● PERSPECTIVES

Two types of auditory glutamatergic synapses and their implications for repairing damaged central auditory pathways

For the mammalian brain to process and decipher the rich panoply of sounds that abound in the world, nature has evolved an elegant collection of neural circuits dedicated to this task. Indeed, the complexity, variety and number of neural pathways devoted to computing auditory information is unique among sensory modalities (Kaas, 2008). After the initial sensorineural encoding of sound at the level of the cochlea, auditory information is processed in several lower brainstem centers and eventually converges in the midbrain, at the level of the inferior colliculus (Wenstrup, 2005). Subsequently, auditory information is transferred through the thalamus, the medial geniculate body, and then the auditory cortex (Winer et al., 2005; Razak and Fuzessery, 2010; Hackett, 2011; Lee and Sherman, 2011; Lee and Winer, 2011; Imaizumi and Lee, 2013; Lee and Imaizumi, 2013). From here, the common view holds that auditory information is processed through a series of corticocortical connections, from which stimulus features such as sound location and identity are extracted (Felleman and Van Essen, 1991; Romanski et al., 1999; Carrasco and Lomber, 2009; Hackett, 2011). In this manner, perceptual features of such sound attributes are computationally decoded across multiple auditory cortical areas (Callan et al., 2006; Tsytsarev et al., 2009; Callan et al., 2012).

Throughout the entirety of the auditory pathway, excitatory glutamatergic projections primarily link neural stations with one another. In addition, inhibitory projections, primarily local glycinergic and GABAergic neurons, act to shape and refine these afferent signals (Winer et al., 1996; Caspary et al., 2008). Although glutamatergic pathways on the whole have been regarded as primarily information-bearing routes, our recent studies suggest an alternative perspective; specifically, that some glutamatergic pathways in the central auditory system instead modulate the information received through the information-bearing glutamatergic pathways (Lee and Sherman, 2008, 2009, 2010a, b, 2011). Furthermore, these distinctions among glutamatergic pathways are not limited to the auditory system and are also found in the visual and somatosensory pathways (Reichova and Sherman, 2004; Tanaka and Miyashita, 2009; Lo et al., 2013).

A constellation of morphological and physiological synaptic properties classifies the auditory glutamatergic pathways into two main types. The first type of glutamatergic projection exhibits thick axons that terminate in large synaptic terminals, ending on dendritic locations proximal to the neuronal cell body (Bartlett et al., 2000; Huang and Winer, 2000; Llano and Sherman, 2008). Furthermore, these projections elicit postsynaptic responses consistent with a role as information-bearing pathways, *i.e.,* large excitatory postsynaptic potentials that depress in response to repetitive stimulation and also lack a metabotropic glutamate receptor component (Bartlett and Smith, 2002; Rose and Metherate, 2005; Lee and Sherman, 2008, 2010a). In contrast, a second type of glutamatergic pathway has diametrically opposite characteristics. Morphologically, these pathways exhibit thin axons that terminate in small terminals and synapse distally on postsynaptic dendrites (Ojima, 1994; Prieto and Winer, 1999; Huang and Winer, 2000; Smith et al., 2007; Llano and Sherman, 2008). Physiologically, these pathways also differ, eliciting small excitatory postsynaptic potentials that facilitate in response to repetitive stimulation and that also activate postsynaptic metabotropic glutamate receptors (Bartlett and Smith, 2002; Lee and Sherman, 2008, 2009, 2010a).

These characteristics apply broadly to glutamatergic pathways in the central auditory system, serving to distinguish pathways that are putatively information-bearing (the first type described above) from those that are modulatory (the second type described above) in nature (**Figure 1**). For example, at the tectothalamic synapse, these criteria identify two distinct types of pathways originating from the inferior colliculus (Bartlett and Smith, 1999; Bartlett et al., 2000; Bartlett and Smith, 2002; Smith et al., 2007; Lee and Sherman, 2010a). The putative information-bearing route originates from the central nucleus of the inferior colliculus (ICc) and terminates in the ventral division of the medial geniculate body (MGBv) (red pathways in **Figure 1**). In contrast, the surrounding nuclei, *e.g.,* dorsal cortex (ICd) and lateral nucleus (ICl), send putative modulatory glutamatergic projections to the non-lemniscal nuclei of the medial geniculate body (MGBd and MGBm) (green pathways in **Figure 1**). Thus, we have suggested that these properties classify the lemniscal pathway from the ICc to the MGBv as the principal route for conveying information from the inferior colliculus to the medial geniculate body, rather than multiple parallel ascending pathways (Lee and Sherman, 2010a, 2011). Instead, in this framework, we suggest that the tectothalamic projections originating from the ICl and ICd to the MGBd and MGBm, respectively, serve a modulatory role, rather than a primarily information-bearing role (Bartlett and Smith, 2002; Hu, 2003; Smith et al., 2007; Lee and Sherman, 2010a).

At the auditory thalamocortical synapse, we posit that these criteria promote an even more intriguing theory. That is, we have found that the projections from higher-order thalamic nuclei, *e.g.* the dorsal division of the medial geniculate body (MGBd), are similar functionally to the projections from the first-order thalamic nucleus, *i.e.* the ventral division of the medial geniculate body (MGBv) (Lee and Sherman, 2008). Thus, both of these pathways from the thalamus exhibit morphological and physiological properties consistent with roles as information-bearing conduits to auditory cortical areas, *i.e.,* the first type of glutamatergic pathway described above (**Figure 1**) (Huang and Winer, 2000; Rose and Metherate, 2005; Lee and Sherman, 2008; Smith et al., 2012), in contrast with the prevailing notion that the higher-order thalamocortical projections serve only a modulatory role (Olshausen et al., 1993).

The notion that the higher-order thalamocortical projections are similar functionally to the first-order thalamocortical projection raises an obvious question: what is the source of information being transferred from the higher-order auditory thalamus to the higher auditory cortical areas? As noted above, the inputs from the inferior colliculus to the higher-order thalamus (MGBd and MGBm) appear modulatory in nature (Bartlett et al., 2000; Bartlett and Smith, 2002;

Lee and Sherman, 2010a). But, rather than promulgating information from the midbrain, the higher-order thalamic nuclei instead receive information from layer 5 of a lower cortical area, *e.g.,* the layer 5 projection from the primary auditory cortex (AI) to MGBd (Figure 1: red pathway from layer 5) (Ojima, 1994; Winer et al., 1999; Llano and Sherman, 2008). These *feedforward* corticothalamic projections from cortical layer 5 are distinct from the *feedback* corticothalamic projections from cortical layer 6, which exhibit properties associated with modulatory glutamatergic projections (**Figure 1**: green pathways). This arrangement establishes an alternate route for communication between cortical areas *via* a *cortico-thalamo-cortical* route. In comparison to the direct corticocortical connections, *e.g.,* the primary auditory cortex (AI) to the secondary auditory cortex (AII), the indirect route, AI to MGBd to AII, may utilize the unique functional properties of thalamic neurons, such as the tonic and burst firing modes (Sherman, 2001; Sherman and Guillery, 2011).

Although this classification of glutamatergic pathways yields new insights into the putative routes of information flow in the central auditory system, open questions remain. For instance, it remains to be determined how these synaptic properties apply to other glutamatergic synapses in the auditory system, such as the descending corticocollicular pathways (Feliciano and Potashner, 1995; Bajo and Moore, 2005; Bajo et al., 2010), which likely modulate ascending auditory information (Clarkson et al., 2012). Perhaps more intriguing is the issue of whether these two types of glutamatergic pathways exhibit different capacities for long-term plasticity. Indeed, the presumption a *priori* is that the putative information-bearing pathways should exhibit a greater resiliency to long-term plastic changes, such that their roles as high-fidelity conduits for auditory information are maintained (Lee and Sherman, 2011). Furthermore, the putative modulatory glutamatergic pathways, with their distal dendritic synaptic locations and activation of metabotropic glutamate receptors might be more ideally constructed to support sustained and longer-term alterations to synaptic strength and efficacy (Froemke et al., 2010; Sherman, 2014). Thus, the relative plasticity of these two types of glutamatergic pathways may inherently limit the regenerative capacity of various components in the auditory processing stream (Ruben, 1996). Consequently, regenerating or repairing damage to the central auditory pathways may benefit from targeting selected glutamatergic synaptic types (Lee et al., 2012, 2013).

Overall, the parcellation of glutamatergic pathways in the central auditory system is ongoing. The aforementioned characterization based on morphological properties and physiological responses establishes a few important metrics for comparison, which is admittedly incomplete and could be expanded to include a range of other synaptic components, such as the varied neurotransmitter transporter systems (Hackett et al., 2011; Storace et al., 2012). In this respect, the differential expression of vesicular glutamate transporter subtypes may further subdivide the classes of glutamatergic synapses describe here, as suggested by their expression in distinct glutamatergic pathways in the brainstem (Zhou et al., 2007), midbrain (Altschuler et al., 2008; Ito and Oliver, 2010), and forebrain (Hackett et al., 2011; Storace et al., 2012). Thus, the exploration and delineation of glutamatergic pathways in the central auditory system will continue to evolve and their subtle functional roles eventually revealed.

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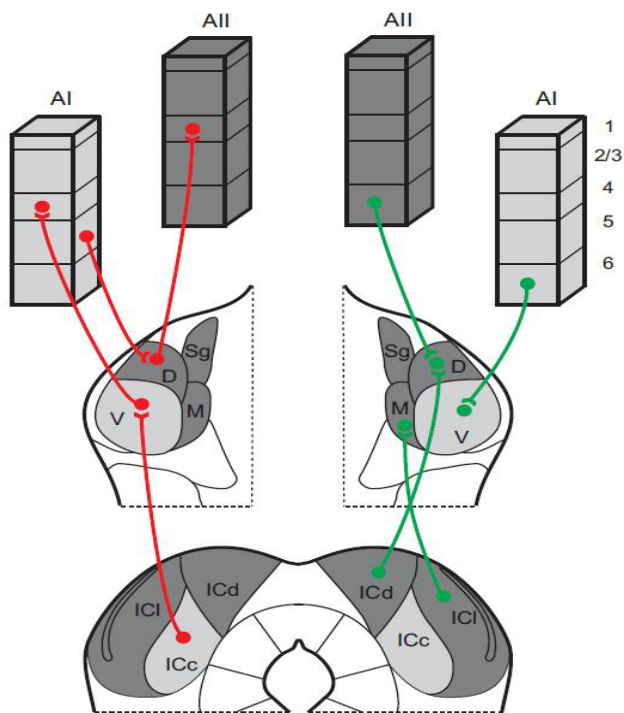
Figure 1 Schematic diagram of glutamatergic pathways from the inferior colliculus, medial geniculate body and auditory cortex.
Pathways are classified on the basis of morphological and physiological criteria, which identify putative information-bearing (red) versus modulatory (green) pathways. These pathways are found bilaterally but are depicted in separate hemispheres for clarity. Portions of the figure adapted from (Paxinos and Franklin, 2001).
Abbreviations: AI, primary auditory cortex; AII, secondary auditory cortex; D, dorsal division of the medial geniculate body (MGB); ICc, central nucleus of the inferior colliculus (IC); ICd, dorsal cortex of the IC; ICl, lateral nucleus of the IC; M, medial division of the MGB; V, ventral division of the MGB; 1–6, cortical layers 1–6.

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