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

Shitij Kapur, M.D., Ph.D., F.R.C.P.C.

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 reflect 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.

(Am J Psychiatry 2003; 160:13–23)

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 reviewed, 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 D_2 receptor, providing a mechanistic basis for the dopamine hypothesis of antipsychotic action. A central role for D_2 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 motivational 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 *désintéressement* 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 "police 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.

Received Jan. 16, 2002; revision received June 12, 2002; accepted June 21, 2002. From the Schizophrenia Program and PET Centre, Centre for Addiction and Mental Health; and the Department of Psychiatry, University of Toronto. Address reprint requests to Dr. Kapur, PET Centre, The Clarke Division of the Centre for Addiction and Mental Health, 250 College St., Toronto, Ont. M5T 1R8, Canada; skapur@camhpet.on.ca (e-mail).

Supported by a Canada Research Chair in Schizophrenia and Therapeutic Neuroscience and by operating grants from the Canadian Institutes of Health Research (Canada), the Stanley Foundation (United States), and the EJLB Foundation (Canada).

The author thanks Drs. Robert Zipursky, Gary Remington, and Paul Fletcher for the intellectual environment in which these thoughts were conceived and nurtured; Drs. Mary Seeman, Kent Berridge, and Robin Murray for comments about the substance and style of this article; and Dr. Eric Kandel for his recent writings calling for a "new framework" to link brain-mind phenomena.

References

1. Davis KL, Kahn RS, Ko G, Davidson M: Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 1991; 148:1474–1486
2. Seeman P, Kapur S: Schizophrenia: more dopamine, more D_2 receptors. Proc Natl Acad Sci USA 2000; 97:7673–7675
3. Seeman P: Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987; 1:133–152
4. Carlsson A, Lindquist M: Effect of chlorpromazine or haloperidol on the formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol 1963; 20: 140–144
5. Anden NE, Butcher SG, Corrodi H, Fuxe K, Ungerstedt U: Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Eur J Pharmacol 1970; 11:303–314
6. van Rossum J: The significance of dopamine-receptor blockade for the action of neuroleptic drugs, in Neuropsychopharmacology: Proceedings of the 5th Collegium Internationale Neuropsychopharmacologicum. Edited by Brill H, Cole J, Deniker P, Hippius H, Bradley P. Amsterdam, Excerpta Medica, 1967, pp 321–329
7. Seeman P, Lee T, Chau-Wong M, Wong K: Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 1976; 261: 717–719
8. Seeman P, Chau-Wong M, Tedesco J, Wong K: Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci USA 1975; 72:4376–4380
9. Farde L, Wiesel FA, Halldin C, Sedvall G: Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry 1988; 45:71–76
10. Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G: Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects—a double-blind PET study of schizophrenic patients. Biol Psychiatry 1993; 33:227–235
11. Kapur SJ, Zipursky R, Jones C, Remington G, Houle S: Relationship between dopamine D_2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000; 157:514–520
12. Kapur S, Remington G: Dopamine D_2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 2001; 50:873–883
13. Angrist B, Sathananthan G, Wilk S, Gershon S: Amphetamine psychosis: behavioral and biochemical aspects. J Psychiatr Res 1974; 11:13–23
14. Angrist BM, Gershon S: The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol Psychiatry 1970; 2:95–107
15. Harris D, Batki SL: Stimulant psychosis: symptom profile and acute clinical course. Am J Addict 2000; 9:28–37
16. Angrist B, Rotrosen J, Gershon S: Responses to apomorphine, amphetamine, and neuroleptics in schizophrenic subjects. Psychopharmacology (Berl) 1980; 67:31–38
17. Soares JC, Innis RB: Neurochemical brain imaging investigations of schizophrenia. Biol Psychiatry 1999; 46:600–615
18. Laruelle M, Abi-Dargham A: Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. J Psychopharmacol 1999; 13:358–371
19. Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE, Etienne P, Evans AC, Lal S, Shevell M, Savard G, Wong DF, Chouinard G, Gjedde A: Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci USA 1994; 91: 11651–11654
20. Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Kirvela O, Ruotsalainen U, Salokangas RKR: Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 1995; 346: 1130–1131
21. Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, Artiges E, Feline A, Syrota A, Martinot JL: Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr Res 1997; 23:167–174
22. Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, Langstrom B: Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 1999; 46: 681–688
23. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB: Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci USA 1996; 93:9235–9240
24. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M: Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 1998; 155:761–767
25. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D: Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci USA 1997; 94:2569–2574
26. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M: From the cover: increased baseline occupancy of D_2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci USA 2000; 97:8104–8109
27. Gjedde A, Wong DF: Quantification of neuroreceptors in living human brain, V: endogenous neurotransmitter inhibition of haloperidol binding in psychosis. J Cereb Blood Flow Metab 2001; 21:982–994
28. Wong DF, Wagner HN Jr, Tune L, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, Toung JKT, Malat J, Williams JA, O'Tuama LA, Snyder SH, Kuhar MJ, Gjedde A: Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naive schizophrenics. Science 1986; 234:1558–1563
29. Wong DF, Pearlson GD, Tune LE, Young LT, Meltzer CC, Dannals RF, Ravert HT, Reith J, Kuhar MJ, Gjedde A: Quantification of neuroreceptors in the living human brain, IV: effect of aging and elevations of D-2-like receptors in schizophrenia and bipolar illness. J Cereb Blood Flow Metab 1997; 17:331–342
30. Andreasen NC, Carson R, Diksic M, Evans A, Farde L, Gjedde A, Hakim A, Lal S, Nair N, Sedvall G, et al: Workshop on schizophrenia, PET, and dopamine D2 receptors in the human neostriatum. Schizophr Bull 1988; 14:471–484
31. Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordstrom AL, Hall H, Sedvall G: D2 dopamine receptors in neuroleptic-naive schizophrenic patients. Arch Gen Psychiatry 1990; 47:213–219

32. Nordstrom AL, Farde L, Eriksson L, Halldin C: No elevated D2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [11C]N-methylspiperone. Psychiatry Res Neuroimaging 1995; 61:67–83
33. Carlsson A, Hansson LO, Waters N, Carlsson ML: Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic implications. Life Sci 1997; 61:75–94
34. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R: Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry 1999; 46:56–72
35. Anand A, Verhoeff P, Seneca N, Zoghbi SS, Seibyl JP, Charney DS, Innis RB: Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. Am J Psychiatry 2000; 157:1108–1114
36. Pearlson GD, Wong DF, Tune LE, Ross CA, Chase GA, Links JM, Dannals RF, Wilson AA, Ravert HT, Wagner HN, Depaulo JR: In vivo D-2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. Arch Gen Psychiatry 1995; 52:471–477
37. Wise RA: Neuroleptic attenuation of intracranial self-stimulation: reward or performance deficits? Life Sci 1978; 22:535–542
38. Wise RA, Colle LM: Pimozide attenuates free feeding: best scores analysis reveals a motivational deficit. Psychopharmacology (Berl) 1984; 84:446–451
39. Wise RA, Spindler J, deWit H, Gerberg GJ: Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science 1978; 201:262–264
40. Markou A, Koob GF: Postcocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 1991; 4: 17–26
41. Koob GF, Le Moal M: Drug abuse: hedonic homeostatic dysregulation. Science 1997; 278:52–58
42. Gardner EL, Lowinson JH: Drug craving and positive-negative hedonic brain substrates activated by addicting drugs. Semin Neurosci 1993; 5:359–368
43. Wise RA: Neuroleptics and operant behavior: the anhedonia hypothesis. Behav Brain Sci 1982; 5:39–87
44. Salamone JD, Cousins MS, Snyder BJ: Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci Biobehav Rev 1997; 21:341–359
45. Salamone JD: The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav Brain Res 1994; 61:117–133
46. Blackburn JR, Phillips AG, Jakubovic A, Fibiger HC: Dopamine and preparatory behavior, II: a neurochemical analysis. Behav Neurosci 1989; 103:15–23
47. Schultz W, Apicella P, Scarnati E, Ljungberg T: Neuronal activity in monkey ventral striatum related to the expectation of reward. J Neurosci 1992; 12:4595–4610
48. Ljungberg T, Apicella P, Schultz W: Responses of monkey dopamine neurons during learning of behavioral reactions. J Neurophysiol 1992; 67:145–163
49. Apicella P, Scarnati E, Schultz W: Tonically discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. Exp Brain Res 1991; 84:672–675
50. Richardson NR, Gratton A: Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. J Neurosci 1996; 16:8160–8169
51. Wenkstern D, Pfaus JG, Fibiger HC: Dopamine transmission increases in the nucleus accumbens of male rats during their first exposure to sexually receptive female rats. Brain Res 1993; 618:41–46
52. Lopez HH, Ettenberg A: Dopamine antagonism attenuates the unconditioned incentive value of estrous female cues. Pharmacol Biochem Behav 2001; 68:411–416
53. Berridge KC, Robinson TE: What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998; 28:309–369
54. Schultz W, Dayan P, Montague PR: A neural substrate of prediction and reward. Science 1997; 275:1593–1599
55. Schultz W: Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol 1997; 7:191–197
56. Waelti P, Dickinson A, Schultz W: Dopamine responses comply with basic assumptions of formal learning theory. Nature 2001; 412:43–48
57. Redgrave P, Prescott TJ, Gurney K: Is the short-latency dopamine response too short to signal reward error? Trends Neurosci 1999; 22:146–151
58. Horvitz JC: Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 2000; 96: 651–656
59. Martin-Soelch C, Leenders KL, Chevalley AF, Missimer J, Kunig G, Magyar S, Mino A, Schultz W: Reward mechanisms in the brain and their role in dependence: evidence from neurophysiological and neuroimaging studies. Brain Res Brain Res Rev 2001; 36:139–149
60. Di Chiara G: A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J Psychopharmacol 1998; 12:54–67
61. Bindra D: A motivational view of learning, performance, and behavior modification. Psychol Rev 1974; 81:199–213
62. Bindra D: How adaptive behaviour is produced: a perceptual-motivational alternative to response-reinforcement. Behavioural Brain Sciences 1978; 1:41–91
63. Toates F: The interaction of cognitive and stimulus-response processes in the control of behaviour. Neurosci Biobehav Rev 1998; 22:59–83
64. Fibiger HC, Phillips AG: Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems, in Handbook of Physiology, Section 1: The Nervous System, vol 4: Intrinsic Regulatory Systems of the Brain. Edited by Bloom FE. New York, Oxford University Press, 1986, pp 647–675
65. Fibiger HC, Phillips AG: Mesocorticolimbic dopamine systems and reward. Ann NY Acad Sci 1988; 537:206–215
66. Robbins TW, Everitt BJ: Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 1996; 6:228–236
67. Robbins TW, Everitt BJ: Functional studies of the central catecholamines. Int Rev Neurobiol 1982; 23:303–365
68. Di Chiara G: Drug addiction as dopamine-dependent associative learning disorder. Eur J Pharmacol 1999; 375:13–30
69. Panksepp J: Affective Neuroscience: The Foundations of Human and Animal Emotions. New York, Oxford University Press, 1998
70. Berridge KC: Pleasure, pain, desire and dread: hidden core processes of emotion, in Well Being: The Foundations of Hedonic Psychology. Edited by Kahneman D, Diener E, Schwarz N. New York, Russell Sage Foundation, 1999, pp 525–557
71. Shizgal P: Neural basis of utility estimation. Curr Opin Neurobiol 1997; 7:198–208
72. Yung AR, McGorry PD: The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 1996; 22:353–370
73. Bowers MB Jr, Freedman DX: "Psychedelic" experiences in acute psychoses. Arch Gen Psychiatry 1966; 15:240–248
74. Bowers MB Jr: Pathogenesis of acute schizophrenic psychosis: an experimental approach. Arch Gen Psychiatry 1968; 19:348–355
75. Roberts G: The origins of delusion. Br J Psychiatry 1992; 161: 298–308

76. Yui K, Goto K, Ikemoto S, Ishiguro T, Angrist B, Duncan GE, Sheitman BB, Lieberman JA, Bracha SH, Ali SF: Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. Mol Psychiatry 1999; 4:512–523
77. Angrist B, Lee HK, Gershon S: The antagonism of amphetamine-induced symptomatology by a neuroleptic. Am J Psychiatry 1974; 131:817–819
78. David AS: Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. Acta Psychiatr Scand Suppl 1999; 395:95–104
79. Bentall RP: The illusion of reality: a review and integration of psychological research on hallucinations. Psychol Bull 1990; 107:82–95
80. Grossberg S: How hallucinations may arise from brain mechanisms of learning, attention, and volition. J Int Neuropsychol Soc 2000; 6:583–592
81. Heinz A: [Anhedonia—a general nosology surmounting correlate of a dysfunctional dopaminergic reward system?]. Nervenarzt 1999; 70:391–398 (German)
82. McDonald N: Living with schizophrenia. Can Med Assoc J 1960; 82:218–221
83. An autobiography of a schizophrenic experience. J Abnorm Soc Psychiatry 1955; 51:677–680
84. Johns LC, van Os J: The continuity of psychotic experiences in the general population. Clin Psychol Rev 2001; 21:1125–1141
85. van Os J, Hanssen M, Bijl RV, Vollebergh W: Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Arch Gen Psychiatry 2001; 58:663–668
86. Heinrich RW: In Search of Madness: Schizophrenia and Neuroscience. Oxford, UK, Oxford University Press, 2001
87. Tsuang MT, Stone WS, Faraone SV: Toward reformulating the diagnosis of schizophrenia. Am J Psychiatry 2000; 157:1041–1050
88. Faraone SV, Green AI, Seidman LJ, Tsuang MT: "Schizotaxia": clinical implications and new directions for research. Schizophr Bull 2001; 27:1–18
89. Walker EF, Grimes KE, Davis DM, Smith AJ: Childhood precursors of schizophrenia: facial expressions of emotion. Am J Psychiatry 1993; 150:1654–1660
90. Ellison Z, van Os J, Murray R: Special feature: childhood personality characteristics of schizophrenia: manifestations of, or risk factors for, the disorder? J Personal Disord 1998; 12:247–261
91. Rabinowitz J, Reichenberg A, Weiser M, Mark M, Kaplan Z, Davidson M: Cognitive and behavioural functioning in men with schizophrenia both before and shortly after first admission to hospital: cross-sectional analysis. Br J Psychiatry 2000; 177:26–32
92. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H: Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000; 57:1053–1058
93. Cannon M, Walsh E, Hollis C, Kargin M, Taylor E, Murray RM, Jones PB: Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. Br J Psychiatry 2001; 178:420–426
94. Garety PA, Hemsley DR, Wessely S: Reasoning in deluded schizophrenic and paranoid patients: biases in performance on a probabilistic inference task. J Nerv Ment Dis 1991; 179: 194–201
95. Freeman D, Garety PA, Kuipers E: Persecutory delusions: developing the understanding of belief maintenance and emotional distress. Psychol Med 2001; 31:1293–1306
96. Bentall RP, Kinderman P, Kaney S: The self, attributional processes and abnormal beliefs: towards a model of persecutory delusions. Behav Res Ther 1994; 32:331–341
97. Bentall RP, Corcoran R, Howard R, Blackwood N, Kinderman P: Persecutory delusions: a review and theoretical integration. Clin Psychol Rev 2001; 21:1143–1192
98. Frith CD, Blakemore S, Wolpert DM: Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. Brain Res Brain Res Rev 2000; 31:357–363
99. Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser MC: Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol 1994; 103:171–183
100. Miller R: The time course of neuroleptic therapy for psychosis: role of learning processes and implications for concepts of psychotic illness. Psychopharmacology (Berl) 1987; 92:405–415
101. Kuhar MJ, Joyce AR: Slow onset of CNS drugs: can changes in protein concentration account for the delay? Trends Pharmacol Sci 2001; 22:450–456
102. Lewander T: Neuroleptics and the neuroleptic-induced deficit syndrome. Acta Psychiatr Scand Suppl 1994; 380:8–13
103. King DJ, Burke M, Lucas RA: Antipsychotic drug-induced dysphoria. Br J Psychiatry 1995; 167:480–482
104. Gerlach J, Larsen EB: Subjective experience and mental side-effects of antipsychotic treatment. Acta Psychiatr Scand Suppl 1999; 395:113–117
105. Voruganti L, Cortese L, Oyewumi L, Cernovsky Z, Zirul S, Awad A: Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. Schizophr Res 2000; 43:135–145
106. Gilbert PL, Harris MJ, McAdams LA, Jeste DV: Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry 1995; 52:173–188
107. Kapur S, Seeman P: Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry 2001; 158:360–369
108. Strange PG: Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. Pharmacol Rev 2001; 53:119–133
109. Courvoisier S: Pharmacodynamic basis for the use of chlorpromazine in psychiatry. Q Rev Psychiatry Neurol 1956; 17:25–37
110. Dews PB, Morse WH: Behavioural pharmacology. Annu Rev Pharmacol 1961; 1:145–174
111. Johnson FN: Stimulus significance and chlorpromazine effects on the expression of avoidance learning in mice. Neuropharmacology 1971; 10:267–272
112. Johnson FN: Stimulus significance and chlorpromazine-induced impairment of avoidance learning in mice. Neuropharmacology 1971; 10:9–14
113. Clody DE, Carlton PL: Stimulus efficacy, chlorpromazine, and schizophrenia. Psychopharmacology (Berl) 1980; 69:127–131
114. Killcross AS, Everitt BJ, Robins TW: Symmetrical effects of amphetamine and alpha-flupenthixol on conditioned punishment and conditioned reinforcement: contrasts with midazolam. Psychopharmacology (Berl) 1997; 129:141–152
115. Crow TJ: Catecholamine reward pathways and schizophrenia: the mechanism of the antipsychotic effect and the site of the primary disturbance. Fed Proc 1979; 38:2462–2467
116. Laborit H, Huguenard P: L'hibernation artificielle par moyens pharmacodynamiques et physiques. Presse Med 1951; 59: 1329
117. Delay J, Deniker P, Harl J: Traitment des états d'excitation et d'agitation par une méthode médicamenteuse dérivée de l'hibernothérapie. Ann Med Psychol 1952; 110:267–273
118. Meurice E: [The effect of neuroleptics in a attempt at understanding the vulnerability to schizophrenia]. Acta Psychiatr Belg 1992; 92:339–354 (French)
119. Belmaker RH, Wald D: Haloperidol in normals. Br J Psychiatry 1977; 131:222–223

120. Miller R: Hyperactivity of associations in psychosis. Aust NZ J Psychiatry 1989; 23:241–248
121. Winkelman NW: Chlorpromazine in the treatment of neuropsychiatric disorders. JAMA 1954; 155:18–21
122. Elkes J, Elkes C: Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. Br Med J 1954; 2: 560–565
123. Opler LA, Kay SR, Lindenmayer JP, Fisxbein A: Structured Clinical Interview for the Positive and Negative Symptom Scale. Toronto, Multi-Health Systems, 1992
124. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799–812
125. Chouinard G, Miller R: A rating scale for psychotic symptoms (RSPS), part I: theoretical principles and subscale 1: perception symptoms (illusions and hallucinations). Schizophr Res 1999; 38:101–122
126. Harrow M, Silverstein ML: Psychotic symptoms in schizophrenia after the acute phase. Schizophr Bull 1977; 3:608–616
127. Harrow M, MacDonald AW III, Sands JR, Silverstein ML: Vulnerability to delusions over time in schizophrenia and affective disorders. Schizophr Bull 1995; 21:95–109
128. Hole RW, Rush AJ, Beck AT: A cognitive investigation of schizophrenic delusions. Psychiatry 1979; 42:312–319
129. Levy ST, McGlashan TH, Carpenter WT Jr: Integration and sealing-over as recovery styles from acute psychosis. J Nerv Ment Dis 1975; 161:307–312
130. McGlashan TH, Levy ST, Carpenter WT Jr: Integration and sealing over: clinically distinct recovery styles from schizophrenia. Arch Gen Psychiatry 1975; 32:1269–1272
131. Drayton M, Birchwood M, Trower P: Early attachment experience and recovery from psychosis. Br J Clin Psychol 1998; 37(part 3):269–284
132. Sacks MH, Carpenter WT Jr, Strauss JS: Recovery from delusions: three phases documented by patient's interpretation of research procedures. Arch Gen Psychiatry 1974; 30:117–120
133. Nuechterlein GK, Subotnik KL, Ventura J, Mintz J, Fogelson DL, Bartzokis G, Aravagiri M: Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. Am J Psychiatry 2001; 158:1835–1842
134. Kapur S, Remington G: Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annu Rev Med 2001; 52:503–517
135. Janowsky DS, Davis JM: Methylphenidate, dextroamphetamine, and levamfetamine: effects on schizophrenic symptoms. Arch Gen Psychiatry 1976; 33:304–308
136. Malhotra AK, Adler CM, Kennison SD, Elman I, Pickar D, Breier A: Clozapine blunts N-methyl-D-aspartate antagonist-induced psychosis: a study with ketamine. Biol Psychiatry 1997; 42: 664–668
137. Angrist B, Rotrosen J, Gershon S: Differential effects of amphetamine and neuroleptics on negative vs positive symptoms in schizophrenia. Psychopharmacology (Berl) 1980; 72:17–19
138. Angrist B, Thompson H, Shopsin B, Gershon S: Clinical studies with dopamine-receptor stimulants. Psychopharmacologia 1975; 44:273–280
139. Wilson EO: Consilience: The Unity of Knowledge. New York, Vintage, 1999
140. Miller R: Major psychosis and dopamine: controversial features and some suggestions. Psychol Med 1984; 14:779–789
141. Garety PA, Freeman D: Cognitive approaches to delusions: a critical review of theories and evidence. Br J Clin Psychol 1999; 38(part 2):113–154
142. Gould RA, Mueser KT, Bolton E, Mays V, Goff D: Cognitive therapy for psychosis in schizophrenia: an effect size analysis. Schizophr Res 2001; 48:335–342
143. Garety P: Delusions: problems in definition and measurement. Br J Med Psychol 1985; 58(part 1):25–34
144. Naber D: A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. Int Clin Psychopharmacol 1995; 10(suppl 3):133–138
145. Van Putten T, Marder SR: Behavioral toxicity of antipsychotic drugs. J Clin Psychiatry 1987; 48(Sept suppl):13–19
146. McCartan D, Bell R, Green JF, Campbell C, Trimble K, Pickering A, King DJ: The differential effects of chlorpromazine and haloperidol on latent inhibition in healthy volunteers. J Psychopharmacol 2001; 15:96–104
147. Acquas E, Carboni E, Leone P, Di Chiara G: SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? Psychopharmacology (Berl) 1989; 99:151–155
148. Killcross AS, Dickinson A, Robbins TW: Effects of the neuroleptic alpha-flupenthixol on latent inhibition in aversively- and appetitively-motivated paradigms: evidence for dopamine-reinforcer interactions. Psychopharmacology (Berl) 1994; 115: 196–205
149. Killcross S, Robbins TW, Everitt BJ: Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. Nature 1997; 388:377–380
150. Ettenberg A: Dopamine, neuroleptics and reinforced behavior. Neurosci Biobehav Rev 1989; 13:105–111
151. Fonberg E: Chlorpromazine exerts stronger suppressive action on the instrumental responses motivated by social than by alimentary reward. Acta Neurobiol Exp 1992; 52:57–69
152. Boye S, Rompre P-P: Behavioural evidence of depolarization block of dopamine neurons after chronic treatment with haloperidol and clozapine. J Neurosci 2000; 20:1–11
153. Phillips P, Johnson S: How does drug and alcohol misuse develop among people with psychotic illness? a literature review. Soc Psychiatry Psychiatr Epidemiol 2001; 36:269–276
154. Voruganti LN, Heslegrave RJ, Awad AG: Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. J Nerv Ment Dis 1997; 185:463–465
155. Mueser KT, Drake RE, Wallach MA: Dual diagnosis: a review of etiological theories. Addict Behav 1998; 23:717–734
156. Grace AA: Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 1991; 41:1–24
157. Javitt DC: Glutamate receptors and schizophrenia: opportunities and caveats. Mol Psychiatry 1996; 1:16–17
158. Goff DC, Coyle JT: The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001; 158:1367–1377
159. Weinberger DR: On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. Neuropsychopharmacology 1996; 14(3 suppl):1S–11S
160. Harrison PJ: Schizophrenia: a disorder of neurodevelopment? Curr Opin Neurobiol 1997; 7:285–289
161. Keshavan MS: Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. J Psychiatr Res 1999; 33:513–521
162. Hamm AO, Weike AI, Schupp HT: The effect of neuroleptic medication on prepulse inhibition in schizophrenia patients: current status and future issues. Psychopharmacology (Berl) 2001; 156:259–265
163. Braff DL, Geyer MA, Swerdlow NR: Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology (Berl) 2001; 156:234–258
164. Parwani A, Duncan EJ, Bartlett E, Madonick SH, Efferen TR, Rajan R, Sanfilipo M, Chappell PB, Chakravorty S, Gonzenbach S, Ko GN, Rotrosen JP: Impaired prepulse inhibition of acoustic startle in schizophrenia. Biol Psychiatry 2000; 47:662–669

165. Feldon J, Weiner I: From an animal model of an attentional deficit towards new insights into the pathophysiology of schizophrenia. J Psychiatr Res 1992; 26:345–366
166. Grace AA: Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res Brain Res Rev 2000; 31:330–341
167. Braff DL, Geyer MA: Sensorimotor gating and schizophrenia: human and animal model studies. Arch Gen Psychiatry 1990; 47:181–188
168. Kendler KS: A psychiatric dialogue on the mind-body problem. Am J Psychiatry 2001; 158:989–1000
169. Gabbard GO: Mind and brain in psychiatric treatment. Bull Menninger Clin 1994; 58:427–446
170. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT Jr: A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry 2001; 58:165–171
171. Peralta V, Cuesta MJ: How many and which are the psychopathological dimensions in schizophrenia? issues influencing their ascertainment. Schizophr Res 2001; 49:269–285
172. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M: Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry 1999; 46:908–920
173. Johnstone EC, Crow TJ, Frith CD, Owens DG: The Northwick Park "functional" psychosis study: diagnosis and treatment response. Lancet 1988; 2:119–125
174. Carlsson A, Waters N, Waters S, Carlsson ML: Network interactions in schizophrenia—therapeutic implications. Brain Res Brain Res Rev 2000; 31:342–349
175. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML: Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu Rev Pharmacol Toxicol 2001; 41:237–260