Ionotropic Glutamate Receptors Show Unique Distribution and Localization in the Dorsal Cochlear Nucleus of the Rhesus Monkey

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Ionotropic Glutamate Receptors Show Unique Distribution and Localization in the Dorsal Cochlear Nucleus of the Rhesus Monkey

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ABSTRACT

The dorsal cochlear nucleus (DCN) receives auditory information via the auditory nerve coming from the cochlea. It is responsible for much of the integration of auditory information, and it projects this auditory information to higher auditory brain centers for further processing. This study focuses on the DCN of adult Rhesus monkeys to characterize two specific cell types, the fusiform and cartwheel cell, based on morphometric parameters and type of glutamate receptor they express. The fusiform cell is the main projection neuron, while the cartwheel cell is the main inhibitory interneuron. Expression of AMPA glutamate receptor subunits is localized to certain cell types. The activity of the CN depends on the AMPA receptor subunit composition and expression.

Immunocytochemistry, using specific antibodies for AMPA glutamate receptor subunits GluR1, GluR2/3 and GluR4, was used in conjunction with morphometry to determine the location, morphological characteristics and expression of AMPA receptor subunits in fusiform and cartwheel cells in the primate DCN. Qualitative as well as quantitative data indicates that there are important morphological differences in cell location and expression of AMPA glutamate receptor subunits between the rodent DCN and that of primates. GluR2/3 is widely expressed in the primate DCN. GluR1 is also widely expressed in the primate DCN. GluR4 is diffusely expressed. Expression of GluR2/3 and GluR4 in the primate is similar to that of the rodent. However, expression of GluR1 is different. GluR1 is only expressed by cartwheel cells in the rodent DCN, but is expressed by a variety of cells, including fusiform cells, in the DCN of the primate.

The cochlear nucleus (CN) is located in the angle pontocerebellosum of the brainstem. It is innervated by the Auditory Nerve coming from the cochlea of the inner ear and is divided into the anteroventral (AVCN), posteroventral (PVCN), and dorsal regions. The CN is the first stopping place for auditory information in the Central Nervous System (CNS).

The dorsal cochlear nucleus (DCN) is located in the dorsal region of the cochlear nucleus (CN) of the brainstem. The dorsal branch of the auditory nerve coming from the cochlea terminates in the DCN. It is involved in the initial integration of auditory
information in the mammalian brain (Petralia, et al., 1996; Rubio, 2004). Its structural organization is thought to resemble that of the cerebellum, having a somewhat laminar arrangement of cells (Manis, et al., 1993). This layered arrangement of cells confers functional organization to the DCN, allowing for integration of auditory information in a highly organized manner, and the final projection of auditory information from the DCN to higher auditory brain centers. Primates, however, do not have the same degree of laminar arrangement that other animals do, including cats and rodents (Heiman and Strominger, 1985).

There are two main cell types in the DCN: the fusiform cell and the cartwheel cell. The fusiform cell is the major excitatory projection neuron of the DCN (Petralia, et al., 1996), and has a large, elongated cell body that is located in the deeper pyramidal (fusiform) cell layer of the DCN (Bell, 2002). The fusiform cell is bipolar in structure, having an apical and basilar dendrite. Primary afferent fibers of the auditory nerve coming from the cochlea terminate at excitatory synapses on the basilar dendrite of the fusiform cell (Bell, 2002), which are believed to be glutamatergic (Petralia, et al., 1996), in other words, using glutamate as its neurotransmitter received by glutamate receptors in the post-synaptic densities of the fusiform cells. The cartwheel cell is the major intrinsic inhibitory interneuron and has a smaller, more spherical cell body that is found more superficially in the pyramidal cell layer. The dendrites of the cartwheel cells can be found in the molecular layer, where they make inhibitory contacts on the apical dendrites of excitatory fusiform cells (Bell, 2002; Rubio, 2004).

Activity of the DCN is dictated by the localization of excitatory synapses in the neurons of the DCN and the timing of their activation. Glutamate is the primary excitatory neurotransmitter found in the central nervous system of mammals (Petralia, et al. 2000) and in the DCN. The activation of the \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) glutamate receptor subunits results in fast excitatory responses of many cell types in the central nervous system (Caicedo and Eybalin 1999; Petralia et al., 2000), including the fusiform and cartwheel cells of the DCN. The auditory nerve provides the major extrinsic excitatory input to the DCN through the termination of its dorsal branch on the fusiform cells of the DCN. The auditory nerve uses glutamate as its neurotransmitter; activating the AMPA glutamate receptors on the postsynaptic densities of the fusiform basilar dendrites located within the deep layers of the DCN (Rubio, 2004). Though the importance of the DCN using glutamate as its primary excitatory neurotransmitter is not fully understood, it is possible that it could function in the regulation of growth, differentiation, and migration during development (Caicedo and Eybalin, 1999). In addition to this, studies in the developing rat have shown AMPA receptors’ possible role in plasticity and creation of specific connections in the ascending auditory pathway (Caicedo and Eybalin, 1999).

The function of the DCN is not completely understood. Several auditory processing activities are attributed to the action of the DCN. Some proposed functions include the use of paired tone facilitation in order to fine tune the auditory system’s ability to focus on a repeated sound, as well as the integration of auditory information and sensory information in the localization of sound (Petralia, et al., 1996).

Much research is focused on the characterization of glutamate receptors in rodents, and anatomical studies have shown that rodents possess very different cell organization in the CN than primates and humans. Humans are more neurobiologically
similar to primates than they are to rodents. However, there is a lack of information about the localization of AMPA receptor subunits in the DCN of primates. Therefore, we used primate DCN to characterize its cytoarchitecture and cellular expression, localization, and distribution of AMPA glutamate receptor subunits, aiming to relate this information to research done in rodents. In doing this, we hoped to gain more insight into the structure and function of the human DCN.

In this study, immunocytochemistry was used in combination with morphometric analysis to determine the differential expression of AMPA glutamate receptors in the cartwheel and fusiform cells of the primate DCN. Antibodies specific to the intracellular carboxy-terminus of GluR1, GluR2/3, and GluR4 were used to characterize the intracellular expression of these AMPA subunits.

**MATERIALS AND METHODS**

**Tissue Preparation**

Brainstem with cerebellum from three adult rhesus monkeys were obtained from the Yerkes National Primate Research Center and used in these experiments. The ages of the monkeys were as follows: MR 98 was 7 years old, MR 99 was 11 years old, and MR 100 was 6 years old. MR 98 and 99 were perfused with 4% paraformaldehyde (PFA) and 0.5% glutaraldehyde (GA) for fixation of the brain. MR 100 was perfused with 4% PFA and 0.1% GA. The brains were stored in buffer.

Coronal sections of 70 µm thickness were obtained using the Vibrotome, to be used for immunocytochemistry to neurotransmitter receptor subunits and light microscopy analysis. Half of MR 99 was kept in 1.5% PFA and 1.5% GA in 0.1M PBS for later Vibrotome sectioning. The other half appeared to have a CN that was separated from the brainstem, which possibly happened during shipment of the brains. Half of MR 100 was cut in coronal sections and preserved in cryosolution 4°C for two weeks, and later in -20°C.

After storage, further coronal sections of all three brains were cut with a thickness of 72 µm using the Vibrotome and stored in PBS to be used in this study.

**Immunocytochemistry**

Coronal sections were chosen from approximately the same level of section allowing analysis of similar populations of cells. Sections, antibodies used, dilutions, and sources are found in Table 1. The following protocol was used for each immunocytochemical preparation. Tissue sections were washed with PBS buffer every ten minutes for a total of thirty minutes. The tissue was then blocked with 10% normal goat serum in PBS (blocking solution for polyclonal antibodies) for 1 hour. Rabbit polyclonal primary antibodies were then introduced into the separate wells and incubated for 48 hours at 4°C. Once incubation was complete, the primary antibodies were recovered and the tissue sections were again washed in PBS every 20 minutes for 1 hour. Biotinylated secondary antibody (Vectastain kit) was prepared using to make a 1:1000 concentration and incubated for 45 minutes. The sections were washed in PBS every 20 minutes for 1 hour. ABC Reagent (Vectastain Elite Kit) was introduced to the sections and incubated for 45 minutes. The sections were then washed in PBS every 15 minutes for a total of 45 minutes. We then developed the sections using diaminobenzidine (DAB)
Substrate (Vector DAB Substrate Kit). Development was done for 3 minutes for the GluR1 wells, 6 minutes for the GluR2/3 wells, and 3 minutes for the GluR4 wells. The sections were then washed in PBS every 10 minutes for a total of 30 minutes. Once these sections had been washed, they were then mounted onto slides using Gelatin mounting solution and allowed to dry overnight. They were then cleared with clearing solution, and covered with cover slips using Permount sealant.

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>PRIMARY ANTIBODY</th>
<th>DILUTION</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR 99 (5 sections)</td>
<td>GluR1</td>
<td>1:1000 1:2000</td>
<td>Upstate</td>
</tr>
<tr>
<td>MR 100 (4 sections)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR 99 (5 sections)</td>
<td>GluR2/3</td>
<td>1:1000 1:2000</td>
<td>Gift from Dr. Wenthold of NIDCD/NIH</td>
</tr>
<tr>
<td>MR 100 (6 sections)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR 100 (10 sections)</td>
<td>GluR4</td>
<td>1:1000 (3 sections) 1:500 (6 sections)</td>
<td>Gift from Dr. Wenthold of NIDCD/NIH</td>
</tr>
</tbody>
</table>

Table 1. Sections, primary antibody, dilutions for immunocytochemistry procedure. Sections from different animals were separated and analyzed using the stated primary antibodies with corresponding dilutions. Sources of these primary antibodies are stated.

### Tissue Analysis and Image Capture

Tissue sections were analyzed using an Olympus BX51 Brightfield Light Microscope. Images were captured using a QImage Retiga EX CCD Camera. Images were taken with 1.25x, 2x, 4x, and 10x objectives for reference. For morphometric analysis, images were taken with 20x and an oil 40x objectives. They were analyzed using Analysis Soft-Imaging System software.

### Morphometric Analysis

Criteria for identification of cell types were location in the DCN, shape of the cell body, maximum and minimum diameters and area of the cell body. Fusiform cells were identified as having a larger, more elongated cell body, and located between the superficial and deep layers of the DCN. Cartwheel cells were identified as having a smaller, more spherical cell body, and located more superficially in the DCN. Measurements were made around the cell bodies, and the computer analyzed maximum and minimum diameters as well as area (Figure 1). Previous research conducted in the macaque monkey using Nissl staining, provided morphometric data from cells identified in the DCN (Heiman and Strominger, 1985). In that study, small cells (cartwheel cells) had an average cell area of 111.7 µm² (SD = 29.9), and an average maximum diameter of 16.2 µm (SD = 2.6). Pyramidal cell (fusiform cell): average area = 256.0 µm² (SD = 85.9), average maximum diameter = 32.8 µm (SD = 7.0). These measurements were used to rule out small or giant cells in this study. Cells that fit the criteria to be classified as cartwheel cells were found with an average area of approximately 200 µm² and a maximum diameter of approximately 20 µm. Cells that were thought to be fusiform had
an area of approximately 320 µm² and a maximum diameter of approximately 30 µm. It is recognized that there are differences between the size of the macaque monkey and the rhesus monkey, allowing for some differences in cell sizes.

![Image of cell bodies within the DCN](image)

**Figure 1. Method of measuring cell bodies within the DCN.** (a) Red and blue outlines represent method of measuring fusiform and cartwheel cells, respectively. (b) Cartoon of elongated fusiform cell body shape (red outline) and spherical cartwheel cell body shape (blue outline). Green double arrows represent minimum diameter, black double arrows represent maximum diameter which the computer software measured and calculated.

**RESULTS**

Using light microscopy, the DCN was distinguished from the other segments of the CN in most sections. Some sections showed a more homogenous CN, with the DCN portion only distinguishable from the AVCN and PVCN by closer examination of the cell types present.

Cartwheel and fusiform cells showed expression of specific glutamate receptors in the DCN and could be distinguished among other cell types. GluR2/3 showed widespread expression in many cell types of the DCN. GluR1 also showed widespread expression among both fusiform and cartwheel cells. GluR4 showed diffuse expression throughout the DCN. Using the morphometric parameters as described in the Methods section of this paper, cartwheel and fusiform cells were distinguished from other cell types in the DCN.

**Cellular Expression of GluR2/3**

Using light microscopy, staining with the antibody specific to GluR2/3 was seen to be widespread among a variety of cell types in the DCN. Staining was moderate and allowed us to visualize cell bodies and part of their dendrites within the DCN.

**Fusiform cells** expressing GluR2/3 were found in the middle layer (fusiform cell layer, FCL) of the DCN. Those cells thought to be fusiform showed the characteristic
large, elongated cell body, and the beginning segments of the basal dendrites could also be seen in some cases (Figure 2b, 2c). Though there were some cell types in the deep layer of the DCN that had a pyramidal shape to their cell body, the fusiform cells in the FCL were found to be somewhat smaller and more elongated. The fusiform cells in the FCL were observed most often in clusters and groups, and occasionally in a line formation (Figure 2b, 2c).
Cartwheel cells expressing GluR2/3 were usually found more superficially in the DCN, in the molecular cell layer (MCL), but were also found in the FCL (Figure 2b, 2c). Cells that were thought to be cartwheel had the characteristically smaller and more rounded spherical cell body. They were often observed to be interspersed among fusiform cells within the FCL and were not found to be present in tight clusters as the fusiform cells were (Figure 2b). The fact that cartwheel cells were found in both the FCL and the MCL led to the observation that the fusiform and cartwheel cells were not arranged in a highly structured laminar organization, but rather interspersed in a more random fashion.

Morphometric analysis, based on the parameters detailed previously, was used for further characterization of the fusiform and cartwheel cell expression of GluR2/3. After qualitative analysis using statistical tests, it was found that fusiform cells expressing GluR2/3 had an average area of 372.84 µm² (SD= 102.55) and an average maximum diameter of 29.37 µm (SD= 5.02). The large standard deviation of the average area of fusiform cells could result from the varied orientation of cells in the different sections.
Cartwheel cells expressing GluR2/3 had an average area of 197.14 µm² (SD= 18.24) and an average maximum diameter of 17.12 µm (SD=1.85).

There were many other cell types that were labeled, having cell bodies larger and smaller in size than the fusiform and cartwheel cells. These cells were found in the deep layer as well as the more superficial FCL and lower MCL, and often had elongated or spherical cell body shape, similar to the cell body shape of the fusiform and cartwheel cell, respectively (Figure 3). These cells were most likely a combination of giant, multipolar, vertical, stellate, and granule cell types. They were later eliminated from morphometric statistical analysis when they fell outside of the parameters described in the methods portion of this paper.

**Cellular Expression of GluR1**

Light microscopy revealed widespread expression of the GluR1 subunit in the cell bodies and dendrites of a variety of cell types in the DCN. The pattern of staining was similar to that of GluR2/3, but somewhat darker.

**Fusiform cells** were seen clearly expressing the GluR1 subunit, and were observed in a significant number. Expression was very similar to that of GluR2/3. The fusiform cells observed had the characteristic larger and more elongated cell body and were found mostly in the FCL (Figure 4b, 4d). Basal and apical dendrites could also be seen in some cases.

**Cartwheel cells** were seen to express the GluR1 subunit as well. They were found interspersed among the fusiform cells, similar to what was seen in the staining of GluR2/3 subunit expression. They had a smaller and more spherical cell body. They were found in both the MCL as well as interspersed in the FCL (Figure 4b, 4d).
Ionotropic Glutamate Receptors Show Unique Distribution

GluR1

PVCN

AVCN

DCN

GluR1

ML FCL DL

60 µm
Figure 4. Cartwheel cells, fusiform cells, and other cell types express GluR1 subunit. (a), (c) GluR1 staining of two different sections of DCN viewed through 20x objective. Red box indicates the portion of the DCN visualized in panel b and d, respectively. In a, the DCN is distinguished from the AVCN and PVCN by the black dashed outline. (b), (d) 20x objective. Red arrows point to examples of fusiform cells. Blue arrows point to examples of cartwheel cells. Green arrows point to other cell types found in the deep layer of the DCN. Key: ML: Molecular Layer. FCL: Fusiform Cell Layer. DL: Deep Layer.
Like in GluR2/3 characterization, cartwheel and fusiform cells expressing GluR1 were often found in close proximity to each other and were not necessarily found in a laminar arrangement. In other words, expression of GluR1 by fusiform and cartwheel cells was not strictly confined to the FCL and MCL, respectively. There were fusiform cells labeled in the MCL and cartwheel cells labeled in the FCL.

Morphometric analysis using statistical analysis gave qualitative results to our visual findings. Fusiform cells expressing GluR1 had an average area of 327.02 µm$^2$ (SD= 13.99) and an average maximum diameter of 30.47 µm (SD= 4.91). Cartwheel cells expressing GluR1 had an average area of 201.87 µm$^2$ (SD= 17.55) and an average maximum diameter of 19.27 µm (SD= 1.68).

Similar to GluR2/3 expression, there were other cell types that were labeled which had both smaller and larger cell size than the fusiform and cartwheel cells. As in the GluR2/3 analysis, the measurements corresponding to these cells were not considered for morphometric statistical analysis, because they fell outside the morphometric parameters for fusiform and cartwheel cells, as stated previously.

**Cellular Expression of GluR4**

GluR4 was expressed by a small number of cells stained in a light manner throughout the DCN (Figure 5). This diffuse expression is similar to what is seen in studies in the rodent (Petralia et al., 1996). In this study, the staining was very light, making it difficult to distinguish and morphometrically characterize cell types in the DCN. As a result, this study was not focused on this receptor subunit expression. It was noted that structures could be identified, but cellular expression of the GluR4 subunit was not quantifiable or easily discerned.

![Figure 5. GluR4 subunit is expressed in a diffuse manner. 2x objective. Light staining of the DCN.](image)
Similarities found between populations of cells expressing GluR2/3 and GluR1

Similarities between the cell sizes in the two immunostained populations could be seen. Fusiform cell populations expressing GluR2/3 and GluR1 had similar maximum diameters. Cartwheel cells expressing GluR2/3 and GluR1 also had similar maximum diameters. The average area for fusiform cells was consistent between populations expressing GluR2/3 and GluR1. Cartwheel cells also had similar average areas between populations expressing GluR2/3 and GluR1 (Figure 6).

Figure 6. Statistical results show similar populations of fusiform and cartwheel cells expressing both GluR2/3 and GluR1. Top graph shows similar average maximum diameters between populations of cartwheel cells expressing GluR2/3 and GluR1. It also shows similar populations of fusiform cells expressing GluR2/3 and GluR1. Bottom graph shows the same results, but with the characterization of average area. Again, populations of cartwheel and fusiform cells expressing GluR2/3 and GluR1 had similar average area. These graphical results are further confirmation that there are analogous cartwheel and fusiform cell populations expressing GluR2/3 and GluR1.
DISCUSSION

The localization and distribution of glutamate receptor subunits is important in understanding the function of the variety of cells found in the DCN. The activity and response of the DCN depends on the excitation of the projection fusiform neurons as well as the inhibitory interneuron cartwheel cells.

Glutamate is known to be one of the major excitatory neurotransmitters in the central nervous system and the DCN (Caicedo, Eybalin, 1999; Petralia et al., 2000; Rubio, 2004). Characterizing cells that express specific AMPA-type ionotropic glutamate receptor subunits is important to understanding the activity of the DCN. Though there has been some characterization in primates, much of what is known about expression of glutamate receptors in the DCN has been learned from studies in rodents. Research in primates has shown apparent anatomical differences between the DCN of primates and that of rodents and even cats.

Results indicate that AMPA glutamate receptor expression, distribution and localization are highly diversified in the DCN of the rhesus monkey as compared to rodents.

**GluR2/3**

The expression of GluR2/3 is widespread in the DCN of the rhesus monkey. This study showed expression of GluR2/3 subunit by fusiform, cartwheel, and many other cell types; including stellate, granule, and giant cell types. These results are consistent with similar characterizations done in the rat. There are many neurons in the DCN of the rat that express GluR2/3 (Petralia et al., 1996; Petralia et al., 2000). Dense staining in the deep DCN is seen in the rodent (Petralia et al., 1996), whereas in this study, the densest staining was seen more superficially in the cell bodies and dendrites of fusiform and cartwheel cells, though there was staining of cell bodies of a variety of different cell types observed in the deep layer.

**GluR1**

GluR1 staining, however, showed a very different characterization than that of rodents. Observations and morphological characterization showed expression of GluR1 in both cartwheel and fusiform cells. The antibody to the GluR1 subunit clearly labeled both fusiform and cartwheel cell bodies, in contrast to the rat which shows expression of GluR1 usually limited to cartwheel cells. The rodent usually shows little to no expression of GluR1 by fusiform cells and most often expresses GluR1 in its cartwheel cells in the outer layers (molecular and fusiform cell layers) of the DCN (Petralia et al., 1996; Petralia et al., 2000). Further, GluR1 is thought to be developmentally down-regulated in the rodent, specifically in fusiform cells. Decrease in expression with increase in age indicates possible redistribution among cell types during development (Caicedo and Eybalin, 1999). This leads one to conclude that GluR1 might be involved in plasticity in the DCN of the rodent by being involved in the establishment of the earliest synaptic connections and regulation of maturation and synaptogenesis during development (Caicedo and Eybalin, 1999). Based on this information, expression of GluR1 by a variety of cell types in the DCN of an adult rhesus monkey was unexpected and interesting to observe.
GluR4

The diffuse expression of GluR4 was expected, since rodents also exhibit diffuse expression of the GluR4 subunit (Petralia et al., 1996). Though there were some cell types seen, there were not many. The cells that did express GluR4 were stained very lightly in the cell bodies and were found in all of the layers of the DCN. Additional data from immunostaining of synapses would be required to further analyze the expression of this subunit in the primate.

Summary table is pictured in Table 2.

<table>
<thead>
<tr>
<th>GluR2/3</th>
<th>Fusiform</th>
<th>Cartwheel</th>
<th>Other</th>
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<tbody>
<tr>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>GluR1</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>GluR4</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Table 2. Summary Table. This table details the differences and similarities of expression of AMPA glutamate receptor subunit expression in the primates as compared to research done in the rodents. “+” signs indicate the receptor is expressed by cell type. “-” signs indicate the receptor is not expressed by cell type. “+/-” indicates diffuse expression in cell type.

Decrease in Laminar Organization

In addition to the unique glutamate receptor localization and distribution among the cell types of the DCN, the observation that there was more of a random organization of cell types than a clearly laminar one, supports other studies done in primates. Primates characteristically lack a highly laminar organization of fusiform cells, which are often arranged in a perpendicular fashion to the outer surface of the DCN in cats (Heiman and Strominger, 1985). The reason for this decrease in laminar organization is not known.

CONCLUSIONS

Unique pattern of expression of GluR1 subunits by fusiform cells in the primate gives rise to some interesting speculation as to why these differences occur between the rodent and the primate.
• The increase in glutamate receptor subunit expression could be a result of the different sound processing that occurs in the primate as compared to the rodent. Ionotropic glutamate receptors, when activated by the glutamate neurotransmitter, allow an influx of ions, including Ca\(^{2+}\), which is a key regulator of synaptic transmission of the action potential. Perhaps the primate has an increased demand for faster transmission or integration than does the rodent, and therefore has increased expression of excitatory glutamate receptors.

• Modification in the regulation of GluR1 expression could mean that there is an increased capacity for plasticity in the DCN of the adult rhesus monkey. GluR1 is believed to be involved in synaptic plasticity in the rat and its known down-regulation during development. Modifications in the developmentally controlled pattern of expression of GluR1 subunits could allow for an increase in its expression in the adult DCN to include fusiform as well as cartwheel cells, allowing for a greater role in the synaptogenesis and migration of synapses in the adult DCN, perhaps playing a part in plasticity of the DCN.

Since primates and humans are closely related in many neurobiological aspects, these conclusions in the primate could give insight into the characterization, localization, distribution, and transmission of these cell types expressing AMPA glutamate receptor subunits within the DCN of humans, further allowing for a greater understanding of the true function of the human DCN.

ACKNOWLEDGMENTS

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LITERATURE CITED


