Elevated Excitatory Input to the Nucleus Accumbens in Schizophrenia:
A Postmortem Ultrastructural Study

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The cause of schizophrenia (SZ) is unknown and no single region of the brain can be pinpointed as an area of primary pathology. Rather, SZ results from dysfunction of multiple neurotransmitter systems and miswiring between brain regions. It is necessary to elucidate how communication between regions is disrupted to advance our understanding of SZ pathology. The nucleus accumbens (NAcc) is a prime region of interest, where inputs from numerous brain areas altered in SZ are integrated. Aberrant signaling in the NAcc is hypothesized to cause symptoms of SZ, but it is unknown if these abnormalities are actually present. Electron microscopy was used to study the morphology of synaptic connections in SZ. The NAcc core and shell of 6 SZ subjects and 8 matched controls were compared in this pilot study. SZ subjects had a 19% increase in the density of asymmetric axospinous synapses (characteristic of excitatory inputs) in the core, but not the shell. Both groups had similar densities of symmetric synapses (characteristic of inhibitory inputs). The postsynaptic densities of asymmetric synapses had 22% smaller areas in the core, but not the shell. These results indicate that the core receives increased excitatory input in SZ, potentially leading to dysfunctional dopamine neurotransmission and cortico-striatal-thalamic stimulus processing. The reduced postsynaptic density size of asymmetric synapses suggests impaired signaling at these synapses. These findings enhance our understanding of the role the NAcc might play in SZ and the interaction of glutamatergic and dopaminergic abnormalities in SZ.

Key words: electron microscopy/anatomy/striatum/synapse

The exact pathophysiology for the origin of schizophrenia (SZ) is unknown, however evidence from decades of research implies that interactions between multiple brain regions and multiple neurotransmitter systems are likely at play. One region that is implicated in SZ pathology is the nucleus accumbens (NAcc). The NAcc integrates signaling from multiple regions of the brain, receiving input from areas including the prefrontal cortex, hippocampus, amygdala, thalamus, and midbrain. Importantly, all of these areas have been associated with SZ, making the NAcc a prime region for integrating multiple disrupted areas to provide a comprehensive understanding of SZ pathology. Reciprocal connections between the NAcc and substantia nigra/ventral tegmental area (SN/VTA) indicate further importance of this region. Via these connections, the NAcc modulates dopaminergic input to the dorsal striatum, and striatal dopamine (DA) dysfunction is a hallmark characteristic of the disorder. Though many studies have implicated the NAcc in SZ, none have been able to describe its circuitry.

The purpose of this study was to provide the first ultrastructural analysis in postmortem human NAcc, and examine the neurocircuitry in the NAcc in SZ to establish the role this region may play in the disorder. We used stereological analysis of electron micrographs in postmortem SZ to analyze the organization and composition of synapse types in the NAcc.

Methods

Brain Tissue

Postmortem human tissue was obtained from the Alabama and Maryland Brain Collections, with consent from the next of kin. The tissue was collected from 8 control and 6 SZ subjects. Cases were diagnosed based on patient medical records, family interviews, autopsy reports, and neuropathologic assessments. DSM-IV diagnosis of SZ was confirmed independently by two psychiatrists. All SZ cases except one were on antipsychotic drugs (APD) at the time of death. Control cases had no history of psychiatric or neurological disease.
Pairs of control and SZ cases were chosen based on the best match of age, race, sex, postmortem interval (PMI), and tissue pH level. Some of the control \( (n = 3) \) and SZ \( (n = 5) \) cases used in this study have also been used in previous studies analyzing synaptic density of the dorsal striatum. \(^{5-9} \) Coronal blocks of the striatum were immersed in 4% paraformaldehyde and 1% glutaraldehyde in 0.1 M phosphate buffer for at least 1 week (4°C). Striatal tissue was then sectioned at a thickness of 40 µm with a Vibratome into 6 free-floating series.

**Core/Shell Mask**

To visualize subregions of the NAcc, 1 series from each case was processed for immunolabeling of calbindin. This series was then used to create a mask of the NAcc core and shell boundary for use when blocking tissue for electron microscopy (figure 1A).

The primary antibody was mouse monoclonal anti-calbindin (Sigma, C9848; 1:1000). The secondary antibody was biotinylated horse anti-mouse IgG (Vector Laboratories; 1:400). Antibodies were prepared in 3% normal horse serum in phosphate buffered saline containing 0.3% triton X-100. The tissue was pretreated in citrate buffer for 30 min in an 80°C water bath for antigen retrieval. The immunohistochemistry protocol was performed as detailed previously. \(^{10} \)

**Electron Microscopy**

A second series was flat embedded for electron microscopic analysis using standard techniques, as detailed previously. \(^{10} \) Regions from the core and shell were blocked using the calbindin-stained sections as a guide. For each region, 3 blocks per case, at least 240 µm apart rostrocaudally, were used to obtain semithin sections.

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**Fig. 1.** Ultrastructure of the human NAcc. (A) A representative calbindin-stained section used as a mask for the core/shell boundary. Blocks from each region were then taken from an adjacent embedded section for EM. (B) A spine (SP) receives convergent input from axon terminals (AT) making asymmetric (black arrowhead) and symmetric (white arrowhead) synapses. (C) An AT forms a symmetric synapse (arrowhead) with a dendrite (DEN). (D) An AT forms an asymmetric synapse (arrowhead) with a DEN. (E) An AT forms an elaborate multi-perforated synapse with a SP. The SP was observed through multiple serial sections and synaptic contact was made at each of the arrowheads. The neck of the SP is marked by the white arrows. M, mitochondrion. Scale bar (B–E) = 500 nm.
These sections (250 nm thickness) were collected using an ultramicrotome, mounted on glass slides, stained with Toluidine Blue and coverslipped for reference. Serial ultrathin sections (90 nm thickness) from each block were mounted on Formvar-coated copper grids, and photographed at 80 kV on a Hitachi transmission electron microscope, as detailed previously.10

Data collection and statistical analyses
To determine the number of synapses in the neuropil, serial sections were analyzed using the disector technique.11,12 An average of seven consecutive sections per block were used as disector reference sections, yielding a combined total of 540 sections analyzed for this study. The average sampling volume was 294 μm³ per block. All synapses in this study were identified by the first and last authors. Micrographs were cropped and adjusted for brightness and contrast for presentation in the figures. Criteria for distinguishing a synapse were the presence of (1) parallel pre- and postsynaptic membranes, (2) a postsynaptic density (PSD), and (3) synaptic vesicles at the membrane in the presynaptic terminal. Synaptic features quantified using stereology included the symmetry of the PSD and the postsynaptic target. Neuropil only was quantified, cell bodies were not photographed. Using stereology, an average of 176 ± 34 synapses were counted in 869.5 ± 55.7 μm³ of the core, and 160 ± 30 synapses in 844.8 ± 104.9 μm³ of the shell, per case. This yielded a total of 2459 synapses in 12173.5 μm³ of the core, and 2076 synapses in 10982.2 μm³ of the shell.

Additionally, serial images were used to quantify PSD and mitochondrial measurements. For PSD measurements, 2 sets of 8 serial electron micrographs per region per case were analyzed resulting in approximately 60 synapses measured per case. The length along the postsynaptic membrane and outline of the PSD were traced by hand using NIH ImageJ. Average thickness was calculated by dividing the area of the PSD by the measured length.13 Mitochondria were analyzed in 1 micrograph per region per case, yielding an average of 296 mitochondria analyzed per case. Mitochondria were counted and normalized to an area of 1000 μm². Their diameters were measured along the short axis using ImageJ. Calcium deposits within mitochondria were counted. For PSD and mitochondrial measurements, serial images were used to verify that measurements were taken from a full cross-section of the synapse.

Striatal area was measured in the adjacent, calbindin-stained sections in ImageJ. The full outlines of the striatal sections were traced and area was measured in cm². Cases in which the complete striatum was not available were excluded from this analysis, resulting in a final sample size for striatal area of n = 4 and n = 5 for control and SZ groups, respectively.

For all analyses, core and shell were analyzed separately. Data from all cases within a group were averaged for each region and statistical tests were performed on average values. All data sets were assessed for normality with the Kolmogorov–Smirnov test, then the corresponding parametric (t-test) or nonparametric (Wilcoxon) tests were performed for group comparisons. All statistical tests were 2-tailed with significance of P < 0.05.

Results
The control and SZ groups were well matched for age, race, gender, PMI, and pH (table 1). The quality of ultrastructural preservation in control and SZ cases was similar and no obvious morphological pathology was present in the SZ cases. The core and shell subregions within each group were qualitatively similar. Asymmetric axosominous (AS) synapses were most frequently observed in both regions of the groups, though symmetric axosominous (SS), asymmetric axodendritic (AD), and symmetric axodendritic (SD) were also observed (figures 1B–D). Very few (<1%) synapses that met all of the criteria listed above were too ambiguous to be classified as a specific synapse type. Some spines received convergent asymmetric and symmetric input from two distinct terminals (figure 1B). Large elaborate synapses with multiple perforations made up 4% of synapses in the core and 2.5% in the shell (figure 1E). Their densities were consistent between groups in both regions, as were other characteristics such as PSD length, area, and number of perforations. There was no difference in the area of the entire striatum between groups (control: 3.72 ± 0.64 cm², SZ: 3.58 ± 0.64 cm², P = 0.76).

Synapse Types
Within the core, there was an increased density of total synapses in the SZ group (figure 2A): 0.18 ± 0.01 per μm³ in control compared to 0.22 ± 0.04 per μm³ in SZ (P = 0.04). This increased density was found only in asymmetric synapses; symmetric synapses had a similar density between the 2 groups. Further, when analyzing synapse subtypes, the increased density was found

Table 1. Case Demographics

<table>
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<tr>
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<td>pH</td>
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Note: Mean ± SD. PMI, postmortem interval; AA, African American; C, Caucasian; M, male; F, female; CTRL, control; SZ, schizophrenia.
exclusively in AS synapses (figure 2B); 0.13 ± 0.01 per µm$^3$ in control compared to 0.16 ± 0.03 per µm$^3$ in SZ ($P = 0.04$). The density of all axosynaptic synapses was increased at a trend level ($P = 0.054$). These differences were unique to the core region; the shell had similar densities of all synapse types between the 2 groups (figures 2A and 2B). Although the density of only one synapse type was significantly increased in SZ, there was a trend for an increase in all types in the core (figure 2C).

**Postsynaptic Density**

Analysis of PSDs revealed a significant reduction in PSD area in both the core and shell (figure 3B). In the synapse subtypes of the core, there was a significant reduction in PSD area of AS synapses (figure 3C), and in PSD thickness of AD synapses (thickness data not shown). Analysis of individual subtypes in the shell revealed no significant differences in the control and SZ groups (figure 3C). These differences were unique to asymmetric synapses;

![Figure 2](image2.png)

**Fig. 2.** Synaptic density in the core and shell. (A) Density of all synapses (Total), and grouped by symmetry of PSD: all asymmetric (Total Asym) and symmetric (Total Sym) synapses, or by postsynaptic target: all axospinous (Total Sp) and axodendritic (Total Den) synapses. (B) Density of synapse types: asymmetric axospinous (AS), asymmetric axodendritic (AD), symmetric axospinous (SS), and symmetric axodendritic (SD). (C) Synapse density relative to control. The dotted line represents the control level. *$P < .05$.

![Figure 3](image3.png)

**Fig. 3.** Area of the PSD in the core and shell. (A) Example AS synapses from control (CTRL) and SZ electron micrographs that were analyzed for PSD size. Scale bar = 500 nm. (B) PSD area of all synapses (Total), and grouped by symmetry of PSD: all axosynaptic (Total Asym) and symmetric (Total Sym) synapses, or by postsynaptic target: all axospinous (Total Sp) and axodendritic (Total Den) synapses. (C) PSD area of each synapse type: asymmetric axospinous (AS), asymmetric axodendritic (AD), symmetric axospinous (SS), and symmetric axodendritic (SD). *$P < .05$. 

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symmetric synapses had similar PSD size between groups in both the core and shell.

**Mitochondria**

The qualitative health and general appearance of the mitochondria were normal in both groups. Quantification of the number of mitochondria in the neuropil (per 1000 μm²) and their average diameter was similar for both groups in the core and shell (table 2). Similarly, the number of calcium deposits per mitochondrion in SZ was similar to that in controls in both regions (table 2).

**Discussion**

This study is the first to examine the neurocircuitry of the NAcc in healthy or diseased postmortem human tissue at the electron microscopic level. Our findings in the SZ subjects suggest an increase in glutamatergic-type input and a similar density of dopaminergic-type input in SZ. The differences identified at the ultrastructural level indicate abnormal wiring in the circuitry of the NAcc in SZ which could be contributing to the pathophysiology of the disease.

**Overview of Human NAcc Ultrastructure**

The ultrastructure of the human NAcc was similar to that described in nonhuman primates and rodents. The elaborate multi-perforated synapses, however, have not been reported in other species or in other regions of the human brain. Increased spine volume, synapse length, and perforations are all associated with increased synaptic activity. Thus, these synapses could be a manifestation of the complex interconnectivity of the NAcc with many other brain regions. Since they were present in both groups they seem to be a unique characteristic of the human NAcc, independent of the disease state.

**Elevated Excitatory Input in SZ**

The increase in AS synapses indicates an increase in glutamatergic-type input to the region. This is consistent with findings in the dorsal striatum which also found an increase in AS synapses in SZ. In agreement with this finding is evidence for an increased expression of the excitatory PSD protein SAP90/PSD-95-associated protein 1 (SAPAP1) in the NAcc in postmortem SZ. Rodent models of SZ also exhibit increased indices of glutamatergic-type input in the NAcc; rats treated with psychomimetics have increased mRNA expression of excitatory PSD genes and increased dendritic spine density in the NAcc which is tightly correlated with the density of AS synapses. A likely source of this elevated input in SZ and its functional implications are discussed below.

**Reduced PSD Size**

Our findings indicate a reduction in the PSD size of excitatory synapses in SZ. The PSD consists of many different proteins for scaffolding and signaling at the synapse. The size and composition of PSDs are dynamic, changing with activity of the synapse and are proportional to the area of the spine head. A reduction in the size of asymmetric PSDs could indicate abnormalities in membrane receptors or signaling molecules of glutamatergic synapses. Several studies have investigated glutamatergic receptors in the NAcc in SZ, and have consistently found no difference in mGluR, NMDA, AMPA, or kainate receptor expression and binding. Thus, it is unlikely that the reduced PSD size found in this study is due to a reduction in glutamate receptor expression. Very few studies have investigated signaling molecules of glutamatergic synapses in the NAcc, and do not report conclusive findings to explain the reduced PSD size found in the present study.

It is possible that the reduced PSD size is a consequence of overstimulation from the excessive glutamatergic afferents also found in this study. If elevated glutamatergic input to the NAcc is indeed involved in the pathophysiology of SZ, it is possible that this excessive excitation could result in the degeneration or reorganization of synaptic structure over time. While no morphological signs were observed in the tissue that indicated excitotoxic degeneration, many PSD proteins are involved in the mechanism of excitotoxicity, and this could provide an explanation for the reduced PSD size at excitatory synapses reported here.

**Similar Inhibitory Input in SZ**

A similar density of symmetric synapses (axodendritic and axospinous) was found in the control and SZ groups. Within the striatum, symmetric synapses are formed by interneurons and dopaminergic projections from the SN/VTA. DA inputs form symmetric synapses on both dendrites and spines. Thus, the similar density of these synapses suggests that the NAcc does not have increased inhibitory input from intrinsic interneurons, nor does it receive increased dopaminergic input from the SN/VTA.
in SZ. While this suggests that dopaminergic input to the
region is normal in SZ, it remains possible that DA is
being abnormally produced in the same number of axon
terminals, or that abnormal modulation by glutamatergic
afferents could result in the dysregulation of its release,
as discussed below.

**Similar Morphological State of Mitochondria**
The structural integrity of the mitochondria in the NAcc
does not indicate drastic abnormalities in metabolic
demand of the region in SZ. This finding contrasts previ-
ous ultrastructural studies in the dorsal striatum which
found differences in the number and distribution of
mitochondria in SZ subjects compared to controls.\(^{45-48}\)
Few studies have considered the structure and function
of mitochondria in the NAcc in SZ.\(^ {49-52}\) Differential
alterations in the basal ganglia have been reported in SZ,
including increased mitochondrial activity in the NAcc
of paranoid SZ subjects that was attributed to APD
effects.\(^ {51}\) Despite the evidence for mitochondrial pathol-
ology in dorsal striatum in SZ, our structural findings do
not indicate this pathology is present in the NAcc.

**Differences in NAcc Core and Shell**
An interesting finding to emerge in this study was that
group differences were primarily found in the core. The
shell of control and SZ subjects was similar across nearly
all measures. The afferent and efferent connections of
the core and shell regions have been identified in rats
and nonhuman primates.\(^ {1,53,54}\) While many of the con-
nections overlap, there are distinct differences that lead to
different functional roles of the 2 subregions.\(^ {1,55}\) Studies
in animal models have found the regions respond differ-
ently to APD, and have often concluded that the shell
must play a larger role in SZ due to the strength of APD
action here compared to the core.\(^ {56-58}\) It is interesting then
that our findings are sequesstered to the core. The af-
ferent and efferent connections of the core parallel those
of the dorsal striatum, while the shell has been considered
a transition zone between the striatum and the extended
amygdala.\(^ {59-61}\) Thus, our findings localized to the core fur-
ther support the redefined hypothesis for the role of the
associative striatum, rather than the limbic striatum, in
SZ.\(^ {62}\)

**Evaluating the Role of the NAcc in SZ**
The NAcc has long been implicated in the etiology of
SZ, and is often assumed to be the locus of elevated
striatal DA characteristic of SZ. This assumption was
typically founded on evidence for antipsychotic action
in the NAcc,\(^ {56-58,63}\) as well as its functional role in the
brain which provided a logical link between the pathol-
ology and symptomatology of SZ. Recent imaging stud-
ies, however, have found the associative striatum, not
the limbic striatum, to be the locus of elevated striatal
DA.\(^ {64,65}\) The morphological findings in postmortem tis-
sue from the present study support the imaging findings
by suggesting that the NAcc does not receive elevated
dopaminergic input.

While this is an interesting development in under-
standing the critical role that striatal DA plays in both
the pathology and treatment of SZ, it does not exclude
the NAcc from the equation of SZ etiology. The evidence
for elevated glutamatergic-type input to the NAcc in the
present study indicates abnormal signaling in the region.
The findings reported here are highly consistent with the
hypothesis for excessive glutamatergic input to the NAcc
driving symptoms of SZ.\(^ {66-69}\)

The NAcc receives glutamatergic input from the cor-
tex, thalamus, hippocampus, and amygdala. Afferent
connections from each of these regions have similar ultra-
structural morphology in the NAcc, typically forming AS
synapses.\(^ {70}\) Thus, the elevated input seen in SZ could be
arising from any of these regions. A possible source for
the increased input is the hippocampus. There is evidence
for a reduction in GABAergic interneurons in the hippo-
campus in SZ\(^ {71,74}\) as well as an increase in hippocampal
activity at rest.\(^ {75,76}\) In this context, one might expect to
see elevated input in the shell rather than the core since
the shell receives denser hippocampal input than the core.
However, anterograde tracing studies show that the hip-
campus projects to all of the NAcc in a topographi-
cal manner,\(^ {77,78}\) so it is possible that the increased input
results from abnormalities of a specific hippocampal sub-
region projecting to the core.

Excessive excitatory input to the NAcc would result
in significant consequences for the flow of information
through this region. DA is released in the NAcc upon
stimulation of the ventral subiculum of the hippocam-
pus,\(^ {79,81}\) and increased activity in the ventral hippocam-
pus drives DA dysfunction in an animal model of SZ.\(^ {59}\)
Further, glutamatergic input from the hippocampus
and amygdala provide a gating mechanism for informa-
tion flow through the NAcc; input from either of these
regions is required for signals from the prefrontal cortex
to continue its flow through the cortico-striato-thalamic
loop.\(^ {82}\) Thus, elevated glutamatergic input to the NAcc
could result in increased dopaminergic release and/or a
hyperresponsive system.\(^ {2}\)

These hypotheses implicate glutamatergic dysregula-
tion of NAcc in positive symptoms of SZ, however it is
also well established that the NAcc is involved in reward
and motivation, the loss of which constitute some of the
negative symptoms of SZ. It has been hypothesized that
a loss of gating in the NAcc, possibly due to elevated
 glutamatergic input and subsequent DA dysregulation,
could result in increased signal noise in the region; this
would effectively diminish the response to stimuli oth-
erwise eliciting reward or motivated behavior.\(^ {83,84}\) The
elevated glutamatergic-type input and similar density of
dopaminergic-type input provide the first structural data in the NAcc of SZ subjects to support the hypothesis that excessive hippocampal input to the NAcc could be a pathological mechanism of SZ.\textsuperscript{5,66-69}

\textit{Limitations}

While the functional consequences of these structural findings can only be speculated, this study provides vital insight for understanding the structural pathology that leads to symptoms in SZ. Forming a link between pathology of the neurocircuitry in SZ and the functional outcomes will be a powerful tool for moving forward in our understanding of the cause, as well as improving treatment for SZ.

The small sample size should be taken into consideration with the interpretation of these findings. With the heterogeneity of SZ, it is likely that the cohort analyzed for this study does not represent all aspects of the disorder. However, the results agree with studies of synaptic density in the dorsal striatum in SZ\textsuperscript{6} and are consistent with hypotheses of SZ. Postmortem SZ subjects suitable for electron microscopy are rare, so the cohort collected for this study, although small, provides a unique analysis of postmortem SZ.

All but one of the subjects in the present study were chronically medicated at the time of death, thus it is possible that our results are due to APD treatment. Ultrastructural studies of APD effects in the striatum primarily focus on the dorsal striatum, where chronic (6 months or longer) haloperidol treatment results in reduced asymmetric synapse density\textsuperscript{85,86} and reduced spine number.\textsuperscript{87} Other studies of APD treatment have reported an increased percentage of perforated synapses in the caudate with no change in total number, and no differences present in the NAcc.\textsuperscript{88-90} These studies do not indicate our results are due to APD treatment. Past studies also indicate that APDs increase striatal volume.\textsuperscript{91-95} Thus, our finding of increased AS synaptic density is likely not an effect of medication, since a larger volume would reduce synaptic density rather than increase it. Rather, it is possible that an increased striatal volume in SZ subjects could result in false negatives or dampen measured increases in density in our study.

Stereological studies provide the advantage of estimating total object number and thus avoiding volume discrepancies. The estimation of total number, however, requires distinct regional boundaries, and it is well established that no distinct boundary exists between the NAcc core and ventral caudate/putamen regions.\textsuperscript{54,60,96-98} Thus, an analysis of total object number would have required introducing arbitrary and nonreplicable region boundaries due to the variability between human brains. This issue was addressed by using unbiased stereology to measure object density paired with measuring striatal volume. The striatal volumes did not significantly differ between the two groups which further confirms that our findings are not due to volume differences.

\textit{Conclusions}

This study provides not only the first ultrastructural quantitative analysis performed in human NAcc, but also an analysis of the NAcc ultrastructure in SZ. Our findings indicate miswiring of the neurocircuitry in the NAcc core in SZ, specifically an increase in glutamatergic-type input. We argue that this is unique to the etiology of the disorder and may provide a morphological link between glutamatergic pathology and striatal DA pathology in SZ.

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