Sensory Processing Dysfunction in the Personal Experience and Neuronal Machinery of Schizophrenia

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Sensory processing deficits, first investigated by Kraepelin and Bleuler as possible pathophysiological mechanisms in schizophrenia, are now being recharacterized in the context of our current understanding of the molecular and neurobiological brain mechanisms involved. The National Institute of Mental Health Research Domain Criteria position these deficits as intermediaries between molecular and cellular mechanisms and clinical symptoms of schizophrenia, such as hallucinations. The prepulse inhibition of startle responses by a weaker preceding tone, the inhibitory gating of response to paired sensory stimuli characterized using the auditory P50 evoked response, and the detection of slight deviations in patterns of sensory stimulation eliciting the cortical mismatch negativity potential demonstrate deficits in early sensory processing mechanisms, whose molecular and neurobiological bases are increasingly well understood. Deficits in sensory processing underlie more complex cognitive dysfunction and are in turn affected by higher-level cognitive difficulties. These deficits are now being used to identify genes involved in familial transmission of schizophrenia and to monitor potentially therapeutic drug effects for both treatment and prevention. This research also provides a clinical reminder that patients' sensory perception of the surrounding world, even during treatment sessions, may differ considerably from others' perceptions. A person's ability to understand and interact effectively with the surrounding world ultimately depends on an underlying sensory experience of it.

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When patients tell us that they are hearing voices or seeing visions, we often assume that these experiences are layered onto a perception of the world that is basically similar to our own. Yet patients report instead more globally distorted perceptions of their world, which underlie their psychotic symptoms. Elyn Saks thus describes the first day that she became psychotic (1):

> One morning in class, I suddenly decided that I needed to get up, leave school, and walk home…. As I walked along, I began to notice that the colors and shapes of everything around me were becoming more intense. And, at some point, I began to realize that the houses I was passing were sending special messages to me: *Look closely. You are special. You are especially bad. Look closely and ye shall find. There are many things you must see. See. See.*

Her suddenly heightened perception of her familiar neighborhood quickly became delusional. We may easily overlook these basic perceptual disturbances in diagnostic interviews, yet they are a basis for the more bizarre distortions of reality that lead to clinical diagnosis of schizophrenia and other psychoses. Deficits in auditory and visual sensory processing may not fully explain patients' psychotic experiences, but they are a paradigmatic example of research that has been guided by patients' own descriptions of their experience of the world. Clinicians who have listened to their own patients describe similar experiences of sensory overload may find that their understanding of their patients' experience of the world around them is sharpened (2).

Although both Kraepelin and Bleuler included descriptions of perceptual abnormalities in schizophrenia in their textbooks (3), the detailed methodology involved in their characterization often makes the research advances in their characterization obscure. The strategy of using simple stimuli—tones or light patterns—helps isolate specific mechanisms, but it can also leave the impression that only initial sensation is being tested. The processing of such simple stimuli is actually complex and involves both cortical and subcortical circuitry. Deficits in processing the simplest stimuli found in schizophrenia may underlie more complex hallucinations and delusions, as for Dr. Saks, in two ways: neuropsychologically, failure to register basic sensory information correctly makes poor decisions about it inevitable; and neurobiologically, the same neuronal mechanisms that register the information are utilized throughout the brain, so that deficits in neuronal mechanisms detected in sensory areas are likely to be present also in regions that have more complex executive functions. Accordingly, many of the neurotransmitter mechanisms most associated with schizophrenia, such as glutamate, GABA, dopamine, and acetylcholine, as well as their receptors, are widely distributed throughout brain, as are many of the associated risk genes, which suggests that their effects on brain function should be equally detectable across brain regions.

David Hubel and Torsten Wiesel similarly described their Nobel Prize research in vision (4):

> To examine the workings of this visual pathway our strategy since the late 1950's has been (in principle) simple. Beginning, say, with the fibers of the optic nerve, we record with microelectrodes from a single nerve fiber and try to find out how we can most effectively influence the firing by stimulating the retina with light….
>
> There was a time, not so long ago, when one looked at the millions of neurons in the various layers of the cortex and wondered if anyone would ever have any idea of their function…. For the visual cortex the answer seems now to be known in broad outline: Particular stimuli turn neurons on or off; groups of neurons do indeed perform particular transformations. It seems reasonable to think that if the secrets of a few regions such as this one can be unlocked, other regions will also in time give up their secrets.

Elementary sensations, such as auditory detection thresholds or visual acuity, are generally considered to be normal in patients, reflecting integrity of the peripheral sensory apparatus. However, research like that of Hubel and Wiesel points to the many stages of processing that occur as sight and sound pass from the eyes and ears through successive brain regions before becoming recognizable as images and words. Much of this processing occurs outside the realm of conscious awareness, so unless it is specifically tested, patients will be unaware of their deficits. Moreover, because basic sensory systems have been extensively characterized not only in humans but also in animal models, patterns of deficit can be directly linked to underlying biology.

Over recent decades, both the nature of the deficits and their consequences for function have become increasingly clear. In this review, we highlight the important role played by sensory deficits in both the subjective and objective functioning of individuals with schizophrenia, as well as how an increasing focus on sensory dysfunction may improve functional outcomes for patients with schizophrenia and other severe neuropsychiatric disorders.

Deficits in sensory processing are most effectively demonstrated using neurophysiological measures, such as event-related potentials, which uniquely trace the flow of information from sense organs through brainstem and subcortical regions and into sensory and then higher cortical brain regions. Results of event-related-potential studies, however, are strongly corroborated by both behavioral and neuroimaging measures that provide additional information regarding the location and nature of underlying cortical impairments (Table 1).

AUDITORY DYSFUNCTION IN SCHIZOPHRENIA

It is well known that humans are distinguished from other primates by our superior reasoning and problem-solving ability, both of which are related to a dramatic expansion in frontal brain regions as compared with other primates (Figure 1). It is less appreciated that an equally marked evolutionary expansion has occurred in the human auditory system (5). This expansion underlies not only our unique linguistic abilities but also our greatly expanded ability to appreciate pitch, rhythm, and other musical features relative to other primates. Like other recently evolving regions, the auditory cortex completes its maturation late in human development (5). Thus, like prefrontal regions, these systems may remain vulnerable to disruption even during late adolescence and early adulthood, when schizophrenia typically develops. In general, sensory systems play a dual role—first, to orient attention to critical regions and features of the environment, and second, to decode the information emanating from those regions to enable subsequent voluntary processing. In schizophrenia, both the attentional and informational roles of the sensory systems are impaired, contributing to the overall pattern of symptoms and neurocognitive deficits we frequently associate with the disorder.

Normal Auditory Physiology

Most clinical tests of auditory function, such as audiological assessments and far-field brainstem potentials, are tests of the most peripheral portions of the system in the inner ear and the auditory nerve leading to the brainstem, which do not appear to be affected in schizophrenia (6). The auditory information from the inner ear is initially processed in brainstem relay neurons, primarily to separate tones and regulate sensitivity to high and low volumes and to orient the person to the location of sound (Figure 2). Auditory information then ascends through the medial geniculate nucleus to the auditory cerebral cortex, which plays a critical role in the decoding of simple auditory features such as pitch, intensity, and location, which are then elaborated in subsequent auditory regions into more complex auditory percepts such as language and tonality. Dysfunction within the cortical regions may thus contribute to the complex patterns of social and communicative disturbances seen in schizophrenia.

Sensory and Sensorimotor Gating Dysfunction

Auditory gating relies on the interplay of auditory input and brainstem reticular formation function. Reticular neurons have rapidly habituating responses to repeated stimulation and thus form the brain's initial sensory gating mechanism, which prevents other brain regions from being flooded with repeated and presumed less important sensory information, such as in a noisy environment. The habituation to repeated stimulation leaves the brain ready to respond to more novel and thus potentially more meaningful sensory stimuli.

The effect of the brainstem's habituation is observed experimentally in two ways. First, a descending spinal pathway from the larger reticular neurons initiates the startle response. A weak tone initiates habituation of the reticular neurons' response to a subsequent louder tone, leading to the phenomenon of prepulse inhibition (PPI) of the acoustic startle response (7, 8).

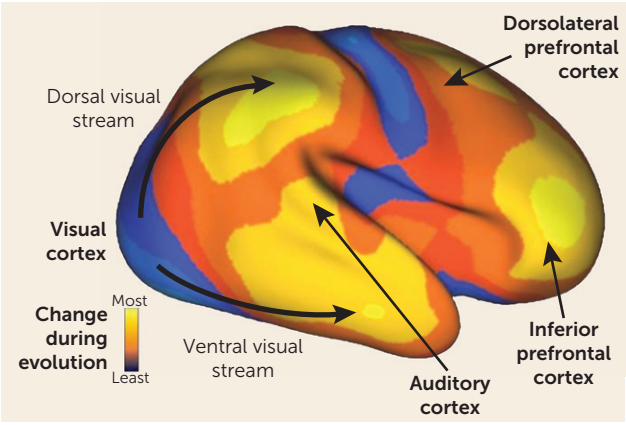
In parallel, projections from other reticular neurons ascend to the midbrain, where they contact cholinergic neurons

TABLE 1. Sensory Processing Dysfunctions in Schizophrenia[a]

Modality	Patient Experience	Neurocognitive Disturbance	Neurophysiological Paradigms	Neuroimaging Paradigms	Neurotransmitter Mechanisms	Candidate Genes
Auditory	Noises appear louder; misperception of sounds; hallucinations (6); reduced response to environmental change as a chronic adaptation (110)	Decreased detection of target signals in digit-vigilance and digit-coding tasks; poor pitch perception; phonological reading deficits (74); amusia (121)	Diminished PPI (7, 11) and P50/N100 sensory gating (10); reduced N100, MMN, and P300 amplitude (12, 71)	Increased frontotemporal/ thalamic activity during gating (14); reduced auditory activation to deviant auditory stimuli (68)	Diminished nicotinic cholinergic and NMDAR glutamate activation of inhibitory interneurons; increased catecholaminergic sensitization of neuron responses (36, 37)	CHRNA7, NRG1, COMT, DISC1 (122)
Visual	Objects appear fragmented and distorted (102); decreased sensitivity to dim, rapidly presented, or moving objects (48)	Reduced "closure" ability (98); impaired face emotion recognition (99); visual reading deficits (104, 105)	Diminished visual P1 to low-spatial-frequency stimuli (89, 123, 94); diminished event-related desynchronization of ongoing rhythms (121)	Reduced activation of low-spatial-frequency regions of visual cortex (91, 92)	Nonlinear amplification failure in subcortical visual pathways; decreased glutamate NMDAR activation (90)	DTNBP1 (124); NOS1 (125)

[a] PPI=prepulse inhibition; MMN=mismatch negativity; NMDAR=*N*-methyl-D-aspartate-type glutamate receptor.

FIGURE 1. The Cortical Areas Responsible for Perception and Executive Function Have Both Experienced Especially Enhanced Expansion in the Evolution of the Human Brain[a]



[a] Reprinted with permission, from Hill J, Inder T, Neil J, Dierker D, Harwell J, Van Essen D: Similar patterns of cortical expansion during human development and evolution. Proc Natl Acad Sci USA 2010; 107: 13135–13140.

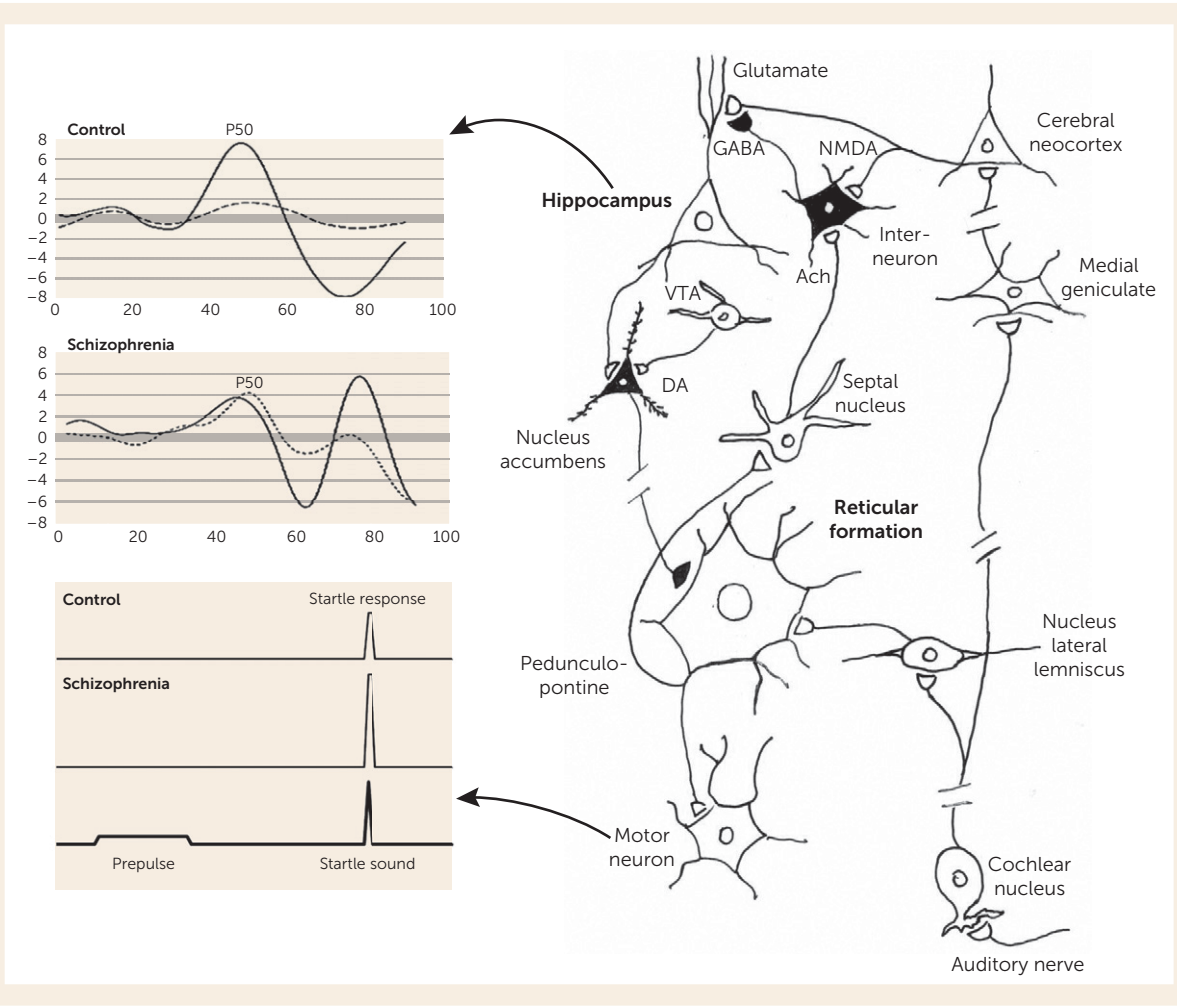
in the medial septal nucleus, which in turn project to the hippocampus, thalamus, and neocortex. These cholinergic projections activate inhibitory interneurons in the hippocampus and other areas that modulate local excitatory glutamatergic neurotransmission (9). The hippocampus then inhibits response to less important information coming from the auditory cortex and other sensory regions, funneled to it through the superior temporal gyrus. In humans, the largest initial cerebral response to an auditory stimulus is a positive wave that occurs at 50 ms and is thus termed the P50 potential. The P50 response to the second of paired stimuli is decreased relative to the first in healthy persons, an example of inhibitory sensory gating (10).

Deficits in the integrity of both PPI and P50 gating in schizophrenia have been extensively replicated since they were first demonstrated, pointing to dysfunction even within these low-level circuits. The deficit in PPI is most prominent in schizophrenia when the weaker tone precedes the startling sound by 60 ms (7). The deficit is more pronounced in women, who normally show less inhibition than men. Patients with schizophrenia, either unmedicated or treated with most antipsychotic drugs, also have reduced inhibition of the P50 auditory evoked potential (see Figure 2). The inhibition of the second stimulus is maximal at 500 ms, later than the maximal PPI interval of 60 ms. In many patients, the two deficits do not occur together, and thus they represent distinct aspects of pathophysiology (11). The N100 also shows impaired gating in schizophrenia (12).

For both PPI and P50 gating, despite the origin of the effect in reticular brainstem neurons, the response engages an entire network of brain circuits—the dopaminergic circuits of the basal ganglia for PPI and the basal cholinergic nuclei and cortex for P50 gating (8, 9). Rodent models of P50 gating emphasize the response in the hippocampus, but sources for human P50 have been found in the superior temporal gyrus, and cortical rhythms are altered during the sensory gating paradigm, with a decrease in EEG beta waves (13). Deficits in the response to repeated sounds have also been localized to the hippocampus and dorsal lateral prefrontal cortex by both dipole analysis and functional MRI (fMRI) (14, 15).

P50 inhibitory gating deficits in schizophrenia have been associated with the frequency and intensity of auditory hallucinations and with neurocognitive measures of decreased

FIGURE 2. P50 Sensory Gating and Prepulse Inhibition of Startle Share Common Circuits, for Which Most of the Neurons and Transmitters Have Been Identified[a]



[a] Breaks in pathways indicate where some relay neurons in the brainstem and the many layers of processing in the neocortex have been omitted. Sound activates the auditory nerve in the ear, which is primarily processed by a pathway from the cochlear nucleus through the medial geniculate nucleus in the thalamus to the cerebral neocortex, from which the entorhinal cortex sends the information to hippocampus neurons via glutamate synapses. This pathway carries detailed auditory information that is eventually processed as words, music, and so on. (Figure 3 describes physiological deficits in the cerebral cortex itself in schizophrenia.) In the brainstem, a branch of the auditory pathway activates the nucleus of the lateral lemniscus, which then activates the reticular formation, which controls attentional activation in the brain. Reticular formation neurons activate the medial septal nucleus in the basal forebrain, which is the source of acetylcholine (Ach) to alpha-7 nicotinic receptors on inhibitory interneurons of the hippocampus (shown in black). These neurons are also activated by the entorhinal cortex via *N*-methyl-D-aspartate (NMDA) type glutamate receptors. When paired sounds stimulate the brain, the first travels through the main auditory pathways to activate glutamate synapses on the hippocampal neurons, which process the information. The reticulo-septal-interneuron pathway is also activated, which initiates γ-aminobutyric acid (GABA) presynaptic inhibition of the glutamate inputs to the hippocampus neurons, so that a second stimulus cannot excite them as strongly. This inhibitory sensory gating regulates the flow of information to the hippocampus to ensure that repetitive, less important information does not overwhelm the limited capacity of hippocampus neurons to process information into memory. Deficits in the inhibitory mechanism are common in schizophrenia. The top left inset demonstrates this physiology using the P50 auditory evoked response, partially generated by the hippocampal neurons and recorded from the scalp. Sounds are repeated at a 500-ms interval. The control subject inhibits most of the response to the second sound (dotted line), whereas the patient with schizophrenia does not. Startle occurs when loud sounds activate reticular formation neurons, which then activate motor neurons to produce startle reactions. A weaker tone preceding the loud sound activates a circuit from the hippocampus to nucleus accumbens neurons, which inhibit the startle response. Decreased inhibition of the hippocampal response and increased dopaminergic (DA) activation from the ventral tegmental area (VTA), converging on the nucleus accumbens, produces deficits in prepulse inhibition in schizophrenia. The nucleus accumbens neurons inhibit pedunculopontine neurons (not shown), which modulate the excitability of reticular formation neurons during startle. The bottom left inset shows the blink response recorded from the orbicularis oculi after a loud, startling sound. This startle response is partly inhibited in the control subject because of the weaker 20-ms prepulse tone preceding the startle sound by 60 ms. The schizophrenia startle response shows significantly less prepulse inhibition (PPI). (For further details on these circuits, see references 129–131.)

vigilance and attention, consistent with the role of inhibitory sensory gating in protecting the brain from being responsive to extraneous stimuli while it is trying to focus attention on a task (16, 17). The association between patients' self-report of sensory phenomena and physiological measures is confounded by the patients' psychopathology (18). Thus, several investigations in patients have not shown association between P50 inhibition and self-reports of sensory gating difficulties (19), but in schizotypal adults, deficiencies in P50 inhibition are associated with difficulties in "hearing everything at once" and with a sense of unreality, including perceptual anomalies and magical beliefs (20, 21). PPI deficits have been correlated with deficient social perception (22).

Genetic Endophenotypes

Inhibitory gating measures have also contributed significantly to the search for genes involved in schizophrenia. Deficits in both PPI and P50 gating are found in schizotypal individuals who have a family history of schizophrenia and in adolescents at high risk for schizophrenia (23–25). As a complex genetic illness, schizophrenia has not been linked to a single major gene. However, these specific endophenotype measures, each thought to underlie one aspect of the genetic basis of schizophrenia, were hypothesized to have a closer relationship to particular elements of genetic risk (20).

In families affected with multiple cases of schizophrenia, the deficit in P50 gating segregates as an autosomal dominant trait and is linked to the CHRNA7 gene complex, which forms the α7-nicotinic acetylcholine receptor (26). Polymorphisms of CHRNA7 have been associated with PPI as well (27). Another related gene is NRG1, which forms neuregulin (28, 29). Neuregulin helps assemble both α-nicotinic and *N*-methyl-D-aspartate-type glutamate receptors (NMDARs) (30), and thus its association with both sensory processing deficits is not surprising. The α7-nicotinic receptor is found presynaptically on glutamate nerve terminals and postsynaptically on inhibitory interneurons (see Figure 2), particularly in the hippocampus and nucleus reticularis thalami (9). Thus, there is convergence between the genetic findings and the neurobiological model, corroborated by postmortem findings of decreased α7-nicotinic receptors in schizophrenia (31). As the scope of genomic analysis has increased, both deficits have been associated with entire networks of genetic variants in schizophrenia in the NIMH Consortium on the Genetics of Schizophrenia study, which examines the relationships of these phenotypes to the cognitive and genetic aspects of schizophrenia (28).

Drug Development

Although schizophrenia cannot be reproduced in animals, mouse and rat analogues of PPI and P50 deficits can be produced. Increased dopaminergic neurotransmission from stimulants and psychotomimetic antagonists of NMDARs such as phencyclidine (PCP) induce the deficit pharmacologically (8). Deficits in CHRNA7 null mutant mice for P50 gating (32) and in NRG1 null mutants for PPI have also been reported (8). Intriguingly, the NRG1-induced deficits do not appear until adolescence (33), modeling the time course for onset of schizophrenia (34).

Animal models were first used to examine effects of nicotine and clozapine, with good corroboration in clinical observations (10). Cigarette smoking increases P50 inhibition and PPI in schizophrenia (35). Further animal and clinical investigation confirmed nicotine's activation of α7-nicotinic receptors as the mechanism of its effects on P50 inhibition (36, 37). Clozapine, unlike other antipsychotics, significantly normalizes P50 inhibition, through increased release of acetylcholine in the hippocampus and the resultant indirect activation of α7-nicotinic receptors on inhibitory interneurons (38).

Investigational therapeutics followed, to develop specific α7-nicotinic receptor agonists to enhance cognition. The initial proof of principle for several of the agents included the demonstration of normalization of P50 inhibition in schizophrenia (39). Results of human studies have been mixed, with some but not all showing enhancement of cognition and relief of negative symptoms (39–41). Nevertheless, at least one compound is currently in late-stage clinical testing, with definitive results expected within the next several years (42).

Development

P50 deficits are already present in many newborns of parents with schizophrenia (Table 2) (43). In the perinatal period, α7-nicotinic receptors are critical to the development of cerebral inhibition. However, cholinergic inputs do not reach the hippocampus until shortly before birth. Therefore, they are not stimulated by synaptically released acetylcholine. Choline, in the millimolar concentrations found in amniotic fluid, activates α7-nicotinic receptors. Dietary supplementation of choline stimulates the development of cerebral inhibition as measured by P50 inhibition after birth (44). Deficits in development of P50 inhibition in newborns are correlated with the first appearance of attention deficit symptoms in later childhood (45).

Deficits in Neocortical Discrimination of Auditory Stimuli

The brainstem-based gating mechanisms operate at a basic filtering level to enable people to operate effectively in noisy, stimulus-filled environments. Once information reaches the cerebral cortex, fine discrimination of differences is needed for the complex feature extraction necessary for uses like language and the more emotive features of sound, including voice tone and music. The primary auditory cortex contains different regions that support the extraction of these different features, including the localization of the source versus the content of sounds (46).

Sound Localization in Schizophrenia

One of the strongest clues to auditory dysfunction in schizophrenia is the presence of auditory hallucinations. Although neural substrates of hallucinations remain incompletely

TABLE 2. Development of Sensory Processing Dysfunctions

Period	Fetal or Newborn Offspring of Parent With Schizophrenia	Adolescents at Risk for Schizophrenia	Schizophrenia, Childhood and Adult	Unaffected Adult Relatives	Schizotypal Adults
Deficit in PPI	Increased incidence of poor startle habituation	Increased prevalence	Increased prevalence, decreased with second-generation antipsychotics, smoking	Increased prevalence	Increased prevalence
Deficit in P50 gating	Increased incidence	Increased prevalence	Increased prevalence, decreased with clozapine and nicotinic agonists	Increased prevalence, segregates as autosomal dominant	Increased prevalence, particularly with positive family history
Deficits in MMN		Increased prevalence	Increased prevalence, unaffected by antipsychotics	Variable results (126, 127)	Increased prevalence (127, 128)
Deficits in visual P1		Unknown	Increased prevalence, unaffected by antipsychotics	Increased prevalence	

understood, it has been known since Penfield (47) that stimulation of auditory regions induces auditory hallucinations similar to those of schizophrenia. Consistent with this literature, auditory hallucinations in schizophrenia are increasingly tied to auditory cortex dysfunction. For example, hallucinations are accompanied by objective hyperactivity of left-sided auditory regions (48). Similarly, increased ability of the left hemisphere to localize sound in the right side of space is correlated with greater severity of hallucinations (49). Increased development of the superior longitudinal fasciculi white matter fiber tracts connecting the auditory areas in the temporal lobe with the prefrontal cortex is also correlated with greater severity of auditory hallucinations and provides a possible anatomical correlate (50).

Neither sound localization nor the cortical anatomical substrate is enhanced in schizophrenia, compared with healthy subjects, but their preservation in patients with more severe hallucinations compared with those without this symptom intensity may reflect the output of a relatively intact cerebral cortex that is attempting to analyze an unregulated stream of sensory information resulting from earlier gating dysfunctions and from specific synaptic dysfunction within the cortex itself. Consistent with this hypothesis, deficits in P50 gating and PPI are both associated with increased severity of auditory hallucinations (51, 52).

Tone Matching Ability

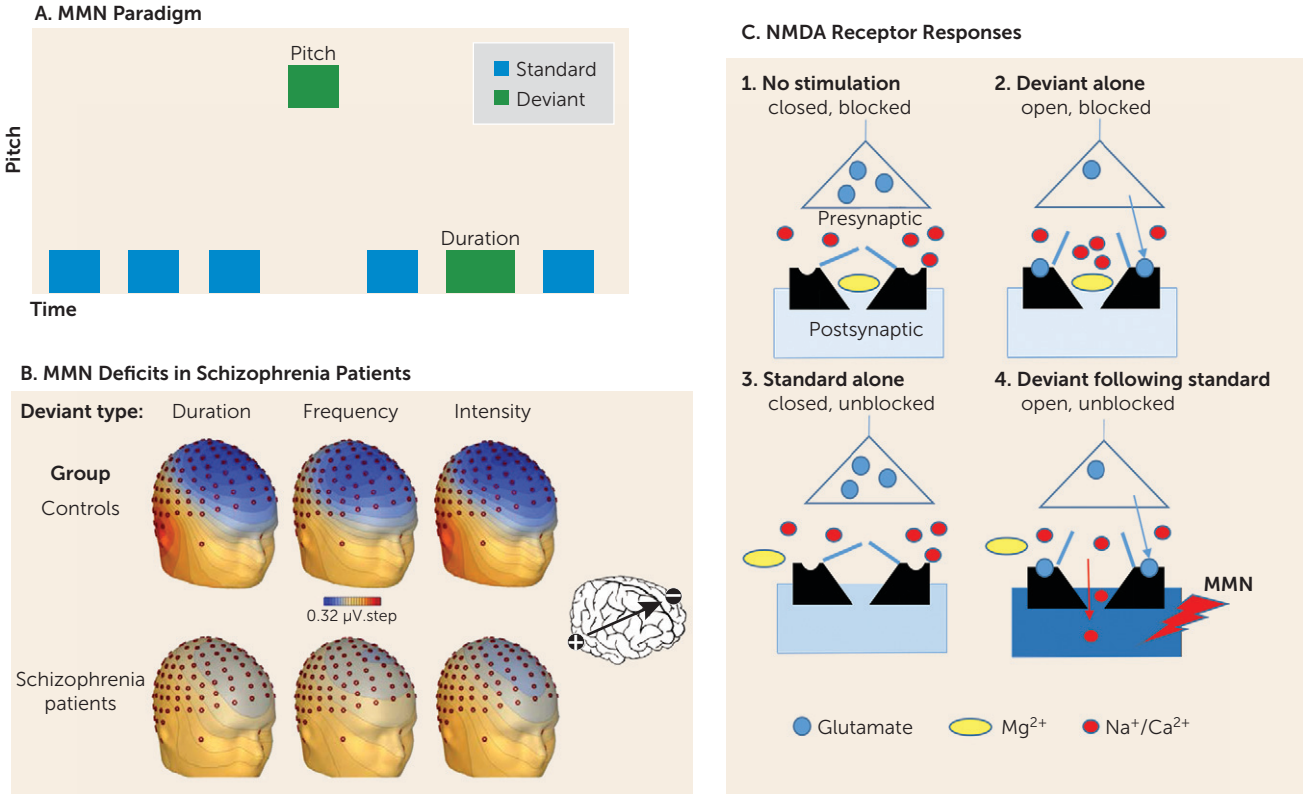
One of the most widely studied measures of cortical auditory dysfunction is the mismatch negativity (MMN), which is elicited whenever a stimulus differs from what is expected based on recent auditory experience. MMN is elicited most frequently in an auditory "oddball" task, in which a series of repetitive stimuli is interrupted infrequently by a physically deviant "oddball" stimulus. Deviant stimuli can differ on any of several physical dimensions, including pitch, duration, intensity, and location (53) (Figure 3A**)**.

MMN has been tied to impaired neurotransmission at NMDARs in both intracranial (54) and surface (55) recordings in nonhuman primates and in ketamine challenge studies in healthy human volunteers (3). Unlike PPI, MMN generation is little affected by either dopaminergic or serotonergic manipulations (56). However, as with P50 gating, ketamine-induced deficits in MMN generation are reversed by nicotinic agonists (57), possibly by presynaptic stimulation of nicotinic receptors on the glutamate nerve terminals (40, 58), with similar effects observed in schizophrenia (39). Other compounds that may reverse MMN deficits in schizophrenia include *N*-acetylcysteine, a precursor of the brain antioxidant glutathione (59), and D-serine, an endogenous NMDAR modulator (60).

Deficits in MMN generation were first reported in the early 1990s, and this finding has since been a widely replicated neurophysiological finding in schizophrenia (3, 61–63) (Figure 3B). Deficits in MMN generation correlate highly with overall level of function (64) and age at which symptoms of the illness first appeared (65). Like P50 and PPI deficits, MMN deficits are heritable across the general population (66). In persons at high clinical risk for schizophrenia, MMN has emerged as a predictor of who will progress to schizophrenia and therefore may require the most intensive remediation (67). Although the majority of studies of auditory dysfunction in schizophrenia have used neurophysiological measures such as MMN, similar deficits may be detected using fMRI to evaluate response to stimulus change within auditory cortical regions (68).

In keeping with the continued maturation of the auditory cortex in adolescence, MMN impairments continue to develop during the initial stages of the illness (69) in parallel with progressive volume reduction in auditory brain regions (70). In addition to MMN deficits, patients with schizophrenia also show deficits in the generation of other cortical auditory responses, such as the auditory steady-state response to rapidly presented stimuli (71). Patients fail to entrain their neuronal response to the rhythm of repeatedly presented stimuli, and so make less efficient use of sensory processing resources (72).

FIGURE 3. Mismatch Negativity (MMN) Paradigm, Deficits in Schizophrenia, and Process in the NMDA Receptor[a]



[a] Panel A is a schematic illustration of the MMN paradigm, showing repetitive standard stimuli along with stimuli that are deviant in frequency (pitch) or duration. Panel B shows the distribution of MMN deficits in schizophrenia patients compared with controls in response to duration, frequency, and intensity deviants; the inset shows the current flow when MMN is generated within the auditory cortex. Panel C is a schematic illustration of the MMN process in the NMDA receptor. Surface-recorded MMN activity reflects current flow through open, unblocked NMDA receptors on pyramidal neurons in the auditory cortex. In panel C1, NMDA receptors are normally blocked by Mg^{2+} at resting membrane potential. In panel C2, when a deviant stimulus is presented without prior standard stimuli, even though the channels open, the blockade prevents current flow. Brain responses therefore occur only through non-NMDA-type glutamate receptors. In panel C3, when repetitive standard stimuli are presented, they depolarize the membrane, leading to unblocking of the channel. In panel C4, once channels are unblocked, presentation of the deviant stimulus leads to NMDA-receptor-mediated current flow. (Panel B is reprinted from T. Friedman et al., "Differential relationships of mismatch negativity and visual P1 deficits to premorbid characteristics and functional outcome in schizophrenia," *Biological Psychiatry,* volume 71, issue 6, pp. 521–529, Copyright 2012, with permission from Elsevier.)

On the behavioral level, deficits in MMN generation are associated with impairments of basic auditory discrimination, such as tone matching (3) and auditory spatial discrimination (49), both underappreciated aspects of the clinical features of schizophrenia. Important social information, including emotion and attitude, is conveyed by variation in vocal intonation ("prosody"). Consequently, impaired ability to detect vocal intonation may contribute significantly to impaired social function (73).

Deficits in tone matching contribute significantly to the ability to detect emotional prosody (74, 75), as well as to communications such as sarcasm that require the individual to appreciate what another person may be thinking (76, 77), a trait called "theory of mind," a form of empathy. On standardized tests of musical ability, such as the Montreal Battery for Evaluation of Amusia (78), nearly 50% of schizophrenia patients show deficits, compared with only 10% of the general population (79).

Deficits in MMN generation, particularly to duration deviants, are also prominent in developmental dyslexia, reflecting impaired ability to perform phonological operations (i.e., "sounding out" words) required for successful reading (80). Recently, similar reductions in phonological reading ability have been observed in patients with established, but not prodromal, schizophrenia, which suggests that progressive reductions in auditory function during the peri-onset period may result in a significant regression in reading ability in schizophrenia from premorbid levels (81). Such findings may identify pathways through which deficits in sensory function lead to impaired functional outcome when schizophrenia itself develops later on.

Although neural circuitry underlying MMN generation has not been fully determined, specific properties of the NMDAR appear to play a key role. NMDARs are unique in that they are controlled by both the resting membrane potential of the postsynaptic cell and glutamate release from

the presynaptic cell. Specifically, at resting membrane potential (approximately −65 mV), NMDARs are blocked by Mg, which binds to a site within the NMDA channel (Figure 3C). Thus, even if glutamate is released from presynaptic terminals in response to a stimulus, no current flows through NMDAR channels even though they are open.

A proposed model of MMN generation (Figure 3C) is that repetitive standard stimuli induce subthreshold depolarization of the resting membrane potential in a population of neurons sensitive to stimulus properties that differ from those of the standard stimuli, leading to unblocking of the channels even though the channels are still closed. Once receptors are unblocked, presentation of the deviant stimulus leads to opening of the channel. Current flow through the open, unblocked NMDAR channel on neurons in the auditory cortex leads to the generation of the surface MMN potential. Although this phenomenon can be studied best in humans by use of sensory stimulation and auditory evoked potentials, similar phenomena occur elsewhere in the brain and lead to the types of cognitive disturbances observed in schizophrenia.

VISUAL SENSORY SYSTEMS

Although sensory studies in schizophrenia to date have focused mostly on auditory dysfunction, visual function is increasingly investigated as well. Like the auditory system, visual function in the brain is subserved by two separate pathways: a dorsal-stream "where" system, which is also termed "perception for action," and a ventral-stream "what" system, which is also termed "perception for identification" (see Figure 1).

Basic Visual Function

The visual system begins in the retina and projects via the visual lateral geniculate nucleus to the cortex. Subcortical visual systems are divided into two main pathways (82). The magnocellular pathway consists of large neurons that rapidly conduct low-resolution visual information to the dorsal visual stream, and thus is most analogous to the brainstem pathways involved in rapid response to auditory stimuli, subserving "where." By contrast, the parvocellular system consists of more numerous smaller neurons that conduct slower but higher-resolution information primarily to the ventral visual stream, subserving "what."

Consistent with their different functions, magnocellular and parvocellular neurons have divergent physiological properties. For example, magnocellular neurons respond strongly even to dim and low-contrast stimuli, giving rise to our familiar ability to detect extremely dim objects in the near dark even if we cannot identify what they are. The rapid, nonlinear increase in the response of magnocellular neurons to increasing stimulus contrast (Figure 4A) has been tied to the physical properties of NMDARs, particularly their need for cooperative binding of two glutamate molecules for activation (see Figure 3C). Magnocellular neurons are also highly sensitive to moving or flickering objects, which accounts for the strong influence of such objects on our attentional systems. These properties depend heavily on function of NMDARs within both subcortical and cortical visual regions (83).

By contrast, parvocellular neurons are smaller and more numerous, and hence are far more able than magnocellular neurons to transmit fine details of the visual scene. The parvocellular system responds in a more graded fashion to shades of gray than the magnocellular system (Figure 4A) and is sensitive to color, permitting fine object recognition (3). Parvocellular neurons show more linear responses than magnocellular neurons, suggesting less engagement of NMDARs. Relative dysfunction of the systems, therefore, will depend on both the pathways involved and the stimulus paradigms used.

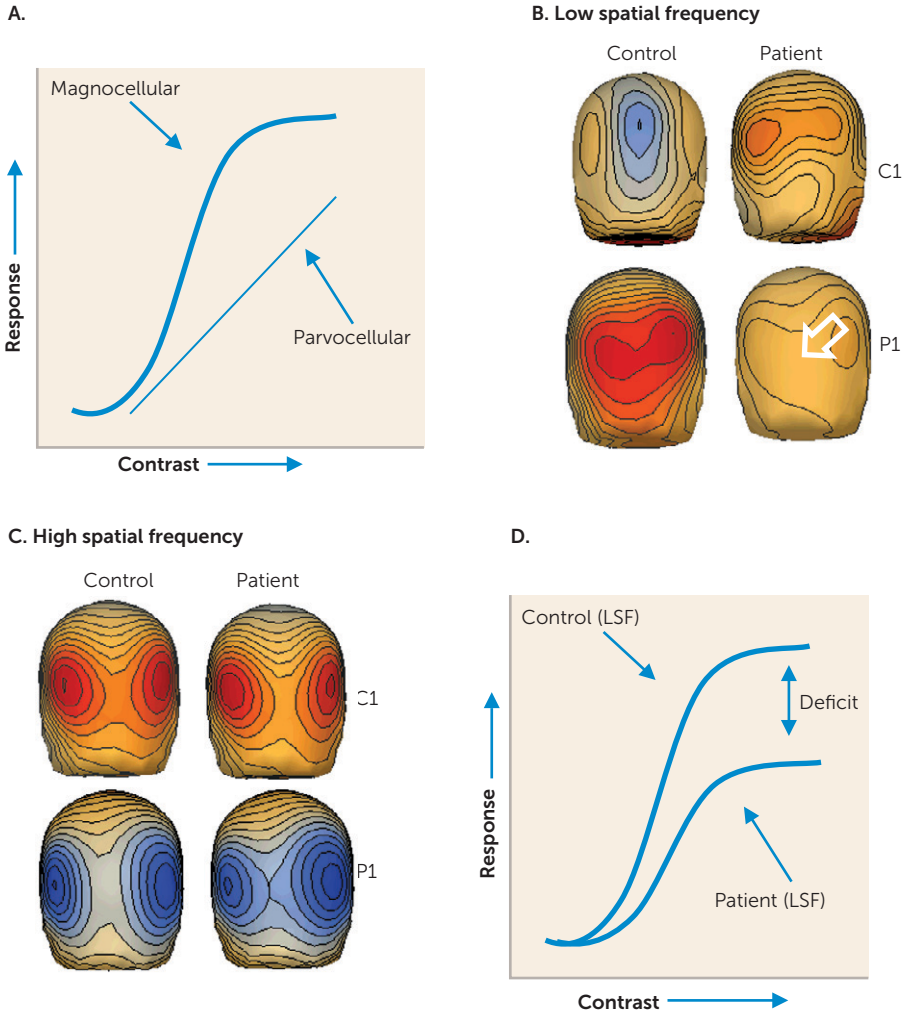
As with the auditory system, routine clinical visual testing, such as use of an eye chart, does not adequately assess potential disturbances in schizophrenia. Magnocellular function can be assessed only through use of specially designed stimuli or tasks, such as measures of contrast sensitivity to low-spatial-frequency stimuli or related neurophysiological measures. Furthermore, although we are consciously aware of events occurring in the ventral visual system, we are typically unaware of processing taking place within our dorsal stream. For example, we may turn our heads in response to a flickering object before we are consciously aware of it. A consequence of such unconscious processing is that patients experiencing dorsal stream dysfunction may be unaware of what they are missing and may not know that their subjective experience differs from that of other people.

Visual Deficits in Schizophrenia

Using the newly invented photographic shutter, Kraepelin and colleagues observed that dementia praecox patients showed severe deficits in detecting stimuli presented for brief intervals (20 ms), confirming earlier findings with a rotating striped drum apparatus (84). Nevertheless, modern studies of visual processing in schizophrenia were not conducted until the 1960s, when Holzman observed that both patients and their unaffected family members showed more variability of eye movement during eye tracking than did healthy volunteers (85, 86). Subsequent studies of visual backward masking (87) demonstrated that patients not only required more time to detect a target—a parameter termed "critical stimulus duration" (as in the earlier Kraepelin studies)—but also showed more sensitivity to masking of the stimulus by a later, more intense stimulus, suggesting impaired interplay between different visual pathways (88).

Since then, more specific paradigms for demonstrating visual dysfunction have been developed on the basis of improved understanding of magnocellular and parvocellular system function (63). Neurophysiological studies have demonstrated impaired generation of the visual P1 potential to stimuli biased toward the magnocellular visual system (65, 89–91) (Figure 4B,C). Other potentially useful paradigms

FIGURE 4. Response Properties of Magnocellular and Parvocellular Neurons in Schizophrenia[a]



[a] Panel A is a schematic illustration of response properties of visual magnocellular and parvocellular neurons. Magnocellular neurons show a nonlinear saturation response pattern (see reference 132), whereas parvocellular neurons show a more linear response pattern. The nonlinear response pattern is thought to depend on properties of the NMDA receptor (see reference 83). Panels B and C show visual event-related-potential responses to low- and high-spatial-frequency stimuli in schizophrenia. Magnocellular and parvocellular pathways are differentially sensitive to low- versus high-spatial-frequency stimuli. Patients show preferential activation impairments in P1 response to low spatial frequencies (arrow), suggesting preferential magnocellular pathway dysfunction (see reference 90). Panel D is an illustration of the response deficit in schizophrenia. In response to low-spatial-frequency (LSF) stimuli, both patients and controls show a nonlinear response pattern with increasing stimulus contrast. In patients, however, the maximum amplitude of the response is lower, consistent with underlying NMDA receptor dysfunction (see reference 3). (Panels B and C are reprinted from P.D. Butler et al., "Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments," *Brain* 2007, volume 130, issue 2, pp. 417–430, by permission of Oxford University Press.)

include steady-state visual evoked potentials (Figure 4D), contour integration, and coherent motion tasks (63). The fMRI literature on early visual deficits is more limited. Nevertheless, impaired activation has been observed in response to low-spatial-frequency stimulation (91, 92), along with visual behavioral deficits. Visual regions are often not assessed in studies of higher cognitive dysfunction; nevertheless, impaired activation of visual regions has been observed in meta-analyses of visual working memory tasks (93), supporting recent suggestions that low-level visual deficits cascade up the system to undermine higher-order cognitive impairments, as in the auditory system (3).

Overall, deficits in sensory response are observed even in the absence of the attentional impairments (94), which suggests that visual deficits are more likely a cause than a consequence of attentional dysfunction. As in the early Holzman studies, deficits in visual processing are consistently observed not only in schizophrenia patients but also in unaffected family members, which suggests that they represent a possible heritable vulnerability factor for the disorder (95).

Functional Implications

As with auditory deficits, visual dysfunction in schizophrenia may go undetected unless specifically evaluated. Nevertheless, as in the auditory system, low-level deficits may cascade up the system to produce higher-order cognitive impairments.

One critical function tied to the early visual system is the ability to "close" or complete fragmented images. This process of perceptual closure, often referred to as the "cat behind the Venetian blind effect," depends on rapid transmission of low-resolution information through the magnocellular/dorsal stream visual system to the prefrontal cortex in advance of more detailed information reaching the ventral stream visual cortex via the parvocellular visual system (96, 97). In schizophrenia, this framing function is lost because of impaired transmission within the magnocellular visual system (98), leading not only to impaired ability to recognize fragmented objects but also to impaired ability to discriminate facial emotion (99) or to engage in tasks that require sustained attention to visual information (91, 100). Patients in the early stages of schizophrenia often experience visual illusions and feelings that images are fragmentary (101, 102). Loss of this framing function may serve as a physiological substrate for this common perceptual experience.

Similarly, the magnocellular visual system plays a critical role in organizing visual space during reading of connected passages of text, such as paragraphs (103, 104). Although single-word reading has been extensively studied in schizophrenia, studies of paragraph reading have only recently been initiated based on emerging "whole brain" theories of schizophrenia. As predicted, schizophrenia patients show severe deficits in passage reading but not single-word reading (105), and these deficits correlate with both behavioral (106, 107) and fMRI-based (108) assessment of visual magnocellular function. Consistent with other visual findings, visual reading deficits extend to individuals at clinical high risk for schizophrenia (81) as well as to unaffected family members (106).

AUDITORY-VISUAL INTERACTION

Given the parallel deficits in auditory and visual function, processes that rely on the synergistic interplay between these systems should be those most affected in schizophrenia. To date, these interactions have been studied mostly in regard to social cognition and, more recently, reading, where expected synergistic consequences have been observed.

In social cognition, subjects infer emotion from both auditory cues and facial expression. Like schizophrenia patients, individuals with congenital amusia show impaired auditory emotion recognition (79) but may compensate by using visual cues and higher-order cognitive reasoning. In schizophrenia, the auditory and visual emotion-processing deficits are correlated but independent (74), which suggests that the confluence of deficits contributes in parallel to the social disconnection of schizophrenia patients.

Similarly, with regard to reading, individuals with isolated visual (as opposed to phonological) deficits may compensate by becoming "auditory" rather than "visual" readers. In schizophrenia, the parallel deficits in auditory and visual processing combine to produce a "double deficit" pattern of dyslexia that leads to significant impairments and poor socioeconomic outcomes (81). Such relationships are observed even in individuals who do not suffer from schizophrenia. However, whereas developmental dyslexia occurs during school years, permitting early detection and remediation, schizophrenia-related dyslexia represents a regression from a higher level of function and thus may go undetected unless specifically assessed.

DEFICITS IN NONSCHIZOPHRENIA DISORDERS

Sensory dysfunction has been studied most extensively in the context of schizophrenia, but additional studies suggest that sensory deficits may also be present dimensionally across other neuropsychiatric disorders. For example, deficits in PPI appear in bipolar disorder (109) and Huntington's disease (110), consistent with the hyperarousal often seen in these conditions. Similarly, P50 deficits may be associated with psychotic mania and childhood autism spectrum disorder (ASD), consistent with impairments in excitatory/inhibitory balance (111, 112). By contrast, MMN appears to be differentially impaired in schizophrenia relative to either bipolar disorder or depression (113). In higher-functioning ASD, alterations are found in the consistency, although not in the overall amplitude, of unimodal sensory response (114). Similarly, patients may have superior, rather than impaired, performance in basic unimodal functions such as pitch processing (115) and visual search capabilities (116) that are impaired in schizophrenia. ASD patients show particular deficits in multisensory facilitation, perhaps leading to a fragmented experience of the environment (117, 118). The National Institute of Mental Health has recently proposed the Research Domain Criteria initiative (119), which views neurocognitive deficits as being present dimensionally across neuropsychiatric disorders. Sensory processing measures are included in this initiative and may make appropriate targets for intervention across, as well as within, specific nosological entities.

DISCUSSION

The cognitive dysfunction of schizophrenia encompasses a profound disturbance in sensory processing. As Hubel and Wiesel found in their investigations, the understanding of how sensory information is processed has proven to be a valuable strategy for identifying specific neuronal dysfunctions. Assessments of sensory dysfunction, including PPI, P50 inhibitory gating, auditory MMN, and visual P1, steady-state, and magnocellular responses reveal heritable neurobiological abnormalities in schizophrenia that include deficits in nicotinic cholinergic, NMDA glutamatergic, dopaminergic, and GABA-ergic synaptic mechanisms. Many of these abnormalities are manifest before the onset of clinical signs of psychosis. The synaptic mechanisms and associated genes are now targets for new drug development to improve cognitive function in schizophrenia, one of the disorder's most limiting clinical features.

While research tools for assessing sensory dysfunction are not used in clinical practice, clinical observations of patients' sensory function have a role in treatment. The first clinical report of chlorpromazine's effects in schizophrenia included its effects on patients' sensory perception of their environment, described by Delay and Deniker (120) as "apparent indifference or the slowing of responses to external stimuli," in contrast to their baseline state of hyperexcitability. Clinicians treating acutely ill patients look for the subsidence of the hypervigilant state as an early therapeutic milestone. Both isolation in a quiet environment and antipsychotic drugs are used to achieve this initial therapeutic effect. Dr. Saks's description of her hyperawareness of her neighborhood is an example of a personal experience of this phase of psychosis.

Patients are often disturbed by their sensory distortions, but they may not volunteer this information to clinicians, particularly if they are already developing paranoia. When

the clinician explains that many patients find that colors may seem more intense, visual perception may be more fragmented, and sounds may seem too loud or too intrusive, patients are often relieved to learn that their situation is understood. These topics may be simpler to explore with patients than their more cognitively elaborated hallucinations and paranoid delusions. Clinicians must be aware as well that patients may be unable to detect the variations in tonality that are used to communicate information, such as emotion or even attitude (e.g., humor and sarcasm), or to process the visual information needed to correctly interpret facial expression, contributing to their difficulty in interpersonal and social interactions.

Because available first- and second-generation antidopaminergic antipsychotics do not affect all the mechanisms that are associated with sensory disturbance in schizophrenia, many aspects of patients' sensory dysfunction will persist chronically. Persistent abnormalities in P50 gating are associated with impaired ability to focus attention on specific tasks, a cognitive deficit associated with poor psychosocial rehabilitation (16). MMN deficits are tied to impairments in both orientation to critical environmental events and detection of the sensory modulations that are used to communicate social information such as emotion or attitude by tone of voice (3). Deficits in visual function are tied to impaired facial discrimination and reading. The result is a loss of connection to people and the environment, especially during the chronic phases of illness. Clinicians and families, as well as patients themselves, who are aware of these impairments may be able to compensate for them by more explicit explanations of communications, with the realization that patients may easily misperceive even the most helpful intent.

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