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Review

From sensation to percept: The neural signature of auditory event-related potentials

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ABSTRACT

An external auditory stimulus induces an auditory sensation which may lead to a conscious auditory perception. Although the sensory aspect is well known, it is still a question how an auditory stimulus results in an individual's conscious percept. To unravel the uncertainties concerning the neural correlates of a conscious auditory percept, event-related potentials may serve as a useful tool. In the current review we mainly wanted to shed light on the perceptual aspects of auditory processing and therefore we mainly focused on the auditory late-latency responses. Moreover, there is increasing evidence that perception is an active process in which the brain searches for the information it expects to be present, suggesting that auditory perception requires the presence of both bottom-up, i.e. sensory and top-down, i.e. prediction-driven processing. Therefore, the auditory evoked potentials will be interpreted in the context of the Bayesian brain model, in which the brain predicts which information it expects and when this will happen. The internal representation of the auditory environment will be verified by sensation samples of the environment (P50, N100). When this incoming information violates the expectation, it will induce the emission of a prediction error signal (Mismatch Negativity), activating higher-order neural networks and inducing the update of prior internal representations of the environment (P300).

Contents

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1. Introduction

Sounds enter the auditory canal, travel through to the tympanic membrane and cause vibration of the auditory ossicles. The ossicles, comprising the malleus, incus and stapes transmit the sound from the air-filled ear canal to the fluid-filled cochlea. The inner hair cells of the cochlea innervate the afferent nerve fibers of the cochlear nerve, which joins the vestibular nerves to form the vestibulocochlear nerve (i.e. cranial nerve VIII) after which the now re-encoded information travels through the brain, passing intermediate stations from brainstem up to the primary auditory cortex and associated brain areas. The auditory stimuli are processed by the brain, comprising not only the classical pathway, which has a tonotopic distribution and projects to the auditory cortex, but also the non-classical pathway. The non-classical pathway, also known as the extralemniscal system, is phylogenetically the oldest system and has a non-tonotopic distribution. It starts at the brainstem in the cochlear nucleus (Cervera-Paz et al., 2007) and via connections at the inferior colliculus, it projects to the medial and dorsal division of the medial geniculate body of the thalamus to the amygdala, which connects to the secondary auditory cortex and association cortices (Aitkin, 1986; Møller, 2003).

Two different models of perception have been developed (Freeman, 2003). One which assumes that the brain passively absorbs sensory input, processes this information and reacts with a motor and autonomic response to these passively obtained sensory stimuli (Freeman, 2003). However, a second model of perception posits that the brain actively looks for the information it predicts to be present in the environment, based on an intention or goal (Freeman, 2003). This goal or intention can drive action which will influence perception. Perception in this latter model can be seen as the result of top-down indirect information creation, depending on what is expected in the sensory environment and relying on what is stored in memory (Hume, 1739; Merleau-Ponty, 1945). The major difference between passive perception and active perception is that active perception critically depends on predictions of what is likely to occur in the environment, based on intentions or goals arising from experience.

In the following sections we will discuss the auditory processes from sensation to perception by making use of auditory evoked potentials (AEPs), in which we hypothesize that auditory perception is derived by bottom-up and top-down processes jointly. We will interpret this in the light of the Bayesian brain model (Friston, 2010; Knill and Pouget, 2004), in which the brain predicts which information will arrive and when this will happen. Moreover, we will focus on the alterations of latency and amplitude of AEPs in tinnitus, i.e. the perception of a sound in the absence of an external auditory stimulus, as it can further unravel the underlying neurophysiological model and it might give us further insights in the influence of tinnitus on the processing of incoming sounds. But for a good comprehension of these sections, we first give a short overview of the neural correlates of the (late) auditory evoked potentials.

2. Auditory evoked potentials

AEPs are the correlates of neural activity elicited by the application of an external sound. In the presence of an intact auditory pathway, the application of an external stimulus will induce an electrical potential at multiple cortical areas, representing the summation of synchronized electrical activity of thousands of neurons in auditory and non-auditory brain regions. The following overview will mainly focus on the neural correlates of the late AEPs obtained with electro-encephalography (EEG) and magneto-encephalography (MEG). In addition, we explicitly mention the brain areas identified with fMRI and intracerebral electrodes to emphasize that the determined areas are almost identical and, hence, not only identified by dipole models. Depending on the latency, AEPs are divided in early, middle or late responses, which are respectively named auditory brainstem responses (ABRs), auditory middle latency responses and auditory late-latency responses (see Fig. 1).

The ABRs, derived from an acoustic stimulus occurring within the first 0–10 ms post-stimulus, are well defined (Moller, 2006b) and comprise five to six consecutive waves reflecting the trajectory of the sound through the brainstem. ABRs are stated not to be influenced by attention (Naatanen and Teder, 1991) and they can be measured in an unconscious state (Moller, 2006b). However, this does not mean that attentional modulation of brainstem activity is not possible. Attention can modulate the brainstem component of the auditory frequency-following responses (FFRs) (Du et al., 2012), which are the sustained evoked potentials generated by continuous presentation of low-frequency tone stimuli based on phase-locked responses of neuron populations, suggesting it is possible to modulate brainstem activity via top-down mechanisms.

The auditory middle latency responses occur within the latency range of 10–50 ms post-stimulus and consist of five peaks (see Fig. 1): P0, Na, Pa, Nb and Pb, of which the P0 is considered to be generated at the higher nuclei of the brainstem and the others right below the auditory cortex. These middle latency responses show a higher variability than the ABRs (Moller, 2006a) and can be modulated by attention (Hansen and Woldorff, 1991) or suppressed by anesthesia (Moller, 2006a).

Although activation of the auditory cortex is a necessary element in the perception of sound, it does not necessarily imply the conscious awareness of the auditory signal. For a stimulus to gain access to the consciousness, a higher-order “awareness” and “salience” neural network has to be co-activated (Langguth et al., 2012; van der Loo et al., 2009). The neural networks underlying the conscious perception of auditory stimuli are more complex and less uniformly identified; therefore, we are mainly interested in the auditory late-latency responses, including the P50, N100, N1–P2 complex, Mismatch Negativity (MMN) and P300.

The P50 is involved in sensory gating and has two main neural generators, the auditory cortex and the dorsal anterior cingulate cortex (dACC) (Grunwald et al., 2003), and possibly the ventrolateral prefrontal cortex (VLPFC) (Korzyukov et al., 2007) (see Fig. 2). This observation suggests that auditory stimuli are processed in parallel, analog to the observations in the somatosensory system (Frot et al., 2008). Moreover, it has been proposed that the extralemniscal system, which projects to the secondary auditory cortex and association cortices, signals that something changes in the auditory environment, the content of which is then processed by the lemniscal tonotopic system ending in the primary auditory cortex. (Jones, 2001; Sherman, 2001). By measuring the P50 amplitude, previous research could not demonstrate significant differences between tinnitus patients and controls, concerning level of arousal or habituation to repetitive sensory stimulation, but they could observe attentional deficits in tinnitus patients compared to controls (Dornhoffer et al., 2006).

The N100 is an event-related potential (ERP) component primarily determined by sensory processing and it has been unambiguously posited that the primary (Huotilainen et al., 1998; Picton et al., 1999; Woods, 1995) and secondary auditory cortices (Lu et al., 1992; Pantev et al., 1995) are the main neural generators. Other involved brain areas are the dACC, as well as the inferior parietal (supramarginal gyrus) and ventrolateral prefrontal cortices (Grau et al., 2007) (see Fig. 2). The N100 is an index of sound detection and is associated with attention-catching properties (Parasuraman and Beatty, 1980; Winkler et al., 1997), rather than subjective contents of perception or discrimination capacities. Furthermore, the

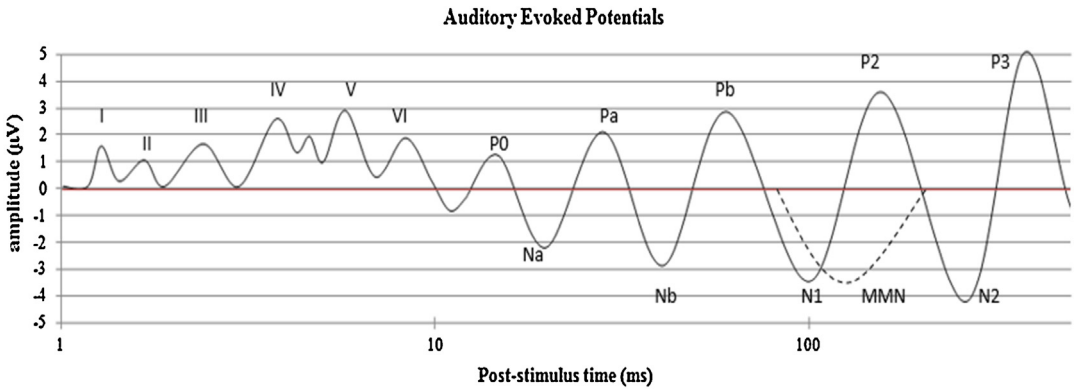

Fig. 1. Overview of the auditory evoked potentials, including the auditory brainstem responses (waves I–VI), the auditory middle latency responses (P0–Pb) and the auditory late-latency responses (N100–P300).

N100, combined with the P200 component, also known as N1–P2, represents the late phase of sensory gating. The specific brain areas involved in sensory gating are still actively discussed, but the areas most often mentioned are the superior temporal gyrus (Thoma et al., 2003), as well as the hippocampus, dorsolateral prefrontal cortex (DLPFC), and thalamus (Alho, 1995; Boutros et al., 2008; Freedman et al., 1996; Korzyukov et al., 2007). Although the N100 is defined as an exogenous component determined by a bottom-up process, previous studies demonstrate that attention can influence the characteristics of this component (Hillyard et al., 1973; Sanders and Astheimer, 2008), suggesting a top-down modulation is possible. In tinnitus patients, mainly increased latencies of the N100 were observed for the targeted (Jacobson et al., 1996; Santos Filha and Matas, 2010) and non-targeted ERP components (Attias et al., 1996), as well as reduced amplitudes (Delb et al., 2008; Jacobson and McCaslin, 2003). Furthermore, it has been shown that tinnitus patients with a mild hearing loss at tinnitus pitch have a more amplitude-dependent N1–P2 response in the tinnitus frequency relative to controls (Kadner et al., 2002).

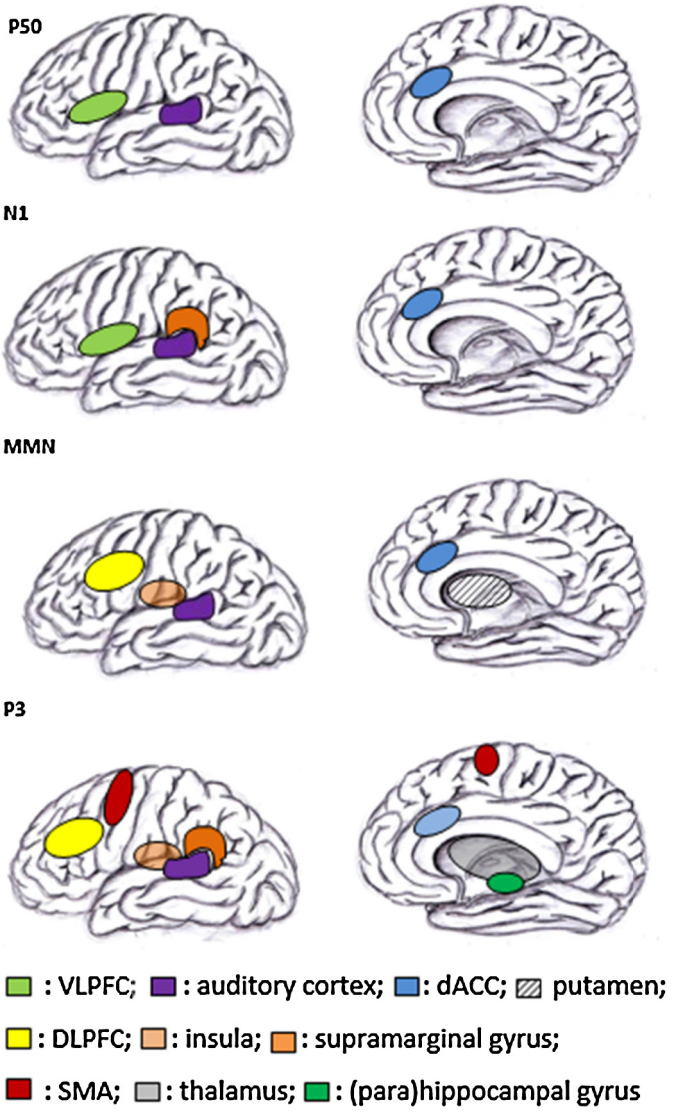

Fig. 2. Neural generators of the P50, N100, MMN and P300.

To delineate MMN the ERPs evoked by the standard stimuli are subtracted from the ERPs evoked by the deviant stimuli of the same sequence (Naatanen et al., 2004). This potential, usually peaking at 150–200 ms, can be elicited by any discriminable change in auditory stimulation, reflecting the neural reaction induced by the deviant stimulus in contrast to the sensory memory trace of the preceding stimuli, even in the absence of a person's attention or in situations of impaired consciousness, i.e. minimal consciousness state and vegetative state. Hence, it is assumed that MMN reflects the automatic auditory change detection process (Escera et al., 1998, 2003). The underlying network involved in eliciting MMN comprises multiple brain areas (see Fig. 2): an auditory-cortex and a fronto-parietal component, as well as the dACC and insula (i.e. salience network) (Alho, 1995; Marco-Pallares et al., 2005; Molholm et al., 2005; Takahashi et al., 2012; Woldorff et al., 1991). In addition to these cortical regions, evidence has been raised about the involvement of the putamen. A recent fMRI study demonstrated increased activity in the anterior putamen reflecting prediction error responses to target omission after predictive versus uninformative cues in different sensory modalities, including auditory (Langner et al., 2011). In tinnitus patients only a few studies looked at MMN using auditory stimuli in different frequency domains. Interestingly, subjects with the most abnormal mismatch patterns were those with the lowest distress values, but even patients with more normal mismatch patterns were not comparable to normal hearing controls as there was a considerable shift in focus of neuronal activation in an anterior direction (Weisz et al., 2004). A recent study, however, demonstrated a decreased amplitude in tinnitus patients in response to deviant stimuli, suggesting that there is a possible deficit in auditory memory mechanisms involved in pre-attentive change detection in tinnitus subjects (Mahmoudian et al., 2013).

The P300 is characterized by a large positive-going wave typically peaking at 300 ms or more after the onset of a rare stimulus,

provoked by a standard oddball paradigm. In contrast to the exogenous potentials previously described, the P300 is an endogenous component, meaning that it is highly dependent on the cognitive context in which a stimulus occurs and the level of attention and arousal (Halgren et al., 1980; Polich and Kok, 1995). In addition, the P300 component has been shown to be insensitive to interstimulus intervals exceeding tens of seconds, implying an active maintenance of previous stimuli in conscious working memory (Polich, 1998; Rugg and Coles, 1995). Moreover, the P300 is widely believed to be a neural signature of the mechanisms required to change the mental model of the environment to make an appropriate response (Polich, 2003). Currently, the underlying brain generators of the P300 are still indecisive. Based on intracerebral recordings, one of the main neural generators is the hippocampus (Halgren et al., 1980; McCarthy et al., 1989). However, the degree of contribution to the scalp P300 is less clear (Halgren et al., 2007) and P300 scalp-recordings did not alter much after medial temporal lobe lesions (Naatanen et al., 2005). Besides the hippocampus, early studies making use of intracranial recorded evoked potentials, EEG or MEG demonstrated the involvement of the thalamus, insula and superior temporal gyrus (Katayama et al., 1985; Okada et al., 1983; Paller et al., 1992; Rogers et al., 1991; Tarkka et al., 1995). Some studies combined EEG with fMRI demonstrating that both techniques indicated nearly the same brain areas involved in the P300 component, i.e. the temporoparietal junctions, supplementary motor areas (SMA), anterior cingulate cortex, insula and medial frontal gyrus (Menon et al., 1997; Mulert et al., 2004) (see Fig. 2). In addition, EEG demonstrated the presence of the P300 component at the left inferior frontal gyrus and right medial temporal gyrus, while fMRI could identify the P300 component in deeper seeded structures, including the thalamus and striatum (Mulert et al., 2004). Two previous studies demonstrated alterations of the P300 in tinnitus patients, in which mainly an increased latency was found without alterations in amplitude (Gabr et al., 2011; Santos Filha and Matas, 2010). Interestingly, many of the brain areas involved in tinnitus overlay the P300 related regions, i.e. insula, SMA, dACC and (para)hippocampal region.

The interpretation of AEPs, and mainly the late AEPs, as well as the meaning of alterations in tinnitus patients, is still under debate. Neurophysiologically, tinnitus has been related to either auditory deafferentation (Eggermont and Roberts, 2004; Jastreboff, 1990; Norena and Eggermont, 2006; Roberts et al., 2010; Weisz et al., 2007), a deficit in noise-canceling (Leaver et al., 2011; Rauschecker et al., 2010), or a combination of both (De Ridder et al., 2013), all of which resulted in an increase of neural excitability of the auditory cortex. Furthermore, tinnitus has been linked to increased synchronization (Tass and Popovych, 2012). Applying this to AEPs, one would expect increased amplitudes of the AEPs, with a possible influence on latency, as well. Moreover, differences in AEP characteristics and its composing frequencies can be expected when sound stimuli correspond with tinnitus pitch, edge frequency or are presented in the frequency domain without hearing loss (Sereda et al., 2013). Currently, however, studies in tinnitus patients are limited and results are rather diverse.

3. From sensation to perception

Currently, the neural pathways of how auditory information reaches the auditory cortex, i.e. sensing the stimulus, are well known, this is in contrast to the limited knowledge about how the auditory stimulus results in a conscious percept. Whereas sensation can be defined as the detection and processing of sensory information, perception is the act of interpreting and organizing this sensory information to produce a meaningful experience of the world and of oneself (De Ridder et al., 2011). Auditory cortex activation evoked by an acoustic stimulus does not necessarily produce conscious auditory perception (Colder and Tanenbaum, 1999). However, auditory perception is possible in the absence of auditory input. More than 80% of people with normal hearing perceive phantom sounds when placed in a soundproof room (Del Bo et al., 2008). Furthermore, some sensations do not reach the level of consciousness. That is, for perception without awareness, the meaning of a stimulus is extracted while the subject cannot consciously identify it or even detect its presence (Dehaene et al., 1998).

Investigating brain activity in patients in a vegetative state or sleep state demonstrated that auditory cortical activity is a prerequisite, but is not sufficient for auditory consciousness (Boly et al., 2005; Laureys et al., 2000). The activity has to be linked to a global workspace in order to gain access to consciousness (Bekinschtein et al., 2009; Dehaene et al., 2006). The global workspace has not been anatomically specified, and might involve multiple subnetworks in order to bring stimulus-related sensory cortex activity to consciousness. This could be related to the fact that a stimulus only has relevance, irrespectively of whether it is externally triggered or pulled from memory, if this stimulus is referenced to the self (Damasio and Meyer, 2009). In this sense, salience refers to the top-down intentionality-driven behavioral relevance of the stimulus (Fecteau and Munoz, 2006).

4. The sensory and perceptual aspects of the late auditory evoked potentials

When we relate the difference between sensation and perception to AEPs, ABRs and auditory middle latency responses might be associated to an auditory sensation, while auditory late-latency responses might be related to the transition from sensation to perception. The sensory aspect can also be defined as the bottom-up process, while perception can be seen as the top-down processing, as it requires input from higher order neural networks (Boly et al., 2011). To obtain a conscious percept, both the strength of the bottom-up process and the top-down attentional amplification, is jointly needed to traverse the conscious threshold. Based on the strength of these different processes, a tripartite model has been proposed, distinguishing subliminal, preconscious, and conscious processing of visual stimuli in the related brain areas (Dehaene et al., 2006). Previous studies have been primarily suggesting that the P50, N1–P2 and MMN are exogenous ERP components with less or no interference of higher order neural networks, while the P300 should be seen as an endogenous component mediated by top-down mechanisms (Bekinschtein et al., 2009). This cut-off between exogenous and endogenous, i.e. sensory and perceptual, is not very sharp and should rather be seen as a transitional process. For example, auditory FFRs are electrical potentials based on precisely phase-locked responses of neuron populations originating in the rostral brainstem (Moushegian et al., 1973; Worden and Marsh, 1968), reflecting the waveform and frequency of the presented sound stimulus. These FFRs are influenced by selective attention, suggesting that top-down perceptual preprocessing in the brainstem, mediated via extensive efferent descending pathways from the cortex, is possible (Galbraith and Arroyo, 1993; Galbraith and Doan, 1995). But, a relevant difference between FFRs and ABRs is that FFRs are generated by the continuous presentation of a low-frequency tone, while ABRs are evoked by a click stimulus. Therefore, it is most likely that the observed top-down processing in the brainstem might be the result of an anticipatory reaction, which can only be present when the stimulus is expected to be present. These observations indicate that even the earliest auditory processes can be influenced by top-down attentional processes.

It should be noted that attention has to be distinguished from consciousness, as selective attention can influence the N1

amplitude (Hillyard et al., 1973; Sanders and Astheimer, 2008), even when the stimulus is only subliminally processed, i.e. without a conscious percept of the stimulus (Dehaene et al., 2006). Attention should rather be considered as a prerequisite of conscious processing. Mainly in the presence of multiple stimuli, selective attention, i.e. the distinction of relevant from irrelevant stimuli based on its saliency or relevance, is required to culminate in a conscious percept (Dehaene et al., 2006). Both the inferior parietal and ventrolateral prefrontal cortices, i.e. the main neural generators of the N1 component, belong to the ventral frontoparietal network, which can send a "circuit breaking" signal when attention needs to be redirected from a cognitive ongoing activity toward a salient or unexpected behaviorally relevant stimulus (Corbetta and Shulman, 2002). This ventral network can therefore, mainly be seen as a stimulus driven, i.e. bottom-up, network influencing higher-order attentional processes. Additionally, activity in both the anterior cingulate cortex and superior temporal gyrus in the N1 time-frame correlated with task difficulty and mental effort, suggesting the representation of early top-down influences to information processing in the sensory areas (Mulert et al., 2007).

In addition, MMN reflects the process of automatic error detection, i.e. the neural expression of a conflicting internal representation of the environment with the incoming sensory stimulus, even present in states of impaired consciousness. MMN is initially generated at the auditory cortex (Giard et al., 1990) and as a result frontal processes, including the dACC (Marco-Pallares et al., 2005; Molholm et al., 2005; Takahashi et al., 2012) and DLPFC, are triggered (Dittmann-Balcar et al., 2001; Molnar et al., 1995; Naatanen et al., 2005). The DLPFC is activated with a delay of approximately 8 ms (Rinne et al., 2000), which might underlie the involuntary attention switch to deviant auditory stimuli preperceptually detected in the auditory cortices (Giard et al., 1990). The insula, on the other hand, is known to be involved in representing bodily states (Craig, 2002), including arousal induced by mental or physical stressors (Critchley et al., 2000; Pollatos et al., 2007), which suggests that this cue-induced insula activity may reflect the general alerting property of the cue (Langner et al., 2011). In addition, it should be noted that although this change-detection process is considered an automatic process, top-down influences are present, and even MMN amplitude alterations are observed during anesthesia and sleep (Heinke et al., 2004; Ruby et al., 2008).

The P300 is primarily determined by higher order cognitive, top-down processes and can only be elicited in a state of awareness, although stimuli characteristics have an impact on the P300 response as well (Jeon and Polich, 2003). The early outcome of comatose patients in terms of consciousness was remarkably better if a rule violation effect, i.e. a P300 response, was present (Faugeras et al., 2011). Additionally, it was demonstrated that mainly the backward, i.e. top-down, connection from frontal to superior temporal cortex correlated with the level of consciousness (Boly et al., 2011) and that only in vegetative state patients a significant impairment of this top-down connection was observed. Based on these observations, it has been hypothesized that these patients have an impaired top-down prediction of sensory stimuli, resulting in an impaired perception and the absence of endogenous ERP components (Boly et al., 2011). Moreover, the insula, together with the dACC, have been referred to as the salience network (Seeley et al., 2007), implicated in the top-down detection of salient events and coordinating appropriate responses (Medford and Critchley, 2010; Menon and Uddin, 2010). Additionally, frontal areas including the SMA are assumed to be related to the perception of sound, similar to their involvement in the conscious perception of somatosensory stimuli, as it has been hypothesized that theta oscillations in the SMA are essential for conscious perception during maintenance intervals of visual stimuli (Melloni et al., 2007).

As previously mentioned, these bottom-up and top-down processes are jointly needed to gain a conscious percept. The sensory stimulus has to contain sufficient power in order to cross a dynamic threshold, consequently inducing a higher order top-down amplification process. A sensory stimulus incapable of crossing this threshold will be subliminally processed, i.e. without the activation of a more global, higher order neural network. Even when a strong stimulus is present, a lack of top-down attentional amplification will lead to pre-consciousness processing of the stimulus, with a temporary buffering of the stimulus until the more global neural network has been released (Kouider and Dehaene, 2007). Only activation of the global, frontoparietal neural network will result in the conscious percept of a sensory or auditory stimulus.

5. Bayesian surprise

It has been proposed that a Bayesian system might be a basic principle for brain function. The model of the active brain corroborates with the idea of the Bayesian brain. The basic idea is that the brain uses probabilistic inference for perception and perceptual learning (Doya, 2007). That is, Bayesian inferences are made based on an internal generative model, which comprises a distribution over sensory data given an external cause (the sensory data likelihood) and a prior distribution over different causes (Friston, 2010). It has been suggested that these Bayesian mechanisms are encoded by neuronal populations whose responses to novel sensory input are interpreted as dynamics induced by the violation of prior expectations (Mumford, 1992; Rao and Ballard, 1999; Strange et al., 2005). MMN (Naatanen et al., 2011) and P300 (Polich, 2007) are identified as the typical neurobiological markers of violation of prior expectations. These two ERP components have recently been associated with Bayesian surprise (Baldi and Itti, 2010; Itti and Baldi, 2009). Bayesian surprise quantifies the effect sensory input has on the internal generative model as the divergence between the encoded prior and posterior distribution over causes, in other words the prediction error. Representing Bayesian surprise enables an observer like the brain to efficiently and dynamically encode the statistical (ir)regularities of its environment (Ostwald et al., 2012). Interestingly, the unexpected omission of an environmental factor induces an error prediction response, as well (den Ouden et al., 2009; Langner et al., 2011), indicating that the observed neural activity changes are not solitarily related to characteristics of the sensory input, i.e. the bottom-up process, but rather a detection of a mismatch between the internal expectations and the incoming information. Furthermore, when the expectations of the brain conflict with the sensory input, the dACC and anterior insula are activated (Ullsperger and von Cramon, 2003), although only an activation of the dACC will be present if this mismatch leads to a change in behavior (Bush et al., 2002). Thus, comparing the representations of intended and actual responses leads to error detection by mechanisms analogous to the error detection based on external feedback (Ullsperger and von Cramon, 2003). Activation of these areas will focus attention toward contextual, novel auditory, visual and somatosensory stimuli (Downar et al., 2000; Huettel et al., 2002; Ranganath and Rainer, 2003). Hence, both brain areas have a significant influence on a person's behavior as they appear to form a salience network, differentiating essential internal and extra-personal stimuli. This salience network not only guides behavior (Mekhail et al., 2011; Seeley et al., 2007), but it also brings the relevant, externally presented stimuli to awareness (Wiech et al., 2010).

Based on the Bayesian brain model even the early processing of sensory stimuli has to be influenced by higher-order neural networks, as they are the results of the active search for a certain goal or intention. Furthermore, it has been shown that top-down

processing from higher-order areas plays an unequivocal role in an individual's conscious perception (Boly et al., 2011). This top-down processing requires an internal, high-level model of the acoustic environment as well as prior knowledge of the properties and dependencies of the objects in it. It even has been shown that modality-specific expectancy induces activation of relevant and inhibition of irrelevant brain areas, leading to a reduction of the detection threshold (Langner et al., 2011). This has been stated to be partially related to an anticipatory suppression of irrelevant noise (Mozolic et al., 2008), i.e. an active filtering of unwanted information, resulting in a more efficient processing of relevant environmental information. Moreover, while bottom-up sensory input would specify the state of the brain, the subsequent top-down activation (i.e. consciousness) would be an expression of the existing dispositions of the brain to be active (Llinas and Pare, 1991). As such, the brain can be viewed as a system that basically responds to changing eventualities and statistical regularities, with information interacting with, rather than determining the operation of the system (Raichle and Mintun, 2006). Consequently, this Bayesian prediction can be verified by sensation samples (P50, N100) of the environment and the updated prediction (based on the MMN prediction error) can subsequently be used as the basis for context based perception (P300).

6. Tinnitus interpreted in the context of the Bayesian brain model

The aforementioned Bayesian brain model can be applied to the concept of tinnitus, as well (De Ridder et al., in press). The Bayesian brain concept proposes that the brain holds a prior belief, a template, of what it is going to encounter in the environment. It makes a prediction, which is updated by active sampling of the environment. This updated, posterior belief then becomes the new reference, the new prior belief for the next information-seeking cycle. This suggests that the brain processes whatever is different from what is expected by comparing sensory input to the prior belief. This involves a frequency, amplitude and location specific auditory memory (Naatanen et al., 1993). It has been suggested that the auditory MMN is a multicellular representation of auditory memory at a single cell level in the auditory cortex (Ulanovsky et al., 2003). Moreover, it has been proposed that the extralemniscal system samples the environment for any change, and that the lemniscal system subsequently transmits the content of this change (Jones, 2001; Sherman, 2001). Thus, only the extralemniscal system is required to maintain an auditory memory trace, as has been shown before (Kraus et al., 1994). The extralemniscal or non-specific auditory system connects to the dACC and insula (Langers and Melcher, 2011), where the detected change is translated into salience (Seeley et al., 2007) required for perception of the external auditory stimulus (Sadaghiani et al., 2009). Thus any prediction must be processed in the dACC and auditory cortex, which is indeed noted in the P50 component of the AEP (Kurthen et al., 2007). But, the detection of a change is probably already detected in the brainstem, as the FFR demonstrates (Galbraith and Arroyo, 1993; Galbraith and Doan, 1995). Although, it should be noticed that the detection of a change does not imply that the stimulus passes the threshold of auditory awareness, as suggested by Dehaene's version (Dehaene et al., 2006) or Baars' global workspace model (Baars, 2005). It requires reverberating activity with other consciousness permitting brain areas. These can be retrieved in the longer latency AEPs.

The N1 component has been related to selective attention, mediated by the VLPFC. Mainly, by actively switching attention to behavioral relevant sound stimuli, incoming stimuli will constantly update the brain's internal representation of the acoustic environment based on a certain attention or goal. One of the most consistent findings in tinnitus patients are the reduced N1 amplitudes and increased N1 latencies possibly reflecting the decreased ability of switching attention (from their tinnitus) to externally applied stimuli (Delb et al., 2008; Jacobson and McCaslin, 2003), resulting in a suboptimal internal representation of the environment.

After detection of the incoming stimulus, the auditory input will be automatically compared with the internal representation of the environment, inducing a cortical error detection response if incoming information does not match prior expectations. A recent study demonstrated that tinnitus patients have decreased MMN amplitudes when auditory stimuli outside the deafferented frequency domain were presented, which the authors interpreted as an abnormality in automated central auditory processing involved in pre-attentive change detection (Mahmoudian et al., 2013). They further stated that tinnitus reduces the duration of sensory memory in the auditory cortex. Moreover, the presence of auditory deafferentation in most tinnitus patients leads to topographically restricted prediction errors, related to memory-based temporal or spatial incongruity. However, the absence of an expected stimulus induces a cortical prediction error signal, as well (Arnal and Giraud, 2012; Arnal et al., 2011). As the brain functions in a way to minimize uncertainty, it will attempt to reduce the deprived input by filling-in mechanisms, mediated by inhibition and/or map plasticity of the auditory cortex. Kadner et al. demonstrated that tinnitus patients with a mild hearing loss at tinnitus pitch have a more amplitude-dependent N1–P2 response in the tinnitus frequency, relative to controls (Kadner et al., 2002). This might be the consequence of the underlying neural reorganization of the tonotopic areas induced by auditory deafferentation. If uncertainty cannot be reduced by getting information from the adjacent cortical regions, the missing information can be recalled from the memory stored in the (para)hippocampal region (De Ridder et al., 2012). The involvement of the parahippocampus in tinnitus might be related to the constant updating of the tinnitus percept from memory, thereby preventing habituation (De Ridder et al., 2006). An important observation is that the auditory cortices and the parahippocampal area, the gatekeeper to the hippocampus (Tulving and Markowitsch, 1997), are reciprocally connected (Munoz-Lopez et al., 2010). The parahippocampal region has been suggested to play an important role in the sensory gating mechanism, a process which has been suggested to be impaired in tinnitus patients. Mainly in suffering tinnitus patients, the elicited N1 response, a marker for late sensory gating, was less decreased when repetitive auditory stimuli were presented (Walpurger et al., 2003), meaning that there is less habituation of irrelevant stimuli.

Filling in as a repair for missing information also activates the dACC and insula (Shahin et al., 2009), brain areas that have been associated with MMN and P300. Additionally, the limited studies investigating the P300 in tinnitus patients identified an increased latency while no amplitude changes could be identified, suggesting the overall delay in top-down processing of auditory stimuli.

7. Conclusion and future directions

The goal of this manuscript was to give a short overview of the current knowledge of the neural correlates of the late auditory evoked potentials and to interpret these observations in the concept of the Bayesian brain, which we further applied to the currently limited results in tinnitus patients. Based on these interpretations, we propose some further studies and caveats for AEP studies in tinnitus. We mainly focused on the sequentially activated brain areas in auditory processing by making use of EEG or MEG measurement. As these techniques have a rather low spatial resolution and

the identification of subcortical regions is still a matter of debate, results should be interpreted carefully. Although notion should be made that many of these regions are identified by intracerebral recordings or fMRI, as well.

Based on the current results, it should be said that there is no clear cut-off between bottom-up and top-down processing; it should rather be seen as a transitional, or interactive, process. This corresponds to the Bayesian predictive brain model. If the brain is truly predictive, there should be brainstem evoked potentials that are already influenced by top-down processes even before perception is possible, i.e. filtering auditory input at an early stage, compatible with a Bayesian model of information processing, as has been proposed for the visual system (Lee and Mumford, 2003). The FFR can indeed be attentionally modulated, even at the level of the brainstem (Du et al., 2012).

In conclusion, future research making use of AEPs could be of great interest to further unravel the fundamental neurobiological mechanisms of tinnitus and auditory perception. But, future studies should take into account that the presented tones should be adjusted to the individual tinnitus pitch and frequency region of hearing loss, one of the most prominent shortcomings of the currently published studies. In addition, it would be of great interest to not only look at the AEP characteristics, but also at different composing frequencies.

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