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

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Abstract

Sensory processing deficits, first investigated by Kraepelin and Bleuler as possible pathophysiological mechanisms in schizophrenia, are now being re-characterized in the context of modern understanding of the involved molecular and neurobiological brain mechanisms. 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 pre-pulse 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 slightly different stimuli that elicits 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, vice versa, are affected by higher-level cognitive difficulties. These deficits are now being used to identify genes involved in familial transmission of the illness 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 surrounding world ultimately depends upon an underlying sensory experience of it.

Keywords

Schizophrenia; Sensory Gating; Startle; Evoked Response Auditory; Mismatch Negativity; Evoked Response Visual

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 that

underlie their psychotic symptoms. Elyn Saks thus describes the first day that she became psychotic:

“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.*” (1)

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 experience, but they are a paradigmatic example of research that has been guided by patients’ own descriptions of their experience of the world. Clinicians attuned to similar descriptions from their own patients of their 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 Professor Saks, in two ways: [1] neuropsychologically, failure to register basic sensory information correctly makes poor decisions about it inevitable, and [2] 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, suggesting 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:

“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 (p. 152)...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 (4).”

Elementary sensation, such as auditory detection thresholds or visual acuity, is generally considered to be normal in patients, reflecting integrity of the peripheral sensory apparatus. However, research like Hubel and Wiesel’s 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. This review highlights the important role played by sensory deficits in both the subjective and objective functioning of individuals with schizophrenia, and how an increasing focus on sensory dysfunction may improve functional outcome 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 these event-related potential studies, however, are strongly corroborated by both behavioral and neuroimaging based measures that provide additional information regarding location and nature of underlying cortical impairments (Table 1).

Auditory dysfunction in schizophrenia

Brain functions that differentiate humans from other primates include our superior reasoning and problem solving ability. These functions related to a dramatic expansion of human frontal brain regions as compared to other primates (Figure 1A). It is less appreciated that an equally marked evolutionary expansion has occurred within 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. Like other recently evolving regions, 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 schizophrenia

Normal auditory physiology (Figure 1B)

Most clinical tests of auditory function, such as audiological assessments or 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. Auditory information then ascends through the medial geniculate nucleus to the auditory cerebral cortex, which plays a critical role in decoding of simple auditory features such as pitch, intensity or location, which then get elaborated in subsequent auditory regions into more complex auditory percepts such as language or tonality. Dysfunction within the cortical regions may thus contribute to the complex patterns of social and communicative disturbance observed 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, e.g., 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 (Table 1). 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 successive 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 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 normal 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 their first demonstrations, 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 msec (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 (Figure 2A). The inhibition of the second stimulus is maximal at 500 msec, later than the maximal PPI interval of 60 msec. 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 brain stem 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 beta electroencephalographic 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 magnetic resonance imaging (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 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 their psychopathology (18). Thus, several investigations in patients themselves 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 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 and is linked to the CHRNA7 gene complex, which forms the $\alpha 7$ -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 $\alpha 7$ -nicotinic receptor is found presynaptically on glutamate nerve terminals and postsynaptically on inhibitory interneurons (Figure 2B), particularly in the hippocampus and nucleus reticularis thalamis (9). Thus, there is convergence between the genetic findings and the neurobiological model, corroborated by postmortem findings of

decreased $\alpha 7$ -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 of Genetics Studies 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 re-produced 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 *NRG-1* null mutants for PPI have also been reported (8). Intriguingly, the *NRG1*-induced deficits do not appear until adolescence (33), modeling the time course of 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 itself, acting through $\alpha 7$ -nicotinic receptors, as the mechanism of 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 $\alpha 7$ -nicotinic receptors on inhibitory interneurons (38).

Investigational therapeutics followed to develop specific $\alpha 7$ -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). Human studies are mixed with several but not all showing enhancement of cognition and relief of negative symptoms (39–41). Nevertheless, at least one compound is presently in late stage clinical testing, with definitive results expected within the next several years (42).

Development

P50 deficits are already present in many newborn infants of parents with schizophrenia Table 2; (43). In the perinatal period, $\alpha 7$ -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 $\alpha 7$ -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, then fine discrimination of differences is needed for complex feature

extraction needed for uses like language and more emotive features of sound, including voice tone and music. The primary auditory cortex contains different regions, which support the extraction of these different features, including the localization of the source vs. 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 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 function. 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 correlate with increased 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 also correlate with increased severity of auditory hallucinations and provide a possible anatomical correlate (50).

Neither sound localization nor the cortical anatomical substrate are enhanced in schizophrenia, compared to controls, but their preservation in patients with more severe hallucinations compared to 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 upon recent auditory experience. MMN is elicited most frequently in an auditory “oddball” task, in which a series of repetitive stimuli are interrupted infrequently by a physically deviant “oddball” stimulus. Deviants can differ on any of several physical dimensions, including pitch, duration, intensity, or location (53) (Figure 2C).

MMN has been tied to impaired neurotransmission at NMDARs based upon both intracranial (54) and surface (55) recordings in non-human primates and ketamine challenge studies in healthy human volunteers (rev. in 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) (Figure 2B), 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 1990's, and this finding has since been a widely replicated neurophysiological finding in schizophrenia (rev. in 3, 61, 62, 63) (Figure 2D). Deficits in MMN generation correlate highly with overall level of function (64) and age at which symptoms of the illness first appear (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 (rev. in 67), and therefore may require most intensive remediation. 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 auditory cortex in adolescence (Figure 1A), impairments in MMN continue to develop over initial stages of the illness (69) in parallel with progressive volume reduction within auditory brain regions (70). In addition to MMN deficits, patients with schizophrenia also show deficits in generation of other cortical auditory responses, such as the auditory steady-state response to rapidly presented stimuli (rev. in 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).

On a 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 ability to detect emotional prosody (74, 75), as well as to communications such as sarcasm that require patients to appreciate what another person may be thinking (76, 77), a trait called "theory of mind", a form of empathy. When tested on a standardized tests of musical ability, such as the Montreal Battery for Evaluation of Amusia (78), nearly 50% of schizophrenia patients test positive vs. 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, suggesting 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 in life.

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 that is also termed “perception for action”, and a ventral stream “what” system that is also termed “perception for identification” (Figure 1A).

Basic visual function

The visual system begins in the retina and projects via the visual lateral geniculate nucleus to cortex. Subcortical visual systems are divided into two main pathways (82). The magnocellular pathways 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 smaller, more numerous neurons that conduct slower but higher resolution information primarily to ventral visual stream, subserving “what.”

Consistent with their different functions, magnocellular and parvocellular neurons have divergent physiological properties. For example, magnocellular neurons are uniquely sensitive 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 those objects are. Furthermore, magnocellular neurons are highly sensitive to moving or flickering objects, accounting for the strong influence of such objects on our attentional systems. These properties depend heavily upon function of NMDARs within both subcortical and cortical visual regions (83).

By contrast, parvocellular neurons are smaller and more numerous, and so far more able than magnocellular neurons to transmit fine details of the visual scene. Furthermore, the parvocellular system responds in a more graded fashion to shades of grey than the magnocellular system, and is sensitive to color, permitting fine object recognition (3). Parvocellular neurons show more linear responses than magnocellular neurons, suggesting relatively lesser engagement of NMDARs. Relative dysfunction of the systems, therefore, will depend upon both the pathways involved and 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 even 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 (20 ms) durations, confirming even earlier findings with a rotating striped drum apparatus (84). Nevertheless, modern studies of visual processing in schizophrenia were not conducted until

the 1960's 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 longer 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 based upon 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). Other potentially useful paradigms include steady-state visual evoked potentials, contour integration and coherent motion tasks (63). fMRI literature regarding early visual deficits is more limited. Nevertheless, impaired activation have been observed 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), suggesting that visual deficits are more likely a cause than 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, suggesting 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" objects based upon fragmented information. This process, often referred to as the "cat behind the Venetian blind effect," depends upon rapid transmission of low resolution information through the magnocellular/dorsal stream visual system to prefrontal cortex even in advance of more detailed information reaching ventral stream visual cortex via the parvocellular visual system (96, 97). In schizophrenia, this framing function is lost due to 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 during 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 upon emerging “whole brain” theories of schizophrenia. As predicted, schizophrenia patients show severe deficits in passage, but not single word, reading (105) that 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 most affected in schizophrenia. To date, these interactions have been mostly studied in regard to social cognition and, more recently reading, where expected synergistic consequences have been observed.

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

Similarly, with regard to reading, individuals with isolated visual vs. phonological deficits may compensate by becoming “auditory” vs. “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 in socioeconomic outcome (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 non-schizophrenia 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 appears in conditions other than schizophrenia, including 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 consistency, although not in overall amplitude, of unimodal sensory response (114). Similarly, patients may have superior, rather than reduced, performance in basic unimodal functions such as pitch processing (115) or 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 NIMH has recently proposed the Research Domain Criterion initiative (119), which views neurocognitive deficits as being present dimensionally across neuropsychiatric disorders. Sensory processing measures are included within 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 GABAergic 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 its most limiting clinical features.

While research tools for assessing sensory dysfunction are not used in clinical practice, clinical observations of patients' sensory function also have a role in treatment. The first clinical report of chlorpromazine's effects in schizophrenia included its effects on the patients' sensory perception of their environment, described by Delay and Deniker as "apparent indifference or the slowing of responses to external stimuli," in contrast to their baseline state of hyper-excitability (120). Clinicians treating acutely ill patients look for the subsidence of the hyper-vigilant 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 hyper-awareness of her neighborhood is an example of a personal experience of this phase of psychosis.

Patients are often disturbed by their sensory distortions, but may not volunteer this information to clinicians, particularly if they are already developing paranoia. If the clinician can communicate that many patients find colors may seem more intense, visual perception may be more fragmented, and sounds may seem too loud or too intrusive, patients are often relieved 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 current first and second generation anti-dopaminergic antipsychotic drugs 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 deficits associated with poor psychosocial rehabilitation (16). Deficits in MMN 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 experienced by many patients especially during the chronic phases. 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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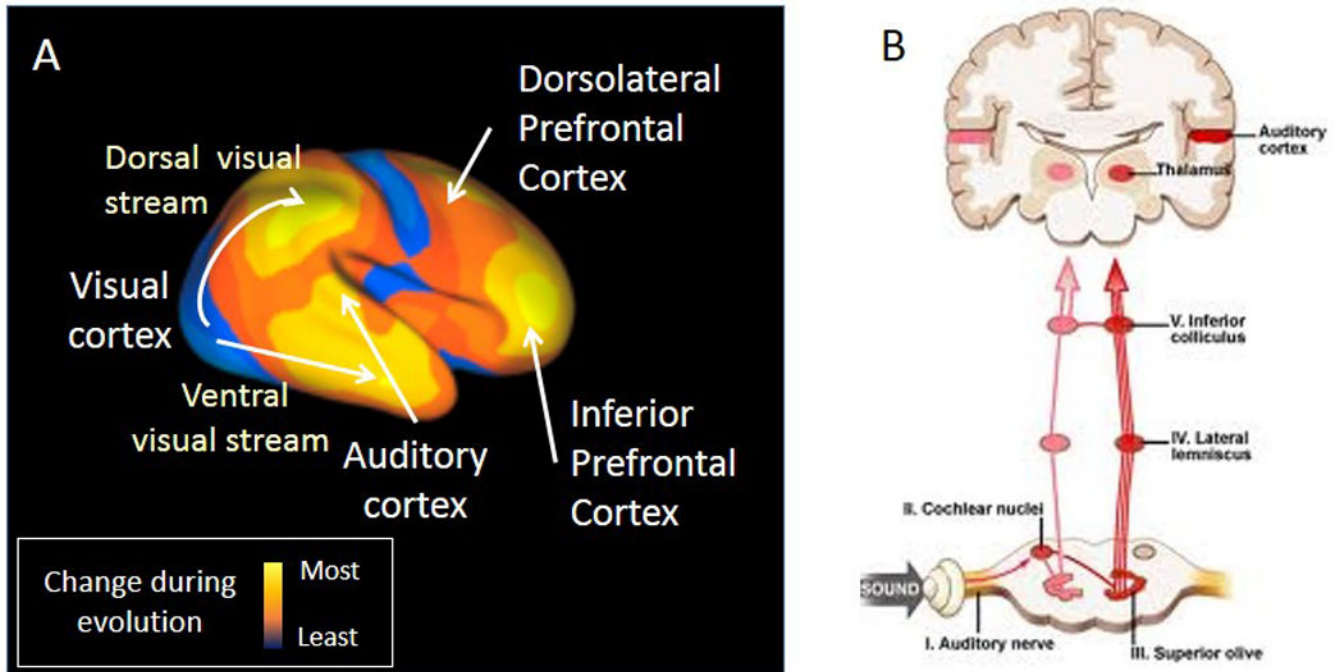


Figure 1. Anatomy of brain sensory systems, A. Cortical areas responsible for perception and executive function have both experienced especially enhanced expansion in the evolution of human brain (from 5). B. Right side of the brain shows auditory responses from the inner ear, conveyed through brainstem relay nuclei, arriving at the auditory cortex through the medial geniculate nucleus. Left side shows how a branch from the brainstem relay nuclei contact the reticular brainstem formation, which in turns activates the medial septal nucleus. The medial septal nucleus cholinergic input acts in the hippocampus to help filter all the sensory information from the cortex, including auditory cortex, that is funneled to it through the Superior Temporal Gyrus.

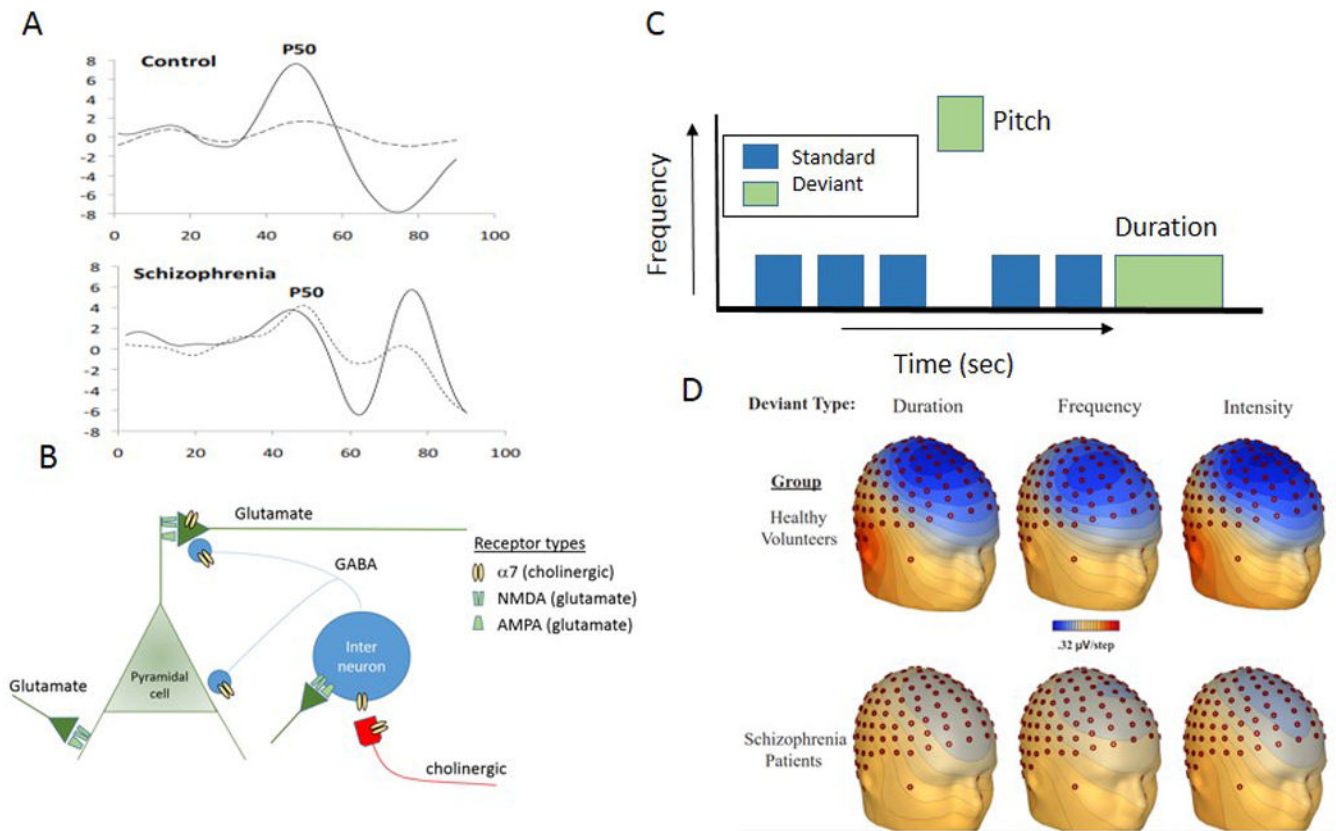


Figure 2.

Dysfunctions in auditory sensory processing in schizophrenia.

A. Representative tracing of the P50 sensory gating deficit in schizophrenia. Voltage in microvolts is shown on the vertical axis, time in milliseconds after each stimulus is shown on the horizontal. The response to the first stimulus is solid line and the response to the second is dashed. The second response is less inhibited in the schizophrenia patient.

B. Brain circuits responsible for sensory processing in the neocortex or hippocampus. AMPA-type glutamate receptors are responsible for the excitatory transmission of sensory input to the pyramidal cells, where integration into images and memory occurs. Inhibitory feedback to help the pyramidal cells' selective focusing of their response occurs through GABA transmission from inhibitory interneurons. Interneuron function is modulated by $\alpha 7$ -nicotinic cholinergic receptors that are activated by subcortical midbrain cholinergic pathways, which convey sensory gating responses from subcortical mechanisms, such as those shown in Figure 1, and NMDA-type glutamate receptors that convey information about unusual or mismatched stimulus characteristics.

C. Paradigm for mismatch negativity (MMN) generation; the detection of the deviant tone generates the MMN. Diminished MMN is seen in schizophrenia regardless of whether the tone is deviant in duration, pitch or frequency, or intensity from a train of otherwise identical stimuli.

D. Topographical distribution of MMN deficits in schizophrenia (65).

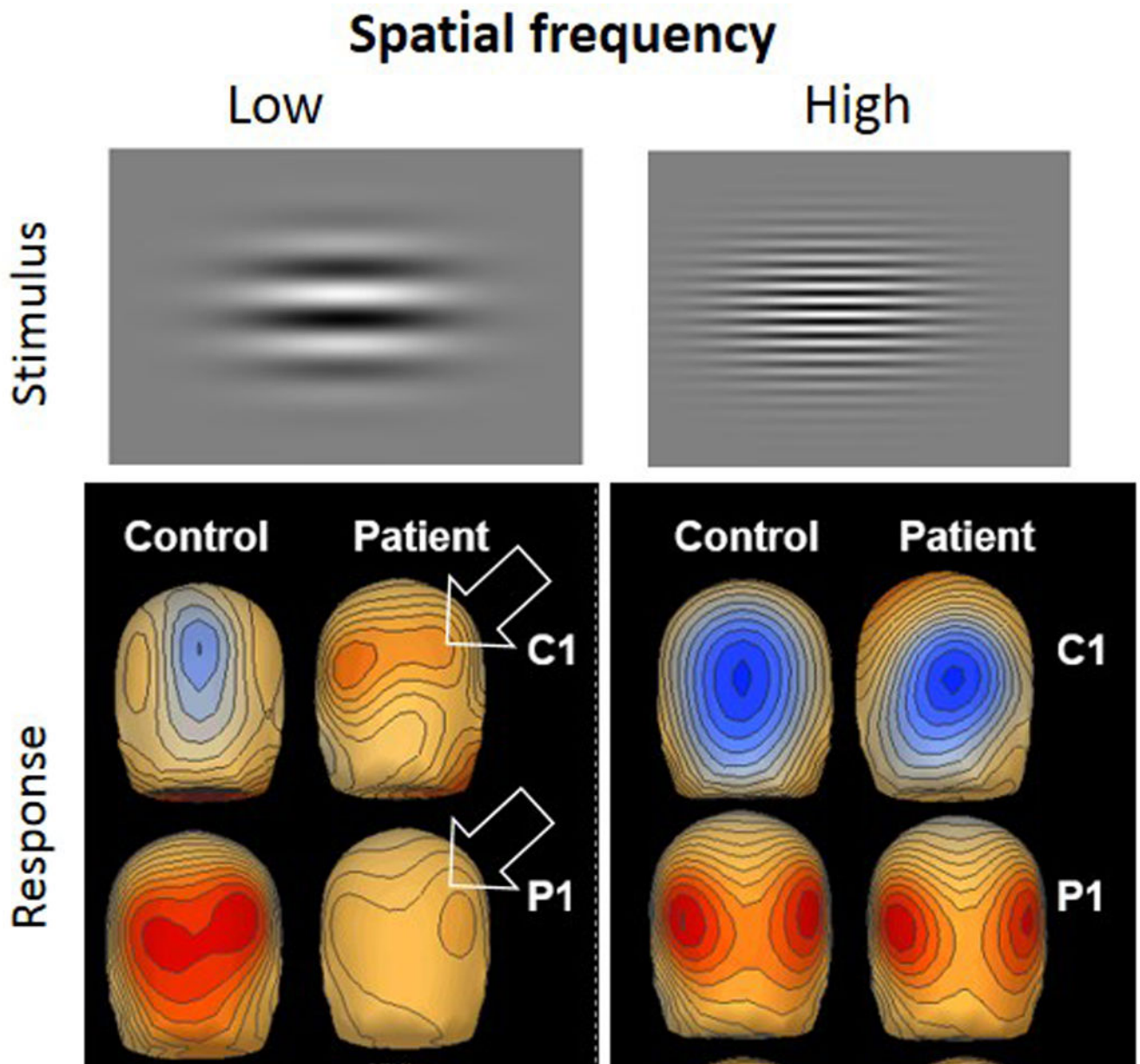


Figure 3. Visual event-related potential deficits in schizophrenia in response to low versus high spatial frequency stimuli in schizophrenia. Top panel shows example of these visual stimuli, which appear as waves. The C1 component of the response at 94 msec is followed by the P1 at 138 msec. The arrows show lower amplitudes of both early components in the patients at low frequency stimulation. The lower frequency stimuli preferentially activate the neuronal mechanisms that help draw patients' attention to more important features of their surroundings (from 90)

Table 1

Sensory processing dysfunctions in schizophrenia

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 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, 124); diminished event-related desynchronization of ongoing rhythms (121)	Reduced activation of low spatial frequency regions of visual cortex (91, 92)	Non-linear amplification failure in subcortical visual pathways ; decreased glutamate NMDAR activation (90)	DTNBP1 (125); NOS1 (126)

Table 2

Development of sensory processing dysfunctions

Period	Fetal newborn offspring of parent with schizophrenia	Adolescents at risk for schizophrenia	Schizophrenia childhood and adult	Unaffected adult relatives	Adult schizotypal persons
Deficit in PPI	Increased incidence of poor startle habituation	Increased prevalence	Increased prevalence, decreased with second generation drugs, 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 or clozapine	Variable results (127, 128)	Increased Prevalence (128, 129)
Deficits in visual P1		Unknown	Increased prevalence, unaffected by antipsychotics or clozapine	Increased prevalence	