On the classification of pathways in the auditory midbrain, thalamus, and cortex

Charles C. Lee and **S. Murray Sherman**
*Department of Neurobiology, University of Chicago, Chicago, IL 60637

Abstract

Auditory forebrain pathways exhibit several morphological and physiological properties that underlie their specific neurobiological roles in auditory processing. Anatomically, such projections can be distinguished by their terminal size, arborization patterns, and postsynaptic dendritic locations. These structural features correlate with several postsynaptic physiological properties, such as EPSP amplitude, short-term plasticity, and postsynaptic receptor types. Altogether, these synaptic properties segregate into two main classes that are associated with either primarily information-bearing (Class 1) or modulatory (Class 2) roles, and have been used to delineate the principle routes of information flow through the auditory midbrain, thalamus, and cortex. Moreover, these synaptic properties engender as yet unexplored issues regarding the neuronal processing of auditory information, such as the convergent integration and long-term plasticity of auditory forebrain inputs.

Keywords

cortex; thalamus; midbrain; auditory cortex; medial geniculate body; inferior colliculus

1. Introduction

Acoustic information from the cochlea is processed successively through brainstem nuclei (Young et al., 1992), the inferior colliculus (Oliver and Huerta, 1992), medial geniculate body (Winer, 1992), and eventually the auditory cortex (Hackett, 2011), and many of the synaptic mechanisms by which this information is transferred, transmitted, and transformed are now being revealed (Atencio et al., 2009; Tan et al., 2007; Zhou et al., 2010). In each of these auditory structures, neurons receive convergent synaptic inputs from several extrinsic and intrinsic sources whose influences on neuronal excitability vary considerably according to neurotransmitter type and postsynaptic mode of action (Lee and Winer, 2010; Winer et al., 1999). For example, neurons in layer 4 of the primary auditory cortex (AI) receive convergent synaptic inputs from thalamic, cortical and brainstem sources that utilize glutamate (Lee and Sherman, 2008), GABA (Yuan et al., 2010), acetylcholine (Weinberger, 2007), dopamine (Bao et al., 2001), and other neurotransmitters. While each of these systems affect the target recipient neurons, most are not principally involved in transmitting

Correspondence to: Charles C. Lee, Department of Neurobiology, University of Chicago, Chicago, IL 60637, clee@bsd.uchicago.edu, Telephone: (773) 834-8764, Fax: (773) 702-3774.

auditory information, but instead the bulk of these inputs act to modulate neuronal responsiveness (Gil et al., 1997; Metherate and Hsieh, 2003; Sherman and Guillery, 1998).

Even among glutamatergic inputs, heterogeneous postsynaptic effects and morphologies distinguish many afferent pathways (Bartlett and Smith, 2002; Lee and Sherman, 2008; Llano and Sherman, 2008; Smith et al., 2007). At several major auditory forebrain structures, glutamatergic pathways can be segregated into two main classes: Class 1 (previously called driver) and Class 2 (previously called modulator) (Table 1) (Lee and Sherman, 2010a; Sherman and Guillery, 2006). Class 1 inputs are characterized by properties suited for the reliable and efficient transfer of information across the synapse (Bartlett and Smith, 2002; Lee and Sherman, 2008, 2010b), while those of Class 2 are not primarily information bearing, but instead are best suited to modulate the transmission of Class 1 inputs (Lee and Sherman, 2009c; Reichova and Sherman, 2004; Sherman and Guillery, 2006). And, such a classification has proven useful for delineating the major information-bearing pathways (Lee and Sherman, 2008, 2009c, 2010b; Llano and Sherman, 2008).

These recent findings provoke several questions: To what extent do these two afferent types exist in the auditory forebrain? What is their role in auditory information flow? Do differences exist in their long-term plasticity? And, how do neurons integrate these convergent synaptic inputs? Pertinent to these questions, we here review the anatomical and physiological properties of these pathways, their relative distribution in the auditory forebrain, and their relationship to the transmission of auditory information.

2. Properties of Class 1 and 2 pathways

Class 1 and 2 input types have been described broadly in forebrain circuitry and are not limited to auditory pathways (Lee and Sherman, 2008; Llano and Sherman, 2008; MacLean et al., 2006; Reichova and Sherman, 2004), and they seem to represent the vast majority of pathways in the various circuits so far tested. Table 1 summarizes their properties. Class 1 inputs are exemplified by the retinogeniculate afferents (Guillery, 1966; Li et al., 2003; Reichova and Sherman, 2004) and the thalamocortical inputs to layer 4 (Huang and Winer, 2000; Lee and Sherman, 2008), while Class 2 inputs are represented by the layer 6 corticothalamic and certain intracortical inputs (Lee and Sherman, 2009c; Llano and Sherman, 2008; Reichova and Sherman, 2004).

Anatomically, axonal and terminal structure distinguishes the Class 1 and 2 inputs (Table 1, e.g. Fig 2). Class 1 afferents, such as the retinal inputs to the lateral geniculate nucleus (Guillery, 1966), have thick axons, dense arbors (Famiglietti and Peters, 1972; Guillery, 1966; Ralston, 1971), and large terminals that synapse on proximal dendrites (Llano and Sherman, 2008; Winer et al., 1999). By comparison, Class 2 inputs, like the layer 6 corticothalamic projection, have thin axons, sparse arbors, and small terminals ending on distal dendrites (Bartlett and Smith, 1999; Llano and Sherman, 2008; Sherman and Guillery, 2006; Smith et al., 2007).

Physiologically, Class 1 inputs produce large EPSPs, exhibit synaptic depression, and only activate ionotropic glutamate receptors (iGluRs) (Bartlett and Smith, 2002; Li et al., 2003; Reichova and Sherman, 2004) (Fig. 1). In contrast, Class 2 inputs exhibit facilitation of small EPSPs, and activate iGluRs and metabotropic glutamate receptors (mGluRs) (Bartlett and Smith, 2002; Li et al., 2003; Reichova and Sherman, 2004).

3. Prevalence of Class 1 and 2 pathways in the auditory system

Pathways throughout the central auditory system exhibit either Class 1 or 2 properties (Bartlett and Smith, 2002; Huang and Winer, 2000; Lee and Sherman, 2008, 2009c, 2010b; Llano and Sherman, 2008; Winer et al., 1999). Although both classes are found across different stages of the auditory pathway, their distribution varies, as discussed below.

3.1. Tectothalamic pathways

The inferior colliculus (IC) is the source of glutamatergic and GABAergic inputs to the medial geniculate body (MGB) (Peruzzi et al., 1997; Winer et al., 1996). These are topographically organized and originate from lemniscal and non-lemniscal IC subdivisions (Lee and Sherman, 2010b). Among the tectal projections, those from the central nucleus of the inferior colliculus (ICc) terminate primarily in the ventral division of the MGB (MGBv), while non-lemniscal projections from the dorsal (ICd), lateral (ICl), and caudal cortices of the IC (ICca) terminate respectively in the dorsal (MGBd) and medial (MGBm) divisions of the MGB (Malmierca et al., 2008; Romand and Ehret, 1990; Wenstrup, 2005; Winer, 2005).

However, the synaptic properties of lemniscal and non-lemniscal glutamatergic inputs differ (Fig. 1). ICc projections exhibit Class 1 properties, such as large terminations and depressing synapses with only iGluR activation (Table 1; Fig. 1B: red) (Bartlett and Smith, 1999,2002;Lee and Sherman, 2010b). In contrast, projections from ICd and ICl exhibit Class 2 properties, such as small terminal arbors, facilitating synapses and recruitment of mGluRs (Fig. 1B: green) (Bartlett and Smith, 2002;Lee and Sherman, 2010b;Smith et al., 2007). Thus, both Class 1 and 2 inputs are found in the auditory tectothalamic system and distinguish the lemniscal and non-lemniscal pathways.

3.2. Thalamocortical pathways

Two major projection systems from the medial geniculate body terminate in the auditory cortex (Huang and Winer, 2000; Jones, 2009). One terminates in layer 4 with some branches to layer 6, as exemplified by the MGBv and MGBd projections to the primary (AI) and secondary (AII) auditory areas (Kaas and Hackett, 2000; Lee and Winer, 2008a; Llano and Sherman, 2008; Theyel et al., 2010). The other terminates most densely in layers 2/3, as seen primarily with projections from the MGBm to AI and AII (Huang and Winer, 2000; Jones, 2009).

These thalamocortical afferents differ in their synaptic properties. The projections to layer 4 of AI and AII, respectively, demonstrate Class 1 properties: dense arborizations (Huang and Winer, 2000; Llano and Sherman, 2008), large EPSPs that depress and activate only iGluRs (Lee and Sherman, 2008; Rose and Metherate, 2001). By comparison, the projections to layers 2/3 display primarily Class 2 properties, although a minority (~20%) have Class 1 or mixed properties (Viaene et al., 2011).

3.3. Corticothalamic pathways

The MGB itself receives descending corticothalamic (CT) projections from layers 5 and 6 of the auditory cortex (Llano and Sherman, 2008; Ojima, 1994; Winer et al., 2001; Winer et al., 1999). The layer 6 CT projection feeds back to the same nucleus from which it receives its main core TC input, e.g., the layer 6 AI to MGBv projection (Fig. 2A). In contrast, layer 5 sends a non-reciprocal feedforward CT projection to the MGB, e.g., the layer 5 AI to MGBd projection (Fig. 2A). Thus both MGBv and MGBd receive feedback layer 6 projections (from AI and AII, respectively), and MGBd but not MGBv receives CT inputs from layer 5 (Llano and Sherman, 2008; Winer et al., 2001). This non-reciprocal layer 5 CT projection displays Class 1 characteristics, i.e., thick axons and large terminations in the MGBd (Fig.

2B: red box) with triadic structures in the cat[1] (Llano and Sherman, 2008; Ojima and Murakami, 2010; Winer et al., 2001), distinguishing it from the feedback layer 6 CT projection exhibiting Class 2 properties, i.e. thin axons and small terminations in MGBv (Fig 2B: green box) and facilitating EPSPs (Bartlett and Smith, 2002; Cappe et al., 2009; Llano and Sherman, 2008; Ojima, 1994; Winer et al., 2001). By extrapolation from studies in the visual and somatosensory systems, because similar experiments have not been fully carried out in the auditory system, we expect that the layer 5 projection should evoke large, depressing EPSPs with no mGluR component (Li et al., 2003; Reichova and Sherman, 2004).

3.4. Local intracortical pathways

Within each auditory area, inter- and intra-laminar projections connect neurons within and across cortical columns (Lee and Sherman, 2009b; Matsubara and Phillips, 1988; Read et al., 2001; Yuan et al., 2010). Glutamatergic pyramidal cells predominate across all layers in the auditory cortex, including layer 4, where they assume the role of the spiny stellate cells in the visual cortex (Smith and Populin, 2001). GABAergic interneurons provide approximately 20% of the intracortical inputs (Yuan et al., 2010). Cortical neurons interconnect prolifically (Binzegger et al., 2004; Lee and Winer, 2008c, 2010), with glutamatergic projections extending across wider cortical territories than do GABAergic inputs (Barbour and Callaway, 2008; Lee and Sherman, 2009b; Yuan et al., 2010).

Interestingly, Class 1 and 2 synaptic properties distinguish some of the intracortical glutamatergic projections (Lee and Sherman, 2008, 2009b, c). Among these, the layer 6 projection to layer 4 is notable for its anatomical robustness, providing approximately 30% of synaptic inputs (Binzegger et al., 2004), and exhibiting Class 2 synaptic properties, i.e. paired-pulse facilitation and recruitment of Groups I and II mGluRs (Fig.3) (Lee and Sherman, 2008, 2009a, c). This contrasts with the glutamatergic projections from layer 4 to layer 3 and those from layer 3 to layer 5, which instead exhibit Class 1 synaptic properties (Lee and Sherman, 2009b). However, the copious interconnectivity of the intracortical projection system still leaves many intrinsic inputs as yet uncharacterized.

3.5. Corticocortical pathways between areas

Auditory cortical areas are linked by an expansive corticocortical (CC) network (Hackett, 2011; Lee and Winer, 2008b, c; Shi and Cassell, 1997), which contributes nearly half of the extrinsic input to a cortical area (Lee and Winer, 2010). The laminar sources of these CC projections differ according to areal origins, with supragranular, infragranular, and bilaminar origins often defining hierarchical relationships among auditory areas (Hackett, 2011; Lee and Winer, 2010; Rouiller et al., 1991) whose number varies on a species-specific basis (Bizley et al., 2005; Budinger et al., 2000; Fitzpatrick et al., 1998; Stiebler et al., 1997).

Among conserved areas, AI and AII are reciprocally connected by pyramidal neurons in layers 2-6 (Winer, 1992). Befitting their abundant connections, the organization of CC synaptic properties between AI and AII is the most complex, varying according to laminar origins and terminations. In general, neurons in layers 5b receive Class 1 synaptic inputs, layers 5a and 6 receive Class 2 inputs, and layers 2-4 receive a combination of Class 1 and 2 inputs (Covic et al., 2009). Interestingly, the origins of these projections are generally mixed across each layer, i.e. layers 2-6 are the sources of both Class 1 and 2 projections (Covic et

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[1]Triadic arrangements are special synaptic structures associated with Class 1 input. A prominent example is the retinal input to the LGN (reviewed in Sherman and Guillery, 2006). However, a key element to these arrangements is a terminal from an interneuronal dendrite. Since interneurons are absent from the thalamus of rats and mice outside of the LGN (Arcelli et al., 1997), triads are not found in the thalamus of these rodent species outside of the LGN.

al., 2009). Such microtopographic distributions further enhance and complicate CC synaptic organization (Lee and Winer, 2008c, 2010).

4. Functional implications

4.1. Role in information processing

The distinct properties of Class 1 and 2 pathways suggest different roles for each in the processing of auditory information. Class 1 inputs, with their large terminal morphologies, postsynaptic positioning close to the cell body, and high probability of release (associated with paired-pulse depression) (Gil et al., 1999), should be proficient as information-bearing inputs (Sherman and Guillery, 1998). Moreover, a key feature of Class 1 inputs, paired-pulse depression, appears to act as a gain control mechanism during high levels of activity (Abbott et al., 1997), a useful property for an information channel. By contrast, the characteristics of Class 2 inputs suggest a vastly different role, one as a modulator of information flow (Lee and Sherman, 2009c, 2010a; Sherman and Guillery, 2006). In particular, Class 2 synaptic activation of mGluRs results in protracted changes in membrane potential, which, in addition to providing efficient control of various time- and voltage-dependent ionic conductances (reviewed in Sherman and Guillery, 2006), often significantly outlasts activity in the afferent inputs (Lee and Sherman, 2009a, c); this is useful for modulation but would serve to distort information flow. Thus, these features, when added to their smaller terminal morphology, postsynaptic positioning far from the cell body, and lower release probability, lead us to conclude that Class 2 inputs likely subserve a modulatory role (Gil et al., 1999; Sherman and Guillery, 2006; Stratford et al., 1996).

However, it should be noted that this does not imply that Class 2 inputs convey zero information. Instead, we suggest that Class 2 inputs operate like other classic modulatory inputs, such as cholinergic or serotonergic inputs. The point is that, while all of these inputs convey some information, a distinction should be made among glutamatergic pathways between those that are primarily information-bearing (Class 1) and those that are primarily modulatory (Class 2).

4.2. Parceling of thalamic nuclei

MGB nuclei, like other sensory thalamic nuclei, can be divided into two groups based on the source of their Class 1 inputs (Reichova and Sherman, 2004; Sherman and Guillery, 2006). In this scheme, the MGBv is classified as a first order (FO) nucleus, since it receives Class 1 synaptic input from ascending tectothalamic streams that originate at the sensory periphery (Fig.3) (Lee and Sherman, 2010b). In this way, the MGBv is analogous to both the lateral geniculate nucleus, which receives Class 1 input from the retina, and the ventroposterior nucleus, which receives Class 1 input from the medial lemniscal system (Sherman and Guillery, 2006). In contrast, the MGBd is classified as a higher order (HO) nucleus, since its Class 1 input originates from layer 5 of the auditory cortex (Fig. 2), similar to the LP-pulvinar complex (vision) and posterior medial nucleus (somatosensory), which also receive Class 1 inputs from layer 5 of cortex (Li et al., 2003; Llano and Sherman, 2008; Reichova and Sherman, 2004; Sherman and Guillery, 2006).

Class 1 inputs to thalamic relay cells represent the major source of information to be relayed, e.g. the retinal input to the lateral geniculate nucleus. FO relays, like the MGBv, then, represent the first relay to cortex of a particular type of input (e.g., auditory or visual), whereas HO relays, because they receive Class 1 input from cortex, serve as a relay station of information already in cortex between cortical areas (Sherman and Guillery, 2002, 2006). This is in addition to any direct CC projections, and it is curious that many, and perhaps all, areas of cortex appear to have parallel direct (CC) and indirect (cortico-thalamo-cortical)

pathways. The possible difference in information content of these parallel pathways between cortical areas has been discussed elsewhere (Sherman and Guillery, 2006; Guillery and Sherman, 2011).

4.3. Information-bearing routes

Given the putative information-bearing function of Class 1 inputs and their prevalence in the central auditory system, a model of information flow from the inferior colliculus to the auditory cortex arises naturally (Fig. 3: red) (Lee and Sherman, 2010a). In this model, auditory information from the cochlea reaches the ICc and is sent to the MGBv and then to AI (Bartlett and Smith, 2002;Lee and Sherman, 2008,2010b). From here, layer 5 of AI transmits information to MGBd, which then advances it to AII (Fig. 3: red) (Lee and Sherman, 2008;Llano and Sherman, 2008). As shown in Fig. 3, this cortico-thalamo-cortical pathway parallels a direct CC pathway. However, the resultant transthalamic route for information flow between AI and AII via MGBd contrasts with the canonical models for intraareal communication mediated strictly by corticocortical connections (Felleman and Van Essen, 1991;Rouiller et al., 1991).

Furthermore, this model proposes that Class 2 projections largely modulate the flow of information in recipient neurons (Fig 3: green) (Lee and Sherman, 2010a). Thus, the ascending pathway from the ICd may not behave as a parallel route for auditory information reaching the MGBd (Hu, 2003;Syka et al., 2000) but instead act to modulate transmission of the layer 5 input to MGBd. Similarly, the TC projections from MGB to layers 2/3 as well as the layer 6 projections both to layer 4 and back to the MGB, in this model, act as modulators of information flow (Lee and Sherman, 2009b;Llano and Sherman, 2008;Viaene et al., 2011), which extends previous models of lemniscal and non-lemniscal parallel pathways for ascending auditory information (Calford and Aitkin, 1983;Lorente de Nó, 1938), and posits a role for the non-specific thalamocortical projection system(Jones, 2007). Finally, the direct CC pathway also has modulatory components (Covic et al., 2009).

5. Unresolved features

5.1. Ubiquity

The relative pervasiveness of Class 1 and 2 properties in these central auditory projections generates an obvious question: Are such features ubiquitous throughout the auditory system? Conceivably, such classifications could be extended and tentatively applied to very early stages of the auditory pathway (Gulley et al., 1978; Hoffpauir et al., 2006; Rowland et al., 2000). For example, in the cochlear nucleus at the bulb of held, bushy cells receive large terminations from type I spiral ganglion cells (Gulley et al., 1978), whose synapses have high release probabilities (Isaacson and Walmsley, 1995). And, these Class 1-like features are even more prominent in the medial nucleus of the trapezoid body at the calyx of held (Hoffpauir et al., 2006; Müller et al., 2010; Rowland et al., 2000), one of the largest synaptic terminals in the brain. Such properties are practically de rigueur for these synapses to faithfully transmit information, particularly at the calyx of held, where accurate timing is critical for sound localization (Kopp-Scheinpflug et al., 2003; Mc Laughlin et al., 2008).

More questionable, though, is the extension to those pathways whose properties are as yet uncharacterized, e.g., very local, intrinsic cortical (Barbour and Callaway, 2008; Tan and Wehr, 2009) or commissural (Chadderton et al., 2009; Lee and Winer, 2008b). Perhaps, among the most intriguing are the numerous corticofugal projections (Winer, 2006), whose targets include the IC (Winer et al., 1998), pons (Schuller et al., 1991), striatum (Beneyto and Prieto, 2001), amygdala (Romanski and LeDoux, 1993), and as remote even as the cochlear nucleus (Schofield and Coomes, 2005). The remarkable breadth of these descending cortical projections affect not only direct auditory processing streams, but also

motor and limbic processes (Winer, 2006). Thus, whether such projections have the properties and attendant functional significance of Class 1 and 2 inputs, or properties quite different involving other classes, would have profound consequences for the cortical control of auditory processing through these regions.

5.2. Convergent integration

While the characterization of these pathways highlights their potential functional roles, a broader perspective recognizes naturally that they are not isolated and that their combined effects largely govern neuronal activity. Indeed, multiple synaptic sources converge, combine and integrate temporally and spatially to generate a neuronal output (Mel, 1993; Polsky et al., 2004; Trevelyan and Jack, 2002). Neurons in layer 4, for example, receive convergent Class 1 and 2 inputs from thalamic (Lee and Sherman, 2008), intrinsic cortical (Lee and Sherman, 2009c) and corticocortical (Covic et al., 2009) sources. And, the MGB receives convergent inputs from the cortex (Llano and Sherman, 2008) and IC (Lee and Sherman, 2010b). Simple passive biophysical models predict that these various synaptic inputs should summate linearly (Polsky et al., 2004; Trevelyan and Jack, 2002). Yet, the Class 2 synaptic activation of mGluRs, with their longer time-scale and downstream modifications to time- and voltage gated channels (Francesconi and Duvoisin, 2000; Stefani et al., 1996), may introduce unexpected non-linearities (Wyart et al., 2005). This broader issue is further complicated by the effects of convergent inhibitory (Yuan et al., 2010) and neuromodulatory (Varela and Sherman, 2007, 2009) projections, whose effects on the integration of Class 1 and 2 inputs are also as yet unknown and remain to be investigated.

5.3. Divergent projections

Axonal branching is prevalent throughout the auditory system, from the projections of type I spiral ganglion cells to the cochlear nucleus (Fekete et al., 1984) to the thalamocortical (Kishan et al., 2008; Lee and Winer, 2008a) and corticothalamic (Kimura et al., 2005; Ojima, 1994) pathways. At their simplest, terminal arborizations allow one axon to form multiple terminal boutons, as in the olivocochlear collaterals to the interstitial nucleus of the vestibular nerve root (Brown et al., 1988). At the other extreme, axons branch to targets millimeters apart, as with some thalamocortical fibers (Cetas et al., 1999; Hashikawa et al., 1995; Huang and Winer, 2000). These divergent projections may create feedback–gain loops (Ye et al., 2000), establish lateral inhibition (de la Rocha et al., 2008; Tan and Wehr, 2009), propagate similar computational processes to remote locations (Guillery and Sherman, 2011; Kuwabara et al., 1991), or synchronize temporal aspects of neural discharge (Ojima et al., 1991).

Such branching poses particular issues with regards to Class 1 and 2 synaptic properties. Do all neuronal branches have similar properties? For instance, layer 5 inputs to MGBd exhibit Class 1 properties, but the layer 5 axons branch to innervate multiple extrathalamic targets as well (Bajo et al., 2007; Ojima, 1994; Winer, 2006). Do the other targets of these axons respond to inputs with Class 1, or other, properties? If not, what does this imply for the function of separate branches? In the one case, layer 6 neurons send branched projections to the MGB and layer 4 of the cortex (Thomson, 2010), which both exhibit Class 2 synaptic properties (Bartlett and Smith, 2002; Lee and Sherman, 2009c; Llano and Sherman, 2008). The shared attributes of these separate branches suggests that layer 6 neurons modulate both the thalamic relay neuron and its layer 4 target (Lee and Sherman, 2009c; Thomson, 2010).

5.4. Long-term plasticity

The ability of auditory neurons to plastically reorganize their receptive field properties is somewhat contradictory from an information processing standpoint (Kilgard and Merzenich, 1998; Weinberger, 2007). On the one hand, auditory information is encoded with high-

fidelity, yet on the other hand, it is malleable to enable learning (Bakin and Weinberger, 1990). This large-scale reorganization of physiological parameters is enabled by plastic changes occurring at the synapse. While long-term potentiation (LTP) and depression (LTD) of the synapse in response to tetanic stimulation protocols has been actively studied for several decades (Malenka and Bear, 2004), more recent investigations of spike-timing dependent plasticity (STDP) have defined the critical windows for initiating plasticity at the synaptic level (Dan and Poo, 2004).

An open question is whether such plasticity is equally expressed at all synapses in the auditory system. For example, should the Class 1 thalamocortical input to layer 4 of auditory cortex be more or less plastic than the Class 2 intrinsic cortical input from layer 6? Or, are they similar? Although reorganization of physiological map parameters has been observed at multiple levels of the auditory pathway (Edeline and Weinberger, 1991; Ma and Suga, 2009; Weinberger et al., 1984; Zhang and Suga, 2000), the literature remains unresolved on the issue of the relative plasticity of central auditory synapses (Dan and Poo, 2004; Malenka and Bear, 2004). The demonstration of STDP is scattered across numerous systems and preparations, which differ in methodology and measures (Bell et al., 1997; Boettiger and Doupe, 2001; Debanne et al., 1998; Magee and Johnston, 1997; Markram et al., 1997). Interestingly, Group 1 mGluRs (Lüscher and Huber, 2010) and dendritic synapse location (Froemke et al., 2010) are likely factors mediating such plasticity, suggesting that plastic differences indeed should exist among Class 1 and 2 pathways. With regard to the auditory system, there has not been a systematic study of the changes in synaptic strength from STDP or neuromodulator activation across multiple levels of the central auditory pathway. Thus, it remains to be resolved whether the Class 1 and 2 auditory pathways exhibit different capacities for plastic reorganization.

6. Conclusions

The diverse morphological and physiological properties of Class 1 and 2 pathways underscore their functional importance in the transmission and modulation of information through the central auditory system. These differences also should make clear that treating these various inputs as functionally homogeneous is counterproductive. Further distinctions among these pathways may emerge, such as with receptor subunit composition (Hermida et al., 2010; Hunter et al., 1993; Petralia et al., 2000), vesicular glutamate transporters (Altschuler et al., 2008; Zhou et al., 2007), and their interactions with inhibitory pathways (Ito et al., 2009; Yuan et al., 2010). The current classification of two types, with Class 1 suggesting the subset of inputs involved primarily in information transfer, has revealed unexpected routes for auditory information flow and adds insight to the higher order computational processes occurring in the mammalian brain, perhaps ones fundamental to the organization of such neuronal circuits across systems and species, but whose ontogeny and pervasiveness remain to be discovered.

Acknowledgments

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Abbreviations

|	
AC	Auditory cortex
AI	Primary auditory cortex
AII	Second auditory area
CN	Central nucleus of the inferior colliculus
D	Dorsal division of the medial geniculate body, or dorsal
DN	Dorsal nucleus of the inferior colliculus
IC	Inferior colliculus
La	Lateral nucleus of the inferior colliculus
M	Medial division of the medial geniculate body, or medial
MGB	Medial geniculate body
Sg	Suprageniculate nucleus
V	Ventral division of the medial geniculate body, or ventral
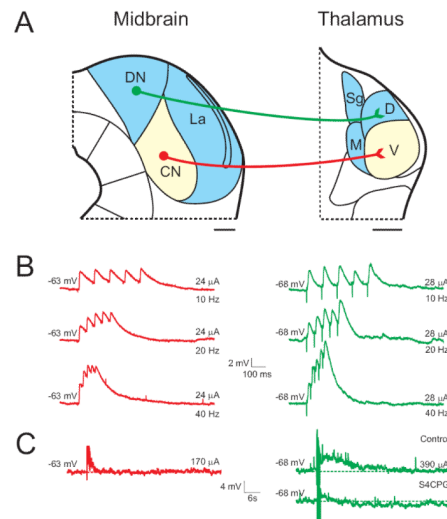
Fig. 1.
Physiology of the ascending tectothalamic projection, as an example illustrating the synaptic properties of Class 1 and 2 glutamatergic inputs in the auditory forebrain. **(A)** Schematic illustration of the connectivity between tonotopic (light yellow) and non-tonotopic (ice blue) regions of the inferior colliculus (IC; left) and the medial geniculate body (MGB; right). Class 1 glutamatergic projections (red) originate from the central nucleus of the IC (CN) and terminate in the ventral division (V) of the MGB, while Class 2 projections originate from non-tonotopic shell regions, such as the dorsal (DN) and lateral (La) nuclei of the IC and terminate in the dorsal (D) and medial (M) divisions of the MGB. Scale bars = 250μm. **(B)** Class 1 postsynaptic responses (red) exhibit large EPSPs that depress in response to paired-pulse stimulation, while Class 2 responses (green) facilitate in response to paired-pulses. **(C)** After blocking iGluRs and stimulation with a high frequency tetanus, the Class 2 tectothalamic input (green) exhibits a long-lasting depolarization that is blocked by group 1 mGluR antagonists. Portions of the figure adapted from Paxinos and Franklin (2001) and Lee and Sherman (2010). See list for abbreviations.
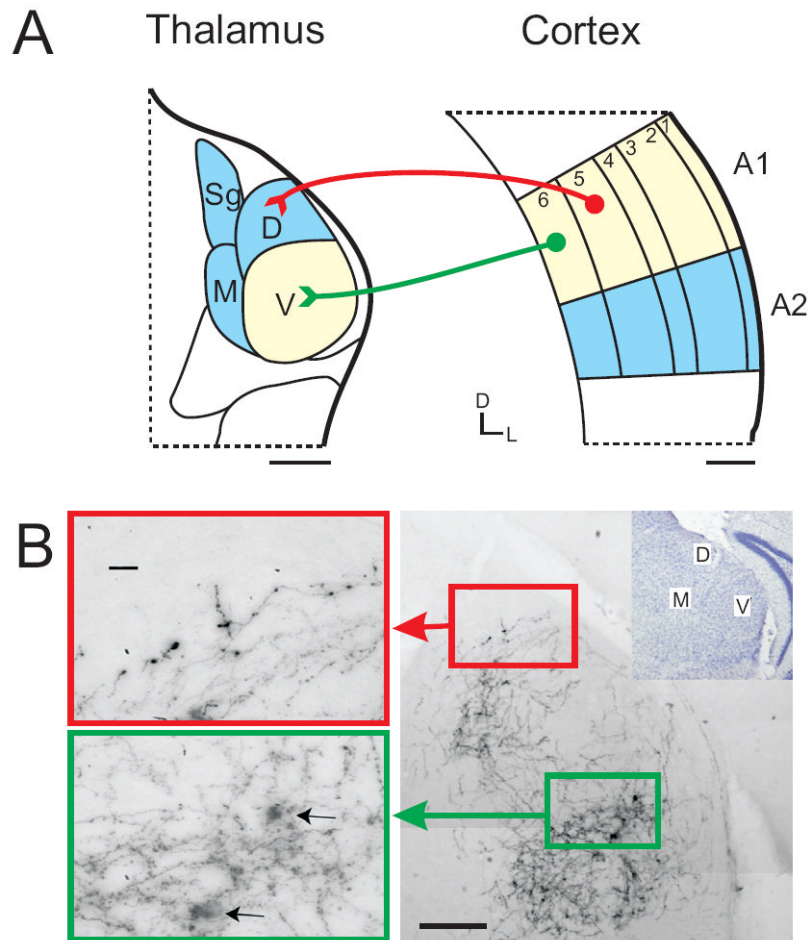
Fig. 2.
Anatomy of the descending corticothalamic projections, as an example to illustrate the morphology of Class 1 and 2 glutamatergic inputs. **(A)** Two CT pathways originate from the primary auditory cortex (AI). Class 1 feedforward projections originate from layer 5 of AI and terminate in MGBd, while Class 2 feedback projections originate from layer 6 of AI and terminate in MGBv. Scale bars = 250μm. **(B)** Class 1 projections (red box) exhibit thick axons with large synaptic terminals compared with Class 2 terminals (green box) which exhibit thin axons and small terminals. Scale bars: left = 20μm, right = 200μm. Portions of the figure adapted from Paxinos and Franklin (2001) and Llano and Sherman (2008). See list for abbreviations.
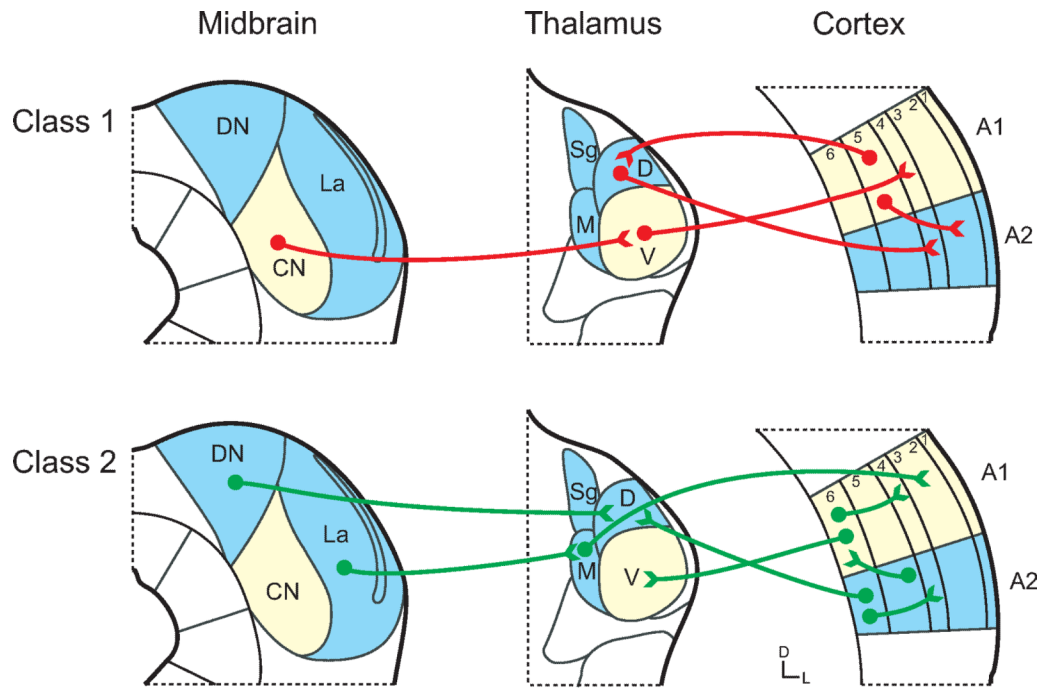
Fig. 3.
Summary of the major Class 1 (red) and Class 2 (green) glutamatergic inputs in the auditory forebrain. Class 1 projections (red) establish a novel route for the interareal transfer of information between AI and AII via a corticothalmocortical route. Class 2 projections (green) are not likely the primary conduits for information in the auditory system, but rather act to modulate that information. Scale bars = 250μm. Portions of the figure adapted from Paxinos and Franklin (2001). See list for abbreviations.

Table 1

Anatomical and physiological features of auditory pathways

	Class 1	Class 2
Terminal Size[1,3,8,9,11,12,13]	Large	Small
Axonal diameter[1,3,8,9,11,12,13]	Thick	Thin
Arborization pattern[1,3,8,9,11,12,13]	Dense	Sparse
Dendritic location[1,3,8,9,11,12,13]	Proximal	Distal
Postsynaptic receptors[2,4,5,6,7,10,11]	iGluR	iGluR and mGluR
EPSP amplitude[2,4,5,6,7,10,11]	Large	Small
Short-term plasticity[2,4,5,6,7,10,11]	Depressing synapse	Facilitating synapse

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