

Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia

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Objective: The clinical hallmark of schizophrenia is psychosis. The objective of this overview is to link the neurobiology (brain), the phenomenological experience (mind), and pharmacological aspects of psychosis-in-schizophrenia into a unitary framework.

Method: Current ideas regarding the neurobiology and phenomenology of psychosis and schizophrenia, the role of dopamine, and the mechanism of action of antipsychotic medication were integrated to develop this framework.

Results: A central role of dopamine is to mediate the “salience” of environmental events and internal representations. It is proposed that a dysregulated, hyperdopaminergic state, at a “brain” level of description and analysis, leads to an aberrant assignment of salience to the elements of one’s experience, at a “mind” level. Delusions are a cognitive effort by the patient to make sense of these aberrantly salient experiences, whereas hallucinations re-

fect a direct experience of the aberrant salience of internal representations. Antipsychotics “dampen the salience” of these abnormal experiences and by doing so permit the resolution of symptoms. The antipsychotics do not erase the symptoms but provide the platform for a process of psychological resolution. However, if antipsychotic treatment is stopped, the dysregulated neurochemistry returns, the dormant ideas and experiences become reinvested with aberrant salience, and a relapse occurs.

Conclusions: The article provides a heuristic framework for linking the psychological and biological in psychosis. Predictions of this hypothesis, particularly regarding the possibility of synergy between psychological and pharmacological therapies, are presented. The author describes how the hypothesis is complementary to other ideas about psychosis and also discusses its limitations.

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Patients with psychosis seek help because of disturbing experiences: odd beliefs, altered perceptions, and distressing emotions. Clinicians using DSM-IV characterize these patients on the basis of phenomenology. Thus, at a clinical level the doctor-patient interaction proceeds mainly at a “mind” or “behavioral” level of description and analysis. On the other hand, the preeminent theories regarding psychosis and schizophrenia are mainly neurobiological, and the centerpiece of intervention is pharmacological. Thus, theorizing and therapeutics proceed largely at a “brain” level of description and analysis. So, when the patient asks, “Doctor, how does my chemical imbalance lead to my delusions?” the doctor has no simple framework within which to cast an answer. In this article I attempt to provide a heuristic framework that could provide a basis for uniting the patient’s experience, the clinical presentation, the neurobiological theories, and the pharmacological interventions.

The article will first briefly review the concept of psychosis and the evidence linking psychosis to an abnormality in dopamine transmission in schizophrenia. Leading ideas about the role of dopamine in behavior will be re-

viewed, with a special focus on the emerging understanding regarding the role of dopamine as a mediator of motivational “salience.” It will be shown how the concept of aberrant salience can give a cogent account of the clinical features of psychosis. Next it will be shown how antipsychotics, by dampening dopamine transmission, dampen this aberrant salience and assist in the resolution of the psychosis. Any effort to bridge these different levels of analysis cannot, given the current stage of our epistemic development, explain all facts in all domains of either psychosis or schizophrenia. This is only a beginning. Therefore, I will end the article by acknowledging the limitations of this framework, relating it to the other prominent models in the field, and pointing out some conceptual predictions and testable implications of this hypothesis.

Dopamine as the “Wind of the Psychotic Fire”

The dopamine hypothesis of schizophrenia (1–3) has comprised two distinct ideas: a dopamine hypothesis of antipsychotic action and a dopamine hypothesis of psy-

chosis. The two are related but different. The dopamine hypothesis of antipsychotic medications can be traced to the early observation that antipsychotics increase the turnover of monoamines (4), more specifically, dopamine (5), and this observation anticipated the discovery of the “neuroleptic receptor” (6–8), now called the dopamine D₂ receptor, providing a mechanistic basis for the dopamine hypothesis of antipsychotic action. A central role for D₂ receptor occupancy in antipsychotic action is now well established, buttressed by neuroimaging studies using positron emission tomography and single photon emission computed tomography (9–12). However, the importance of dopamine receptors in the treatment of psychosis does not by itself constitute proof of the involvement of dopamine in psychosis (12).

Early evidence for a role of dopamine in psychosis was the observation that psychostimulant agents that trigger release of dopamine are associated with *de novo* psychosis (13–15) and cause the worsening of psychotic symptoms in patients with partial remissions (16). Further evidence came from postmortem studies that showed abnormalities in dopaminergic indexes in schizophrenia, although the interpretation of these data was always confounded by drug effects (1, 3). The most compelling evidence in favor of the dopamine hypothesis emerges from neuroimaging studies (details reviewed in references 2, 17, 18). Several studies have shown that patients with schizophrenia, when psychotic, show a heightened synthesis of dopamine (19–22), a heightened dopamine release in response to an impulse (23–25), and a heightened level of synaptic dopamine (26, 27). While there are some indications of a change in the number of receptors (28, 29), the claim remains controversial (30–32). Thus, on balance there is reasonable evidence of heightened dopaminergic transmission, more likely a presynaptic dysregulation than a change in receptor number, in patients with schizophrenia. This role of dopamine in psychosis and schizophrenia needs to be put in perspective. First, it is quite likely that the dopaminergic abnormality in schizophrenia is not exclusive (as other systems are involved), and it may not even be primary (17, 33). Second, the dopaminergic disturbance is likely a “state” abnormality associated with the dimension of psychosis-in-schizophrenia (27, 34, 35), as opposed to being the fundamental abnormality in schizophrenia (27, 36). As suggested by Laruelle and Abi-Dargham (18), “Dopamine [is] the wind of the psychotic fire.” If so, how does dopamine, a neurochemical, stoke the experience of psychosis?

Dopamine as a Mediator of Motivational Salience

There is nearly universal agreement on a central role of dopamine in “reward” and “reinforcement.” However, precisely what these terms mean, and exactly what dopamine contributes to their realization, is a subject of competing

hypotheses. One prominent hypothesis has been the “anhedonia” hypothesis of dopamine, proposed by Wise et al. (37–39) and endorsed by several others (40–42), according to which dopamine is a neurochemical mediator of “life’s pleasures” aroused by naturally rewarding experiences (such as food, sex, and drugs of abuse) and by neutral stimuli that become associated with them (43). While the hypothesis accounts for a number of aspects of dopamine functioning, particularly in relationship to drug abuse, some important observations called for modification. First, dopamine is involved not only in appetitive and rewarding events but also in aversive ones (44, 45). Second, the firing of dopamine neurons and dopamine release precede the consummation of pleasure and are seen in the anticipatory phase, regardless of eventual consummation (46–51). Finally, it can be shown that dopamine blockers, mainly antipsychotics, change the drive to obtain food and sex (52), even when there is no ostensible change in the hedonic pleasure associated with these objects, i.e., they change the “wanting” without necessarily changing the “liking” (53). To deal with these observations, alternative ideas have emerged. According to one idea, the firing of dopamine neurons is important for “predicting rewarding events, and in coding expectancies about outcomes” (54–56). While this can account well for electrophysiological data regarding dopamine firing in the context of appetitive rewards, it does not deal well with aversive events and does not account well for the longer-term modulatory role of dopamine in behaviors (53–55, 57). Another account of the roles of dopamine is the incentive/motivational salience hypothesis of Berridge and Robinson (53) and similar proposals by others (58–60). This latter conceptualization provides the most plausible framework for the current discussion and will be detailed further in this article.

The motivational salience hypothesis in its current form builds on the previous ideas of Bindra (61, 62) and Toates (63), who have written about incentive motivation, and of neurobiologists such as Fibiger and Phillips (64, 65), Robbins and Everitt (66, 67), Di Chiara (60, 68), Panksepp (69), and others who have speculated on the role of dopamine in these motivated behaviors. According to this hypothesis, dopamine mediates the conversion of the neural representation of an external stimulus from a neutral and cold bit of information into an attractive or aversive entity (53, 70). In particular, the mesolimbic dopamine system is seen as a critical component in the “attribution of salience,” a process whereby events and thoughts come to grab attention, drive action, and influence goal-directed behavior because of their association with reward or punishment (53, 70). This role of dopamine in the attribution of motivational salience does not exclude the roles suggested by previous theorists; instead it provides an interface whereby the hedonic subjective pleasure, the ability to predict reward, and the learning mechanisms allow the organism to focus its efforts on what it deems valuable and allows for the seamless conversion of motivation into ac-

tion (53, 70). When used in this sense, the concept of motivational salience brings us a step closer to concepts such as “decision utility” that are used to explain and understand the evaluations and choices that humans make (70, 71). Conceived in this way, the role of dopamine as a mediator of motivational salience provides a valuable heuristic bridge to address the brain-mind question of psychosis-in-schizophrenia (53, 70).

Psychosis as a Disorder of Aberrant Salience

I use “psychosis” in this paper to refer to the experience of delusions (fixed, false beliefs) and hallucinations (aberrant perceptions) and the secondarily related behavior. Several empirical observations about psychosis demand explanation. First, endogenous psychosis evolves slowly (not overnight) (72). For many patients it evolves through a series of stages: a stage of heightened awareness and emotionality combined with a sense of anxiety and impasse, a drive to “make sense” of the situation, and then usually relief and a “new awareness” as the delusion crystallizes and hallucinations emerge (72–75). Second, drugs such as amphetamine (dopamine releasers) do not cause psychosis in a single exposure for most normal humans (76), although after chronic administration they do produce a picture resembling schizophrenia (15). However, for patients who have experienced psychosis before, even a single dose of amphetamine causes a predictable, but temporary, exacerbation and return of the patient’s own symptoms (13, 76, 77). Third, once the symptoms are manifest, delusions are essentially disorders of inferential logic, as most delusional beliefs are not impossible, just highly improbable (75). Hallucinations by most accounts are exaggerated, amplified, and aberrantly recognized internal percepts (78–80).

Under normal circumstances, it is the stimulus-linked release of dopamine that mediates the acquisition and expression of appropriate motivational saliences in response to the subject’s experiences and predispositions (53, 70, 71, 81). Dopamine *mediates* the process of salience acquisition and expression, but under normal circumstances it *does not create* this process. It is proposed that in psychosis there is a dysregulated dopamine transmission that leads to stimulus-independent release of dopamine. This neurochemical aberration usurps the normal process of contextually driven salience attribution and leads to *aberrant assignment of salience to external objects and internal representations*. Thus, dopamine, which under normal conditions is a mediator of contextually relevant saliences, in the psychotic state becomes a creator of saliences, albeit aberrant ones.

It is postulated that before experiencing psychosis, patients develop an exaggerated release of dopamine, independent of and out of synchrony with the context. This leads to the assignment of inappropriate salience and mo-

tivational significance to external and internal stimuli. At its earliest stage this induces a somewhat novel and perplexing state marked by exaggerated importance of certain percepts and ideas. Given that most patients come to the attention of clinicians after the onset of psychosis, phenomenological accounts of the onset of psychosis are largely anecdotal or post hoc. However, patients report experiences such as, “I developed a greater awareness of... My senses were sharpened. I became fascinated by the little insignificant things around me” (from case 3 in reference 73); “Sights and sounds possessed a keenness that he had never experienced before” (from case 5 in reference 73); “It was as if parts of my brain awoke, which had been dormant” (82); or “My senses seemed alive.... Things seemed clearcut, I noticed things I had never noticed before” (74). Most patients report that something in the world around them is changing, leaving them somewhat confused and looking for an explanation. This stage of perplexity and anxiety has been recognized by several authors and is best captured in the accounts of patients: “I felt that there was some overwhelming significance in this” (82); “I felt like I was putting a piece of the puzzle together” (from case 4 in reference 74).

If this were an isolated incident, perhaps it would be no different from the everyday life experience of having one’s attention drawn to or distracted by something that is momentarily salient and then passes. What is unique about the aberrant saliences that lead to psychosis is their persistence in the absence of sustaining stimuli. This experience of aberrant salience is well captured by this patient’s account: “My capacities for aesthetic appreciation and heightened sensory receptiveness...were very keen at this time. I had had the same intensity of experience at other times when I was normal, but such periods were not sustained for long and had also been integrated with other feelings” (83). From days to years (the prodrome) (72), patients continue in this state of subtly altered experience of the world, accumulating experiences of aberrant salience without a clear reason or explanation for the patient.

Delusions in this framework are a “top-down” cognitive explanation that the individual imposes on these experiences of aberrant salience in an effort to make sense of them. Since delusions are constructed by the individual, they are imbued with the psychodynamic themes relevant to the individual and are embedded in the cultural context of the individual. This explains how the same neurochemical dysregulation leads to variable phenomenological expression: a patient in Africa struggling to make sense of aberrant saliences is much more likely to accord them to the evil ministrations of a shaman, while the one living in Toronto is more likely to see them as the machinations of the Royal Canadian Mounted Police. Once the patient arrives at such an explanation, it provides an “insight relief” or a “psychotic insight” (74, 75) and serves as a guiding cognitive scheme for further thoughts and actions. It drives the patients to find further confirmatory evidence—in the

glances of strangers, in the headlines of newspapers, and in the lapel pins of newscasters.

Hallucinations in this framework arise from a conceptually similar and more direct process: the abnormal salience of the internal representations of percepts and memories. This could account for the gradation in the severity of hallucinations, whereby to some people they seem like their own “internal thoughts,” to others their own “voice,” to others the voice of a third party, and to some others the voice of an alien coming from without (73, 74). So long as these events (delusions and hallucinations) remain private affairs, they are not an illness by society’s standards (84, 85). It is only when the patient chooses to share these mental experiences with others, or when these thoughts and percepts become so salient that they start affecting the behavior of the individual, that they cross over into the domain of clinical psychosis.

The development of delusions and hallucinations may be further abetted by the fact that patients with schizophrenia show abnormalities in cognitive, interpersonal, and psychosocial functioning (12, 86–93) even before the development of frank psychosis. It has been suggested that patients prone to psychosis, especially in the context of schizophrenia, show biases in probabilistic reasoning and a tendency to “jump to conclusions” (94, 95), alterations in attributional styles (96, 97), differences in their “theory of mind” (98), and abnormal levels of perceptual aberrations and magical ideation (99). These cognitive and interpersonal factors likely interact with the aberrant neurochemistry and determine the different phenomenology of psychosis across different individuals and different disorders (e.g., schizophrenia, mania, and drug abuse).

Dampening of Aberrant Salience by Antipsychotics

Antipsychotics lead to a resolution of psychotic symptoms, but here again a number of well-recognized clinical features need explanation. First, dopamine receptor blockade reaches steady state in the first few days, but the improvement of psychotic symptoms is slow and cumulative (100, 101). Second, one of the first subjective improvements reported by patients is that “it doesn’t bother me as much anymore.” The core belief in the truth of the delusion, the belief that the perception actually occurred (“the voice actually said those words”), often persists for years even though these delusions may stop interfering with thought and function (100). Third, patients do not like taking antipsychotics even when there are no overt observable side effects. While the newer “atypical” antipsychotics are better tolerated, antipsychotics as a class are associated with an element of “dysphoria” or a “deficit-like state” (102–105). Finally, antipsychotics provide only symptomatic control, because when antipsychotic treatment is stopped, symptoms return in the vast majority of cases, although not instantaneously (106). In these cases

of relapse, the phenomenology of the returning symptoms tends to remain relatively stable across episodes.

Antipsychotics now encompass over 100 drugs, all of which block neurotransmitter receptors and have a particular dopamine-blocking action (12, 107, 108). How does a drug that acts on receptors on a cell surface reverse this complex neurochemical-phenomenological experience called psychosis? It is proposed that antipsychotics are efficacious in psychosis because they all share a common property of “dampening salience.” Two important aspects of this idea need to be highlighted. First, while antipsychotics may differ in chemical structure or receptor affinity (which are physical properties of the drug), they share a psychological effect—dampening salience—which is the final common pathway of improvement. Second, in this scheme antipsychotics only provide a platform (of attenuated salience); the process of symptomatic improvement of delusions requires further psychological and cognitive resolution.

The concept of dampening salience can trace its conceptual origins to the very first behavioral studies of antipsychotics in animals and humans in the 1950s. In pivotal experiments in 1956, which are relevant to this day, Courvoisier (109) observed that rats who had come to associate a ringing bell with a shock would try to avoid the mere sound of the bell. However, when these rats received an antipsychotic they stopped avoiding the bell, even though they were motorically capable of doing so and still responded to the shock. This led her to suggest that antipsychotics induce “a forgetfulness of motive” (109), a central finding that has been echoed over the succeeding decades, although the terminology used to describe it has changed: antipsychotics decrease the “efficacy of stimuli in controlling and directing behavior” (110), lead to “decreased stimulus significance” (111, 112), “decrease [inappropriate] stimulus efficacy” (113), “modulate the behavioral impact of...aversively motivated conditioned stimuli” (114), engender “counteraction of positive feedback processes” (115), or most recently, “impair incentive salience attributions” (53). Regardless of changing trends in behavioral psychology or the changing types of antipsychotics, this core finding has been replicated in hundreds of different paradigms over half a century and remains the single fundamental property shared by all effective antipsychotics. Similar observations of humans were made by the earliest observers; Laborit and Huguenard (116) reported in 1951 that patients given these drugs showed *dés-intéressement* in their surroundings even in the absence of any sedation, while Delay et al. (117) observed in 1952 an *état d’indifférence* resembling in this respect the effects of lobotomy, which was prevalent in those times. This concept was captured by others, who have used terms such as “psychic indifference” (E. Meurice, unpublished article, 2000), “distanciating agents” (118), and “emotional restriction” (119). I propose that antipsychotics, when administered to a patient who labors under aberrantly salient

ideas (delusions) or aberrantly salient perceptions (hallucinations), block the underlying aberrant dopaminergic drive, and given the critical role of dopamine in salience (as already noted), this leads to an attenuation of the salience of these ideas and perceptions.

This view of the action of antipsychotics helps us understand why even though the dopamine system gets blocked at the onset, the antipsychotic response does not show any such categorical on/off but shows a slow, gradually incremental response, like most healing responses (100, 120). According to the idea of salience attenuation, antipsychotics do not primarily change thoughts or ideas; instead, they provide a neurochemical milieu wherein new aberrant saliences are less likely to form and previously aberrant saliences are more likely to extinguish (100, 113, 120). This is consistent with how patients experience their improvement. Patients do not immediately abandon the psychotic idea or percept but report that the idea or percept “doesn’t bother me as much” (121, 122). In fact, for many patients this is as good a resolution as antipsychotics can provide. This concept is implicitly accepted by the field, as on most rating scales for psychosis the severity of psychosis is rated not so much on the content of the idea/percept as on the degree to which it preoccupies the mind and affects behavior (123–125). Thus, antipsychotics at first remove not the core content of the symptom but the degree to which the symptoms occupy the mind, distress the patient, and drive action (125). It is only later, over the ensuing weeks, that the fundamental content of the delusions and hallucinations is deconstructed and (only for some) recedes entirely from awareness (126, 127).

The resolution of symptoms then is a dynamic process: antipsychotics lessen the salience of the concerns, and the patient “works through” her symptoms toward a psychological resolution (120, 125). Symptom resolution may have much in common with the mechanisms whereby all humans give up on cherished beliefs or frightening dreads, and it may involve processes of extinction, encapsulation, and belief transformation—fundamentally psychological concepts (120, 125, 128–132). Thus, antipsychotics do not excise symptoms; rather, they attenuate the salience of the distressing ideas and percepts, allowing patients to reach their own private resolution of these matters.

This conception accounts well for the phenomenon of relapse, exacerbation, and recurrence of psychosis that almost inevitably occurs in schizophrenia (133). Antipsychotics are seen in this model as blocking the expression of abnormal dopaminergic transmission, but they do not fundamentally alter the dopaminergic dysregulation (12, 134). Therefore, I propose that when antipsychotic treatment is stopped (or sometimes even when it is not) endogenous dopaminergic dysregulation gets reinstated. The same ideas and percepts that were previously part of the patient’s symptoms become reinvested with salience and come to direct thought and behavior. This might explain why a patient whose paranoid delusions concerned “po-

lice from the 52nd division” is very likely to have the same concerns rekindled in a relapse. When a patient’s symptoms are “in remission” during antipsychotic treatment the delusions and hallucinations from a previous episode are not erased but recede to the background of consciousness. The resurgence of an abnormally heightened dopaminergic state, whether due to drugs (135, 138), stress, or endogenous dysregulation, reinvests these dormant symptoms with salience, making them clinically relevant again.

Implications and Predictions of This Model

The framework provides a heuristic for “consilience” (139) between the neurochemical biology of psychosis and the undeniably personal nature of the experience of psychosis. Dopamine dysregulation may provide the driving force, but the subject’s own cognitive, psychodynamic, and cultural context gives form to the experience. Psychosis is seen as a dynamic interaction between a bottom-up neurochemical drive and a top-down psychological process (140), not as an inescapably determined outcome of a biology. If this is the case, then specific psychotherapies for psychosis not only should be feasible but would be synergistic with pharmacotherapies. At present, for most patients we provide modifiers of the biological process (antipsychotic drugs) but provide no specific help for the cognitive-psychological resolution. Patients “work through” their delusions and hallucinations by themselves using, perhaps, the innate psychological processes that allow humans to give up on cherished beliefs and overcome dreaded fears. As these processes are better understood (97) and implemented in specific psychotherapies, an antipsychotic effect will rely not only on receptor blockade but also on cognitive and psychological restructuring (141). Early studies using specific cognitive therapies for psychosis are showing additional efficacy separate from drug effects (142).

A logical extrapolation of this model is the idea that it is implausible to seek an “overnight” treatment that will lead to instantaneous resolution of psychosis (parallel to a drug that immediately stops status epilepticus). Patients who have been psychotic for some time incorporate their psychotic beliefs into their larger cognitive schemas (75, 143). In such a situation, blocking the neurochemical abnormality (no matter how quickly and completely) will only take away the driving force but will not demolish the schemas already constructed. Improvement of psychosis, although assisted by drugs, finally involves psychological strategies that have timelines of weeks and months, rather than seconds and minutes. Thus, the current framework poses a conceptual challenge to an expectation of an antipsychotic that works overnight.

Neither normal volunteers nor patients find antipsychotics pleasant; in both populations they are associated

with a plethora of unpleasant subjective effects, captured under the rubric of “neuroleptic-induced dysphoria,” “decreased motivational drive,” or “neuroleptic-induced deficit state” (102–104, 144–146). These side effects may be the other edge of the fundamental mechanism of antipsychotics—dampened salience. A high salience of the objects and ideas that one loves and desires is the important force that drives humans and their social interactions (70). It is quite conceivable that the same mechanism (i.e., dampened salience) that takes the fire out of the symptoms also dampens the drives of life’s normal motivations, desires, and pleasures. Obviously, the effects are not symmetrical, i.e., drugs do not dampen normal saliences to the same degree they dampen aberrant saliences, yet I know of no drugs that selectively and exclusively affect one and not the other in animals (37, 43, 53, 114, 147–152). Perhaps this dampening of pleasurable drives is why patients with schizophrenia have a much higher incidence of drug abuse, self-medication, and other ways of overcoming this dampening (153–155). Finding a way around this quandary may not be simple. Until one finds something qualitatively different about the anatomy, physiology, or pharmacology of the circuits subserving appetitive versus aversive salience, it may be difficult for biological therapies to exclusively dampen one and spare the other.

Relationship to Other Models and Ideas

While there is general acceptance of a role for a dopaminergic abnormality in psychosis, precisely how this comes about is a matter of debate. It has been postulated that the mesolimbic dopamine abnormality may be a primary neurochemical abnormality (3, 6), a secondary consequence of hypofrontality (1, 156), secondary to a glutamate deficit (33, 157, 158), or secondary to a primary neurodevelopmental disorder (159–161). All these models include a final mesolimbic dopamine dysregulation but do not specify how this dysregulation leads to symptoms. The aberrant-salience hypothesis may provide a link in the explanatory chain going from the biological dysfunction of these other hypotheses to the symptomatic expression of psychosis.

Some other influential ideas about symptom formation have focused on deficient “filtering” as measured by prepulse inhibition (162–164), by latent inhibition (165), or in electrophysiological animal models (166). The idea of aberrant salience differs from these notions of information-gating abnormalities. Prepulse inhibition is a measure of information-gating at a preattentive sensorimotor reflex level (167), latent inhibition is a model of attentional habituation, while information gating as conceived of by Grace et al. (166) is an electrophysiological concept at the level of neuronal firing. Salience, on the other hand, is conceived and operationalized at a level of cognitive associations, reward and reinforcement, and motivational significance. Future research will have to elaborate on how

these electrophysiological and information-gating phenomena relate to the behavioral concept of “salience.”

Qualifications and Boundaries

Any effort at a brain-mind synthesis has to issue a disclaimer: it is not the intent of this article to address the complex ontological issues that relate to this topic (168). The attempt is not to offer a complete synthesis across two levels but to create a framework that provides a reasonable accommodation of the established brain findings and mind findings in psychosis. For the purposes of this article it is sufficient to assume that brain-level and mind-level phenomena constitute empirical regularities that bear a relationship, without necessarily presuming a particular nature of that relationship (169). Second, the dopamine/salience hypothesis is not an etiological hypothesis but a pathophysiological one. It does not try to explain why schizophrenia happens, only how the symptoms of psychosis arise given certain neurochemical abnormalities. As our understanding of etiology advances, this account could serve as a link in the explanatory chain linking etiology to experience. Third, the hypothesis addresses itself mainly to the psychotic symptoms of schizophrenia, not to the more enduring deficit and cognitive abnormalities of this illness (170–172). Thus, the present hypothesis is more a hypothesis of psychosis-in-schizophrenia. As such, it may have more implications for understanding the occurrence of psychosis in other illnesses (for example, manic psychosis) than it does for understanding the nonpsychotic (i.e., negative and cognitive) symptoms in schizophrenia (173). Fourth, schizophrenia is not as simple as abnormal dopamine in a normal brain. Even if aberrant dopamine/aberrant salience has a privileged role in expressing psychosis-in-schizophrenia, this role is played out with other actors—neurodevelopmental, cognitive, and interpersonal deficits—actors that take to the stage before the presumed hyperdopaminergic abnormality. Finally, while I have focused mainly on the role of dopamine in psychosis, I do not intend to claim exclusivity for this one neurotransmitter in the production of the complex human state called psychosis. Other neurotransmitters may collaborate with or contribute to the dopaminergic abnormality giving rise to the complete phenomenological expression of psychosis (174, 175). At the present time, however, the state of knowledge about the dopamine system and psychosis allows for an integrated brain-to-mind framework, whereas this is not yet true for the other transmitter systems.

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