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SYMPOSIUM REVIEW

Functional significance of synaptic terminal size in glutamatergic sensory pathways in thalamus and cortex

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Abstract Glutamatergic pathways are a major information-carrying and -processing network of inputs in the brain. There is considerable evidence suggesting that glutamatergic pathways do not represent a homogeneous group and that they can be segregated into at least two broad categories. Class 1 glutamatergic inputs, which are suggested to be the main information carriers, are characterized by a number of unique synaptic and anatomical features, such as the large synaptic boutons with which they often terminate. On the other hand, Class 2 inputs, which are thought to play a modulatory role, are associated, amongst other features, with exclusively small terminal boutons. Here we summarize and briefly discuss these two classes of glutamatergic input and how their unique features, including their terminal bouton size and anatomy, are related to their suggested function.

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Not all glutamatergic pathways are equal

Following its arrival from the periphery, sensory information is fed forward and back between thalamus and cortex, but also within cortex itself, by a number of glutamatergic pathways. These glutamatergic pathways, however, are not homogeneous, and marked differences have been observed in their anatomy, synaptic properties and, as a consequence, their function. Work by our laboratory and others has shown that, based on these differences, glutamatergic pathways can be placed into one of two broad categories, *Class 1* and *Class 2*.

Class 1 inputs. Differences in the synaptic properties of the two classes of input have been examined primarily *in vitro*, where activation of various glutamatergic pathways has produced dramatically different postsynaptic effects. For instance, >10 Hz electrical stimulation of Class 1 inputs produces large-amplitude, all-or-none, excitatory postsynaptic potentials (EPSPs) exhibiting paired-pulse depression (Fig. 1*Aa*), and these inputs activate ionotropic but not metabotropic glutamate receptors postsynaptically (Fig. 1*Ac*). Typical examples of Class 1 inputs include pathways that convey sensory information from the periphery to thalamus (these pathways are often collectively referred to as 'lemniscal'), such as the medial lemniscal input to the ventral posterior medial nucleus (VPM/L, Castro-Alamancos, 2002), the optic tract input to the lateral geniculate nucleus (LGN, Reichova & Sherman, 2004) or portions of the

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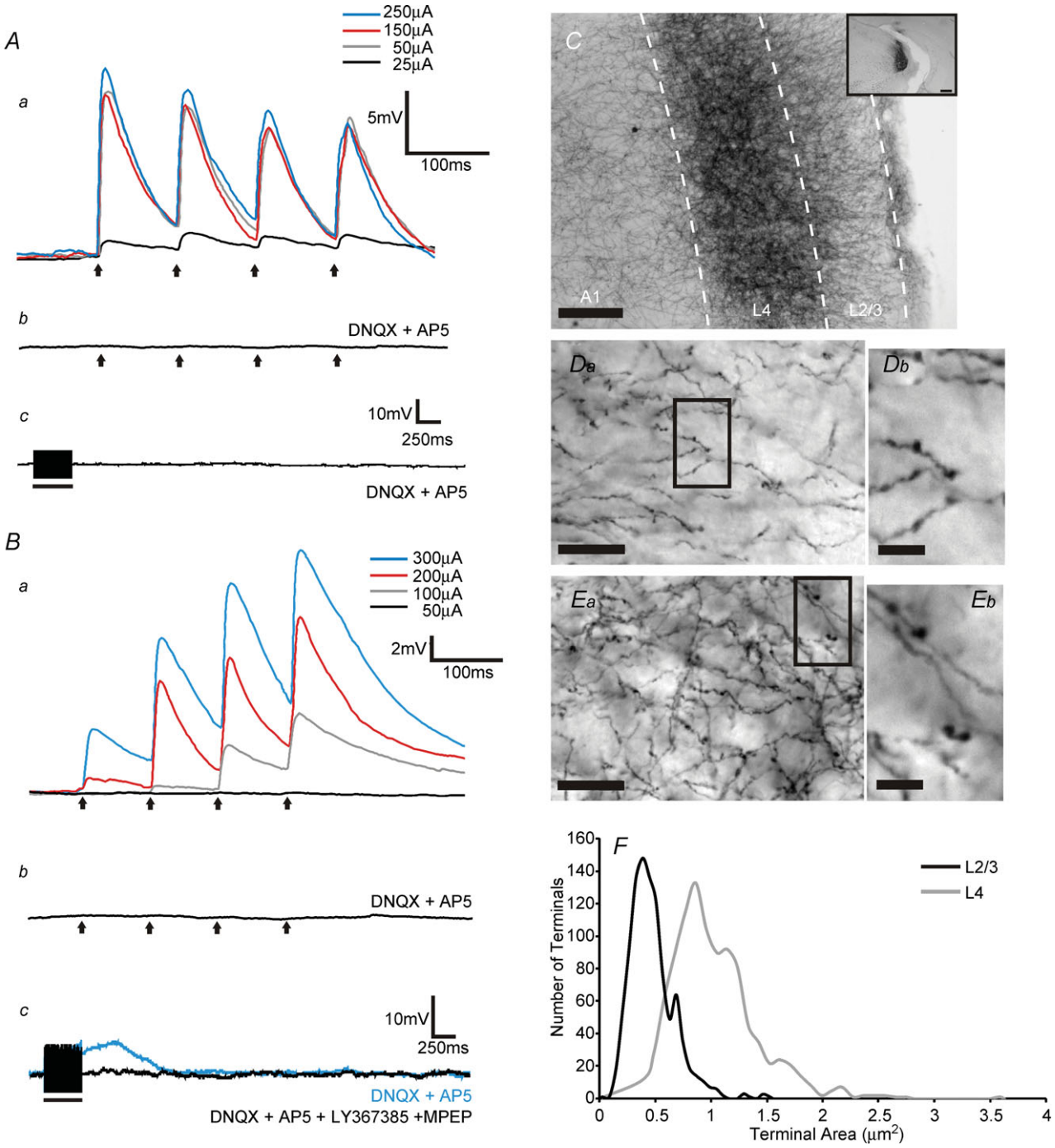

Figure 1. Examples of synaptic and anatomical characteristics of Class 1 and Class 2 inputs to layer 4 and layers 2/3 cells of the mouse primary auditory cortex (A1)

A, Class 1 response (average of 10 sweeps for each trace shown) in a layer 4 cell. *Aa*, this cell responded with paired-pulse depression to stimulation of ventral segment of the medial geniculate nucleus (MGNv) at 10 Hz. Responses were largely 'all-or-none', and EPSP amplitudes were largely unaffected by increases in stimulation intensities, reflecting the lack of convergence of MGNv inputs on layer 4 cells. *Ab*, stimulation at 10 Hz (250 μA), in the presence of the ionotropic glutamate antagonists DNQX and AP5 failed to produce any EPSPs. *Ac*, high frequency stimulation (125 Hz, 200 μA) in the presence of DNQX and AP5 did not produce any membrane potential changes, suggesting a lack of a metabotropic component. Arrows represent timing of stimulation for all 10 Hz trials and black bars represent the duration of stimulation in high frequency stimulation trials. *B*, Class 2 response in a layer 2/3 cell; also average of 10 sweeps for each trace. *Ba*, the cell responded with paired-pulse facilitation to MGNv stimulation at 10 Hz. Increasing stimulation intensities produced increases in EPSP amplitudes, possibly due to the high degree of convergence of these inputs onto a single cell. *Bb*, stimulation at 10 Hz (250 μA), in the

tectothalamic input to the ventral segment of the medial geniculate nucleus (MGNv, Bartlett & Smith, 2002; Lee & Sherman, 2010). Similarly, feedforward corticothalamic pathways originating in layer 5 (Li *et al.* 2003; Reichova & Sherman, 2004) possess characteristics that are highly similar to those of lemniscal Class 1 inputs to thalamus.

Class 1 inputs have also been identified outside of thalamus, such as in certain thalamocortical pathways (Vieane *et al.* 2011*a*,*b*, see Fig. 1*Aa*), some inter-areal corticocortical pathways (Covic & Sherman, 2011; DePasquale & Sherman, 2011), and some local cortical inputs (DePasquale & Sherman, 2012). However, glutamatergic inputs in thalamocortical and intracortical circuitry are somewhat more variable in certain parameters than those described for thalamus, giving rise to three Class 1 subtypes.

Similar to lemniscal Class 1 inputs to thalamus, thalamocortical inputs to layer 4 and some inputs to layers 5 and 6 produce responses that are largely insensitive to increases in stimulation intensity following threshold ('all-or-none' responses), indicative of little or no axon convergence (Class 1A responses, Lee & Sherman, 2008; Viaene *et al.* 2011*a*,*b*,*c*). However, certain corticocortical Class 1 inputs (Covic & Sherman, 2011; DePasquale & Sherman, 2011) and some thalamocortical inputs to layers 5 and 6 (Viaene *et al.* 2011*b*) show a considerable degree of convergence, as suggested by the increased EPSP amplitudes following increases in stimulation intensity (Class 1B). Furthermore some thalamic projections to the subgranular cortical layers produce paired-pulse responses that resemble a mixture of facilitation and depression but do not activate metabotropic glutamate receptors and are thus functionally considered as Class 1 inputs (Class 1C, Viaene *et al.* 2011*b*).

Class 2 inputs. On the other hand, the synaptic properties of Class 2 inputs differ substantially from those of Class 1 inputs. For example, electrical stimulation of the local layer 6 to layer 4 pathway in the primary auditory and somatosensory cortices produces relatively small EPSPs, exhibiting paired-pulse facilitation (Lee & Sherman, 2008, 2009*b*). Similar short-term synaptic plasticity is also evident in other Class 2 pathways, such as the corticothalamic pathways arising in pyramidal cells of layer 6 (Bartlett & Smith, 2002; Li *et al.* 2003), some thalamocortical afferents (Viaene *et al.* 2011*a*,*c*; see Fig. 1*Ba*), some inter-areal corticocortical projections (Covic & Sherman, 2011; DePasquale & Sherman, 2011), as well as some intra-areal corticocortical pathways (Lee & Sherman, 2008, 2009*b*; DePasquale & Sherman, 2012). In addition to ionotropic glutamate receptors, these pathways are also capable of activating metabotropic glutamate receptors, both of Group I types leading to post-synaptic depolarization (Reichova & Sherman, 2004; Lee & Sherman, 2008; Covic & Sherman, 2011; Viaene *et al.* 2011*a*,*c*; see Fig. 1*Bc*) and also Group II types leading to hyperpolarization (Lee & Sherman, 2009*a*; DePasquale & Sherman, 2011). Finally Class 2 pathways are made up of axons with a much greater tendency to converge onto single cells compared to their Class 1 counterparts. This is evident by the monotonic or 'graded' fashion in which EPSPs increase in amplitude when stimulation intensity of these pathways is gradually increased (Fig. 1*Ba*), the result of the recruitment of a progressively larger number of converging axons.

Anatomical features of Class 1 and Class 2 inputs

In addition to the differences in their synaptic profile, Class 1 and Class 2 pathways have been associated with certain anatomical features. For instance, Class 1 pathways in thalamus are characterized by thick axons ending in dense terminal arbors that contain many relatively large ($>2\ \mu m^2$ in cross-sectional area) synaptic boutons. Examples of established Class 1 afferents, for which data about the size of their synaptic boutons is available, include the retinal input to LGN (Szentagothai, 1963; Colonnier & Guillery, 1964; Peters & Palay, 1966; Guillery, 1969; Hajdu *et al.* 1982; So *et al.* 1985; Sur *et al.* 1987; Van Horn *et al.* 2000; Li *et al.* 2003), the lemniscal input to VPM/L (Ralston, 1969), the inferior colliculus input to MGNv (Morest, 1975; Bartlett *et al.* 2000) and the corticothalamic pathways originating in layer 5 (Hoogland *et al.* 1991; Rouiller & Welker, 1991, 2000; Bourassa *et al.* 1995; Vidnyánszky *et al.* 1996; Feig & Harting, 1998; Li *et al.* 2003). A typical and rather interesting feature of thalamic Class 1 pathways is their tendency to contact large, presumably proximal dendrites (see Sherman & Guillery, 2006).

presence of DNQX and AP5, failed to produce any EPSP. *Bc*, high frequency stimulation (125 Hz, 200 μA) in the presence of DNQX and AP5 produced a slow and prolonged membrane depolarization (blue trace) that could be blocked with a cocktail of type 1 (LY367385) and type 5 (2-methyl-6-(phenylethynyl)pyridine; MPEP) metabotropic glutamate receptor antagonists (black trace). *C*, anterograde labelling of axons and boutons in A1 following an injection of biotinylated dextran amine (BDA) in MGNv (inset). *Da*, BDA-labelled axons and boutons in layers 2/3 of A1. Highlighted area in *Da* can be seen at higher magnification in *Db*. *Ea*, BDA-labelled axons and boutons in layer 4 of A1. Highlighted area in *Ea* can be seen at higher magnification in *Eb*. *F*, histogram of bouton area in layers 2/3 and layer 4 of A1 (μm^2). Scale bars: *E*, 125 mm; *E* inset, 0.25 mm; *Da* and *Ea*, 20 μm; *Db* and *Eb*, 5 μm). Reproduced from Viaene *et al.* (2011*a*).

Similarly, cortical Class 1 pathways end in large terminal boutons. Examples of such pathways include a number of thalamocortical pathways (specifically, but not exclusively, those that terminate in layer 4 of cortex) in the auditory, visual and somatosensory systems (Ahmed *et al.* 1994; Lee & Sherman, 2008; Viaene *et al.* 2011*a*,*c*), and some corticocortical pathways (Covic & Sherman, 2011).

Unlike Class 1 inputs to thalamus, thalamic Class 2 inputs, such as those originating in corticothalamic afferents from layer 6 are made up of thin axons that terminate in small synaptic boutons ($<1\ \mu m^2$ in cross-sectional area) (Hoogland *et al.* 1991; Bartlett *et al.* 2000; Ichida & Casagrande, 2002; Li *et al.* 2003). These Class 2 inputs tend to contact their target postsynaptic cells on thinner, presumably distal dendrites (Sheman & Guillery, 2006). Cortical Class 2 inputs also terminate in small synaptic boutons. Examples include some cortico-cortical pathways (Covic & Sherman, 2011), and, as we reported recently, most thalamocortical inputs to layers 2/3 in the primary somatosensory (S1) and auditory (A1) cortices (Viaene *et al.* 2011*a*,*c*). It is also interesting that most of the projection from the posterior medial nucleus of the thalamus (POm) to all the layers of S1 is also Class 2 and is characterized by small terminals (Viaene *et al.* 2011*c*). The POm is considered a higher order thalamic nucleus for somatosensation, mostly involved in relaying information between cortical areas, and it projects mainly to higher order somatosensory cortical areas; its first order equivalent is VPM/L. Other first and higher order examples are, respectively, LGN and pulvinar for vision and the MGNv and MGNd for hearing; for review, see Sherman & Guillery, 2006.

Figure 1*C* shows anterograde labelling in the mouse primary auditory cortex (A1) following injections of biotinylated dextran amine (BDA) in the MGNv. Of particular interest is the comparison of terminal bouton sizes in layers 4 and 2/3. While thalamocortical boutons in layers 2/3, which deliver mainly Class 2 inputs, are relatively small, averaging less than $0.5\ \mu m^2$ in cross-sectional area (Fig. 1*Da*, *Db* and *F*), the boutons in layer 4, which are associated with Class 1 inputs, are considerably larger, averaging more than $1\ \mu m^2$ in cross-sectional area and in some cases as large as $2\ \mu m^2$ or more (Fig. 1*Ea*, *Eb* and *F*). Note that, whereas the Class 1 input to layer 4 was characterized by large boutons, it also contained smaller boutons. It should be clarified that Class 1 and 2 inputs should not be confused with Guillery's (1966) definition of type I and type II axons. This appears to be a feature of other Class 1 pathways as well (Sur *et al.* 1987).

Mechanisms and functional implications

Table 1 summarizes the anatomical and synaptic differences between Class 1 and Class 2 glutamatergic inputs. Due to the large, purely ionotropic EPSPs that they produce, Class 1 inputs can exert strong effects on their postsynaptic targets that temporally match activity in the input, and the paired-pulse depression is plausibly an important property providing a gain control mechanism for synaptic processing (Chung *et al.* 2002), making them ideal for the reliable and faithful relay of information. Because of this, Class 1 inputs are often referred to as *driver* inputs, given that they are the main determinants of a post-synaptic cell's activity by virtue of defining its receptive field (Sherman & Guillery, 2006). Class 2 glutamatergic inputs on the other hand do not possess the required synaptic features for the effective relay of information. Instead, their relatively weak postsynaptic effects, extensive convergence, and their slow, prolonged metabotropic component are better suited for a modulatory role. For instance, the prolonged response is useful for the control of voltage- and time-gated conductances, and the response outlasts activity in the input by 100s of milliseconds to several seconds, features that are inconsistent with effective information flow. For this reason, Class 2 inputs are often referred to as *modulators* (Sherman & Guillery, 2006).

Table 1. A summary of the anatomical and synaptic features of Class 1 and Class 2 inputs

	Class 1 (driver)	Class 2 (modulator)
Anatomical features	Large and small terminals	Small terminals
	Contact proximal dendrites	Contact distant dendrites
	Thick axons	Thin axons
	Less convergence on target	More convergence on target
Synaptic features	Large EPSPs	Small EPSPs
	Paired-pulse depression	Paired-pulse facilitation
	Activate ionotropic glutamate receptors	Activate ionotropic and metabotropic glutamate receptors

An interesting point that needs to be made is that even though Class 1 inputs are the main bearers of information in thalamic and cortical circuits, they are vastly outnumbered by Class 2 inputs, accounting for less than 10% of the total number of synapses in thalamus and cortex, with some estimates putting them as low as 2% (Wang *et al.* 2002; Van Horn & Sherman, 2004). Because in thalamus Class 1 terminals produce ∼10 synapses, and Class 2 rarely more than one, these synaptic ratios imply a much lower ratio of Class 1 to Class 2 terminal boutons (Van Horn *et al.* 2000.) Even though these numbers may somewhat underestimate the total number of Class 1 inputs, as they focus mainly on large boutons, it is evident

that the stronger synaptic effects of Class 1 inputs are not due to a numerical superiority over those of Class 2.

Although glutamatergic pathways tested to date fall clearly into the Class 1 or 2 categories, more classes may well emerge with further testing of other brain circuits.

Figure 2 shows a diagrammatic representation of glutamatergic pathways in the visual, auditory and somatosensory systems, for which both terminal anatomy, especially with regard to bouton size, and synaptic properties are known. Even this overly simplified form reveals that a highly complex matrix of Class 1 and Class 2 input interactions occurs in thalamic and cortical circuits.

An interesting question that has not been addressed is whether the large and small terminals of Class 1 pathways originate from the same cells. Even though some evidence suggests that this may be indeed the case (Sur *et al.* 1987; Tamamaki *et al.* 1995) the exact functional roles of small *versus* large boutons of Class 1 inputs remains unknown. Similarly it is unknown whether synapses from separate branches of a single axon can possess different synaptic properties (Class 1 *vs.* Class 2) or not (e.g. Reyes *et al.* 1998). Answering these questions will provide us with a better understanding of the exact mechanisms behind the function of Class 1 and 2 glutamatergic inputs.

Conclusions

Even though a great number of questions remain about the mechanisms of glutamatergic synaptic transmission, there is considerable evidence to suggest that certain anatomical and functional features of inputs are correlated. Glutamatergic pathways that terminate in large boutons appear to possess properties that enable them to exert strong postsynaptic effects and to be the driving force behind the transmission of information. The postsynaptic effects of pathways associated with small terminal boutons, on the other hand, are substantially more subtle and modulatory, their role largely being to control various aspects of how Class 1 inputs are processed. Nonetheless, given that many glutamatergic pathways have remained

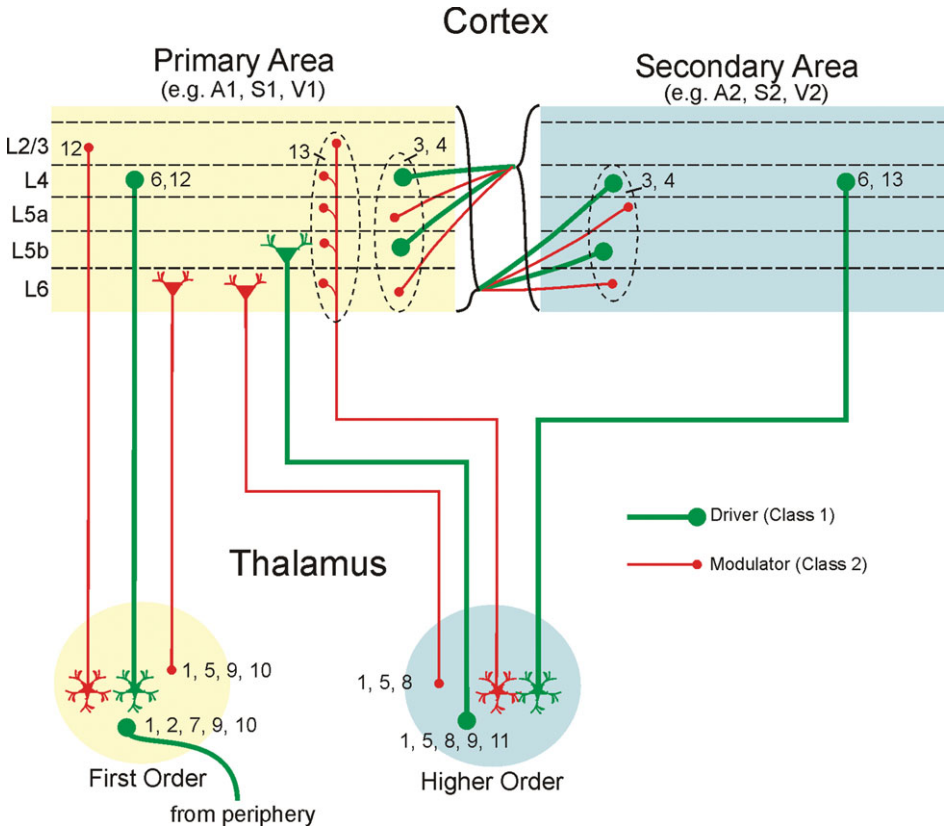

Figure 2. A diagrammatic representation of glutamatergic pathways in thalamic and cortical circuits for which both terminal anatomy, especially with regard to bouton size, and synaptic properties are known

Numbers near boutons reflect literature references providing evidence for the classification of each input: (1) Bartlet *et al.* (2002); (2) Castro-Alamancos (2002); (3) Covic & Sherman (2011); (4) DePasquale & Sherman (2011); (5) Hoogland *et al.* (1991); (6) Lee & Sherman (2008); (7) Lee & Sherman (2010); (8) Li *et al.* (2003); (9) Reichova & Sherman (2004); (10) Van Horn *et al.* (2000); (11) Van Horn & Sherman (2004); (12) Viaene *et al.* (2011a); (13) Viaene *et al.* (2011c).

unexplored with regard to their synaptic properties, parsimony dictates that their identification as Class 1 or 2 should not be assumed purely on their anatomical features, or vice versa. As the number of glutamatergic pathways with known synaptic profiles grows, so does our understanding of the brain circuits and the mechanisms behind their function.

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