy of hypnosis is closely linked to the quality of the relationship between the therapist and the patient, which can be understood as mirroring parental care (in a caretaker–caregiver interaction) in which oxytocin is involved (Zelinka et al., 2014).

Oxytocin can be administered with minimal invasiveness with an intranasal spray, inducing behavioral changes including effects on fear, prosociality (Veening & Olivier, 2013)

and trust (Kosfeld et al., 2005; but see Declerck et al., 2020). These observations motivated a few studies on the effect of oxytocin administration on responsiveness to suggestion. Bryant and colleagues (2012) reported that hypnotic suggestibility was enhanced in a group of low-suggestible male participants after oxytocin administration, compared to a placebo group, with some evidence that this effect was specific to cognitive suggestions. A follow-up study (Bryant & Hung, 2013) involved suggestions for high-suggestible male participants to engage in unorthodox social behaviors (swearing, singing, dancing) following a posthypnotic cue. Participants who had been administered oxytocin were significantly more responsive than those in the placebo group. By contrast, Parris and colleagues (2014) used a posthypnotic suggestion for word blindness. Contrary to their hypothesis, they found that the effect of the suggestion was impaired in the oxytocin group (but not in the placebo group). They proposed that the discrepancy of the results with previous research may be due to the memory impairment effects of oxytocin (Heinrichs et al., 2004). More recently, Liu and colleagues (2020) found no effect of oxytocin administration on placebo and nocebo effects, most particularly in a large sample experiment (N=146) using a verbal suggestion to modulate the perception of nociceptive stimuli.

Others have investigated oxytocin baseline concentration in the body and suggestibility, as well as changes during a hypnosis session, using saliva samples. Varga and Kekecs (2014) measured oxytocin levels before and after administration of a hypnosis scale. No significant changes were found in oxytocin levels in the hypnotist or participant. In addition, no significant correlation between baseline oxytocin or cortisol levels with hypnotic suggestibility was found. In an independent study, the same group reported a decrease in oxytocin levels in the high suggestibility group, and an increase in the low suggestibility group following a hypnotic induction (Kasos et al., 2018). It should be noted however that saliva oxytocin measurement, in particular using enzyme immune assay, has been strongly questioned as an indicator of

bioavailable oxytocin (Horvat-Gordon et al., 2005; Javor et al., 2014; McCullough et al., 2013). The aforementioned results on oxytocin level changes should therefore be taken with great caution.

Bryant and colleagues (2013) investigated the relationship between hypnotic suggestibility and two single nucleotide polymorphisms of the oxytocin receptor gene, implicated in social bonding, maternal behavior and attachment (rs53576) and autism spectrum disorder (rs2254298). They reported a significant effect of the rs53576 polymorphism (with a higher suggestibility for AA than GG participants) as well as a significant effect of rs2254298 on trait absorption (higher in AG/AA than GG), thereby providing further evidence for a role of oxytocin in hypnotic responding.

Taken together, these different results point toward a potential role of oxytocin in responsiveness to suggestion with some caveats. In particular, manipulation of oxytocin levels by intranasal administration may only selectively enhance suggestibility under certain conditions. Similarly, oxytocin receptor polymorphism may partly explain inter-individual differences in trait suggestibility whereas the extent to which a hypnotic induction modifies oxytocin levels is not yet clear. Nevertheless, these different results warrant further attention in order to better characterize a potential oxytocinergic role in suggestibility.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is implicated in a wide array of psychological and neurophysiological functions, and malfunctions of the serotoninergic system has been associated to many disorders including anxiety, schizophrenia, as well as obsessive-compulsive, sleep and eating disorders (Naughton et al., 2000). Among 5-HT receptor subtypes, 5-HT_{2A} is of particular interest, as it appears involved in both schizophrenia (Naughton et al., 2000) and hallucinogenic responses following psychedelic administration (Nichols, 2004). It also mediates the inhibitory role of the serotoninergic system on

dopaminergic neurons (Naughton et al., 2000). The serotonin system, and in particular the 5-HT_{2A} receptor system, may have a key role in the shaping of our subjective reality, balancing external sensory input with internal constructs and interpretations.

The role of serotonin in suggestion has been investigated pharmacologically using classic psychedelics. Early studies suggest these drugs enhance response to suggestion. Sjoberg and Hollister (1965) found that response to verbal suggestions increased following administration of lysergic acid diethylamide (LSD), mescaline, and a combination of LSD+mescaline+psilocybin. Middlefell (1967) used a single suggestion for 'body sway' in three clinical populations (neurotic, depressive and schizophrenic patients) under LSD and reported a significant effect of LSD compared to placebo only for neurotic participants. More recently, Carhart-Harris and colleagues (2015) reported that suggestibility significantly increased following LSD administration in a small sample (N=10), using a single-blind, within-subject placebo-controlled design. Together, these results suggest serotonin receptor agonists increase suggestibility.

If serotonin plays a role in suggestibility, we might expect that the serotonin transporter (SERT) polymorphism 5-HTTLPR is involved in hypnotic suggestibility as one variant of this polymorphism ('*s*') is characterized by a less efficient serotonin reuptake. However, two studies (Katonai et al., 2017; Rominger et al., 2014) failed to find a significant association between variants of this polymorphism and hypnotic suggestibility. By contrast, Ott and colleagues (U. Ott et al., 2005) investigated the 5-HT_{2A} receptor polymorphism T102C, which has been linked to several psychopathologies including schizophrenia (Abdolmaleky, 2004). They observed that the T/T genotype, characterized by a stronger binding potential of the 5-HT_{2A} receptor, showed higher trait absorption, which is often associated with hypnotic suggestibility, thereby suggesting a potential further link. Although these data suggest that suggestibility is not linked to the SERT 5-HTTLPR polymorphism, future research is required

to assess whether hypnotic suggestibility varies across subtypes of the 5-HT_{2A} receptor polymorphism.

Limitations and future directions

The foregoing sections implicate multiple neurochemicals in response to suggestions. However, the *specific* mechanisms underlying these effects should be treated with caution because of neurochemical interactions, downstream effects, and our ignorance regarding the cognitive changes that mediate these putative effects. In addition, nearly all studies have only indirect bearing on neurochemical processes in hypnotic responding as they have not directly measured the respective neurochemicals.

The various neurochemical agents reviewed here have been shown to have complex effects and this complicates our understanding of the precise neurochemical loci of observed changes in suggestibility. Classic psychedelics have downstream effects on glutamate (De Gregorio et al., 2018) that somewhat mirror the effects of NMDA receptor antagonists. In addition, research in non-human animals suggests biphasic neurochemical effects of LSD such that it acts as a dopamine agonist at a late phase (Marona-Lewicka et al., 2005). There is also evidence that NMDA receptor antagonists increase synaptic activity in GABAergic neurons and trigger striatal dopamine release (Gupta et al., 2020). The glutamate and GABA results could potentially be reconciled by recourse to the notion of excitation-inhibition balance (Cavanagh et al., 2020) such that brain states characterized by a relative *lower* excitation-inhibition balance may be conducive to hypnotic responding. By contrast, benzodiazepines, which seem to enhance suggestibility, also reduce 5-HT neurotransmission (Nutt & Cowen, 1987) and dissociative states (Gitlin et al., 2020). This suggests potential points of conflict between the effects of these agents, independent pathways, or complex interactions for suggestibility enhancement. A similar limitation applies to the anatomical specificity of these

effects: to our knowledge, only one study has identified neurochemical-suggestibility associations in a particular brain region (DeSouza et al., 2020), albeit without a control site.

Alongside the diverse neurochemical effects of these different drugs, their heterogeneous phenomenological effects should be considered in future research on the psychopharmacology of verbal suggestion. Insofar as individuals high in absorption display a stronger experiential response to these drugs (Studerus et al., 2012), absorption might moderate the suggestibility-augmenting effects of these drugs. Consideration of absorption in this respect is similarly motivated by evidence for depleted ACC glutamate concentrations in high absorption individuals (DeSouza et al., 2020). Further work on NMDA receptor antagonists in suggestibility enhancement should similarly consider the potential moderating influence of familial alcohol history (Yoon et al., 2016).

Extrapolation from the research studies in this domain are hindered by other methodological limitations and it will be imperative for future research to employ more rigorous methodologies in order to minimize bias, and improve generalizability and replicability. Some of the aforementioned studies did not adhere to a double-blind protocol, thereby opening up the possibility that the effects are shaped by experimenter effects. Future research will need to utilize double-blind methods involving masking of suggestibility status and drug condition. The internal validity of pharmacological studies will be further strengthened through the use of more standardized measures involving audio recordings of suggestions and corrections for compliance (e.g., Acunzo & Terhune, in press; Wieder & Terhune, 2019), which can minimize the impact of various confounds. A related issue is that nearly all scales included in pharmacological studies lacked control conditions for individual suggestions (Acunzo & Terhune, in press). This renders it difficult to distinguish the suggestibility-enhancing effects of a drug from its broader cognitive-perceptual effects. For example, one study observed greater responsiveness to an analgesia suggestion during N_2O

inhalation (Barber et al., 1979). However, the absence of the same pain assessment *without suggestion* renders the results ambiguous: increased analgesia could be attributed to N_2O's well-established analgesic properties (Gitlin et al., 2020) rather than suggestion.

A germane limitation of many of the reviewed studies is that most of the drugs pose a significant challenge for the internal validity of placebo-controlled designs as participants as well as blind experimenters can infer the drug condition to which they've been allocated. This limitation can augment, or interact with, the methodological shortcomings described above and renders it difficult to identify the specific locus of suggestibility augmentation. At least one placebo study showed that verbal suggestions and contextual cues were sufficient to elicit self-reports of psychedelic responses without administering any active substance (Olson et al., 2020). This study itself lacked a control condition so the precise factors underlying these induced effects is unclear but alongside real-life cases of suggestion producing psychedelic responses (Moore & Ramirez, 1998), it demonstrates that contextual factors are at least partly responsible for psychedelic responses in some individuals. This issue can be addressed by administering lower doses that are difficult to detect (Polito & Stevenson, 2019; Yanakieva et al., 2019) coupled with concurrent measurement of response expectancies (Whalley & Brooks, 2009).

A final as of yet understudied question is the impact of drug use on hypnotic suggestibility. Multiple studies have reported that suggestibility positively correlates with recreational drug use (e.g., Van Nuys, 1972) but it will be necessary to target specific drugs and drug classes to examine the neurochemical specificity of these effects. On the basis of the present review, it might be expected that hypnotic suggestibility would be selectively enhanced in users of NMDA receptor antagonists and psychedelics relative to users of other substances. Although the causal inferences of correlational designs are limited, they can be informative alongside controlled pharmacological research and longitudinal assessments of drug users.

Summary and conclusion

Here we reviewed current knowledge regarding the role of five neurochemicals in response to suggestions. These disparate bodies of research suggest that elevated dopamine, serotonin, GABA, and oxytocin and depleted glutamate are conducive to hypnotic responding. Multiple conflicting results have been reported regarding dopamine and oxytocin whereas links between hypnotic suggestibility and GABAergic agonism and glutamatergic hypofunction are relatively consistent. Nevertheless, the evidence bearing on a role for each of these neurochemicals in hypnotic responding is limited by numerous methodological shortcomings and outstanding questions regarding the neurochemical specificity of these effects. These preliminary results warrant further attention from studies applying more rigorous methodologies that control for competing interpretations and evaluate mediating hypothesized cognitive processes.

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