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Contributions of the subcortical auditory system to predictive coding and the neural encoding of speech

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Prevalent views in cognitive neuroscience have highlighted the auditory cortex (AC) as the major neuroanatomical site for auditory cognition. Yet, this view suffers from ‘cortical myopia’ as it neglects the intricate functional architecture of the subcortical auditory pathway. Here, I will review evidence indicating that key anatomical structures in the auditory hierarchy, such as the inferior colliculus and the medial geniculate body, play major roles in statistical learning and predictive processing, thus contributing to auditory perception. Furthermore, mounting evidence supports these subcortical structures as involved in the neural encoding of speech sounds, including categorical perception, and in early language acquisition when the AC is still immature. I will argue that a brain potential known as frequency-following response provides a methodological tool to map high-level cognitive operations to the human subcortical auditory system. Future studies should emphasize the precise interplay between cortical and subcortical structures in supporting auditory cognition.

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Introduction

Deciphering the neural mechanisms of high-level auditory cognition is key to understand speech, to explain the joy of music and its role in organizing many aspects of our social behaviors, and to alleviate developmental disorders such as specific language impairment or dyslexia. For several historical reasons, epistemological assumptions, and methodological limitations [1,2], the prevalent cognitive neuroscience view has attributed these functions to the auditory cortex (AC) [2]. Yet, this view suffers from ‘cortical myopia’ [1], as it neglects the complex functional architecture of the subcortical auditory pathway. Compared with other sensory systems, the auditory pathway entails an intricate network of neurons arranged in five synaptic relays before reaching the cortex, which feature ipsilateral, contralateral, recurrent, feedforward, and feedback projections [3]. Among these, the inferior colliculus (IC) of the auditory midbrain, because of its sophisticated anatomical connectivity [4], is considered the analog to the primary visual cortex [5], and has been shown to play a major role in encoding statistical regularities from the acoustic input [6,7], in gating speech sounds by experience-dependent plasticity [8••], and in reading skills [9]. In turn, the medial geniculate body (MGB) in the thalamus has been implicated — through its anatomical connections to the amygdala — in voice identification and emotion content recognition in speech [10], and also in predictive coding [11] and reading disorders [12].

For their central role in driving complex computations on the acoustic input before it reaches the cortex, this review focusses on the contributions of the IC and the MGB to two prolific areas of research that involve the subcortical auditory system in high-level cognition: predictive perception and the neural encoding of speech. I highlight that a brain potential known as the frequency-following response (FFR), generated in the ascending auditory system, provides a proxy of subcortical auditory function in humans. I further suggest that the FFR can be used to test cognitive auditory function in developing individuals (i.e. neonates and infants), before the AC reaches full maturation. Several other subcortical structures have been implicated in auditory cognition, such as the cerebellum [13,14] and the basal ganglia [15], among others [2], but these are beyond the scope of this review.

Predictive coding in the subcortical auditory system

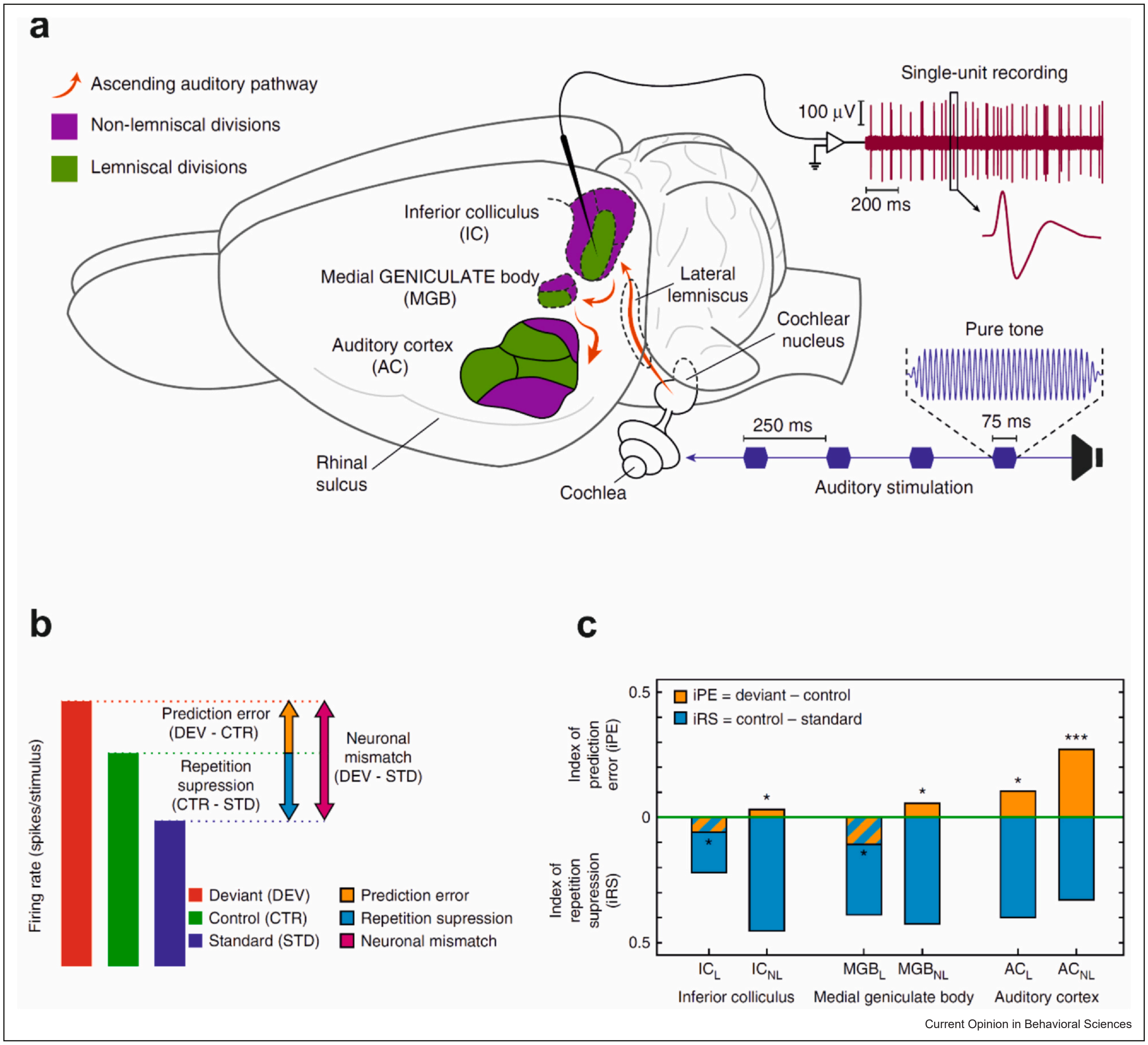
Current views of perception posit that sensory systems rely both on prior experience and contextual factors to adaptively engage with the dynamic external environment, so that neural populations modulate their responses to sound based on stimulus statistics. This is observed as suppressed or attenuated responses to repeated stimuli, whereas unexpected stimuli generate a prediction error signal [16]. According to this view, the brain is a Bayesian inference machine that computes the likelihood of sensory stimuli to occur based on previous history (i.e. predictions), with neural responses representing the mismatch between the expected event and the actual sensory input (i.e. the prediction error) [16]. In the auditory modality, evidence supporting predictive coding comes through the investigation of mismatch responses in neuronal activity in animal models and brain potentials in human studies [17,18], research that has focused mostly on cortical responses [19,20]. However, single-unit recordings in the rat have identified a subset of neurons located in nonlemniscal IC that adapted rapidly to stimulus repetition but displayed strong responses to unexpected stimulus changes [21]. Evidence supporting statistical inference in the IC was subsequently found in humans using functional magnetic resonance imaging (fMRI) [7] and brainstem evoked potentials elicited to speech [6]. Further studies extended these findings to the MGB [7,11], and demonstrated that IC/MGB neurons can encode more complex regularities than simple stimulus repetition (i.e. a violation in a tone-alternation pattern [22] or abstract rules [23]), and that prediction error emerges gradually along the auditory hierarchy, from the IC to the AC [24••] (Figure 1, see [25] for converging results in marmoset monkeys using fMRI and electrocorticography). Compelling evidence supporting that IC neurons encode for sensory predictions comes from a recent study showing neuronal responses to auditory stimuli that were actually not presented but highly predicted (i.e. omission responses) [26•].

A critical aspect in elucidating the role of the IC and MGB in auditory cognition is whether predictive responses and prediction errors are computed in these subcortical structures or otherwise inherited from the AC via the corticofugal pathway, according to the predictive coding view positing top-down propagation of predictions [16]. The corticofugal pathway is a major bundle of descending fibers that project from several auditory cortical areas to distinct portions of the MGB and IC [4], and hence may play a role in driving predictions subcortically in a top-down manner. Existing evidence is inconclusive, though. Cryogenic reversible inactivation of the AC revealed that prediction errors, at least for simple stimulus statistics (i.e. mere stimulus repetition), remained intact in both the IC [27] and the MGB [28]. However, a recent study using a similar design to [24] and optogenetic inactivation of the cortico-collicular bundle in awake mice challenged these findings [29••]. Specifically, it was found that inhibiting AC feedback decreased prediction error in IC, whereas repetition suppression remained unaffected. The results of this study align with comprehensive theoretical views suggesting that predictions in the auditory system would be generated in the AC and propagated as a cascade of generative models to the subcortical pathways via the corticofugal system [30•,31]. However, these results are in contrast with others showing statistical learning of sound patterns in IC independent of corticofugal modulation [32]. Furthermore, methodological differences (animal species vs. human participants, arousal status, and active vs. passive listening) as well as the complexity of the implicit statistics in the acoustic environment investigated, may explain these discrepancies. A recent promising approach entailing the use of two concurrent independent generative models (one based on local statistics, one driven by the task at hand) and computational modeling, suggested that both locally generated and top-down- propagated predictions modulate human neural responses (fMRI) at each level of the auditory hierarchy (IC, MGB, and AC) [33]. Yet, future research is granted to disentangle the interplay between the different levels along the auditory hierarchy in subserving predictive auditory perception.

Neural encoding of speech

Another area of research that has highlighted a major role of the subcortical auditory system to auditory cognition relates to the neural encoding of speech sounds, and its contributions to the thorough analysis of the speech signal, as well as to human communication in a broad sense. A few studies using ultra-high-field fMRI have implicated the left MGB in speech recognition, both in quiet [34] and in noisy acoustic backgrounds [35], even in specific thalamic subdivisions (i.e. the tonotopically organized primary ventral MGB) [36], as well as in reading disorders [12]. The wealth of the evidence comes, however, from studies of the human speech–-brainstem response [37], albeit the anatomical precision of these studies is limited by the intrinsic spatial resolution of the electroencephalography (EEG) approach (see the next section for a thorough discussion on the neural generators of these responses). These studies have shown the (upper) auditory brainstem to be involved in extracting pitch-relevant information [38], in mediating improved auditory discrimination in difficult listening conditions (speech in noise) [39,40], in deficient speech encoding on a number of developmental disorders, such as dyslexia [41] and autism [42], and in boosting speech processing by experience-dependent plasticity, particularly by music training [43,44] and bilingualism [45]. Of particular relevance are the studies that highlighted abnormal brainstem encoding of speech as predictors of future literacy skills [9,46]. Overall, these studies have emphasized the role of the collective auditory experiences along the lifespan [47], as well as the involvement of a cognitive–sensorimotor–reward circuitry in driving top-down plasticity within a distributed but integrated subcortico-cortical network [8••]. Given the anatomical limitations mentioned above, an open question for future research remains whether these

Figure 1



Current Opinion in Behavioral Sciences

Emergence of prediction errors along the auditory hierarchy. **(a)** Schematic illustration of the experimental setup. Isolated neurons in relays along the rat auditory neuraxis were recorded during the presentation of pure- tone sequences. Recordings were carried out in both the lemniscal (green) and nonlemniscal (purple) divisions at each station. Stimulation sequences (not shown) feature oddball conditions (a higher/lower low-probability 'deviant' tone occurring among a frequently occurring 'standard' tone), as well as several control conditions (ascending and descending 'cascade' sequences, and a 'many-standards' sequence, see [24••] for details). **(b)** Neuronal mismatch responses (deviant vs. standard, purple arrow) to the oddball sequence were decomposed using the control conditions, so that the comparison standard control isolated repetition suppression (cyan arrow), whereas the comparison deviant-control yielded the prediction error (orange arrow). **(c)** Prediction error indices (orange) and repetition suppression indices (cyan) were computed, for all hierarchical levels and anatomical divisions, by subtracting neural responses to the control from the deviant and to the standard from control, respectively, and represented as upward-positive for prediction error index (iPEs) and downward-positive for repetition suppression index (iRS). Notice, however, that for IC_L and MGB_L, prediction error yielded negative values (i.e. the control response was larger than the deviant response), and this was represented as orange bars invading the cyan area for repetition suppression. The results unveiled a gradual emergence of prediction error in the nonprimary auditory hierarchy, from IC, to MGB, and to AC, as well as in lemniscal AC, suggesting predictive coding as an intrinsic functional property of the entire auditory system.
Adapted with permission from [24••] under the Creative Commons Attribution 4.0 International License.

plastic changes pertain to the entire network or are implemented at specific levels (i.e. IC, MGB), and whether different experiences impact on different network levels and/or on the encoding of different speech attributes.

A key aspect in disentangling the role of the IC/MGB to high-level auditory cognition is whether they implement complex computational capabilities supporting categorical speech perception. Two approaches have been undertaken.

In one of such approaches, brainstem responses to speech tokens are compared from individuals with different linguistic backgrounds. For example, Mandarin speakers were found to have more robust responses than nontonal language speakers to prototypical pitch contours [48]. Another study presented a very short ambiguous acoustic cue (a voice-onset time of 2 ms followed by 10 ms of silent gap) that was perceived as a different consonant by English (/b/) or Spanish (/p/) native speakers, yielding a linguistic effect on anatomically resolved brainstem responses recorded with magnetoencephalography (MEG) [49]. An alternative approach implements a within-subjects design in which participants are presented with acoustic tokens within the continuum between two vowels. Using active — but not passive [50] — listening in conditions biasing the perceptual system, provided supporting evidence [51••]. Participants had to classify into two phonetic categories seven different tokens along the vowel continuum from /u/ to /a/, presented in random and serial (forward, backward) order conditions. It was hypothesized that serial order would warp the phonetical space, facilitating categorical encoding; accordingly, brainstem responses to the same identical acoustic token were found to be enhanced in the serial compared with the random order condition [51••].

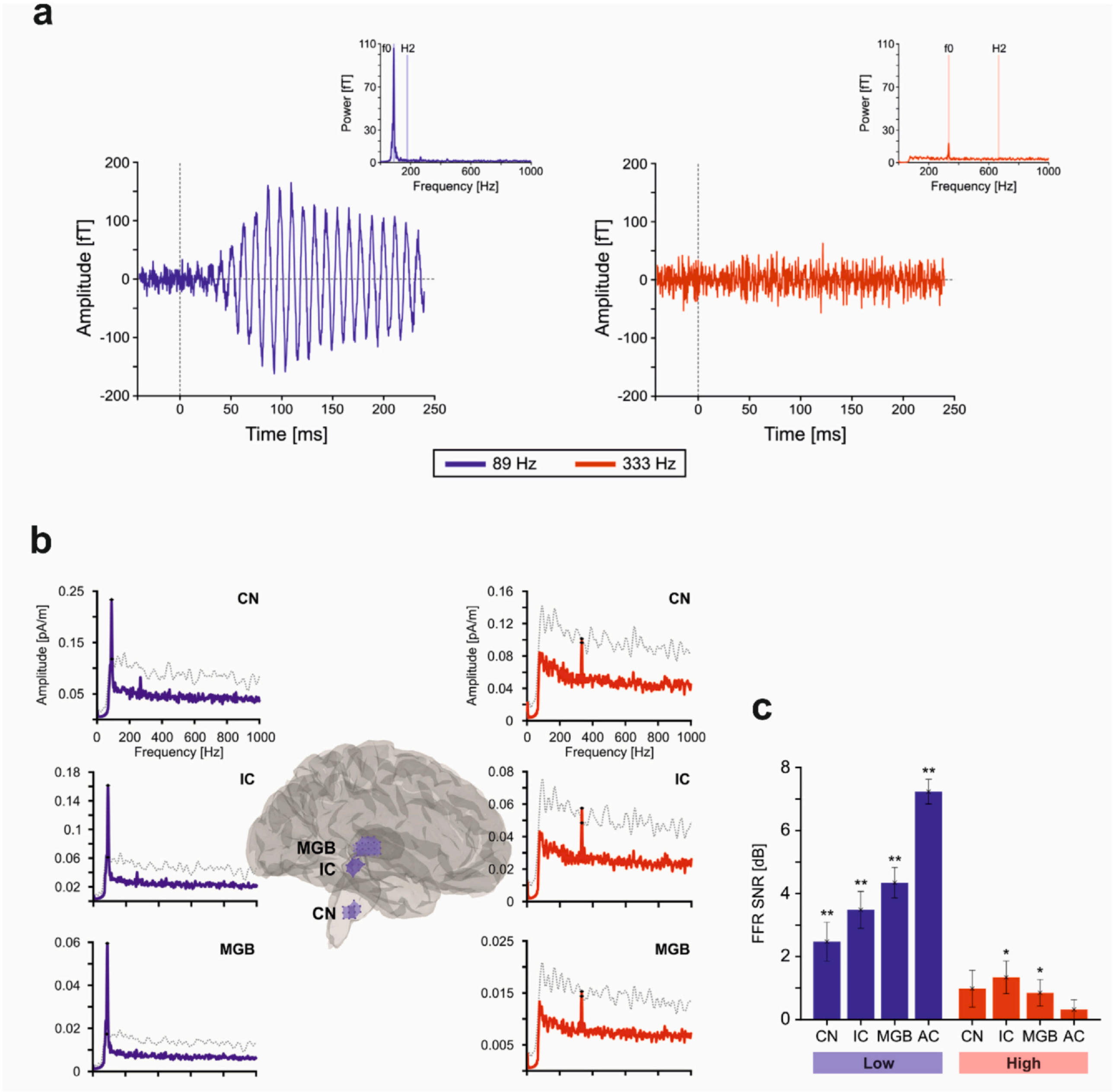
The two approaches discussed above and the results reviewed herein raise two interesting questions regarding the involvement of the subcortical auditory system in categorical speech perception. First, it seems apparent that active listening (i.e. the involvement of high-level cognition through cortical attention) is necessary for the categorical effects to be observed subcortically, hence involving the corticofugal bundles. This is further supported by studies showing enhanced source-level anatomically resolved brainstem responses (EEG) in active versus passive listening in challenging listening conditions (i.e. speech in noise [52•]), and by modulations of the brainstem response in noise according to arousal states, as indicated by cortical alpha [53] (for converging evidence involving task-modulation in gating speech recognition at the level of the MGB, see [35]). Second, studies using the across-groups approach, comparing participants with different linguistic backgrounds, support the long-term plasticity effects discussed above. In turn, studies using the within-subjects design raise the question whether the observed subcortical tuning is, in the same vein, hardwired by the linguistic experience of the participant, or induced or boosted by top-down modulation, or both. The hardwired alternative aligns with the long-term implications of the cross-linguistic studies, and supports the idea that the brainstem performs complex computations on its own, thus releasing cortical resources for higher-order functioning.

A further role of the subcortical auditory system may be in fostering early language acquisition when the entire auditory system is not yet fully mature. Despite the auditory brain being responsive to external sounds during the third trimester of pregnancy, the AC experiences a profound development during the first year of life [54], in parallel with the myelination of the auditory pathway and the acoustic radiation [55]. In these conditions, prenatal hearing [56] as well as early exposure to a rich acoustic environment right after birth may boost rapid induced plasticity in the subcortical auditory system. Recordings of speech–brainstem responses in neonates [57] have shown that infants are born with a full capacity to track voice pitch already at birth [58], that music exposure during pregnancy improves this capacity [59•], and that encoding the temporal fine structure of speech develops rapidly during the first month of life, supporting experience-dependent plasticity through acoustic exposure [60]. Whether or not this plasticity depends on corticofugal influence of an immature AC or is generated de novo by intrinsic subcortical processing awaits future investigation.

The frequency-following response as a proxy of subcortical auditory processing

The majority of the studies reviewed in the preceding section made use of scalp recordings of brainstem responses elicited to speech sounds [37]. Technically, these are called FFR, as they reflect phase-locked compound neuronal activity to the spectrotemporal components of the acoustic signal, while it is transcribed in neuronal aggregates along the auditory neuraxis. Hence, capital for the argumentation above is proving that FFRs are generated in the auditory brainstem, as suggested by seminal studies [61]. A recent influential MEG study reported a major contribution from the AC, with a right dominance [62], yet, source modeling of the scalp-recorded FFR confirmed its anatomically distributed generation, including the cochlear nucleus (CN), the IC, and the AC, and showed that the relative contribution of these sources varied as a function of sound frequency [63], owing to the synchronization cutoff of the AC at ~100 Hz [64]. Confirming evidence comes from a recent study from our group, which investigated the sources of the FFR through MEG recordings elicited to low- (89 Hz) and high- (333 Hz) tone frequencies [65•]. The results confirmed the contribution of the entire auditory hierarchy (CN, IC, MGB, and AC) to the generation of the FFR, with the AC being not significantly activated for the high-frequency tone (Figure 2). Current views support this multiple-generator hypothesis, and posit that their relative contributions may vary depending on factors such as recording techniques, stimulus features, and participant profiles [66••]. By implementing appropriate methods, such as brainstem-constrained inverse solutions (e.g. [52•]), presentation of high-frequency stimuli [65•], or analyzing neuronal activity elicited at very short latencies to

Figure 2



Current Opinion in Behavioral Sciences

The FFR as a proxy of subcortical auditory function. Distributed source modeling of the neural generators of the FFR as resolved with MEG shows neural sources along the entire auditory hierarchy, which contribute to surface responses in a frequency-dependent manner [63•]. **(a)** The time domain MEG FFR elicited to pure tones of low (89 Hz, blue) and high (333 Hz, red). The plots represent the grand-average across n = 19 participants from one single MEG channel; the upper inset shows the FFT transformation of the MEG recordings, displaying maximal spectral power at the eliciting tone frequency. **(b)** Regions of interest (ROIs) in the subcortical auditory system used to compute the amplitude spectrogram during the FFR time course (shown in blue [left] and red [right] for the low- and high-frequency tones, respectively). For statistical analysis, the peak at the frequency of interest was compared with that in the spectrogram of the baseline (i.e. the MEG activity that preceded the stimulus presentation in each trial). Sources were considered activated if the FFR peak exceeded significantly that of the baseline. (ROIs for primary AC as well as control areas are not shown). **(c)** The auditory-to-control ratio — a scalar computed to estimate the degree of activation of each source and to each frequency (see [63•] for details) — highlights the distribution of sources contributing to the generation of the surface FFR. **(d)** Of note, for the high-frequency tone (red), the cortical source was not engaged, suggesting that appropriate manipulations of stimulus frequency yield genuine subcortical FFRs.
Modified with permission from [63•].

continuous speech streams (< 10 ms, precluding cortical contribution) [67,68], I suggest that the FFR still provides a valuable proxy of subcortical auditory processing.

Conclusions and future directions

From the literature reviewed here, there is convincing evidence that both at the levels of midbrain and thalamus, complex computations occur subserving auditory cognition. Two independent areas of research support this view: predictive coding and the encoding of speech sounds, and both were the focus of this review. However, it is also currently unclear whether these computations emerge intrinsically in the subcortical nuclei, or are inherited from the AC via the corticofugal pathways. Novel experimental designs combining predictions driven by local statistics and higher-order contingencies [33], such as those related to expectations or task instructions, may help clarifying the interplay between bottom-up and top-down contributions to these processes. Furthermore, the specific contributions of the IC and the MGB to both predictive coding and speech encoding should be extended, as only few studies have addressed the two structures simultaneously. For example, the FFR described above is a compound response recruiting contributions from the entire neuraxis, but the specific roles of the collicular and thalamic relays to speech encoding remain to be clarified. Other areas of research pertaining to auditory cognition were not addressed here because their previous little interest beyond the cortex, but may provide new perspectives. For example, research on statistical learning of language, particularly of lower-level components (such as phonemes and syllables), entails both the neural encoding of speech and a predictive coding perspective [23,69–71], and may hence bring novel insights. This research has focused on cortical activity [69], with some exceptions involving the hippocampus [72], and therefore invites an examination of the potential role of the subcortical auditory system in driving statistical learning of different linguistic structures.

Several methodological developments have been put forward, such as the recording of anatomically resolved FFRs to speech [52•], the use of MEG [49,62,65•,66••], or brainstem recordings to continuous speech [67,68]. Both animal and human research addressed predictive coding, but animal research was scarce regarding the neural encoding of speech (e.g. [73]), and misses the complexity of linguistic processing carried by humans. However, animal studies have the advantage of allowing direct recording of activity in specific subdivisions of the anatomical stations of the subcortical auditory system (IC, MGB), while human EEG studies have poor spatial resolution, despite similar temporal accuracy. A potential overcoming for this latter limitation may come from the application of ultra-high-field (7 tesla or above) fMRI to map functional activation of resolved subregions of the subcortical auditory system. Although this approach has been used, with regard to auditory cognition, to map speech encoding the primary auditory thalamus [34,36], several studies have shown its potential to map the functional specialization of IC (its spatial frequency selectivity and tuning [74]), and MGB [75]. Furthermore, detailed ultra-high-field MRI 3D atlas with both activation (fMRI) and connectivity (diffusion MRI) maps has been provided [76], which can guide future research. On the other hand, animal studies allow also the direct manipulation of neural activity, while attempts to inhibit the AC in humans to test genuine contributions of IC to speech encoding were unsuccessful [77].

In summary, both human and animal research implementing novel designs combining different generative models of the sensory environment with complex sequences entailing linguistic statistics at different structural levels, appear as a promising strategy. Human research addresses the core of cognitive function, but the EEG methodology has poor spatial resolution, while MRI approaches miss the rich temporal dynamics intrinsic to the acoustic environment. In contrast, animal research is limited about questions pertaining to cognition, but may provide insights regarding the involvement of specific subdivisions of auditory stations, not yet available to human research. Together, these approaches will provide a comprehensive view of the intrinsic computations of the subcortical auditory system that contribute to auditory cognition.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A study that nicely examines the contribution of the corticofugal pathway to predictive coding in the subcortical auditory system. The authors recorded stimulus-specific adaptation and prediction errors in the IC of the awake mouse, and inactivated the corticofugal bundle with optogenetics. Results showed that whereas stimulus-specific adaptation was unaffected by inactivation, predictions errors in IC were decreased, thus supporting the view that subcortical prediction error is driven by top-down modulation.

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An investigation of the effects of the prenatal exposure to music on brainstem responses to speech. The authors recorded FFRs elicited to a speech sound (/da/ for half the sample; /oa/ for the other half) right after birth in neonates, and compared responses from babies that were exposed on a daily basis to music during pregnancy (third trimester) with those from babies not exposed at this rate. Results showed enhanced responses in exposed babies, thus demonstrating that brainstem experience-dependent plasticity relevant for speech processing occurs during the fetal period.

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