The unique role of the non-lemniscal pathway on stimulus-specific adaptation (SSA) in the auditory system

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Stimulus-specific adaptation (SSA) is a special type of adaptation that allows neurons to cease responding only to repetitive, background stimuli, while preserving its responsiveness for other, new upcoming deviant stimuli. It emerges subcortically in non-lemniscal neurons of the inferior colliculi, propagating and evolving throughout the auditory pathway, until reaching its uppermost manifestation in the non-lemniscal areas of the auditory cortex. In this review, we will discuss the fundamental role of the non-lemniscal pathway in the generation of SSA, which is usually disregarded in cortical SSA research, despite being a major anatomical source of the mismatch negativity (MMN).

INTRODUCTION

Stimulus-specific adaptation (SSA) was firstly found in the auditory system by Ulanovsky and colleagues (2003) using mostly multi-unit activity recordings in the cat. In this pioneering study, they proposed that SSA in the primary areas of the auditory cortex (A1) could be the neuronal correlate of the mismatch negativity (MMN), an scalp-recorded evoked potential elicited by rare events that has demonstrated being a great tool for neurocognitive research (Näätänen *et al.*, 2007), with potential clinical applications (Näätänen *et al.*, 2012). They also assumed that SSA had to be a purely cortical activity, like the MMN, since their original recordings in the auditory thalamus failed to show SSA. However, these inceptive suppositions were later proven to be incomplete, inasmuch as (1) there were some notable discrepancies between the dynamics and sources of the MMN and the SSA recorded in A1, and (2) there was SSA being generated subcortically, actually as early as at the midbrain level. Both limitations could be accounted for by the same missing aspect: the fundamental role of the non-lemniscal auditory pathway in the generation of SSA, as we will discuss in the following. With the exception of two classical papers (Irvine and Huebner, 1979; Schreiner and Cynader, 1984), the role of non-lemniscal auditory cortex in adaptation still remains somewhat overlooked as of date, with very few SSA

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studies going beyond A1 (Nieto-Diego and Malmierca, 2016; Parras *et al.*, 2017). In this review, we will illustrate the tight relation between SSA emergence and the non-lemniscal auditory pathway in order to stimulate its inclusion in future SSA research.

SSA AS A HIGHER-ORDER TYPE OF ADAPTATION

Adaptation is an omnipresent property of neurons in the auditory system. It allows neurons to stop responding to redundant stimulation, thus exerting a protective role by avoiding an overload of the processing systems (Megela and Teyler, 1979). Most types of adaptation can be understood as rather basic physiological mechanisms, governed by activity-dependent cellular properties operating at the level of the neuron's output (Gutfreund, 2012; Pérez-González & Malmierca, 2014). SSA defines a higher level type of adaptation, depending more on the history of stimulation of the neuron rather than on its intrinsic properties (Ulanovsky *et al.*, 2004; 2003). Neurons showing SSA are able to adapt to frequently occurring stimuli (standards) selectively, while strongly resuming their firing whenever a rare stimulus (deviant) appears into the scene (Nelken, 2014). In other words, what makes SSA a unique kind of adaptation is that it is based on the input of the neuron, rather than its output, hence constituting an integrative endeavour observable at cellular level. An endeavour that must be critical for survival. With every repetition, a standard stimulus loses informative power. By selectively diminishing the resources devoted to process these standard sounds and dampening its perceptual representation, more resources are available for those novel sounds that are potentially more informative (Malmierca *et al.*, 2015). Consequently, deviant stimuli are automatically more salient and perceptually advantaged, giving rise to psychophysical effects such as attention capture (Tiitinen *et al.*, 1994) or pop-outs (Diliberto *et al.*, 2000), and it could be even at the base of the assembling of perceptual objects (Nelken, 2004).

THE NON-LEMNISCAL PATHWAY PERFORMS A HIGHER-ORDER TYPE OF SENSORY PROCESSING

Auditory information is transmitted along a series of several nuclei organised in a hierarchical manner, where different auditory features are progressively extracted at each level. Along the auditory neuraxis, two parallel pathways can be distinguished marking each station they cross with structural and functional characteristic features. Almost half a century ago, Ann Graybiel (1973) coined and defined the so-called *"lemniscal line system"* and *"lemniscal adjunct system"* as general categorisation of sensory conduction routes referred to the lemniscus. Since then, the distinction between "lemniscal" (also referred as "core" or "primary") and "non-lemniscal" (also referred as "belt" or "nonprimary") pathways have been widely used in auditory research (Hu, 2003; Jones, 2003; Lee and Winer, 2008). Making this simple distinction, we can easily classify and understand the role of the multiple subdivisions present in the inferior colliculus (IC), the medial geniculate body of the thalamus (MGB) and the auditory cortex (AC; Fig. 1).

The lemniscal pathway represents a core of neurons in every auditory nucleus that tend to be sharply tuned and organised in rather clear tonotopic fashion made of

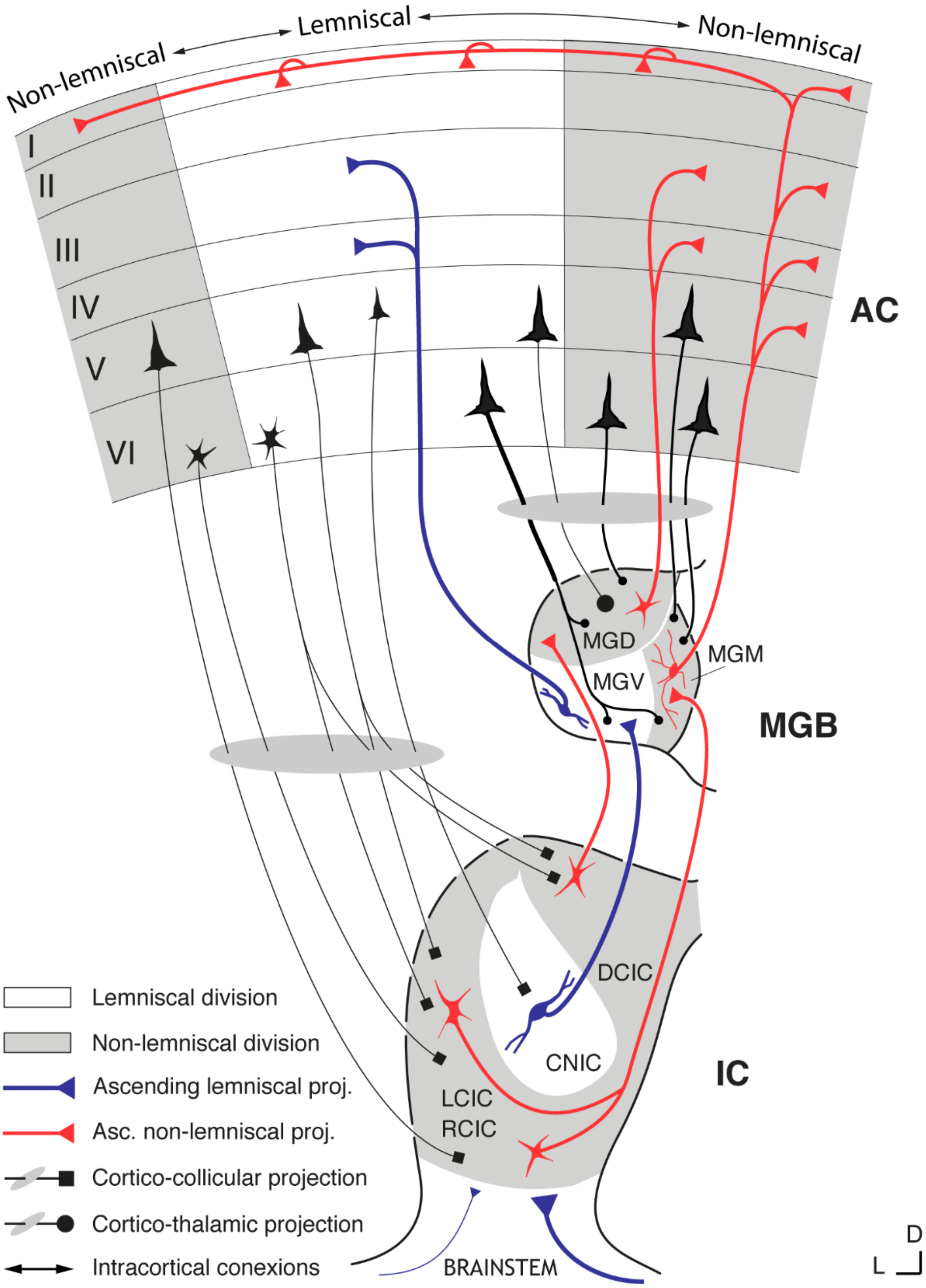

Fig. 1: Schematic diagram of the auditory pathway, showing the major stations and projections that constitute the lemniscal and non-lemniscal pathways. Note that divisions in subcortical nuclei are well preserved across species, while AC fields vary markedly (Malmierca, 2003; Malmierca and Hackett, 2010). Adapted from Malmierca *et al.* (2015).

anatomical laminae or bands. The majority of the neurons in each band project to their homologous band in the next station of the lemniscal pathway (Malmierca *et al.*, 2015). In addition to the precise tuning of their frequency-response areas (FRA; Fig. 2A), lemniscal neurons also show in general a better consistency in their response to the sound, including shorter latencies, greater firing rates, more overall spikes fired per stimulus and higher spontaneous activity than their non-lemniscal counterparts (Malmierca *et al.*, 2015). In other words, the response of these very tonographically organised neurons is fundamentally driven by the physical features of the sound, receiving mostly ascending inputs from lower lemniscal stations in the auditory neuraxis. Because of these characteristics, lemniscal divisions are considered to be part of a first-order stage of processing, forming a primary system more engaged in building up an accurate perceptual representation of the stimulus, disregarding its context or other abstract relations between sounds. The rat lemniscal pathway consists of the central nucleus of the IC (CNIC), the ventral division of the MGB (MGV), and the primary auditory cortex which includes the A1 field, the anterior auditory field (AAF) and the ventral auditory field (VAF) of the AC.

Parallel to the lemniscal pathway, another system referred to as the non-lemniscal pathway lies in which any trace of tonotopical distribution is at its best diffuse. The non-lemniscal pathway constitutes a belt of broadly-tuned neurons that gets inputs from the lemniscal core they are wrapping, and from other non-lemniscal stations: Subcortical non-lemniscal neurons send ascending projections to the next non-lemniscal station (Loftus *et al.*, 2008) while cortical neurons from belt areas send descending projections mostly (albeit not exclusively) to the non-lemniscal divisions of the MGB and the IC (Fig. 1) (Malmierca and Ryugo, 2011). The fact that non-lemniscal neurons shape this loop-like connectivity network with heavy cortical modulation, in addition to their comparatively longer response latencies, the broadness of their FRAs (Fig. 2B) and their adjunct anatomical position relative to the lemniscal stream, strongly indicates that they must exert an integrative function in the auditory system. Consequently, non-lemniscal divisions are part of a higher order stage of processing, constituting a secondary system capable of processing more complex aspects of the auditory scene analysis and tracking the history of stimulation, as required to account for the generation of SSA. The rat non-lemniscal pathway includes the rostral (RCIC), lateral (LCIC) and dorsal (DCIC) cortices of the IC, the dorsal (MGD) and medial (MGM) divisions of the MGB, and the suprarhinal auditory field (SRAF) and the posterior auditory field (PAF) of the AC.

SSA FIRSTLY EMERGES IN THE SUBCORTICAL NON-LEMNISCAL PATHWAY

As mentioned previously, Ulanovsky *et al.* (2003) initially suggested a cortical origin of SSA, since in their original work they could not find any signs of SSA in the auditory thalamus, most probably because they recorded very few neurons, most likely from the ventral (lemniscal) division of the MGB (although no details of the anatomical location of the recordings are given in their study). But this exclusively cortical nature of SSA was soon revisited and conceptualized after the discovery of

SSA in the IC (Ayala et al., 2015; Ayala & Malmierca, 2015, 2017; Duque & Malmierca, 2015; Duque *et al.*, 2012, 2016; Malmierca *et al.*, 2009; Parras *et al.*, 2017; Patel *et al.*, 2012; Pérez-González *et al.*, 2005, 2012; Pérez-González & Malmierca, 2012; Valdés-Baizabal *et al.*, 2017; Zhao *et al.*, 2011) and in the MGB (Anderson & Malmierca, 2013; Anderson *et al.*, 2009; Antunes & Malmierca, 2014; Antunes *et al.*, 2010; Duque *et al.*, 2014; Parras *et al.*, 2017). Significant and strong SSA appeared in the IC cortices, the MGD and intensely in the MGM, so sharply distributed exclusively in the non-lemniscal stations that the mere measurement of population SSA in a subcortical nucleus could provide enough evidence to distinguish between the lemniscal and non-lemniscal divisions of it.

The corticocentric interpretation of SSA was not completely dismissed after proving the existence of SSA in subcortical stations, probably due to the already strong established connection between SSA and MMN. It was suggested then that subcortical SSA might be "imposed" by the cortex (Nelken and Ulanovsky, 2007) given the massive corticocolicular projections that the IC cortices receive, and the impressively dense corticothalamic projections, that outmatch the thalamocortical output by a factor of ten (Malmierca *et al.*, 2015). Descending projections must necessarily exert at least a considerable modulatory function, but the prime source of SSA cannot be pinned down just by investigating connectivity. In order to address this question, studies of reversible deactivation of the AC using a cooling technique were conducted while recording the MGB (Antunes and Malmierca, 2011) and the IC (Anderson and Malmierca, 2013). The general results demonstrated that indeed the AC clearly modulated the firing rate of the non-lemniscal neurons in a gain-control manner (Malmierca *et al.*, 2015; Pérez-González *et al.*, 2012), helping to increase the contrast between standard and deviant stimuli by affecting the discharge rate to both proportionally (Ayala *et al.*, 2016; Duque *et al.*, 2015; Pérez-González *et al.*, 2012).

Nevertheless, the overall subcortical SSA levels and dynamics were mostly unaffected by cortical deactivation, with only about half of the adapting IC neurons and almost none in the MGB showing some change in their SSA sensitivity. In light of these results, it would be more plausible that SSA in A1 were actually inherited from subcortical non-lemniscal structures than viceversa. Although the possibility of SSA being generated *de novo* at the intrinsic microcircuitry of each station cannot be ruled out, it is reasonable to suggest that SSA must be a detection property that firstly emerges in the non-lemniscal IC, given that SSA has not being detected earlier in the auditory pathway (Ayala and Malmierca, 2013; Ayala *et al.*, 2013). From the IC cortices, SSA is transmitted downstream through the non-lemniscal subcortical pathway towards the cortex, where AC neurons work in complex integration of stimulus properties across multiple time scales and are less specialized for feature detection (Nelken, 2004), including the feature of novelty.

SSA IN NON-LEMNISCAL CORTICAL AREAS CAN BETTER ACCOUNT FOR THE GENERATION OF THE MMN

Despite the initial general acceptance of SSA as being the best candidate for the neuronal generator of MMN, there was still a time breach between the relatively long

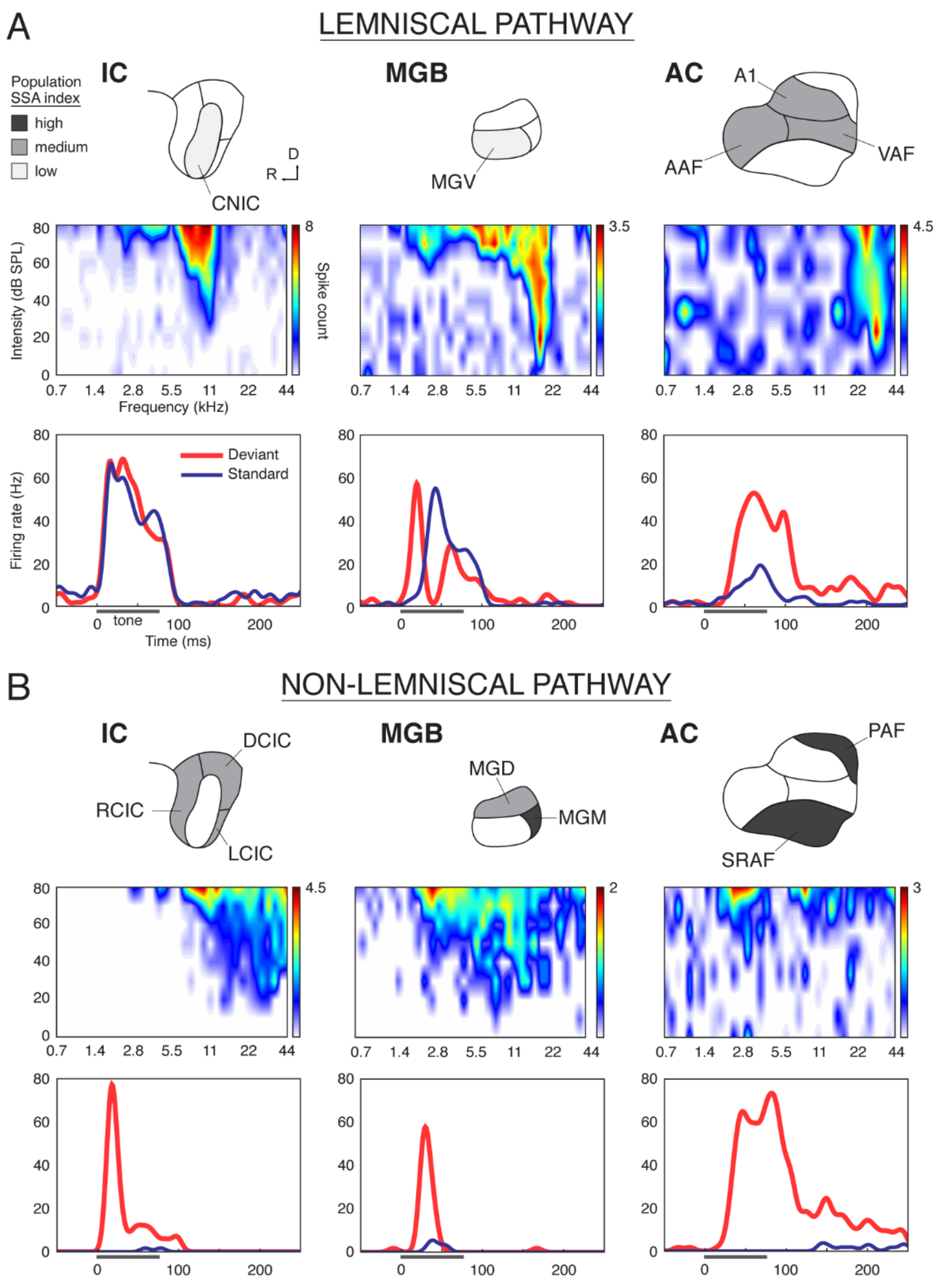

Fig. 2: Distribution of SSA along the rat auditory neuraxis. In the first row of each block, lemniscal (A) and non-lemniscal (B) subdivisions of the main post-lemniscus auditory nuclei are shaded indicating the strength of the population SSA present in it. In the second row, the FRA of a representative neuron of that subdivision is displayed, followed below (third row) by the corresponding responses of that neuron to a certain tone when presented in conditions of high probability (standard) or low probability (deviant).

peak latencies of the MMN and the swift cortical SSA reported in Ulanovsky *et al.* (2003), which sees it maximum rather close to the stimulus onset. Most importantly, the anatomical location of the reported SSA did not fit well with the topography of the change-detection MMN either, whose alleged generators are pinned down in the region of the secondary auditory cortex in humans (Alho, 1995), cats (Pincze *et al.*, 2001) and rats (Shiramatsu *et al.*, 2013). In spite of these considerable limitations, most of SSA research conducted in AC as of date is confined to A1.

Only in two recent studies (Nieto-Diego and Malmierca, 2016; Parras *et al.*, 2017), the lack of detailed studies on SSA beyond A1 is finally addressed by thoroughly recording of single-unit, multi-unit activity and local-field potentials in each of the auditory cortical fields of the rat. Besides confirming SSA presence in lemniscal AC, evidence provided demonstrates that SSA is even more robust in non-lemniscal AC fields. SSA properties differ substantially between lemniscal (primary) and non-lemniscal (nonprimary) fields. Cortical SSA distribution creates a topographic gradient that segregates the highest SSA levels to non-lemniscal fields in a sharp fashion, remarkably paralleling SSA subcortical organisation. Thereby, the continuity of the lemniscal and non-lemniscal pathways in the cortex is reflected by SSA distribution. Within non-lemniscal fields, SSA is much stronger and develops faster due to the more intense suppression and longer delay it produces on the responses to standard stimuli, which is not rare to find utterly obliterated. Levels of SSA within non-lemniscal regions are much higher around the beginning of the response than in the lemniscal ones, remaining strong up to 200 ms after the stimulus onset (Fig. 3A). Therefore, it can be argued that the non-lemniscal cortical regions are more suitable candidates for being mayor contributors in the MMN generation than their lemniscal homologues in the cortex.

Regarding local-field potentials, their difference wave correlated in time and strength with the SSA observed in single-unit and multi-unit activity recordings, confirming greater levels in non-lemniscal fields (Nieto-Diego and Malmierca, 2016; Parras *et al.*, 2017). These difference waves showed the same morphology in all cortical fields, with a fast negative deflection (Nd) followed by a positive one (Pd). On the one hand, the Nd occurred earlier and tended to be larger in lemniscal fields than in the non-lemniscal ones, suggesting a lemniscal origin (Fig. 3B). This early deflection could be related with the modulations of the scalp-recorded middle latency responses that correspond to the first response of the primary AC to a deviant event, which take place previous to the occurrence of the MMN (Escera and Malmierca, 2014). On the other hand, the Pd peaked homogeneously along the AC, so its generation must hinge on intracortical processing and reciprocal interaction between lemniscal and non-lemniscal fields, further suggesting a bottom-up propagation of SSA. Most importantly, the Pd tended to peak between 60 and 80 ms (Fig. 3B), well within the range of MMN-like potentials recorded in the rat (50-100 ms) (Harms *et al.*, 2016). This synchronicity finally allows to overcome the discrepancies in the time course and anatomical source of the SSA and the MMN, thus setting a bridge between both in which the cornerstone is the non-lemniscal contribution.

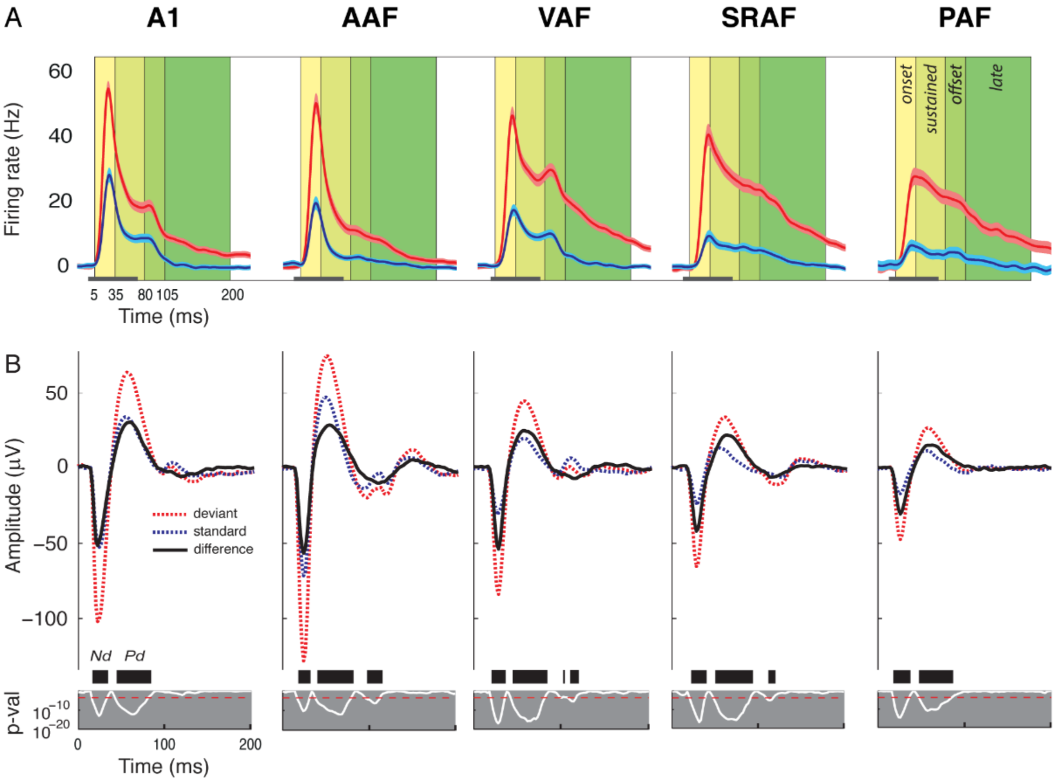

Fig. 3: Grand-average of the responses to standard (STD) and deviant (DEV) tones recorded as multi-unit activity (A) and local-field potentials (B) within each AC cortical field. Adapted from Nieto-Diego and Malmierca (2016).

CONCLUSION

Whether generated in situ in lemniscal AC or just inherited subcortically, the fact is that lemniscal neurons in the cortex show SSA, so it would be imprecise to say that SSA is a purely non-lemniscal property. However, the inverse can definitely be asserted. The SSA is a defining feature of the non-lemniscal auditory pathway, with prevailing presence all along it. The appearance of SSA as early as the level of the midbrain in the cortices of the IC suggests it is an emerging property of the non-lemniscal subcortical structures, while in non-lemniscal cortical areas SSA achieves its most refine manifestation. All this reaffirms the notion of the non-lemniscal pathway as a parallel higher-order stage of sensory processing that goes beyond the faithful representation of auditory stimuli predominant in the lemniscal pathway, being able to extract more complex features in auditory events, like novelty. Thus, it can be argued that regularity encoding and deviance detection are capabilities of the auditory brain that have a non-lemniscal foundation, essential in the generation of SSA and MMN.

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