Auditory event-related potentials

Auditory event-related potential (AERP), auditory evoked potential (AEP), auditory evoked field (AEF)

Auditory event-related potentials are electric potentials (AERP, AEP) and magnetic fields (AEF) generated by the synchronous activity of large neural populations in the brain, which are time-locked to some actual or expected sound event (cf. the definition of ERP in **EEG/MEG Evoked/Spontaneous Activity).**

Measurement and Derivation of AERPs/AEFs

AERPs are derived from the continuous electro-/magnetoencephalogram (EEG/MEG, see **EEG/MEG Evoked/Spontaneous Activity**) by extracting segments of the signal (epochs) time-locked to some actual or expected acoustic event. AERPs were first recorded by Hallowell and Pauline A. Davis in 1935-36 (Davis 1939; Davis et al. 1939). Because EEG/MEG is typically recorded non-invasively (outside the brain, e.g., from/around the scalp), these measures only reflect synchronous activity of large neural populations (for measuring methods and instrumentation, see **EEG/MEG Evoked/Spontaneous Activity**). Consequently, the acoustic events eliciting detectable AERPs consist of relatively large changes of spectral energy occurring within a relatively short time period, such as abrupt sound onsets, offsets, and changes within a continuous sound, because large acoustic changes affect many neurons within the auditory system and the short transition period synchronizes the responses of individual neurons (Nunez and Srinivasan 2006; cf. **Auditory System (Anatomy, Physiology)**). Furthermore, the expectation of such changes in the auditory input can elicit AERP responses even in the absence of actual stimulation (cf. the *Omitted Stimulus Response* in **Long-Latency AERP Responses**, below).

The EEG/MEG signal mixes together on-going (spontaneous) neuroelectric activity with that elicited by the event. In order to better estimate the brain activity evoked by the event, it is usually repeated several times (typically 50 to 200 trials/sweeps, but up to 2000 times for **Auditory Evoked Brainstem Responses**) and the EEG/MEG segments are entered into some mathematical algorithm extracting the common part of the single-trial epochs. The most commonly used method for extracting AERPs aligns the single-trial epochs by their common onset and averages them point by point (the averaging method; Alain and Winkler 2012). There are many other algorithms for extracting ERPs from EEG/MEG, each based on different assumptions regarding the properties of the event-related response and the spontaneous EEG/MEG activity (for a general primer, see Luck, 2005; for detailed discussion of ERPs, see Handy, 2005; Fabiani et al 2007; for special considerations of MEG/AEFs, see Hansen et al 2010; Nagarajan et al 2012; for AERPs, see Picton 2010; Alain and Winkler 2012).

EEG/MEG signals can contain components up to a few kHz with the faster components mainly originating from lower levels of the auditory system (cf. **Auditory System (Anatomy, Physiology)** and **Auditory Evoked Brainstem Responses**). Cortical contributions are much slower, up to a few tens of Hz. Unless one is specifically looking for very slow (Vanhatalo et al. 2010) or fast responses (Curio 2005), AERP recordings are usually made with bandpass filter settings of 0.01-50 Hz (or 250 Hz for extracting the Middle-Latency Response, see below). AERP amplitudes are typically below 10 µV with the reference (zero) level set to a baseline voltage (unless direct current is recorded), which is usually the average signal amplitude in a time interval preceding the AERP-eliciting event. Although in general, there is no unique solution to the inverse problem of finding the origins (the neural generators) of electromagnetic potentials measured outside the brain, by utilizing anatomy/physiology based constraints, the generators of AERPs can be located with reasonable accuracy in the brain (Nunez and Srinivasan 2006; see also **Brain Imaging Methods**). Due to the underlying physics, magnetic AEFs provide more accurate source localization compared with electric AERPs (Nunez and Srinivasan 2006; Nagarajan et al 2012). On the other hand, MEG only allows one to measure the tangential components of the electromagnetic activity in the brain, whereas EEG represents the full activity (Hansen et al 2010; see **EEG/MEG Evoked/Spontaneous Activity**). For AEFs, however, this limitation of the MEG signal is less severe than for other sensory/cognitive systems (Picton 2010; Nagarajan et al 2012). This is because a large part of the human auditory system in the cortex is located in the Sylvian fissure (see **Auditory System (Anatomy, Physiology)**), thus mostly producing magnetic signals which can be picked up by the MEG device.
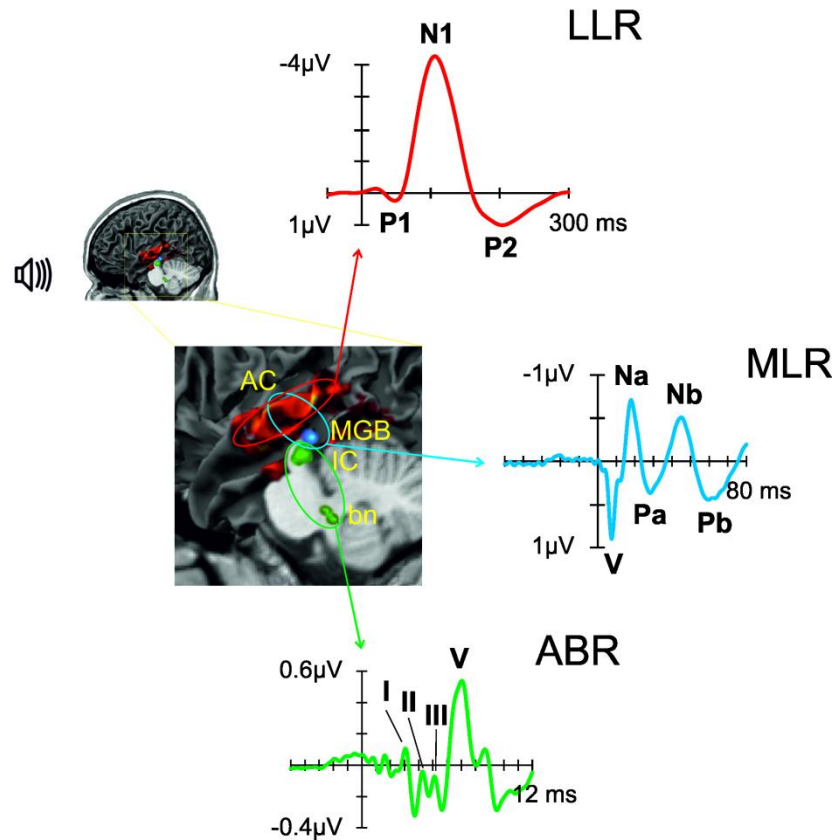
Auditory Event-Related Potentials

Figure 1. The Human Auditory Event-Related Potential (AERP), its main waveforms and its generators in the brain. The human AERP is composed of three groups of waveforms in three different latency ranges: the Auditory Brainstem Response (ABR) elicited within the first 8-10 ms from sound onset (green, bottom panel); the Middle-Latency Response (MLR), elicited within the 12-50 ms interval from sound onset (blue, central panel), and the Long-Latency Responses (LLR) emerging after 50 ms (red, top panel). The anatomical inset (left panel) highlights the main stages of the auditory pathway: "bn", brainstem nuclei (including the cochlear nucleus, the superior olivary nucleus, the nucleus of the lateral lemniscus); "IC", inferior colliculus; "MGB", the medial geniculate body in the thalamus; "AC", auditory cortex. The main assumed brain sources of the different AERPs are marked by colored circles: the ascending auditory pathway of the brainstem for ABRs (green); the thalamo-cortical loops and parts of auditory cortex for MLRs (blue); the auditory cortex for LLRs (red). AERPs can be broken down into a series of waves (see the naming convention in the main text).

Figure 1 illustrates the progression of stimulus-related neuronal activity through the auditory system and the corresponding series of positive and negative waveforms observable in the AERP response. The earliest detectable responses (< ca. 10 ms after the acoustic event) originate from subcortical brain

structures and are termed the *Auditory Brainstem Response* (ABR; cf. **Auditory Evoked Brainstem Responses**). These are followed by AERP responses of thalamo-cortical origin (mainly from the primary auditory cortex), termed the *Middle-Latency Response* (MLR), elicited during the ca. 10-50 ms post-event latency range. The waveforms following are called *Long-Latency Responses* (LLR) and they originate largely from auditory cortex, but may also include contributions from parietal and frontal areas.

ABRs are referred to by Roman numerals set in the order of their elicitation. MLR waveforms are usually denoted by their polarity at the vertex (approximately the top of the head); P for positive and N for negative polarity waves, and a letter or a number (see Figure 1). There are two conventions for the numbers in referring to LLRs: They either denote the serial order of the response starting with the first detected response (Davis 1939; Davis et al. 1939), termed N1, or they denote the typical peak latency of the waveform, such as P50 (the same as Pb or P1). However, as more and more responses elicited with the same polarity and in overlapping latency ranges have been discovered, both notations have become equivocal. Therefore, some recently discovered AERP responses are denoted by acronyms referring to their functional aspects, such as ORN (Object Related Negativity) or MMN (Mismatch Negativity) (for a detailed description of the variety of ERP responses, see Luck and Kappenman 2012; for AERPs, Picton 2010; Alain and Winkler 2012). Magnetic response fields are usually marked by the letter 'm' appended to the name of the corresponding (A)ERP (e.g., N1m or N100m).

Beyond the categorization based on the ERP peak latency there are two other typical distinctions in use. ERPs are termed obligatory or exogenous if they are elicited by each event irrespective of its relation to preceding or concurrent events or the person's task, motivations, knowledge, etc. ERP components elicited only when there is a certain relation between the event and other events or some aspect of the person's mental state are termed endogenous. Another distinction refers to the person's voluntary activity with respect to the given stimulus event. ERP responses only elicited when the person has some explicit task involving the event (task-relevant even) are termed "active" ERP responses, while those elicited irrespective of the person's task (task-irrelevant) are termed "passive" ERP responses.

However, waveforms (peaks and dips) are not the true building blocks of ERP responses. The brain is a massively parallel processing instrument. Therefore, at any given moment of time, multiple processes may contribute to the observable waveform. For a neurophysiologically and functionally more meaningful decomposition of the complex neuroelectric response, one should be able to delineate how each of the concurrent processes contributed to the observed neuroelectric activity. This objective is reflected by Näätänen and Picton's (1987) definition of an ERP component: '... we define an EP "component" as the contribution to the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by a specific pattern of input' (p. 376). Thus a component is defined by two criteria: 1) it should have a specific generator structure (e.g., secondary auditory and frontal cortices) and 2) it should be specific to some experimentally definable stimulus configuration (such as stimulus change after several stimulus repetitions). One could amend this definition with the person's task/goals/knowledge regarding the given stimulus configuration (e.g., instructed to respond to the given stimulus event). However, the criteria set up by the above definition are seldom met in ERP research. This is partly due to limitations in separating generators (i.e., they are

usually distributed over an area in the brain and concurrently active processes often occupy areas very close, possibly even overlapping each other) as well as not knowing what stimulus configurations are handled by the same processes in the brain (are all expectation violations processed in the same way? – probably not). Thus in practice, the majority of ERP research reports use the terms "waveform" and "component" interchangeably, sometimes linking the effects of multiple manipulations to the same waveform, while at other times, attempting to separate the specific generator process affected by a given stimulus or state variable.

There are many different processes, which can be reflected in AERPs. Early, obligatory responses typically reflect processes extracting auditory features, such as pitch, intensity, location, etc. Most AERP responses are sensitive to the amount of sound energy change and also to some aspects of the sound presentation rate or the ratio between sound and silence in time. These attributes of auditory stimuli belong to the primary descriptors of sound events as studied in psychoacoustics (Zwicker and Fastl 1990). There are also AERP responses indicating the presence of automatic memory for sounds (Cowan 1984; Demany and Semal 2007) and predictive processing of the auditory input (Friston and Kiebel 2009; Winkler et al. 2009). Further, some AERP responses reflect processes involved in auditory scene analysis (Bregman 1990), the separation of concurrently active sound sources in the environment and the formation of auditory perceptual objects (Griffiths and Warren 2004; Winkler et al 2009). Many AERP responses are also sensitive to attentional manipulations, including the active storage of sounds, selective attention, and target identification (Cowan 1988; Näätänen 1990). AERP responses specific to music and speech perception are described in the corresponding entries (**Music Processing in the Brain** and **Electrophysiological Indices of Speech Processing**). Therefore, AERPs have been extensively used to test theories of perception (e.g., Bregman 1990; Friston 2005), memory (e.g., Broadbent 1958; Baddeley and Hitch 1974; Cowan 2001), and attention (e.g., Broadbent 1958; Lavie 1995) and in recent years they have received increased interest from computational modelling (e.g., Garrido et al 2009; May and Tiitinen, 2010; Wacongne et al 2011) as well as from clinical applications (e.g., Picton 2010; Näätänen et al 2012).

In the following, we shall describe the most important middle- and long-latency AERP responses (for the auditory brainstem responses, see **Auditory Evoked Brainstem Responses**).

Middle-Latency AERP Responses

Discrete auditory stimuli elicit a sequence of very small (<1 μV) negative and positive waveforms in the 10-50 ms post-stimulus latency range, termed the Middle Latency Response (MLR). These responses can usually be best seen on signals recorded from the vertex with a mastoid or neck electrode as reference. The names and typical latencies of MLRs when elicited by click stimuli are: *N0* (10 ms), *P0* (15 ms), *Na* (20 ms), *Pa* (30 ms), and *Nb* (~40 ms) (see Picton 2010). An additional later waveform, the *Pb*, which peaks at about 50 ms from sound onset, is not always included amongst the MLR components, because it can also be obtained as the P50 or P1 with the filter bandwidth optimised for measuring LLRs (Regan, 1989; see below). Because of their small amplitude and specific spectro-temporal characteristics, recording the MLR requires a) averaging across close to 1000 responses, b) appropriate filter settings (15-200 Hz; Bell et al. 2004), and c) careful removal of electromagnetic interference from power supplies

and lines, as a large part of the power of the MLR responses falls into the 50-60 Hz range. It is also important to avoid artefacts stemming from the myoelectric activity of the postauricular muscle (PAM), which lies behind the ear and is activated by loud sounds. This is usually achieved by placing the reference electrode on the neck or the sternum (Bell et al. 2004). Optimal sounds for eliciting clear MLRs are chirps and clicks, which have sharp onsets and a broad spectrum. Pure tones elicit MLRs of somewhat different morphology and smaller amplitude (Borgmann et al. 2001). However, MLRs can be obtained even with low-intensity tone bursts and relatively independently of the arousal level (Jones and Baxter 1988).

No hemispheric asymmetry was found for MLRs as a function of the stimulated ear (Starr and Don 1988). Based on precise structural maps of individual brains, the spatiotemporal pattern of neural activation giving rise to MLRs has been identified in supratemporal auditory areas using either current estimates derived from intracerebral recordings (Yvert et al. 2005) or equivalent dipole source modelling of scalp-recorded electric brain potentials (Yvert et al. 2001). These studies localized the earliest cortical activity (P0) at 16–19 ms from sound onset in the medial portions of Heschl's sulcus (HS) and Heschl's gyrus (HG), which likely correspond to primary auditory cortex (PAC). Na generation resulted from activity in more posterior regions of the same HS and HG areas. During the Pa/Pb complex, which includes also the Nb, the electric brain activity propagates in postero-anterior and medio-lateral directions in HG to the Planum Temporale (PT) and then to more anterior parts of the Superior Temporal Gyrus (STG), which correspond to secondary auditory areas. Also, frontal and parietal brain regions contribute as early as 30 ms from sound onset (the P30m AEF response) to MLR (Itoh et al. 2000). Animal studies have suggested that MLRs involve parallel thalamocortical activation of areas 41 (PAC), and 36 (parahippocampal gyrus), while human lesion studies have implicated contributions from thalamic projections to Pa (Kraus et al. 1982) and Na (Kaseda et al. 1991), supporting a thalamo-cortical interaction in MLR generation.

With increasing sound intensity, MLR component latencies decrease while the amplitudes increase, although these effects may not uniformly apply to each component (e.g., Na, but not Pa; Seki et al. 1991; Althen et al. 2011). Galambos et al. (1981) found a systematic reversed U-shaped relationship between the MLR amplitudes and stimulus presentation rate. At slow rates (≤10 Hz), peak-to-trough amplitudes are rather small (0.4 μV) and they reach the maximum of 1 μV by about 40 Hz presentation rate. This twofold increase in amplitude is due to superimposition of MLRs elicited by successive sounds. In contrast, at stimulation rates below and above 40 Hz out-of-phase responses to successive MLR responses cancel out each other. Some authors interpret this finding in terms of the "steady state" potentials (oscillatory activity generated in sensory cortical areas that is time-locked to the periodicity of stimulus presentation; typically measured from visual and somatosensory cortical areas; Rees et al. 1986). Other authors assume that this phenomenon reflects the contribution of transient early evoked gamma-band oscillations to the auditory MLR (Basar et al. 1987; Pantev et al. 1991; Müller et al 2001; see **EEG/MEG Evoked/Spontaneous Activity**). Based on the stimulus-driven properties outlined above, MLRs have been considered exogenous AERP components. However, this view has been challenged by studies showing that MLRs are enhanced by strongly focused attention as early as 20 ms from sound onset (Woldorff and Hillyard 1991; Woldorff et al. 1993; cf. ***Attention-Related AERP Responses*** below),

and that MLR amplitudes are modulated as early as 50 ms from sound onset by task difficulty and whether or not a motor response is required (Ninomiya et al. 1997). Further, a recent series of studies has shown that MLRs are sensitive to stimulus probability in a feature-specific manner (Grimm and Escera 2011) with infrequent frequency changes enhancing the Pa (Slabu et al. 2010) and Nb (Grimm et al. 2011; Alho et al. 2012), whereas location changes enhance the Na (Sonnadara et al 2004; Grimm et al. 2012; Cornella et al. 2012). These results suggest that the MLR components reflect processes subserving higher-order sensory/cognitive functions.

Long-Latency AERP Responses

The auditory *P1* (*P50, Pb*; Figure 1) component is at the border between MLR and LLR. In fact, when recorded and analysed with the filter setting most useful for deriving MLRs it is termed the Pb (see ***Middle-Latency AERP Responses***, above). Using the parameters better suited for assessing LLRs, it typically peaks at about 50 ms from stimulus onset, appearing with positive polarity at the vertex and with reversed (negative) polarity at electrodes placed on the other side of the Sylvian fissure (e.g., electrodes placed over the mastoid apophysis). P1 is the first wave of the P1-N1-P2 obligatory exogenous AERP complex. It is thought to be generated bilaterally in primary auditory cortex, somewhat larger contra- than ipsilaterally for pure tones (Godey et al. 2001) and for other types of pitch-evoking sounds (Butler and Trainor 2012), with some spreading of the neuroelectric activity over its time course (Yvert et al. 2005). P1 is often used as a landmark for primary auditory cortex in AERP and AEF studies aimed at localizing the AERP components. Similarly to other obligatory AERP responses, P1 is highly sensitive to stimulus features and presentation rate (fully recovering within a few hundred milliseconds) as well as to attentional manipulations (Picton, 2010). The P1 was initially assumed to reflect neural activity involved in extracting auditory features (e.g. Näätänen and Winkler 1999). Recent evidence also links this response with the automatic separation of auditory streams (Gutschalk et al. 2005; Snyder et al. 2006; Szalárdy et al. 2013; cf. **Auditory Perceptual Organisation**): The amplitude of the P1 component has been found to be modulated by whether a sequence with two interleaved sounds (e.g., ABABAB..., where 'A' and 'B' denote two different sounds) was perceived as a single coherent stream or in terms of two concurrent streams of sound (one made up of the 'A' and the other by the 'B' sounds).

The auditory *N1* (*N100; Figure 1*) wave was the first AERP response discovered historically (Davis et al. 1939) as it is the most prominent deflection at the vertex. It is elicited by abrupt changes in sound energy, such as sound onsets and offsets (Näätänen and Picton, 1987). N1 typically peaks with negative polarity over the vertex ca. 100 ms after the eliciting event. It is also the most widely studied AERP response, having been linked with virtually any and all assumed auditory processing steps. The N1 wave has a complex generator (and thus subcomponent) structure (Näätänen and Picton, 1987). The subcomponent most tightly related to auditory processes (the supratemporal N1) is mostly located in secondary auditory areas (Godey et al. 2001), but it also overlaps the areas active during the P1 component (Yvert et al. 2005). Similarly to the P1, N1 is larger contralaterally to the ear of stimulation and it is highly sensitive to stimulus features, presentation rate, and attentional manipulations. However, unlike the P1, the N1 recovery is much slower, extending beyond 10 s (Cowan et al. 1993). Further, N1 is sensitive to perceived sound features (e.g., pitch), as opposed to raw spectral parameters (such as the harmonic frequencies of a complex tone; Pantev et al. 1989b), although feature extraction

is not yet complete at the time the N1 wave is elicited (Winkler et al. 1997). The supratemporal N1 also shows both tonotopic (Pantev et al. 1988) and ampliotopic organization (Pantev et al. 1989a); that is, the location of its generator varies with the frequency and amplitude of pure tones. However, the N1 generators are not sensitive to combinations of sound features (i.e., feature conjunctions).

The processes reflected by N1 have been linked with onset and acoustic change detection (Näätänen 1992), feature extraction, sensory memory (Lü et al. 1992; at least for sound features, Näätänen and Winkler 1999) and, recently, with auditory stream segregation (Gutschalk et al. 2005; Snyder et al. 2006; Szalárdy et al. 2013). For example, the length of the silent period after which an N1 with maximal amplitude is elicited by a sound is in good correspondence with the behaviourally measurable duration of auditory sensory memory traces (Cowan 1984). When sounds are presented in a train with <10 s silent intervals between them, the N1 amplitude decreases sharply within the first few presentations, reaching an asymptote within 5-10 presentations (e.g., Cowan et al. 1993). Based on this finding, some authors argue that through adaptation (see **Adaptation in Sensory Cortices, Models of**), the neurons underlying the N1 response may retain all sound information and thus provide the basis for detecting violations of auditory regularities (May and Tiitinen 2010; see also **Auditory Change Detection**). However, this hypothesis is debated in the literature (e.g., Näätänen et al. 2011). The sensitivity of the auditory N1 wave to selective attention initially suggested that the difference between the N1 responses elicited by task-relevant (attended) and task-irrelevant (unattended) sounds (the Nd; Hillyard et al. 1973) may reflect an orientation to the attended auditory features and/or maintenance of the memory trace of the target sound. However, others argued that the differential response is separate from the N1, with the early part overlapping the N1 (termed Nd_e) assumed to reflect feature processing, and the later part (Nd_l, also termed the Processing Negativity, PN; Näätänen 1982 see PN in *Attention-Related AERP Responses*) the maintenance of the attentional trace (Koch et al. 2005; Näätänen et al. 2011).

Little is known about the auditory *P2* (*P175, P200*; Figure 1) AERP response. It has been mostly studied within the P1-N1-P2 or N1-P2 complex. P2 typically peaks between 175 and 200 ms from the event onset with positive polarity over the vertex, inverting polarity over the Sylvian fissure. The generators of P2 lie anterior to those of the N1 in secondary auditory areas (Mäkelä et al. 1988; Bosnyak et al. 2004). Lesion (Woods et al. 1993) and maturation studies (Ponton et al. 2000) suggest that P2 may reflect the output of the mesencephalic reticular activating system (see **Auditory System (Anatomy, Physiology)**). Only a few studies have attempted to distinguish P2 from the N1 wave. The P2 amplitude was found to be more sensitive to perturbing the feedback of one's voice than the N1 (Behroozmand et al. 2009) as well as to training with specific types of sounds (e.g., speech: Tremblay et al. 2001; music: Bosnyak et al. 2004; or frequency discrimination: Tong et al. 2009). There are several speculations regarding the functions of the processes reflected by P2. Based on its assumed neural origin, P2 has been suggested to be generated by a pre-attentive alerting mechanism (Tremblay and Kraus 2002). Other suggestions include P2 reflecting stimulus classification (Crowley and Colrain 2004), modulating the threshold for conscious perception (Melara et al. 2002), protecting against interference from irrelevant stimuli (Garcia-Larrea et al. 1992), and the accuracy of memory traces in short-term memory (Atienza et al. 2002).
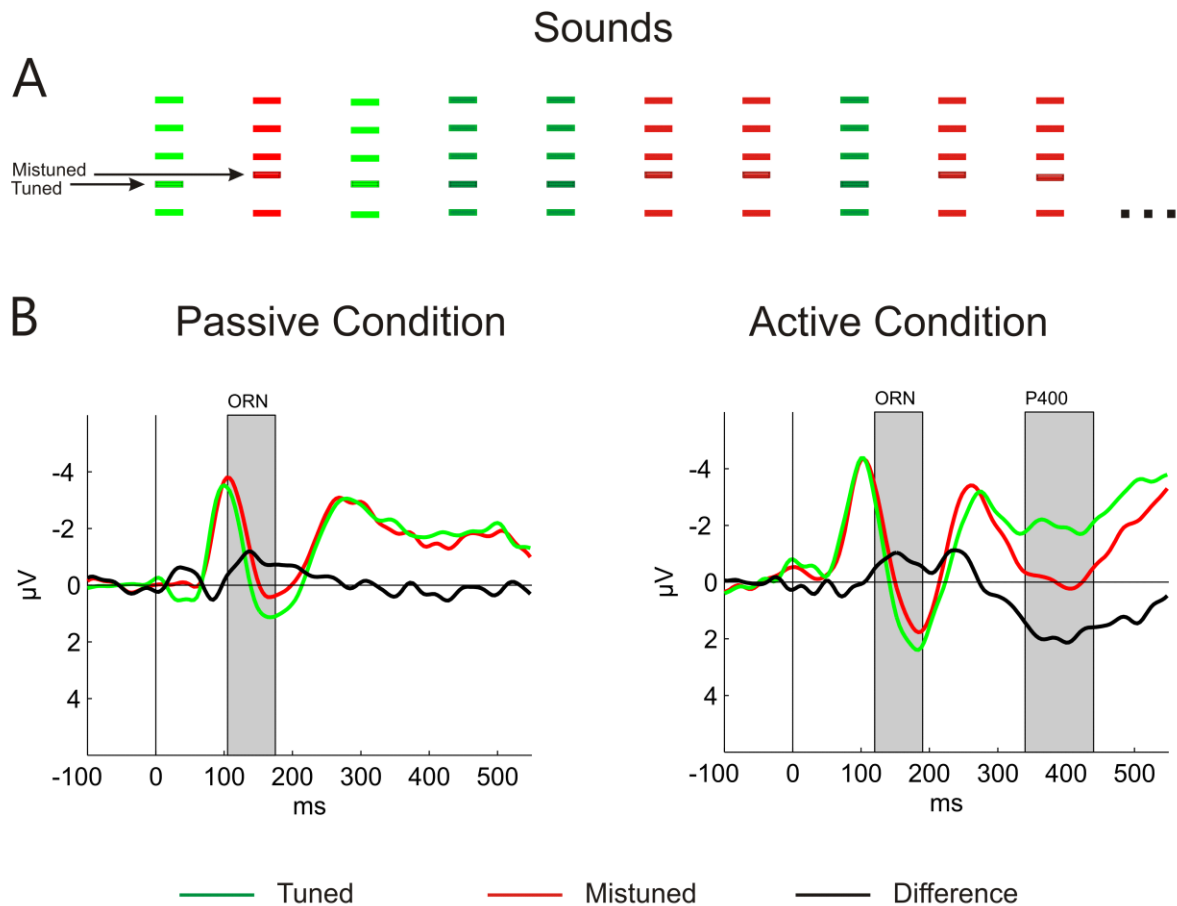
Object Related Negativity (ORN)

Sounds

A

Passive Condition

Active Condition

B

Tuned   Mistuned   Difference

Figure 2. Object Related Negativity (ORN). *(A)* Complex tones with the second of five harmonics tuned (green) or mistuned upwards by 8% (red) were presented equiprobably in a sequence. *(B)* Group-averaged (N=20, left; N=23, right) AERP responses elicited by tuned and mistuned complex tones recorded at the vertex, separately in the passive (participants disregarded the sounds) and the active condition (participants judged whether they heard one or two concurrent tones). Mistuned-minus-tuned difference waveforms (black) show a negative waveform appearing between 100 and 200 ms from sound onset in both task conditions. This is the ORN response (the range is marked by grey shading). The positive difference waveform observed in the 300-500 ms latency range in the Active Condition is termed the P400.

The *Object Related Negativity* (*ORN*) is elicited when more than one sound are simultaneously heard (Alain et al. 2001). Thus ORN reflects the outcome of the analysis of simultaneous (concurrent or vertical) auditory grouping cues (cf. **Auditory Perceptual Organisation**). Components of sounds emitted by a single source usually commence at the same time, they originate from the same spatial location and, if composed of discrete frequencies, they consist of harmonics derived from the same base (i.e., integer multiples of the same frequency). When the acoustic input does not meet these criteria, one usually experiences it as two or more concurrent sounds and ORN is elicited. ORN is typically recorded by presenting complex tones with one harmonic mistuned by 4% or more (Figure 2, panel A) and derived by subtracting the response to the one-sound stimulus (e.g., tuned tone) from that to the

multiple-sound stimulus (e.g., mistuned tone). ORN peaks between 140 and 180 ms from sound onset, with the largest amplitude over the fronto-central region of the scalp (Figure 2, panel B left). ORN has bilateral neural generators in auditory cortex, which are separate from those of the previously described obligatory AERP responses (Arnott et al. 2001). Some studies have indicated the existence of two independent lateralized generator processes, since although ORN is elicited even when most tones in the sequence have been mistuned, the probability of mistuned sounds within the sequence differentially affected the ORN generators in the two hemispheres (Bendixen et al. 2010). If the listener is instructed to respond when he/she hears two concurrent sounds, a late positive response (P400) is elicited in addition to the ORN (Figure 2, panel B right; Alain et al. 2001).

The auditory *N2* (*N200*; Figure 1) wave covers at least three (*N2a or MMN, N2b, N2c*; see Pritchard et al. 1991), possibly more AERP components (Folstein and Van Petten 2008) appearing partly overlapping in time between 150 and 300 ms from the eliciting event. The somewhat earlier N2a or MMN does not require attention to be focused on the event (cf. MMN and **Auditory Change Detection**), whereas the later components are related to attentive monitoring of the acoustic input and they are not specific to sounds.
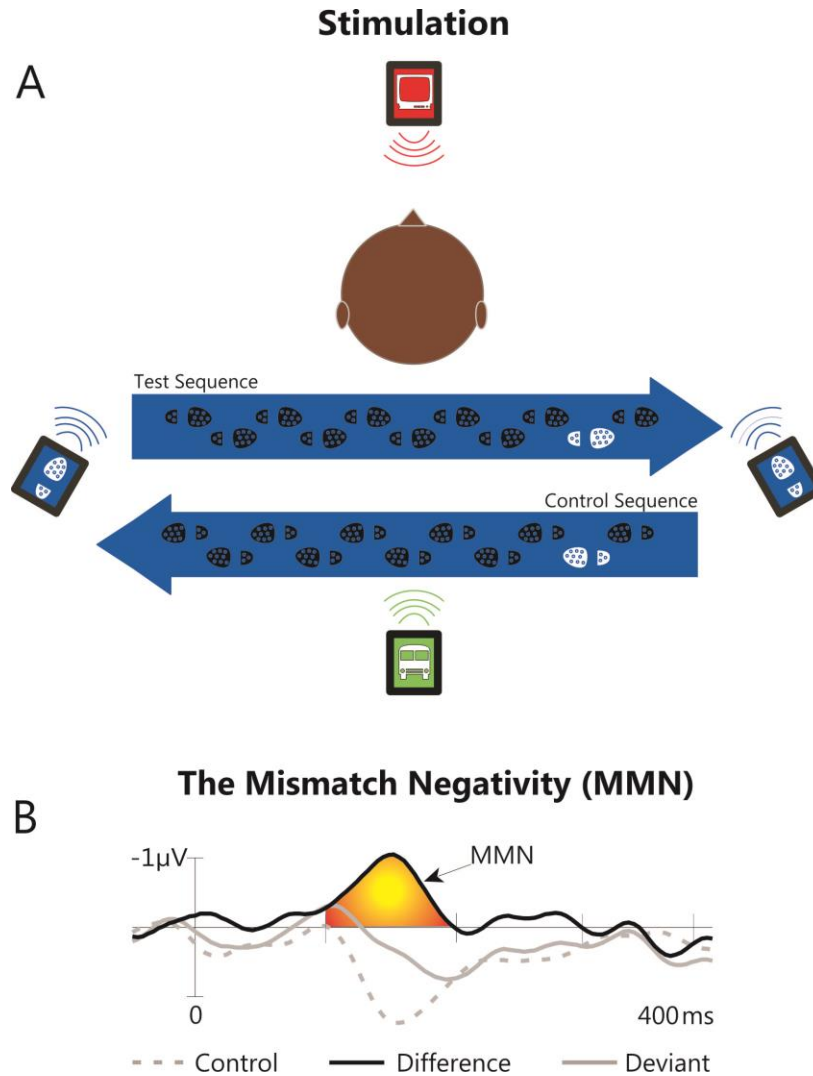
Stimulation

The Mismatch Negativity (MMN)

Figure 3. The Mismatch Negativity (MMN). *(A)* The experimental setup. Participants watched and listened to a movie presented on a TV screen directly in front of them. A series of footsteps perceived as moving from left to right (Test Sequence; upper arrow) or right to left (Control Sequence; lower arrow) were delivered by a pair of loudspeakers placed symmetrically on two sides, slightly behind the participant's head. Ten out of the 11 different digitized natural footstep sounds (marked as black footprints on the blue arrows) could be perceived as a coherent sequence produced by someone walking across a room. The 10th footstep of the Test Sequence ("deviant") and the 2nd footstep of the Control Sequence ("control") however sounded as if the person stepped on a different surface (marked by the white footprint on the blue arrows). Street noise was delivered through a loudspeaker placed directly behind the participant. *(B)* Group-averaged (N=8) AERP responses elicited by the deviant (continuous grey line) and the identical control sound (dashed grey line) measured from the frontal midline electrode. The MMN component, derived by subtracting the control response from that to the deviant (difference: black line) is marked with yellow-orange fill in the MMN latency range. The results illustrate that 1) MMN is only elicited when a sound violates a detected regularity, as the regular progression of footsteps needed to be detected and represented by the brain before it could be violated (which could not happen if only one "regular" footstep sound preceded the different one); 2) regularities can be extracted from acoustic variance as all regular footstep sounds were acoustically different; 3) regularities are separately maintained for concurrent auditory streams, as MMN was elicited for deviation in the footstep stream despite the presence of two other active sound sources; and 4) MMN elicitation does not require one to attend the stream in which a regularity has been violated, as participants in this experiment attended the movie, not the footsteps. (Adapted from Winkler et al. 2003.)

The *Mismatch Negativity* (*MMN, N2a*) is an AERP component elicited by violations of auditory regularities (Winkler 2007; Näätänen et al. 2011; Figure 3). MMN typically emerges between 100 and 200 ms from the onset of deviation with frontocentrally dominant negative polarity that is inverted over the Sylvian fissure. MMN generators are located bilaterally in secondary-auditory and frontal areas (Alho 1995). Although traditionally regarded as a component reflecting auditory change detection, technically, MMN does not reflect acoustic change, as for example, an alternating sequence of sounds does not elicit the MMN, whereas repeating a sound within such a sequence does (Horváth et al. 2001; see further details in **Auditory Change Detection**). MMN is derived by subtracting from the response elicited by the regularity-violating sound (termed "deviant") the response elicited by a control sound. Optimally, the control sound is either identical or very similar to the deviant sound but does not violate any auditory regularity (for a detailed discussion of selecting the correct control, see Kujala et al. 2007). MMN is elicited even when the sounds are task-irrelevant, although it can be suppressed by strongly focusing attention on a parallel auditory channel and/or by contextual information (Sussman 2007). Initially discovered within the oddball paradigm (Näätänen et al. 1978), MMN has since been observed for violations of a large variety of abstract and complex regularities (Näätänen et al. 2001). In parallel, its interpretation shifted from MMN being an AERP correlate of auditory sensory memory (Näätänen and Winkler 1999; Cowan, 1984) tasked with detecting potentially relevant events in the auditory environment (Näätänen 1992) towards the compatible but more general notion of representing a process that updates the detected auditory regularities when their predictions are not met by the incoming sound (Winkler 2007). The latter interpretation links MMN with predictive coding theories (Friston 2005; Winkler and Czigler 2012) and posits that it plays a role in auditory stream segregation (cf. **Auditory Perceptual Organisation**) by maintaining the predictive models underlying auditory perceptual objects (Winkler et al. 2009). For a more detailed discussion of MMN, see the entry **Auditory Change Detection**.

Auditory evoked potential
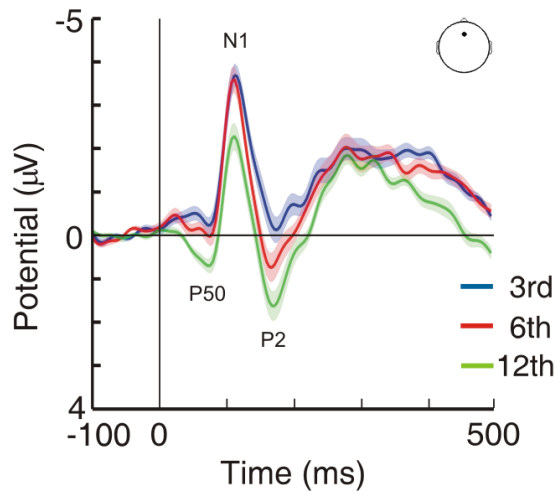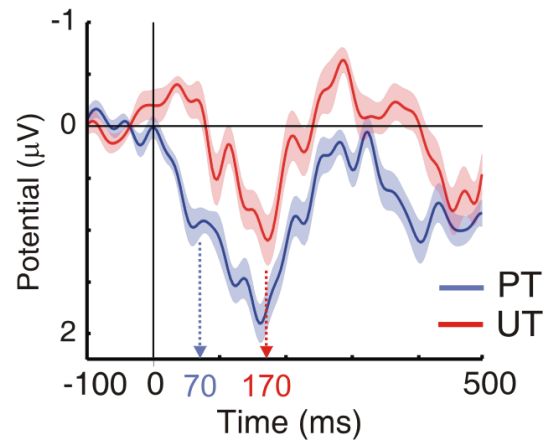
Repetition Positivity

Figure 4. The Repetition Positivity (RP). Left: Group-averaged (N=14) frontal midline (marked on the schematic head drawing at the top right corner) AERPs elicited by pure tones in a roving-standard stimulus paradigm (see in the text). The panel shows AERPs (averaged across different frequencies) elicited for the 3rd (blue), 6th (red) and 12th (green) repetition of the same tone. Note that the positivity covering the latency range of the P50-N1-P2 waveform complex emerges at the 6th repetition and becomes more pronounced by the 12th repetition. Right: Difference waveforms resulting from subtracting the response to the 3rd repetition from that to the 12th repetition under two conditions: Predictable Timing (PT: isochronous presentation, blue) and Unpredictable Timing (UT: the within-train inter-onset interval was varied, red). Note that the onset of RP is earlier (ca. 70 ms post-stimulus) for the predictable than for the unpredictable timing condition (ca. 170 ms). (Adapted from Costa-Faidella et al. 2011a.)

The *Repetition Positivity (RP)* appears as a fronto-central amplitude modulation of the P50, N1 and P2 AERP responses (Figure 4); all three of them overlap the slow positive RP waveform so that the P50 and P2 become more positive and the N1 less negative with increasing number of repetitions of the eliciting sound (Haenschel et al. 2005; Costa-Faidella et al. 2011a; Costa-Faidella et al. 2011b). Similar stimulus repetition effects have been observed even at shorter latencies, during the MLR latency range (Dyson et al. 2005). The RP was first observed by Baldeweg et al. (2004) and characterized by Haenschel et al. (2005) in a study that aimed at investigating the neural correlates of the sensory memory trace implicated in the generation of the MMN. It was argued that the MMN amplitude dependence on the number of standard-stimulus repetitions preceding the deviant (e.g., Sams et al. 1983; Javitt et al. 1998) provides only an indirect measure of the strength of the underlying memory trace. The AERP elicited by the standard sound was expected to show effects of repetition suppression (Desimone 1996), as was observed for individual neurons in the primary auditory cortex of the cat (Ulanovsky et al. 2003), and this could provide a more direct measure of the strength of standard-stimulus memory trace. The typical paradigm use for obtaining the RP is called the "roving-standard" paradigm (introduced by Cowan et al. 1993), as the classical oddball paradigm yields less clear results (Cooper et al. 2013). In the roving-standard paradigm, short trains of a repeating sound are delivered without a break with each train delivering a different sound (e.g., pure tones with different frequencies). The number of sound repetitions can also vary from train to train. To separate the RP from other concurrent AERP

components, the average response elicited by the second or the third sound of the train is subtracted from that elicited by the last tone of the train. The response to the first sound of the train is not used in the subtraction, because, due to the sound change between the trains, it should elicit the MMN (Haenschel et al., 2005; Costa-Faidella et al., 2011a, 2011b). The generator structure of the RP has not yet been fully characterized, but its early onset latency (commencing during the P50) and its long duration (ending during the P2) suggest that it may involve a distributed cortical network spanning from PAC up to auditory association areas (Baldweg 2007). The RP has been shown to simultaneously encode repetitions over multiple time scales (Costa-Faidella et al. 2011b; Cooper et al. 2013) similarly to single neurons observed in the cat's PAC (Ulanovsky et al. 2004). In addition to stimulus repetition, the RP is also sensitive to temporal regularities, such as whether the sounds are presented isochronously or with random timing: Costa-Faidella et al. (2011a) found earlier and larger RP's for isochronous as compared with randomly timed tones in the trains. The latter result supports the predictive coding view of auditory deviance detection (Winkler 2007; Winkler and Czigler 2012), according to which detection of a regularity helps to encode the sensory memory trace of upcoming stimuli. Thus higher levels in the auditory processing hierarchy feed back to lower processing levels (Baldweg 2006).

Auditory brain responses can also be elicited without hearing sounds. By omitting sounds from an isochronous sequence, one can record potentials time-locked to the moment when the sequence would have continued in a regular manner. The responses are termed the *Omitted Stimulus Response* (*OSR*). Some of them are elicited even when listeners don't focus on the sounds, thus demonstrating a basic tendency of the auditory system to generate predictions for incoming sounds (Friston 2005; Winkler et al. 2009). It has been shown that when all features of the upcoming sound can be predicted from the preceding sound sequence, the OSR elicited by sound omission during the first 50 ms does not differ from the AERP elicited by the sound itself; however, when only the timing of the sound can be predicted, but not its features, the OSR starts to differ from the corresponding AERP at an earlier time (Bendixen et al. 2009). When sounds are predictably caused by some action of the listener, occasionally omitting one elicits an AERP that is initially (up to ca. 100 ms) morphologically similar to that elicited by the corresponding self-initiated sound; although the brain generators underlying the two responses partly differ from each other (SanMiguel et al. 2013). There is also an MMN-like OSR (Yabe et al. 1999). Elicitation of these responses is limited to inter-onset-intervals (IOI) shorter than ca. 200 ms (Horváth et al. 2007), except when the omitted sound is part of a pattern (Salisbury 2012). With longer IOIs, an early posterior negative (180 –280 ms) response and a later anterior positive wave have been obtained (Busse and Woldorff 2003). Further, ERP responses can also be elicited by mental imagery of sounds, although the results vary somewhat with the procedure employed (Meyer et al. 2007; Cebrian and Janata 2010; Wu et al. 2011).

Attention-Related AERP Responses

Attention-related AERPs include two distinct groups of responses: those related to involuntary (passive or exogenous) attention, and those related to voluntary, mainly selective attention. Regarding involuntary attention, at least three components have to be considered. The MMN (described above), or at least its frontal component (Giard et al. 1990; Deouell et al. 1998; Escera et al. 2000a; Deouell 2007), has been associated with involuntary attention (Näätänen and Michie 1979; Näätänen 1990; Näätänen

1992). Some studies have also related the activation of the supratemporal MMN generator with behavioural correlates of involuntary attention, i.e., delayed response times to target stimuli on a primary task (Yago et al. 2001). Näätänen and Michie (1979) proposed that the process generating MMN may issue a call for focal attention (Öhman, 1979) upon the detection of an unexpected change in the acoustic environment. Initial supportive evidence was provided by Schröger (1996; Schröger and Wolff 1998a) and Escera et al. (1998), who introduced new auditory-auditory and auditory-visual distraction paradigms (for a more recent design, see Horváth and Winkler 2010). In these paradigms, participants are instructed to perform a primary auditory or visual task while ignoring rare task-irrelevant violations of an auditory regularity. Several studies have shown that these rare deviations prolong the reaction time and reduce the hit rate to target stimuli in the primary task (Escera and Corral 2007), thus demonstrating involuntary attention switching to the task-irrelevant deviations.

Following the MMN, AERPs recorded in the distraction paradigm display a fronto-central positive deflection ca. 250-350 ms from stimulus onset, termed the *P3a* or *novelty-P3*. P3a was first described by Squires et al. (1975) as an earlier and more frontal positive deflection compared to the later and more posterior P3b component (for a review on P3b, see Donchin and Coles 1988). Whereas P3a is elicited by rare task-irrelevant sounds, P3b is elicited by target sounds (for a detailed comparison between the P3a and P3b, see Polich 2007). P3a is also elicited by widely different and "novel" (unique, categorically different from the context) sounds (Knight, 1984), hence it is sometimes referred to as the novelty-P3 (for a discussion of whether the P3a and the novelty-P3 can be considered as the same ERP component, see Simons et al. 2001). Compelling evidence linking the novelty-P3 to the orienting reflex (OR; Sokolov 1963) was obtained by Knight (1996), who found strong correlation between the novelty-P3 and one of the well-known autonomic components of OR, the galvanic skin response (GSR). The P3a is composed of two subcomponents distinctly differing in latency (early and late), scalp distribution, and sensitivity to attentional manipulations (Escera et al. 2000a; Yago et al. 2003). Source modelling of the magnetic counterpart of P3a (P3am) elicited by auditory deviants and novel sounds has revealed a genuine auditory cortical contribution to the early part of P3a (Alho et al. 1998). Whereas the early part of the novelty-P3 appears to be insensitive to attentional manipulations (Escera et al. 1998), the later part is modulated by working memory (SanMiguel et al. 2008) and emotional load (Domínguez-Borràs et al. 2008). The early P3a is sensitive to stimulus-specific information predicting task-irrelevant auditory deviance, whereas the late P3a appears to be more closely correlated with distraction (Horváth et al. 2011). P3a is widely regarded as a correlate of attention switching (Escera et al. 2000a; Friedman et al. 2001). However, some recent studies suggested that although P3a is probably an antecedent of attention switching it can be elicited without a corresponding shift in the focus of attention (Rinne et al. 2006; Horváth et al. 2008b; Horváth and Winkler 2010; Hölig and Berti 2010).

The third involuntary attention related AERP component is the so-called *Reorienting Negativity* (*RON*), first described by Schröger and Wolff (1998b). RON is observed as a negative deflection following the P3a (Escera and Corral 2007). RON has been suggested to reflect processes of reorientation (restoring the task set of the primary task) after a distracting stimulus. RON is composed of two subcomponents (Escera et al. 2001; Munka and Berti 2006; Berti 2008) the functional characterization of which are still debated (Escera et al. 2001; Berti 2008). The cortical generators of RON are not well known. Horváth et

al. (2008a) found contributions from primary motor areas to RON, suggesting that action-selection related activity plays a role in the reorientation process. Both P3a and RON as well as behavioural correlates of distraction (but not MMN) are eliminated or at least strongly diminished when the task-irrelevant deviant is predicted by a visual cue (Sussman et al. 2003; Horváth and Bendixen 2012). Cues that provide more specific information about the distracting stimulus are more effective in preventing distraction and the elicitation of P3a and RON (Horváth et al. 2011).

Selective attention related AERPs have been traditionally studied in the context of the classical "cocktail-party" situation described by Cherry (1953). In the simplified dichotic listening model of this situation, participants are exposed to two concurrent messages (one to each ear). Using this paradigm, many studies attempted to decide between the "early" (Treisman 1964; Treisman 1998; Broadbent 1970) versus "late" selection theories of attention (Deutsch and Deutsch 1963; Norman 1968). These theories of attention primarily differ from each other in the placement of a selective filter within the chain of information processing (Broadbent 1958): whereas early selection theories suggest that stimuli are selected for elaborate processing based on simple sensory features (such as pitch) and unattended stimuli do not receive processing beyond extracting these sensory features, late selection theories propose that all stimuli receive elaborate processing and stimuli can therefore be selected on the basis of higher-order properties. (Note that more recent theories of attention do not posit a single selective filter; see e.g., Lavie 1995.) The seminal observation by Hillyard et al. (1973) that selective attention enhances the N1 amplitude for stimuli presented in the to-be-attended channel favoured the early filtering view. However, the findings of Näätänen et al. (1978) of a long-lasting negativity elicited by all attended stimuli, the *Processing Negativity* (PN; Näätänen 1982) challenged this interpretation providing support to late-selection theories. Subsequent studies confirmed both of these effects (Okita 1979; Hansen and Hillyard 1980; Näätänen et al. 1980) and proposed subtraction of the AERP elicited by the non-attended stimuli from that elicited by the attended stimuli as the method to reveal the *Negative Difference* (*Nd*) potential to isolate the AERP correlates of selective attention (Nd; Hansen and Hillyard 1980). The *Nd* is composed of two parts: the early one, termed Nd_e, associated with a gating mechanism preferentially processing the task-relevant stimulus features, and a later part (Nd_l) related to the maintenance of the attentional trace (correspond to the PN). The functional distinction between the Nd and PN has been debated in detail (Alho et al. 1986a; Alho et al. 1986b; Alho et al. 1994; Teder et al. 1993). Studies showing very early selective attention effects, e.g., at the latency range of the MLR (Woldorff et al. 1987; Woldorff and Hillyard 1991) and possibly even earlier, at the level of the cochlea (Giard et al. 1994) support the interpretation of the Nd_e as a correlate of gating by simple stimulus features. On the other hand, the fact, that the more similar the stimulus to the target the longer the corresponding PN, supports the notion of a comparison with the attentional trace. The frontal scalp distribution of Nd_l (Woods and Clayworth 1987) and the cerebral sources of PN (Giard et al., 1988) are also compatible with the memory-based interpretation of Nd_l. There are several further ERP components related to various facets of attention. However, these are not specific to the auditory modality and thus fall outside the scope of this entry (cf. the entry **EEG/MEG Evoked/Spontaneous Activity**).

AERPs Reflecting Speech and Music processing

The sounds of speech and music may elicit any and all the AERP responses described above. There are, however, also some ERP responses, which arise from events that can be defined in syntactic or semantic terms. It should be noted that most speech-related ERPs can also be elicited through reading. Most AERP responses specific to speech and music have been obtained in paradigms, in which the expectation for the most likely (or simplest) continuation of a sequence of words has been violated. For example, violating the expectation for the first phoneme of the upcoming word elicits a negative shift in the 150-350 ms latency range, termed the *Phonological Mismatch Negativity* (*PMN;* Connolly and Phillips, 1994). It is, however, debated, whether this response can be separated from that elicited by words, which are semantically incongruent with respect to the preceding context (D'Arcy et al. 2004; Van den Brink and Hagoort 2004). Violating speech syntax can lead to the elicitation of the *Early Left Anterior Negativity* (*ELAN*) in the 150-200 or the *Left Anterior Negativity* (*LAN*) in the 300-500 ms latency range, depending on the type of violation, whereas potentially correct but syntactically complex sentences elicit the *Syntactic Positive Shift* (*SPS* or *P600*) (for reviews, see Friederici 2002; Hagoort 2008). Violating semantic expectations in speech elicits the *N400* component (Kutas and Federmeier 2011). Musical syntax violations elicit an ELAN-like but predominantly right-hemispheric response, the *Early Right Anterior Negativity* (*ERAN*) in the 180-200 ms or the *Right Anterior-Temporal Negativity* (*RATN*) in the 200-400 ms latency range and N400 has been also be observed in musical models of semantic incongruence (Koelsch and Siebel 2005). For a more detailed discussion of speech- and music-related ERPs, see **Electrophysiological Indices of Speech Processing** and **Music Processing in the Brain**.

Development of AERPs

Previous sections described the AERP responses elicited in adults. Although AERPs can be recorded immediately after birth and even in foetuses within the womb (Draganova et al. 2005), their morphology and functional characteristics widely differ from the adult responses. Further, different AERP components become mature at different times and they often undergo several intermediate phases before reaching adult-like characteristics. As this topic would require a full entry of its own, here we point the reader to some of the existing literature. The most complete reviews of the maturation of AERPs from infancy to adolescence were provided by Wunderlich et al. (2006) and Coch and Gullick (2012). The early infantile development of the AERP components has been summarized by Kushnerenko (2003); for the maturation of the AERPs reflecting auditory change detection, see Jing and Benasich (2006), for large deviations, see Kushnerenko et al. (2013). The maturation of obligatory AERP components from 5 to 20 years of age is covered in Ponton et al. (2000; 2002). AERP maturation during adolescence is described in Bishop et al. (2007). Summarizing these works, one can conclude that the adult AERP morphology characterizes humans from 17/18 years onward and remains more or less unchanged through ageing. There are, however several findings of differences between elderly and young adults in specific tasks (for a review, see Friedman 2012).

Modelling AERP's - some general principles

Theories that seek to explain some of the LLRs have also been explored using more tightly constrained mathematical and computational models. Here we focus on models of the mismatch negativity (MMN) component, as it has arguably received the most widespread attention. Theoretically, MMN has been

variously associated with change detection, adaptation, prediction error, novelty detection, and model adjustment, although for some years, there has been controversy as to whether anything more than adaptation is required to explain the experimental data (e.g., see May and Tiitinen 2010 vs. Näätänen et al. 2011).

Using a modelling framework in which exemplars of each of the competing explanations, listed above, were expressed as mathematical functions of stimulation-induced changes in an *unobservable* 'internal state' and resulting *observable* (EEG) responses, Lieder et al. (2013) investigated the ability of each model to explain empirical MMN responses on a trial-by-trial basis. The models were expressed in a rather abstract way, as summarized below, with simple expressions for internal state and response functions (intended to predict stimulus-evoked MMN amplitudes), that captured a range of possibilities for each of the categories. Change detection was modelled with the internal state simply a record of the log frequency of the previous tone in the sequence, and response functions as: a) a flag, set if a difference was detected, b) the signed and c) absolute difference between the frequency of the incoming and previous tone; giving three change detection models. Adaptation was modelled by the exponential decay and recovery of the internal state variable associated with each stimulus frequency, and the response function as a read out of the internal state corresponding to the incoming stimulus. The internal state for the prediction error, novelty detection, and model adjustment accounts was modelled as a Bayesian observer's belief in the tone category of the stimulus, with the evolution of tone category modelled according to a transition matrix derived incrementally from the data according to the 'free-energy-minimisation principle' (Friston 2005). Two prediction error response functions were modelled: prediction errors with respect to sensory input and internal state, respectively. Novelty response functions were modelled as surprise about sensory input and temporal structure (tone category), respectively. Model adjustment response functions were modelled in terms of adjustments to the parameters of the internal model, e.g. mean frequency of a category, expected sequence length, transition probabilities between categories. Simulations showed that, at least at this level of detail, prediction error (with respect to tone category) and model adjustment models (change in expected sequence length, change in transition probabilities between categories), accounted best for the data (Lieder et al. 2013).

On the other hand, May and Tiitinen (2010) have argued strongly that their neural model which includes adaptation on the inputs can explain all MMN data to date; the key mechanism being the activation of fresh afferents by stimuli that deviate in some way from the standards. In this account, MMN is seen as a modulation of the N1 component rather than as a separate component in its own right. The model, consisting of a bank of neural oscillators driven via adapting input synapses, can account for the latency as well as the amplitude of the MMN (May et al. 1999). In addition, extending the model to include local inhibitory feedback circuits, results in a set of non-homogeneous band-pass temporal filters that can also support the topographic representation of stimulus presentation rate (May and Tiitinen 2001). Ringing in these filters is argued to account for the MMN elicited by a missing expected sound. Diverse receptive fields, e.g. to frequency modulations, also allow the model to simulate MMN responses elicited by violations of some abstract rules, such as a repeated tone in a random pattern of ascending tone pairs. However, although adaptation is claimed to be the key to MMN, the model responses also

depend upon the amplification of recurrent excitation, lateral inhibition, and the connectivity of the network. The model thus essentially contains within its changing pattern of adaptation and inhibition, a memory trace of recent activation, and in this sense, contains a memory component embedded within it.

Building on their previous work on a brain-inspired architecture for learning long-term representations of action-perception associations, Garagnani and Pulvermüller (2011) proposed a similar model in which, in addition to adaptation and inhibition, spreading activation through circuits strengthened by learning (long term memory) caused MMN responses to familiar deviants to be larger than that to unfamiliar deviants. They pointed out that only through some form of long term memory mechanism could this differential sensitivity of MMN to familiarity/unfamiliarity be explained. By modelling multiple auditory areas they also provided a novel explanation for differences between the N1 and MMN generators, with N1 being generated in primary auditory areas subject to strong adaptation, and MMN in addition to adaptation also being influenced by reverberating excitation within distributed memory circuits. However, the model processes sequences of static patterns, and as presented, it is not able to account for the sensitivity of MMN to unexpected changes in the timing of sequences, such as the omission MMN (Yabe et al. 1997).

A model that explicitly includes a separate memory module to keep track of the short term history of activation and simulates MMN at a finer level of granularity, i.e. at the level of spiking neurons, was proposed by Wacongne et al. (2012). Memory in the model is implemented using a set of neurons organised into a delay line, i.e. their connectivity ensures that activity passes in one direction across the population, and the progress of activity through this population explicitly represents the timing of the previous event, up to 400 ms. Separate delay lines are used for each tone frequency modelled, thereby also recording their identity. The model simulates MMN by means of prediction errors. Through exposure to tone sequences it learns to generate a prediction of the next tone (both its timing and identity) in a repeating pattern. These predictions are compared with the incoming stimuli in the prediction error units, where mismatches result in a larger signal than matches. The model learns transition probabilities between successive events, as long as they fit within its fixed memory span. In contrast to the adaptation account of MMN, the model relies exclusively on prediction errors. An experiment designed to distinguish between these two explanations for MMN found evidence in favour of a predictive error model of MMN (Wacongne et al. 2012), a result compatible with the findings of Lieder et al. (2013).

A predictive coding account of MMN has also been modelled at a more abstract level using a Kalman filtering (Kalman 1960) approach (Kaya and Elhilali 2013). In this case the timing of events is modelled using a separate filter from the one used to model feature distributions. The advantage of the Kalman filter is that provides a well-understood way to recursively estimate the system state, refined through analysis of prediction errors, and has been shown to be implementable in the form of a neural network (Szirtes et al. 2005). The model adapts to the variance in observations and, with time, as its predictions improve so its tolerance decreases, making it more sensitive to outliers. Deviants are detected as events not predicted by any existing filter, and trigger the creation of a new set of Kalman filters intended to

model a potentially new sound source, making this an interesting framework for more general auditory scene analysis problems, e.g. (Chakrabarty and Elhilali 2013).

In summary, computational models of the theoretical accounts of MMN have begun to be explored. However, so far they have either only been implemented at a rather abstract level; e.g. (Garrido et al. 2009; Lieder et al. 2013; Kaya & Elhilali, 2013), focus exclusively on a single mechanism for explaining MMN; e.g. (May and Tiitinen 2001; Wacongne et al. 2012) or account only for MMN responses to unexpected within-event properties (Garagnani and Pulvermüller 2008, 2011). The finding, using dynamic causal modelling, that modifications to both feed forward and feedback connections are required (Garrido et al. 2009), and evidence in auditory cortex for adaptation, short term and long term plasticity, recurrent excitation and inhibition suggests that MMN in the brain may actually depend on the combination of all these factors. Furthermore, while the learning of transition probabilities may be sufficient for some scenarios, in the short term at least, people become sensitive to specific tone patterns; it is unclear whether any of the models discussed here could respond differentially to violations of more extended pattern sequences or more abstract rules.

Utility of AERP for clinical practice

Clinical applications of AERPs range from routine practice in audiology, neurotology, neurology, and neurosurgery by ABRs and MLRs (Picton 2010) to highly promising tools for cognitive assessment by some long-latency endogenous components, of which MMN is a prime example. In audiology, ABRs are used universally for hearing screening in neonates failing the Otoacoustic Emission test (OAEs; Robinette and Glatkke 2007). Currently, about 97% of infants are screened for hearing impairment in the USA (Gaffney et al. 2010). ABRs, elicited by click stimuli, are used as a tool for objective audiometry, and ABRs elicited by pure tones can also be used for assessing frequency-specific thresholds in infants (Stapells and Oates 1997; Stapells et al. 1993). In neurotology and neurology, AERPs are combined with the patient's medical history and with an extensive battery of tests for evaluating the anatomy and functional properties of the ear-brain relationship (Picton, 2010) in search for an extensive range of disorders of the ear and the auditory pathway, such as Ménière's disease and demyelinating lesions such as Multiple Sclerosis. In these applications, AERPs are used to determine conduction times along the auditory pathway and to localize the anatomical locus of the brain damage with the help of the known origin of the different ABR waveforms (see reviews in Baloh 1997; Chiappa 1997; Lustig et al. 2003). In addition, ABRs are used in combination with evoked potentials from other modalities to monitor coma prognosis (Guérit 2005; Fischer et al. 2006; see below), or in isolation to corroborate brain death (Machado et al. 1991). In the surgical theatre, MLR is used to monitor the depth of anaesthesia in adults (Bell et al. 2004) and children (Kuhnle et al. 2013). It has been recently shown that, compared with the traditional clinical assessment of depth of anaesthesia, MLR monitoring led to a reduction in a) the amount anaesthetic drug requirement, b) the use of vasopressors to manage hypotension, and c) consequential cognitive impairment (Jildenstål et al. 2011).

Regarding cognitive AEPRs, MMN (see above and the entry **Auditory Change Detection**) has shown great promise for potential clinical applications (Näätänen and Escera 2000). Part of this expectation stems from the fact that MMN indexes auditory discrimination accuracy without the requirement to

perform some task (i.e., it can be recorded without the patient's collaboration and even in newborn infants; see Alho et al. 1990) and that it can be elicited very reliably, compared with other cognitive event-related potentials (Escera and Grau 1996; Escera et al. 2000b). Yet, after two decades of clinical research (see Näätänen et al. 2012), except for coma monitoring and prognosis no routine clinical application has emerged for the MMN. As for coma monitoring, it has been demonstrated that the presence of MMN in a comatose patient is associated with the return of consciousness (Kane et al. 1993; Fischer et al. 1999), and that as part of a battery of physiological indicators of brain activity, MMN can be used in the decision tree for estimating awakening from coma (Fischer et al. 2006). Given the large variety of disorders and clinical conditions in which impaired MMNs have been observed, it has been suggested that, rather than providing a specific diagnostic measure for any particular disease, the MMN provides an objective index of dysfunction of N-metyl-D-aspartate (NMDA) receptor-mediated cognitive functions (Näätänen et al. 2011). In general, due to their high variability and complex functional and anatomical origin, endogenous AERPs can only be employed within large test batteries for diagnostic and monitoring purposes. However, some of these responses provided new insights into the cognitive and emotional aspects of various neurological and psychiatric disorders (e.g., for schizophrenia research using MMN, see Mondragón-Maya 2011).

AERPs: Advantages and limitations

(A)ERPs provide information about sound-elicited neural activity with millisecond accuracy. Thus they are ideally suited for breaking down the steps of auditory information processing in the brain in the empiricist tradition. It is thus understandable that some of the most recent theoretical developments in the field (e.g., predictive coding theories; Friston, 2005) trace back their roots to Helmholtz' (1860/1962) theories of perception. High temporal resolution coupled with the possibility of finding the neural generators of the various ERP responses is also appealing to neurologists and medical doctors, in general. By finding correlations between AERPs and conscious perception on the one hand (such as the link between ORN and the perception of two concurrent sounds; Alain et al 2001), and discovering the neural mechanisms underlying the observed AERP waveforms on the other hand (e.g., linking SSA and the deviance-detection responses observed in the MLR latency range; Slabu et al. 2010; Grimm et al. 2011; for a review, see Ayala and Malmierca 2013), AERPs can provide a crucial link in understanding the neural mechanisms of perception.

However, there are a number of limitations to the utility of (A)ERPs for research and applications. Firstly, they only reflect a part of the information processing in the brain. When the number of neurons involved in some process is relatively small, or the neurons are distributed over a large area in the brain, or the neural activation is not fully time-locked to the given auditory event, no ERP can be measured. Other methods, such as time-frequency analysis of the EEG, provide better information about these types of processes. AERPs are usually smaller than their visual counterparts. Consequently the signal to noise ratio, where activity not time-locked to the sound onset is regarded as noise, is quite low. This forces one to present many trials to the participant and rely on assumptions which are not fully met by the EEG signal (such as the independence of the signal from the noise, ergodicity, etc.). Further, the accuracy of localizing the sources of neuroelectric activity is limited by the quality of constraints (e.g., anatomical knowledge) required to solve the inverse problem, and the dispersion of the electrical fields.

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Although magnetoencephalography provides a better spatial resolution, as was already mentioned, AEFs only reflect tangential sources, but not radial ones, thus restricting their general usefulness. In terms of spatial accuracy, other neuroimaging methods, such as fMRI, provide a superior alternative (at the cost of much lower temporal resolution). Further, the correspondence between perception and AERP responses is often not straightforward, as can be gleaned from the often controversial psychological interpretations mentioned in the main text of this entry. Few AERP components can be consistently observed across different stimulus paradigms, thus limiting the validity of most process-based interpretations. Efforts to discover the neural bases of ERP responses must overcome many obstacles. One of the most difficult problems is that whereas individual neurons can mainly be studied in animal models due to the invasive nature of such investigations, it is often difficult to assess how well findings in various species can be extended to characterizing the human brain. Finally, the biggest issue for clinical applications is, as was already mentioned, the large inter- and even intra-individual variability of AERPs.

In summary, AERPs can potentially provide much information about sound processing in the brain, but for extracting this information, better theories and more tightly constrained models, which can integrate information from the diverse fields of anatomy, neuroscience, and psychology, are required.

• CROSS-REFERENCES/RELATED TERMS

Adaptation in Sensory Cortices, Models of
Auditory Change Detection
Auditory Evoked Brainstem Responses
Auditory Perceptual Organisation
Auditory System (Anatomy, Physiology)
Brain Imaging Methods
EEG/MEG Evoked/Spontaneous Activity
Electrophysiological Indices of Speech Processing
Music Processing in the Brain

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