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Citation for published version (APA):

Smith, D., Acunzo, D., Deeley, Q., Mehta, M., & Terhune, D. B. (2024). The neurochemical bases of suggestion and hypnosis. In *Routledge international handbook of clinical hypnosis* (pp. 269-286). Routledge.

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The neurochemical bases of verbal suggestion and hypnosis

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Abstract

Characterizing the neurochemical systems involved in responsiveness to hypnotic suggestions has the potential to advance our understanding of the neurocognitive bases of verbal suggestion but also to develop novel interventions for enhancing responsiveness to suggestions in clinical and experimental contexts. In this chapter, we draw on pharmacological, genotyping, neuroimaging, and electrophysiological research to synthesize the available evidence regarding the involvement of different neurochemicals in response to suggestion. We highlight multiple converging lines of evidence that point to potential fruitful targets for future research but we also draw attention to multiple limitations in this body of evidence. We consider the extent to which these results are consistent with different theories of verbal suggestion and hypnosis and outline multiple avenues by which these theories could be discriminated using pharmacological methods. Finally, we conclude by highlighting the clinical implications of this research and how it may help to advance our understanding of the neurocognitive basis of verbal suggestion.

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Smith, D. M., Acunzo, D. J., Deeley, P. Q., Mehta, M., & **Terhune, D. B.** (2024). The neurochemical bases of suggestion and hypnosis (pp. 269-286). In J. H. Linden, G. De Benedittis, L. I. Sugarman, & K. Varga (Ed.), *Routledge international handbook of clinical hypnosis*. Routledge.

Introduction

The most robust finding in both experimental and clinical research on hypnosis is that hypnotic effects and treatment outcomes are constrained by trait verbal suggestibility (Laurence et al., 2008; Montgomery et al., 2011; Terhune et al., 2017). Owing to its clinical and theoretical impact, attempts have been made to modulate direct verbal suggestibility, with varying success (Gorassini, 2004). Pharmacological agents are one promising modulator of direct verbal suggestibility (Acunzo et al., 2021). Determining the neurochemical contributors to hypnosis is of great importance as it offers the possibility to understand and modulate the neurocognitive mechanisms associated with suggestion and devise methods by which treatment outcome can be strengthened.

Our current understanding of the potential role of neurochemical systems in direct verbal suggestibility remains in its infancy (Acunzo et al., 2021), but multiple potentially converging lines of research provisionally implicate different neurochemical systems. Here we aim to build upon our recent synthesis of this research domain (Acunzo et al., 2021). We first briefly review links between four neurochemicals and suggestibility, focusing on more recent research (for historical reviews, see (Moll, 1911; Pettey, 1913; Vingoe, 1973). We next consider the implications of this research for theories of hypnosis and clinical applications of suggestion. Finally, we highlight salient limitations in this research domain and describe challenges and potentially fruitful lines of research in this understudied area.

The Neurochemistry and Psychopharmacology of Hypnosis and Suggestion

Dopamine

Dopamine is a monoamine neurotransmitter belonging to catecholamines, which also include epinephrine and norepinephrine. Dopamine is involved in the neuromodulation of a variety of systems and functions including motivation, reward, reinforcement (Gershman & Uchida, 2019; Wise & Robble, 2020) working memory, cognitive control (Cools, 2019; Ott & Nieder, 2019) and motor control (Joshua et al., 2009).

Dopamine modulation also appears to be key in default mode network integration, suggesting a central role in consciousness maintenance (Spindler et al., 2021).

Preliminary research suggests that dopamine concentration is positively associated with response to suggestion, but some findings are mixed or contradictory (see (Acunzo et al., 2021) for a review). Sensory gating, as measured by the prepulse inhibition of the startle reflex, which is attenuated with dopamine agonist administration, appears to be reduced in highly suggestible individuals (Levin et al., 2011; Lichtenberg et al., 2008; Storozheva et al., 2018). This result has been interpreted to reflect elevated dopamine in these individuals (but see ((De Pascalis & Russo, 2013). Cerebrospinal fluid concentrations of dopamine metabolite homovanillic acid have been positively linked with trait hypnotic suggestibility (Spiegel & King, 1992). More direct and causal evidence for a role of dopamine in increasing suggestibility comes from pharmacological studies: dopamine reuptake inhibitor methylphenidate (MPH) treatment was found to increase hypnotic suggestibility in individuals with ADHD (Lotan et al., 2015) and dextroamphetamine administration, which increases extracellular levels of dopamine, seems to increase response to suggestion compared to a placebo in healthy volunteers (Ulett et al., 1972). Although speculative, one interpretation is that potentiation of dopamine transmission augments suggestibility by promoting focused attention toward verbal suggestions. Proxy measures for dopaminergic function and their association with hypnotic suggestibility have yielded contradictory results (see (Acunzo et al., 2021; Cardeña et al., 2017), although recent analyses have begun to question the sensitivity of these proxies (Sescousse et al., 2018; van den Bosch et al., 2022); similar inconsistencies have been observed with research on the genetic polymorphisms (some implicated in dopamine transmission) related to suggestibility (Lichtenberg et al., 2000; Presciuttini et al., 2014; Rominger et al., 2014; Storozheva et al., 2018; Szekely et al., 2010). Given dopamine's inverted U shaped relationship with cognitive performance it would not be surprising if dopamine exhibited such a relationship with hypnotic suggestibility (Cools & D'Esposito, 2011).

Serotonin

Serotonin (5-HT) plays a broad role in cognition, affect regulation, and social influence (Duerler et al., 2022; Štrac et al., 2016). Additionally, serotonin has a role in the formation of social hierarchy with dominance in primates being associated with higher serotonin levels (Moskowitz et al., 2001; Raleigh et al., 1991; Raleigh et al., 1984).

Multiple studies have reported that classic psychedelics, such as lysergic acid diethylamide (LSD), produce an increase in suggestibility (for a review, see (Acunzo et al., 2021)). The psychoactive effects of classic psychedelics seem to be mostly mediated through 5-HT_{2A} receptor (Carhart-Harris & Nutt, 2017). Insofar as these drugs primarily act as partial serotonin agonists (Nichols, 2016), this research arguably implicates the serotonin system in responsiveness to suggestion. In particular, suggestibility has been shown to be enhanced by LSD, mescaline, and a combination of LSD, mescaline, and psilocybin (Sjoberg & Hollister, 1965) (for similar effects, see (Middlefell, 1967) (Ulett et al., 1972)). More recently, it was reported that suggestibility, as indexed by the *Creative Imagination Scale*, was greater following LSD administration than placebo in a within-subjects single-blind study (Carhart-Harris et al., 2015), a result that was subsequently independently replicated (Wießner et al., 2021). A potentially convergent finding is that a variant of the T102C polymorphism that results in stronger binding potential for the 5-HT_{2A} receptor is associated with higher absorption, a well-established correlate of hypnotic suggestibility (Ott et al., 2005). However, independent research failed to observe an association between the serotonin transporter polymorphism 5-HTTLPR and hypnotic suggestibility (Katonai et al., 2017; Rominger et al., 2014). Although it should be noted that Katonai and colleagues did find an association between 5-HTTLPR and a self-report measure capturing the perceived intimacy of the hypnotic interaction. Limited suggestibility research has been conducted on serotonergic drugs other than psychedelics. In summary, these results imply that suggestibility is potentially associated with the 5-HT_{2A} receptor but its relationship to the serotonin system more broadly is less clear. The cognitive-perceptual

mechanisms that mediate this link are similarly unclear given the broad psychological effects of psychedelic drugs.

GABA

GABA is the primary inhibitory neurochemical in the brain. In addition to a central role in governing neuronal inhibition, it is prominently involved in neuronal plasticity and modulation of cortical network dynamics (Ende, 2015). At the psychological level, GABA is involved in a diverse array of cognitive functions including memory and learning and is aberrant in multiple disorders (Reddy-Thootkur et al., 2022).

Multiple lines of research provide preliminary evidence that elevated GABA is associated with greater (hypnotic) suggestibility (Spiegel, 1980). The most robust evidence for this link comes from a recent magnetic resonance spectroscopy (MRS) study, which found that hypnotic suggestibility was positively associated with GABA concentrations in anterior cingulate cortex (DeSouza et al., 2020), although the lack of a control voxel renders the anatomical specificity of this result ambiguous. To our knowledge, there have been few controlled studies of the impact of GABAergic agents on suggestibility. One placebo-controlled study found that alcohol, a GABA agonist, enhances hypnotic suggestibility (Semmens-Wheeler et al., 2013) (see also (Hull, 1933)). By contrast, a well-powered study reported that another GABA agonist, diazepam, did not significantly enhance hypnotic suggestibility relative to nicotinic acid, although this was potentially attributed to sample heterogeneity (Gibson et al., 1977); see also (Halpern & Merlis, 1961). Multiple anecdotal findings have also suggested that GABA agonists, such as benzodiazepines, enhance responsiveness to suggestion (for a review, see (Acunzo et al., 2021)). Similarly, an uncontrolled study of hypnotic suggestibility in different medicated patient groups suggested that those receiving anti-anxiety medication (typically GABA agonists) tended to display higher hypnotic suggestibility (Spiegel, 1980).

Glutamate

Glutamate is the brain's primary excitatory neurotransmitter and is involved in a wide range of cognitive functions including learning and memory (Olney & Farber, 1995; Riedel et al., 2003). The N-methyl-D-aspartate (NMDA) receptor antagonists ketamine and nitrous oxide are known to induce pronounced dissociative states, such as depersonalization and derealization, as well as a range of psychotomimetic effects, including hallucinations and delusions (Piazza et al., 2022).

Research showing that glutamate concentrations in anterior cingulate cortex are negatively correlated with dissociative absorption provides an indirect association between glutamate and suggestibility (DeSouza et al., 2020). Research has shown that 20–40% nitrous oxide inhalation was associated with greater nonhypnotic (Whalley & Brooks, 2009) and hypnotic (Barber et al., 1979) suggestibility than placebo (medical air or oxygen) inhalation (this is further supported by earlier preliminary research [e.g., (Eysenck & Rees, 1945)]. Importantly, in the Whalley and Brooks study, expectations did not predict suggestibility change although increases in imagination vividness correlated with suggestibility increases. Moreover, participants were unable to reliably identify which condition they were in (Whalley & Brooks, 2009), which suggests that the effects were not attributable to inadequate participant blinding, which is a salient confound in most psychedelic research (Burke & Blumberger, 2021). Preliminary research suggests that ketamine also increases hypnotic suggestibility but possibly only in low suggestible participants (Patterson et al., 2018; (Sklar et al., 1981)). The dissociative effects of NMDA receptor antagonists parallel the elevation in state dissociation (e.g., depersonalization) that accompanies hypnotic inductions (Cleveland et al., 2015). Taken together, these studies provide preliminary evidence for a role of glutamatergic function in suggestibility.

Other Substances

Unfortunately, little attention has been allocated to understanding the influence of other neurochemical systems on suggestibility. Acetylcholine and opioids are prime examples of substances that are understudied (Goldstein & Hilgard, 1975; Spiegel & Albert, 1983; Sternbach, 1982). Research suggests that highly suggestible participants might have lower responsiveness to opioids (Goldstein & Hilgard, 1975; Presciuttini et al., 2018; Spiegel & Albert, 1983). In particular, several research groups have failed to attenuate hypnotic analgesia with the opioid antagonist naloxone (Goldstein & Hilgard, 1975; Spiegel & Albert, 1983) or observe significant changes in beta-endorphin plasma levels during hypnotic suggestions of analgesia (Debeneditis et al., 1989; Moret et al., 1991), suggesting that hypnotic analgesia is not dependent on opioid based mechanisms. Early research implied that cannabis, which targets the cannabinoid system, enhances hypnotic suggestibility (Beahrs et al., 1974). There is also growing interest in the impact of oxytocin, a neuropeptide involved in social cognition and attachment (Shamay-Tsoory & Abu-Akel, 2016) on hypnotic suggestibility (Bryant & Hung, 2013; Bryant et al., 2012; Kasos et al., 2018; Varga & Kekecs, 2014), although the data are inconclusive to date and marked by contradictory findings and caveats (Acunzo et al., 2021).

Implications for Theories of Hypnosis

To our knowledge, no contemporary theories of hypnosis make explicit reference to the neurochemical systems subserving responsiveness to verbal suggestions. In turn, most pharmacological research on verbal suggestion effects has not been theory-driven and thus it is difficult to leverage the foregoing body of research to provide support for, or falsification of, these theories. Nevertheless, in this section we bring these data to bear on contemporary theories and highlight congruencies and inconsistencies (Table 1) with a view toward future interrogation of these models on the basis of systems neuroscience research into these neurochemical systems.

Table 1
Features of prominent hypnosis theories and relevance to neurochemical systems implicated in hypnosis and suggestion.

Mechanisms underlying response to hypnotic suggestion				
Theory	Primary cognitive mechanisms	Primary neurophysiological mechanisms	Primary neurochemical mechanisms	Relevant neurochemical evidence
Cold control	Diminished awareness of intentions	Atypical prefrontal functioning	Not Specified	<p>Consistent: Suggestibility enhancing agents also disrupt prefrontal connectivity (Driesen et al., 2013; Kummerfeld et al., 2020; Pallavicini et al., 2019; Ryu et al., 2017); Ketamine impairs metacognition (Lehmann et al., 2021)</p> <p>Inconsistent: Suggestibility enhancing substances impair cognitive control (Blackman et al., 2013; Kummerfeld et al., 2020; Pokorny et al., 2020; Umbricht et al., 2003)</p>
Dissociated experience	Diminished executive monitoring	Not specified	Not Specified	Consistent/inconsistent: Same as evidence for/against cold control theory
Dissociated control	Diminished executive control	Diminished lateral prefrontal cortex functioning	Not Specified	<p>Consistent: NMDAR antagonism impairs post-error performance adjustments (Skoblenick & Everling, 2014); Suggestibility enhancing agents disrupt prefrontal connectivity (Driesen et al., 2013; Kummerfeld et al., 2020; Pallavicini et al., 2019; Ryu et al., 2017); Suggestibility enhancing agents impair cognitive control (Blackman et al., 2013; Kummerfeld et al., 2020; Pokorny et al., 2020; Umbricht et al., 2003)</p> <p>Inconsistent: None</p>
Second-order dissociated control	Diminished communication between executive monitoring and control	Reduced connectivity between anterior cingulate and lateral prefrontal cortices	Not Specified	<p>Consistent: Same as evidence for dissociated control theory</p> <p>Inconsistent: None</p>
Interoceptive Predictive coding	Diminished interoceptive prediction mismatch fosters a sense of reality/feeling of knowing	Aberrant interoceptive predictive processing in the insula leads to reduced responsiveness in the salience network	Not Specified	<p>Consistent: (Barber et al., 1979; Patterson et al., 2018; Whalley & Brooks, 2009) and may regulate precision (Adams et al., 2013)</p> <p>Inconsistent: None</p>
Predictive coding	Motor suggestions via attention modulate the strength of sensory evidence, proprioceptive predictions, and prediction errors	Not specified	Not Specified	<p>Consistent: same as evidence for interoceptive predictive coding</p> <p>Consistent/Inconsistent: Data on the impact of suggestibility enhancing substances on attention is mixed (Bălăeț, 2022; Fried et al., 1995; Oranje et al., 2000)</p>
Response expectancy	Response expectancies produce subjective experiences	Not specified	Not Specified	<p>Consistent: None</p> <p>Inconsistent: None</p>

Dissociation and Cold Control Theories

Hypnosis has long been conceptually linked to dissociation (Bell et al., 2011; Ellenberger, 1970), which includes various disruptions of normally-integrated cognitive systems, such as those governing awareness, identity, and memory (Kihlstrom et al., 1994). Dissociation theories of hypnosis coalesce around the proposal that responding to hypnotic suggestion involves a disruption or reduction in the coordination of cognitive modules that are normally coupled in the execution of complex behaviours (for a review, see (Woody & Sadler, 2008)). These theories have alternatively proposed that hypnotic responding is supported by a breakdown in the coordination of executive control and monitoring (*Neodissociation* or *Dissociated Experience Theory*), executive control and lower-level systems supporting automatic behaviours (contention scheduling; *Dissociated Control Theory*), or an asymmetrical disruption whereby control cannot be updated from executive monitoring (*Second-order Dissociated Control Theory*). A similar model, *Cold Control Theory*, proposes that responsiveness to suggestion is facilitated by reduced awareness of intentions supporting goal-directed responses (Dienes & Perner, 2007). Although this account does not mechanistically invoke dissociation, and more parsimoniously focuses on metacognition, cold control theory is indistinguishable from dissociation theories at the neurophysiological level (Terhune, 2012).

Congruence with Pharmacological Findings

The pharmacological research reviewed above is broadly consistent with dissociation (and cold control) theories of hypnosis and suggestion but for the most part does not provide preferential support for specific predictions from these accounts. The dissociation theories postulate that there is a critical link between dissociation and suggestibility. At the phenomenological level, it is notable that different pharmacological agents that appear to enhance suggestibility including LSD and nitrous oxide produce dissociative states such as depersonalization (Liechti, 2017; Piazza et al., 2022). Further work should clarify this apparent

association by examining whether suggestibility enhancement depends on the experience of dissociative states in response to these drugs, such as by pharmacological reduction of dissociative states through concurrent administration of GABA agonists (Gitlin et al., 2020). Moreover, suggestion effects have been theorized to share greater mechanistic overlap with compartmentalization states (e.g., functional symptoms) (Brown, 2006) rather than detachment states (e.g., depersonalization) and it will be important to probe this in future research. Conversely, both *Dissociated Control* and *Cold Control*, but not *Neo-Dissociation*, theories predict that prefrontal dysfunction is conducive to hypnotic responding (Coltheart et al., 2018; Dienes & Hutton, 2013). A decoupling between anterior and posterior regions seems to be associated both with high hypnotic suggestibility (Jamieson & Burgess, 2014; Terhune et al., 2011) as well as the impact of NMDA receptor antagonists and classic psychedelics (Pallavicini et al., 2019) and provides a potential neurophysiological mechanism underlying suggestibility enhancement (see also (Reiser et al., 2012). Congruent with these findings, NMDA receptor antagonism reduces the ability to use contextual information held in working memory to determine the correct response to subsequent stimuli (Blackman et al., 2013; Kummerfeld et al., 2020; Umbricht et al., 2000) an effect which is likely mediated by disruptions in prefrontal connectivity (Driesen et al., 2013; Kummerfeld et al., 2020; Ryu et al., 2017) and broadly aligns with the proposal that prefrontal hypofunction is conducive to enhanced suggestibility. NMDA receptor antagonism has also been shown to induce a shift from a cortically-centered to a subcortically-centered connectivity profile; this might imply a greater dependence on basal ganglia and cerebellar mechanisms in action selection and execution, which indirectly aligns with dissociated control theory (Joules et al., 2015; Santarcangelo, 2014).

Dissociation, particularly dissociated control theories, which emphasize compromised executive functioning, and cold control theories, which emphasize compromised metacognition, part ways when it comes to their cognitive predictions. In turn, considering the broader cognitive effects of the drugs considered above may help to clarify the cognitive bases of their suggestibility enhancement. Ketamine has been shown to impair metacognition of episodic memory (Lehmann et al., 2021) – this aligns with

cold control and neo-dissociation theories although it does not explicitly contradict dissociated control theory. By contrast, Dissociated Control Theory predicts some sort of disruption of cognitive control should accompany suggestibility enhancement and this prediction sits well with the cognitive control disruptions induced by NMDA receptor antagonism (Blackman et al., 2013; Kummerfeld et al., 2020; Umbricht et al., 2000) as well as serotonergic psychedelics (Heekeren et al., 2008; Pokorny et al., 2020; Umbricht et al., 2003). Along similar lines, one finding that is especially congruent with the predictions of Second-Order Dissociated Control Theory is that ketamine impairs post error adjustments in non-human primates implying a breakdown of the normal integration of executive monitoring and control (Skoblenick & Everling, 2014). Importantly, cold control and neo-dissociation theories assume that hypnotic suggestions are implemented via executive control without accompanying higher order thoughts and thus pharmacological impairments in cognitive control should reduce hypnotic responding. This has not been observed and thus the available evidence *slightly* favors dissociated control theory. Nevertheless, to our knowledge, the dissociative, decoupling, and control effects of these drugs (Kummerfeld et al., 2020; Pallavicini et al., 2019) have not yet been related to suggestibility enhancement.

Response Expectancy and Predictive Coding Theories

Suggestions can be construed as communications that allow an individual to form specific predictions regarding subsequent experiences. The proposal that one's response expectancies drive, or at least partly shape, responses to hypnotic suggestions is a central tenet within social cognitive theories of hypnosis, including response expectancy theory (Kirsch, 1985) and response set theory (Kirsch & Lynn, 1999). Although a wealth of evidence indicates that response expectancies are a reliable predictor of responsiveness to (hypnotic) suggestions, there are ongoing questions regarding the magnitude of these effects as well as the underlying mechanisms (for reviews, see (Lynn et al., 2022; Lynn et al., 2008; Terhune et al., 2017). Similar ideas are present in more recent theories of hypnotic suggestion (Jamieson, 2018, 2022; Martin & Pacherie, 2019) embedded within the predictive coding framework (Clark, 2013;

Friston, 2010). This framework views the brain as a hierarchical Bayesian inference machine that works to minimize the discrepancy between predictions and sensory evidence while weighting these factors based on their respective confidence levels (precision). Although these accounts differ, they maintain that behavioural and phenomenological responses to suggestions are routed in abnormalities in the precision assigned to priors (predictions) and/or prediction errors (mismatch between priors and sensory evidence), such that behaviour and experience are more strongly shaped by priors engendered by suggestions.

Congruence with Pharmacological Findings

As with other theories, response expectancy and predictive coding theories of hypnosis do not stipulate specific neurochemical processes. How drugs and/or hypnosis modulate precision may depend on the cortical level of a predictive hierarchy thus complicating the interpretation of results. For example, it has been argued that psychedelics exert their effects by dampening the precision of high-level priors leading ascending prediction errors to better update beliefs (Carhart-Harris & Friston, 2019). At first glance, this would seem to be incompatible with predictive coding models of hypnosis, which plausibly would attribute suggestibility enhancement under psychedelics to increased prior precision. However, the latter priors arguably manifest at a lower level in the cortical hierarchy, which would mean that more precise lower level sensorimotor priors would tend to override mismatches in sensory feedback. In keeping with this hypothesis the mismatch negativity amplitude (MMN), an electrophysiological response (difference between deviant and standard events), which is believed to be a manifestation of low-level prediction errors, is attenuated by ketamine and some psychedelic drugs (Heekeren et al., 2008; Timmermann et al., 2018). However, the MMN does not exhibit a consistent relationship with hypnosis and hypnotic suggestibility (Hiltunen et al., 2019; Jamieson et al., 2005). Also, in the framework of predictive coding precision is typically conceived of at a psychological level as attention (Adams et al., 2013; Feldman & Friston, 2010) but the impact of suggestibility enhancing substances on attention is mixed (Bălăeț, 2022; Fried et al., 1995; Oranje et al., 2000). Changes in insula connectivity associated with hypnosis (Jiang et

al., 2017) hint at the possibility of a change in interoceptive predictive coding, as suggested by Jamieson (2022), but these findings should be interpreted with caution. Over-weighting of priors in perception has also been shown to relate to lower glutamate concentrations in insula in psychosis (Leptourgos et al., 2022), which arguably provides preliminary support for the possibility that NMDAR antagonists enhance suggestibility by increasing prior precision. However, more research is required before firmer conclusions can be made regarding how to best explain hypnosis and pharmacologically facilitated suggestibility within a predictive coding framework.

Therapeutic Implications and Applications

Enhanced Suggestibility

There is increasing evidence for the use of targeted suggestions to augment the effectiveness of established psychological treatments for a range of mental health and functional disorders – for example, anxiety disorders, depression, and functional neurological symptoms (Deeley, 2016; Elkins, 2016; Valentine et al., 2019). Improved understanding of the neuropharmacology of suggestive and dissociative processes could potentially lead to additional augmentation of psychological treatments with pharmacotherapy. However, several provisos should be borne in mind. Ideally any pharmacotherapy would need to be evaluated in the context of an existing protocolised psychological treatment using suggestion for which a robust evidence base exists. Although psychological treatments augmented with suggestion have been described in case reports and case series (Lemercier & Terhune, 2018), at present there continues to be a lack of large scale randomized controlled trials demonstrating the safety and effectiveness of specific treatments augmented with suggestion. This limits the justification for the addition of pharmacotherapy to enhance the effectiveness of suggestion to psychological treatments which employ them. However, an alternative approach could be to take conditions for which the safety and effectiveness of pharmacotherapy has been established (e.g., selective serotonin reuptake inhibitors

for depression and anxiety disorders), or those for which there is emerging evidence (e.g., research demonstrating the effectiveness of psilocybin for the treatment of depression with appropriate therapeutic support; (Carhart-Harris et al., 2016) and to evaluate the addition of suggestion to augment treatment (i.e., what was once referred to as the hypnodelic approach [Lemerrier & Terhune, 2018]). With appropriate control conditions this would also allow assessment of drug x condition x suggestion interactions to determine the extent to which the effects of suggestions are modulated by psychoactive agents and neuropsychiatric conditions. In addition to investigating therapeutic efficacy this may provide insights into the neuropharmacology of suggestive processes.

Challenges and Future Directions

Limitations of the Literature

Despite some intriguing convergences across studies, this literature possesses multiple methodological limitations that need to be considered when interpreting their theoretical and therapeutic implications (Acunzo et al., 2021). Perhaps most importantly, most of these studies concerned psychoactive drugs and thus did not adhere to conventional double-blind designs (for a counterexample, see (Whalley & Brooks, 2009) and opens up the possibility that the observed effects are driven, or exacerbated, by expectancy and placebo effects (Burke & Blumberger, 2021). Relatedly, nearly all previous pharmacological studies involved live administration, and experimenter scoring, of suggestibility scales by an experimenter who was not blinded, which can further exacerbate the impact of participant unblinding. To improve the rigour and generalizability of empirical results, future research will benefit from the use of active control agents, double-blind designs, comparisons across psychoactive agents, and standardized recorded scales (for a review, see (Acunzo et al., 2021). The majority of research on the neurochemistry of suggestion has focused on overt responsiveness to suggestion and future research would benefit from more attention being paid to subjective reports, which can provide valuable information regarding the experience of

avolition accompanying responses to suggestion, i.e., the *classic suggestion effect* (Weitzenhoffer, 1974). Another limitation of the literature is that some of the non-pharmacological studies of the neurochemical basis of hypnosis made use of peripheral neurochemical measurements (Kasos et al., 2018; Varga & Kekecs, 2014). Finally, as noted above, relatively few studies have considered the variables that mediate or correlate with suggestibility enhancement, such as dissociative states, aberrant functional decoupling, or other neurocognitive changes, and this limits the mechanistic insights that can be gained from these studies.

Determining Causal Pathways

Targeting specific neurochemical systems with pharmacological agents affords the promise of establishing their causal role in suggestibility enhancement. However, causal inferences are severely limited due to the neurochemical complexity and psychoactive nature of these drugs. Pharmacological agents implicated in suggestibility enhancement rarely target a specific neurochemical system and often have complex neurochemical interactions and downstream effects. For example, both serotonergic psychedelics and glutamatergic dissociatives seem to modulate dopamine release (De Gregorio et al., 2016; Gupta et al., 2019). Perhaps more problematically, rather than suggestibility enhancement being attributable to specific neurochemicals, one possibility is that drugs with psychoactive effects might enhance suggestibility (Spiegel, 1980). That is, suggestibility enhancement might be a product of phenomenological changes shared across these drugs. This proposal can arguably explain why such a diverse set of drugs with markedly different neurochemical profiles from LSD to cannabis (Beahrs et al., 1974) to nitrous oxide seem to enhance suggestibility. A further consideration is phenomenological heterogeneity in response to these agents and how this might differentially impact suggestibility alteration (Acunzo et al., 2021). For example, alcohol, nitrous oxide, and ketamine have stimulant effects in some individuals and sedative effects in others (e.g., (Walsh et al., 2017). Anecdotal research suggests that sedatives might attenuate hypnotic suggestibility (Spiegel, 1980). Greater consideration of these issues is

warranted in future research, such as with active control agents, investigation of mediation and moderating phenomenological and cognitive variables, and investigation of pharmacological agents that attenuate, rather than enhance, suggestibility.

Apples and Oranges

A salient methodological issue for future research is determining whether (high) suggestibility in the absence of pharmacological facilitation and pharmacologically modulated (high) suggestibility depend on overlapping mechanisms. That is, it is not yet clear if the dissociative states and increases in suggestibility associated with the substances covered here share neurocognitive features with those observed in clinical populations or in highly suggestible individuals. Parallels between pharmacological dissociative states and suggestibility enhancement and elevated suggestibility in dissociative psychopathology (Bell et al., 2011; Wieder et al., in press) are intriguing and warrant greater attention. By contrast, if many or all cases of pharmacologically-elevated suggestibility are dissimilar to non-modulated high hypnotic suggestibility, pharmacological research is less likely to yield insights into the nature of suggestion.

Orexin: A new frontier?

A potentially fruitful pathway for future research is the modulatory influence of orexin on suggestibility. Orexin is a neuropeptide that helps regulate arousal and appetite and influences multiple neuromodulatory systems and attentional processing (Brown et al., 2001; Tsujino & Sakurai, 2009). Plasma and cerebrospinal fluid levels of orexin-A have been shown to be lower in PTSD (Higuchi et al., 2002), a condition associated with elevated hypnotic suggestibility (Spiegel et al., 1988) and narcolepsy, which is characterized by the loss of orexin neurons in lateral hypothalamus and elevated dissociative symptoms (Quaedackers et al., 2022). It has been recently proposed that orexin antagonists might facilitate

dissociative experiences and enhance responsiveness to suggestion (Smith & Terhune, 2023), however to our knowledge this remains to be demonstrated.

Non-linear effects

A further challenge is posed by the non-linear effects of neurochemical systems on cognition and perception. Both norepinephrine and dopamine exhibit quadratic relationships with behavioral performance (Aston-Jones et al., 1999; Cools & D'Esposito, 2011) and it is plausible that hypnotic suggestibility might exhibit non-linear relationships with the neurochemical systems considered here, resulting in a sensitivity to drug dose and a 'baseline' dependency (Cools & D'Esposito, 2011). Clearly, the relationships between suggestibility and substances capable of inducing a loss of consciousness (e.g., GABAergic drugs) are non-linear. Accordingly, closer attention should be allocated to more subtle effects by examining multiple doses in future pharmacological studies.

Conclusion

In summary, preliminary research suggests that NMDAR hypofunction, elevated concentrations of dopamine and GABA, a greater serotonin receptor binding affinity, are conducive to responding to (hypnotic) suggestions. Despite multiple converging findings, clear interpretation of these results is limited by methodological considerations and limitations. The results align with several theoretical orientations, signaling the need for greater stipulation of neurochemical mechanisms within theories of hypnosis and greater interrogation of mediating and moderating cognitive factors. We have outlined fruitful avenues for future lines of research. The limited amount of research conducted in this area means that future researchers have an abundance of low hanging fruit to pick from, although there are many caveats and complications to take into consideration. Despite these challenges, a better understanding of the neurochemistry of suggestion will allow us to test theories of hypnosis and potentially develop novel

pharmacological approaches to enhancing the efficacy of hypnotic suggestion in therapeutic and clinical contexts (Lemercier & Terhune, 2018).

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