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The Auditory Cortex in Schizophrenia

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Sweet et al have recently shown that the somal volume of pyramidal cells is reduced in layer 3 of the auditory cortex in schizophrenic patients (Sweet et al 2004; Sweet et al 2003). In this issue of Biological Psychiatry, they report new data showing that the density of axon terminals is also significantly decreased in the same layer (Sweet et al 2006). These results provide direct morphological evidence for altered information processing in the auditory cortex in schizophrenia, and lay a basis for further investigation of how deficits at this early stage of sensory processing may contribute to impairment of higher-order functions thought to involve also other brain areas such as the prefrontal cortex.

Dysfunction of the auditory system has long been suspected to be present in schizophrenic patients, due in part to the high prevalence of auditory hallucinations among these patients. Functional imaging and electrophysiological studies show that the auditory cortex is activated during auditory hallucinations. However, since several other brain areas including the prefrontal cortex and hippocampus also show increased activity during hallucinations (e.g. Shergill et al 2000), it is uncertain whether the role of the auditory cortex is primary or secondary. In a recent imaging study, normal subjects were asked to indicate, by pressing a button, when they heard a sound following a silent period of variable duration (Voisin et al 2006). The activity in the auditory cortex was found to increase while the subjects listened in silence. Frontal cortical areas, believed to play a higher-level role in attention control, were also activated and the activity was correlated with the duration of the period in which the subjects were attentively listening in silence. This raises the possibility that the activation of the auditory cortex in the absence of external auditory stimuli reflects a top-down control of the area by the frontal cortex. Post-mortem and structural imaging studies show, however, that the auditory cortex is reduced in volume in hallucinating subjects compared to control groups. Furthermore, the severity of hallucinations is negatively correlated with the volume of the auditory cortex, suggesting that the symptom is at least partially due to abnormalities within the auditory cortex (e.g., Gaser et al 2004).

Schizophrenic patients also show deficits in several neurophysiological tests involving acoustic stimulation, including auditory P50 suppression, mismatch negativity (MMN), and auditory P300 response.

P50 is a small positive potential in the EEG that occurs about 50 msec after auditory stimulation (clicks) and is typically reduced to the second of two paired clicks. This temporary inhibition, presumably serving to inhibit irrelevant repetitive sensory input, is often absent or reduced in schizophrenic subjects. P50 suppression is thought to be regulated by wide-ranging neural circuitry, prominently involving hippocampal structures. A recent study using Intracranial

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recording in humans suggest, however, that temporo-parietal area near the primary auditory cortex and the prefrontal cortex play a more important role than the hippocampus in P50 sensory gating (Grunwald et al 2003).

MMN is a negative component of auditory evoked potential elicited by any discriminable change in a repetitive background of auditory stimulation. It is considered to operate pre-attentively and reflects the properties of an automatic, memory-based comparison process. MMN deficits are a robust feature in schizophrenia and appear to be relatively specific to the illness since bipolar, major depressive and obsessive-compulsive disorder patients all have normal MMN. Studies using a variety of approaches indicate that the auditory MMN is generated within the primary and secondary auditory cortices with possible contributions from bilateral dorsolateral prefrontal cortices.

P300 is a large positive peak in the EEG about 300 to 500 ms following onset of task-relevant, infrequent auditory stimuli that are randomly interspersed within an ongoing train of a different repeating tone. P300 is thought to reflect cognitive processes related to recognizing and processing the significance of the relatively rare stimulus. Its reduction is one of the most robust neurophysiological abnormalities in schizophrenia. The importance of the auditory cortex in P300 deficits is suggested by the finding that the greatest P300 amplitude separation between schizophrenics and controls is observed at left temporal electrode sites and this focal decrement is correlated with a decreased volume of the left auditory cortex (e.g., McCarley et al 2002).

In spite of the evidence for dysfunction of the auditory cortex in schizophrenia, there have been very few studies examining the anatomical basis underlying the dysfunction. Studies by Sweet at al represent the first such studies. They have recently reported that mean somal volumes of deep layer 3 pyramidal cells are reduced in Brodmann's area 41 and area 42 in subjects with schizophrenia (Sweet et al 2004; Sweet et al 2003). Since somal volume may be affected by the number of axonal terminations onto a neuron and the number of axon terminals maintained by the cell, Sweet et al hypothesized that axon terminal densities in the same areas are also reduced. In this issue of Biological Psychiatry, Sweet et al show that the axon terminals, measured by synaptophysin-mmunoreactive (SY-IR) puncta, are significantly decreased in deep layer 3 of area 41 (Sweet et al 2006). Experiments in macaque monkeys further suggest that long-term antipsychotic treatment does not account for the reduced SY-IR puncta density in subjects with schizophrenia and may even act to offset disease-related reductions in density. These findings by Sweet et al raise two immediate questions. 1) What are the origins of those missing terminals? 2) Are pyramidal cells in layer 3 their only intended targets?

As suggested by Sweet et al, the main sources of innervation to deep layer 3 of area 41 are excitatory projections from intrinsic collaterals from cells in layers 3 and 4 and from the ventral subdivision of the medial geniculate nucleus. Evidence suggests, however, that layer 3 also contains axon terminals derived from cells in layers 2, 5 and 6. More importantly, a significant proportion of terminals in layer 3 are likely to be inhibitory. GABA neurons in the auditory cortex are more numerous than elsewhere in the neocortex (Hendry and Jones 1991; Prieto et al 1994). Layer 3 non-pyramidal cells have been shown to have more local axonal branches than pyramidal neurons in the same layer (Winer 1984). The auditory cortex also receives inputs from norepinephrine neurons in the locus coeruleus, 5-HT neurons in the raphe nuclei, and cholinergic neurons either intrinsic to the area or from other brain regions such as the nucleus basalis. Thus, whether the observed reduction in terminal density is restricted to feedforward excitatory pathways or includes reductions in other terminals remains to be determined.

The decrease in SY-IR puncta density seems to be consistent with the reduction in pyramidal cell somal volume. More detailed analysis shows, however, that changes in the two

measurements are statistically not correlated (Sweet et al 2006). This raises at least two possibilities: 1) the reduced pyramidal cell somal volume is not solely due to reduced excitatory inputs to these cells, and 2) pyramidal cells in layer 3 are not the only intended targets of these missing terminals. Supporting the latter possibility, layer 3 contains a significant number of non-pyramidal cells, most of which are likely to be GABA neurons (Hendry and Jones 1991; Prieto et al 1994). These neurons may provide inhibitory projections to pyramidal neurons in the same layer or in layer 4 (Winer 1984). Layer 3 also contains apical dendrites of pyramidal cells from layers 5 and 6. Some of these cells are known to project back to the medial geniculate nucleus. Thus, if the intended targets of these missing terminals include also non-pyramidal cells and apical dendrites of cells in layers 5 and 6, both feedforward and feedback processing in the auditory cortex would be compromised.

In summary, studies by Sweet et al have provided the first anatomical evidence for laminar specific changes in the auditory cortex of patients with schizophrenia. Further understanding of these changes should provide important insights into how information processing is altered at the level of the auditory cortex in schizophrenia and how the alteration may further contribute to some of the deficits seen in that disease.

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