# The Interaction of Intensity and Deviance on Auditory Event-Related Potentials: Findings Using Principal Component Analysis (PCA) of Current Source Densities (CSDs)

by

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Abstract

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Advisor: Gerard Bruder, Ph.D.

Mismatch negativity (MMN) studies provide insights into the brain's ability to perceive and/or detect deviations from established sensory patterns. Clinical studies investigating the loudness-dependency of auditory evoked potential (LDAEP) have shown a relationship between the intensity of an auditory stimulus and neuro-physiological or -chemical activity of the primary auditory cortex. Unfortunately, these two bodies of literature remain disjointed. The present study integrates elements of each body of literature to a) investigate the impact of varying levels of intensity deviance on N1/P2 with a standard set of intensities used in LDAEP paradigms, and b) assess the extent to which deviance-related processes (indexed by MMN) are affected by louder or softer tones. A passive MMN-paradigm used the same stimuli as deviants and standards in order to separate deviance- from stimulus-specific N1/P2 processes. A CSD-PCA approach was used to identify and quantify reference-independent patterns of activity underlying the ERP. Results show that the intensity dependence of N1/P2 is largely dependent on the context in which a given intensity was cast. Namely, a high rate of repetitions of standard intensities produce significant reductions (adaptations) in N1/P2, while N1/P2 enhancement occurred for louder, but not softer deviants. Moreover, MMN amplitude paralleled intensity disparity; however, louder deviants produced greater MMN activity than softer deviants,

presumably reflecting an attentional modulation of sensory processing. A P3a-like vertex source was elicited by the loudest intensity (100 dB), but was absent for all other intensities. Insights gained from this study have direct implications for both clinical LDAEP and MMN studies. LDAEP studies should consider how overlapping or dynamic processes (e.g., adaptation of N1/P2 or elicitation of MMN) influence the amplitudes of N1 and P2. MMN studies should a) consider how attention may interact with intensity to produce distinctly different MMN responses independent of actual deviance-related processes, b) consider how P3a activity reflects a wider range of functions other than 'attentional signaling,' such as response inhibition or startle-related processes, and c) consider other physiologically plausible and parsimonious explanations of MMN (e.g., sensory adaptation) when interpreting findings.

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## 1.1 Event-Related Potentials.

Event-related brain potentials (ERPs) are fluctuations in voltage that are temporally- and spatially-related to stimulation occurring outside the brain or from mental processes inside the brain, which are extracted, averaged, and filtered from the electroencephalogram (EEG; Picton et al., 2000). An ERP waveform is characterized by a series of peaks and troughs within the averaged epoch, which corresponds to potential differences between recording sites and the recording reference. Peaks or troughs within the ERP waveform are classified according to their polarity, and timing relative to stimulus- or response-onset. For example, an auditory N1 or N100 refers to a negative deflection that reaches a maximum in amplitude near 100 ms after an auditory stimulus (Davis, 1964; Hillyard & Picton, 1978). Functional descriptions are also attributed to certain peaks or troughs in the ERP waveform (e.g., 'novelty P3a,' 'mismatch negativity,' 'error-related negativity,' etc.) and are directly related to the paradigmatic manipulation that elicited the response. For example, an auditory 'mismatch negativity' is usually observed when an aberration occurs within an established (i.e., standard) series/pattern of tones (Näätänen, et al., 1978). ERPs can also be categorized as either exogenously-driven (e.g., by environmental stimuli such as tones) or endogenously-driven brain processes (e.g., stimulus evaluation, classification, memory, and decision-making, etc.; Donchin, Ritter, & McCallum, 1978).

## 1.2 Choice of Recording Reference.

The choice of a recording reference can impact the spatiotemporal characteristics

of surface potentials at individual electrode sites because the measured voltage is the potential difference between a recording site and a reference site (Dien, 1998; Kayser & Tenke, 2006; Nunez & Srinivasan, 2006; Tenke & Kayser, 2005). It is possible for electrical currents from sources activated within the brain to propagate throughout the conductive medium (i.e., brain case) and be measured at any point on the surface of the scalp (Nunez & Srinivasan, 2006). This fact is important as a voltage potential for any given site can vary considerably in amplitude, polarity, signal quality, or peak latency depending on which reference location is chosen (i.e., reference-dependent recordings are not unique), which can bias and mislead an investigator's interpretation about generators underlying ERP components (McCarthy & Wood, 1985). As described by Nunez and Srinivasan (2006), a theoretical reference near infinity that is electrically unaffected by any sources contributing to the recording electrodes is an (obviously) idealized model; the reality is that the reference will inevitably by affected by the same intracranial sources as all other electrodes in a volume conductor model (e.g., the head). Thus, choosing the location of a recording reference is arbitrary (many times it is chosen simply by convention). Short of exploiting reference-independent techniques (Hjorth, 1975; Kayser & Tenke, 2006, Nunez & Srinivasan, 2006; Scherg & Von Cramon, 1985, 1986; Tenke and Kayser, 2005), investigators must grapple with the "reference problem."

### 1.3 Current Source Density

The "reference problem" can be circumvented by techniques that reduce broad volume conducted contributions at each recording site (e.g., Kayser & Tenke, 2006; Scherg & Von Cramon, 1985, 1986; Tenke & Kayser, 2005). Widely distributed activity from distant or disparate sources becomes close to negligible when surface Laplacian

current source density (CSD) analyses are applied to the recorded data (Nunez & Srinivasan, 2006). Surface Laplacian CSD estimates provide a reference-independent measure of the magnitude of current flow entering (source) and leaving (sink) the scalp from superficial cortical regions (Tenke et al., 1998; Tenke & Kayser, 2005). CSDs provide a physically accurate estimate of the orientation, general location, and strength of current generators underlying the ERP topography (Kayser & Tenke, 2006; Kayser, Tenke, Gates, & Bruder, 2007; Tenke & Kayser, 2005). Given the present state of the art, it is impossible to unambiguously localize the activity of all neuronal generators underlying a given ERP topography (i.e., "inverse problem"). However, advanced analytical techniques like brain electrical source analysis (BESA) and CSD-PCA help decompose the recorded data to meaningful source waveforms or current source/sink patterns, respectively, which assist investigators in inferring the locations of neural generators. Many of the techniques used for source localization (e.g., BESA, LORETA) depend on the placement of equivalent dipole sources (not to be confused with the concept of a 'cortical dipole' is introduced below) in terms of their "goodness of fit" (Scherg, Vajsar, & Picton, 1989), but they do not provide unique solutions to the data (Tenke & Kayser, 2005). Inverse modeling is often theoretically driven and depends only on known (or highly plausible) generators. As described by Tenke and Kayser (2005), CSDs are reference-independent, "macroscopic," volume-based estimates of the radial current flow into the scalp, which allow for "cautious inferences about neuronal generators" (p. 2827). Because CSDs are independent of the recording reference, they have an unambiguous component polarity and topography. By eliminating volume-conducted contributions from distant regions, CSD topographies have more sharply

localized peaks than scalp potential (ERP) topographies.

### 1.4 Benefits of temporal PCA

The use of unrestricted, covariance-based temporal PCA (Varimax rotation) provides data-driven characterizations of the sources of variance comprising an ERP waveform (Kayser & Tenke, 2003). A temporal PCA returns orthogonally-related factors that explain the percentage of explained variance as a function of time (factor loadings) and corresponding spatial topographies (factor scores, weighting coefficients). CSD-PCA factors provide a concise, efficient simplification of the temporal pattern and spatial distribution of neuronal generators. The correspondence between the time course and topography of the extracted orthogonal factors, and the observed CSD waveforms allows identification and measurement of complex, physiologically-relevant CSD components for further analysis (i.e., only a limited number of meaningful, high-variance CSD factors are retained for statistical analysis; for arguments and detailed discussion, see Kayser & Tenke 2003, 2006a, 2006b; Tenke & Kayser 2005). The data-driven characteristics of the CSD-PCA approach reduce the amount of subjectivity inherent to conventional methods of component identification (e.g., peak picking, window averaging, etc.). Whereas conventional approaches have difficulty separating temporally overlapping ERP components (e.g., N1 and MMN), the orthogonality of resulting CSD-PCA factors help disentangle the unique spatiotemporal characteristics of superimposed ERPs.

### 1.5 The “Cortical Dipole”

Many techniques used to investigate the location of generators underlying and/or contributing to the ERP rely on the concept of a “cortical dipole.” A dipole is a configuration of equal positive and negative charges with a specific orientation in space.

The concept of a cortical dipole is a plausible simplification of the electrical properties of the human cortex. Pyramidal cell neurons in the cortex have long apical dendrites that are predominantly oriented radial (perpendicular) to the outer surface of the cortex. Large numbers of these aligned dendrites effectively form a dipole (Lorente de No, 1947). According to the superposition theorem, electrical activity recorded at the scalp equals an algebraic sum (spatial average) of all the independent sources of activity in the underlying conductive medium. While scalp recordings will be biased for generators sources near the cortical surface with an orientation normal to the recording site (Nunez & Srinivasan, 2006), they will also linearly index all other activity, regardless of strength and orientation. Consequently, it is important to note that modeling a single dipole from scalp recordings does not necessarily indicate that an actual neuronal generator is strictly isolated to the cortex immediately subjacent to the electrode(s), as it is possible that the generator pattern observed at the scalp may arise from the superposition other electrical brain activity.

The human cortex is characterized by extensive folding all along its several obliquely shaped lobes and the size, shape, and convolution pattern of each individual brain varies considerably. Given this caveat, simplified models of the brain (e.g., spherical shell models) provide a means of calculating underlying generators in terms of a “cortical dipole,” especially when analyzing data averaged over several subjects. However, it is critical to take into account the anatomy of brain structures and the cytoarchitecture associated with these structures when inferring neural generators from surface recordings. For example, gross anatomical characteristics (e.g., gyri and sulci), sublaminar cytoarchitecture (e.g., pyramidal cells), and activation patterns of tissue may

create opened or closed fields (Tenke, Schroeder, Arezzo, & Vaughan, 1993). The field configuration will significantly impact on measures of electrical activity recorded at the scalp. Apical dendrites within sulci will usually be tangential to the recording surface making their electrical activity less visible from the scalp; furthermore, if both sides of the sulci are simultaneously active current will flow in opposite directions resulting in partial-to-full cancellation of current flow outside the local field (i.e., closed field; Tenke & Kayser, 2008). When using techniques (e.g., CSD or BESA) to infer the location of component generators based on simplified head models it is important to consider the plausibility of the inferred generator in light of the known neuroanatomy (Tenke & Kayser, 2005).

# CHAPTER 2: THE AUDITORY N1/P2

## 2.1 Exogenously-Attributed Characteristics of Early Auditory ERP Components (N1/P2)

### 2.1.1 Mediating and Moderating Variables.

AEPs are a series of measurable peaks and troughs that are categorized into three latencies: short-latency (< 10 ms) cochlear and brainstem potentials; mid-latency (10 – 50 ms) thalamocortical potentials; long-latency (> 50 ms) cortical potentials. The most commonly recognized long-latency AEPs are the N1 and P2, which generally peak in amplitude around 100 and 200 ms respectively. N1 and P2 are regarded as a linked biphasic complex due to the similarity in their response to auditory stimuli. Auditory N1/P2 was one of the earliest ERP components to be classified, originally considered a subcomponent of a polyphasic "vertex potential" ($N_0$, $P_1$, $N_1$, $P_2$, and $N_2$). As part of the vertex potential, N1/P2 was regarded as a nonspecific response to alterations in physiological states (Davis 1964; Davis & Zerlin, 1966) that trigger the auditory cortex to process incoming information (Walter, 1964). However, subsequent research demonstrated that specific physical features of stimuli (e.g., intensity, frequency, duration; see Näätänen & Picton, 1987) produce variability in latency, amplitude, and scalp distribution of N1/P2. It is now generally accepted that the N1/P2 is an exogenously generated ERP component mediated by the primary auditory cortex in response to stimulus changes exceeding perceptual threshold and modulated by the physical properties of stimuli, which may be modulated by attentional processes (discussed below)

N1 is mediated by the abrupt change (i.e., rise/fall time of 30 ms or less) in some discriminable auditory feature impinging on the auditory cortices from a stable level within the auditory environment. Generally, N1 is elicited by interruptions in a period of

silence, but it can also be elicited whenever discriminable changes occur in the level of a continuous signal (e.g., when a constant signal at a given frequency is ramped to a different frequency; Clynes, 1969; Kohn, Lifshitz, & Litchfield, 1980), or in response to the offset of a sound exceeding approximately 500 ms in duration (e.g., Hillyard & Picton, 1978). Modulation of N1 can occur through alterations in specific physical features of a stimulus (e.g., intensity, frequency). For example, N1 amplitude is positively related to the level of intensity (discussed in detail below) and approximates a power law function (Keidel & Spreng, 1965); N1 latency increases with softer intensities. In contrast, increases in frequency (e.g., > 2000 Hz) produce decreases in amplitude and shifts in scalp topography (Näätänen, Teder, Alho, & Lavikainen, 1992; Näätänen & Winkler, 1999). The level of repetition and/or presentation rate of stimulus sequences can also affect N1. Repetition of stimuli held at a constant rate produce attenuation of N1 after only a few stimuli (Cowan, Winkler, Teder, & Naatanen, 1993; Ritter, Vaughan, & Costa, 1968), and stimuli separated by long interstimulus intervals (ISIs) produce enhanced N1 (e.g., Hari, Kaila, Katila, Tuomisto, & Varpula, 1982). In contrast, significant reductions in N1 amplitude have been observed for pure tones with presentation rates below 500 ms (May & Tiitinen, 2009; Sussman, Steinschneider, Gumenyuk, Grushko, & Lawson, 2008). N1 attenuation to stimulus repetition is most likely due to a neural refractory process lasting several milliseconds (Budd, Barry, Gordon, Rennie, & Michie, 1998), which maintains a trace of the auditory feature (Lu, Williamson, & Kaufman, 1992; Näätänen & Winkler, 1999). Maintaining a perceptual trace of auditory input may help provide a context for detecting other salient deviations within the incoming auditory stream.

### 2.1.2 Attentional Influences

While the central role of N1/P2 relates to stimulus-specific perceptual processes, attentional factors may have a modulating effect. Early studies of auditory evoked potentials (AEPs) noted increases in N1 amplitude as a result of task difficulty (e.g., Davis & Zerlin, 1966) or when subjects were instructed to attend to stimuli (Hillyard, Hink, Schwent, & Picton, 1973; Picton & Hillyard, 1974). However, this effect was not always observed (e.g., Davis 1964; Hartley, 1970). Some authors have suggested that the magnitude of N1 covaries with the level of attentional resources allocated to incoming stimuli (Schwent & Hillyard, 1975), whereas others have argued that the effect of attention is indexed by ERP components overlapping the N1 (Alho, Paavilainen, Reinikainen, Sams, & Naatanen, 1986; Näätänen, et al., 1992). Attempting to reconcile these theoretical differences, Näätänen (1990) suggested N1 serves as a preattentional signal that an auditory event has occurred without indicating what the stimulus is or what its precise features are. Näätänen suggested the possibility that other components emerge and overlap N1 causing it to appear amplified. As discussed below (Section 2.5), evidence suggests that other ERP components may temporally overlap N1 causing augmented negative deflections in this timeframe, but are attributed to automatic, endogenously-mediated mechanisms such as detecting mismatches within incoming stimuli (Näätänen, Gaillard, & Mantysalo, 1978).

## 2.2 Inferring the Neuroanatomical Generators of N1

Many early investigators assumed the N1 generator was located in the frontal association cortex (Picton, Hillyard, Krausz, & Galambos, 1974) as N1 amplitude was typically observed maximally over frontocentral locations (e.g., Davis & Zerlin, 1966)

with mastoid, ear, or sterno-vertebral references. A frontal generator would have been consistent with early notions that the N1 reflected a generic attentional response to changes in the environment. However, a seminal study conducted by Vaughan and Ritter (1970) convincingly demonstrated that the origin of N1 activity fit a "field configuration expected from a dipole layer source lying in a plane perpendicular to the surface of the skull and parallel to the orientation of the primary auditory cortex…" (p. 365). Specifically, they showed that activity was isopotential with a nose reference at recording sites overlying the auditory cortex and showed maximal activity (negativity) over frontocentral sites with a polarity inversion over posterior temporal sites. This finding not only helped implicate the auditory cortex as the generator of N1, but also underlined the significance of the choice of reference when attempting to infer neural generators of ERPs. While Vaughan and Ritter's interpretation of their findings was initially contested (e.g., Picton, et al., 1974), several studies using various source localization techniques have confirmed the presence of N1 generator patterns in the region of the primary auditory cortex (e.g., Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001; Hari, et al., 1982; Scherg & Von Cramon, 1986; Wood & Wolpaw, 1982).

Heschl's gyri are located on the superior surface of the temporal lobes within the lateral sulcus and run from lateral to insular regions. Intracranial recordings suggest that the scalp recorded N1 is likely the superposition of several generators oriented normal to the planum temporale yielding larger surface potentials at frontal and central locations (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994). Scherg and Von Cramon (1985) successfully simulated the data published by Vaughan and Ritter (1980) by employing a spatiotemporal dipole model with two equivalent dipoles bilaterally

placed in the auditory cortex to index N1 activity. One dipole in the proximity of the superior temporal plane (tangential orientation) and another within the lateral superior temporal gyrus (radial orientation) was sufficient to explain most of the variance in the surface recorded data. The larger amplitude, tangentially-oriented dipole source with a Cz maximum (N100) temporally preceded a smaller amplitude, radial dipole source at temporal sites (N130). A follow-up study using the same dipole configuration was tested in a sample of patients with unilateral lesions involving the primary and secondary auditory cortices (Scherg & Von Cramon, 1986). An asymmetric dipole configuration accurately modeled the complete reduction of N1 ipsilateral to the lesion while retaining the normal dipole source potential in the intact hemisphere. The tangential N1 was also shown to be larger over the hemisphere contralateral to the ear of stimulation, a finding that has been observed elsewhere (see Näätänen & Picton, 1987).

CSD analyses have provided evidence of tangential and radial N1 source generators (e.g., Giard, et al., 1994; Kayser & Tenke, 2006; Tenke, et al., 2008). By virtue of a combined CSD and unrestricted temporal principal component analysis (PCA), Kayser and Tenke (2006) demonstrated the existence of two orthogonal N1 factors related to tones with unique spatial and temporal characteristics. An N1 peaking at 100 ms was characterized by a central sink (e.g., FCz, Cz, C3/4) and lateral-posterior temporoparietal source (e.g., TP9/10. The temporal N1 component had a peak latency of 160 ms with a prominent lateral-central temporal sink (T7/8) and central source (Cz). Animated CSD topographies provided on the author's website (http://psychophysiology.cpmc.columbia.edu/mmedia/Kayser2003b/cn2003csd.html) illustrate "the dynamic temporal-spatial linkage between central N1 and temporal N1… implicating an

N1 dipole rotation using the Sylvian fissure as an axis" (pg. 361).

Magnetoencephalographic (MEG) measurements do not rely on a reference point and they are blind to activity oriented radial to the scalp. Since the magnetic field of N1 (normally referred to as "N1m") shows an anterior to posterior polarity reversal over the perisylvian region, MEG findings also suggest the N1 generator is located within/near-to the superior temporal plane (e.g., primary auditory cortex; Godey, et al., 2001; Hari, Aittoniemi, Järvinen, Katila, & Varpula, 1980; Hari, et al., 1982; Lütkenhöner & Steinsträter, 1998).

Intracranial recordings of the auditory cortex offer the most direct measure of extracellular current sources giving rise to the scalp-recorded N1. For obvious ethical reasons, intracranial recordings in humans are usually limited to samples of patients undergoing presurgical evaluations for medically intractable epilepsy. Due to unique clinical considerations, human intracranial studies often differ as a result of the recording procedure (cf., Brugge, et al., 2008; Liégeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994), the choice of auditory stimuli, and considerable intersubject and interhemispheric variability of the anatomy and cytoarchitecture within the auditory cortices (Howard, et al., 2000). Given the preceding caveat, intracranial studies have shown that multiple auditory cortical fields contribute to the scalp recorded N1. Activity in the timeframe of N1 occurs in subdivisions of the superior temporal cortex, such as the planum temporale, posterior lateral superior temporal area, and Heschl's gyrus (Brugge, et al., 2008; Halgren, et al., 1995; Howard, et al., 2000; Liégeois-Chauvel, et al., 1994).

## 2.3 Intensity Modulation of N1/P2

### 2.3.1 Increases in Stimulus Intensity Reliably Elicit Enhancements of N1/P2.

Intensity modulation of N1/P2 amplitude is commonly referred to as the loudness-dependency of auditory evoked potentials (LDAEPs). Modulation of N1/P2 amplitude using LDAEP paradigms has been rigorously investigated since the earliest reports of the vertex potential (Davis & Zerlin, 1966; Moore & Rose, 1969; Rapin, Schimmel, Tourk, Krasnegor, & Pollak, 1966; Spoor, Timmer, & Odenthal, 1969). Keidel and Spreng (1965) noted that N1 amplitude is positively related to the level of intensity and approximates a power law function (Keidel & Spreng, 1965). Originally, N1/P2 amplitude increases were thought to occur only up to approximately 70-75 dB (Rapin, et al., 1966), where the rise in the intensity/amplitude function to stimuli louder than 75 dB would become asymptotic (e.g., Adler & Adler, 1989; Davis & Zerlin, 1966; Moore & Rose, 1969; Picton, Woods, & Proulx, 1978; Snyder & Hillyard, 1976). However, it was later shown that N1 enhancement for much louder (e.g., 100 dB) intensities could be observed if longer ISIs were employed (Näätänen & Picton, 1987).

The magnitude of the tangentially-oriented N1m dipole (the magnetic equivalent of the electric N1) located near the superior temporal cortex has been shown to increase monotonically with stimulus intensity (e.g., Bak, Lebech, & Saermark, 1985; Eberling, Bak, Kofoed, Lebech, & Saermark, 1981; Hegerl, Gallinat, & Mrowinski, 1994). One MEG study (Pantev, Hoke, Lehnertz, & Lütkenhöner, 1989) noted that louder intensities produced activity further out on the lateral edge of the Sylvian fissure compared to relatively softer tones, however this finding has not been replicated. Intensity modulation of the tangential N1 is also implicated by electrical dipole source modeling. Hegerl, Gallinat, and Morwinski (1994) used BESA to model the sources of N1 elicited by tones (1000 Hz) at five levels of intensity (60, 70, 80, 90, and 100 dB) to help determine which

cortical region was most sensitive to intensity. Source waveforms suggested that the tangential dipole (measured as N1/P2 peak-to-peak) was most sensitive to changes in intensity compared to dipoles with a radial orientation. However, a figure presented in the Hegerl et al paper depicting amplitude-to-stimulus intensity slopes for tangential and radial source activity indicates a substantial increase in amplitude for the radial dipole at intensities above 80 dB; however no statistics were reported for the radial activity. If indeed activity was greater for intensities above 80 dB for radial sources, this finding would dovetail with the previously reported MEG finding (Pantev et al., 1989) showing an anterior-radial shift in tangentially-oriented N1 activity with louder intensities, and suggest that loud tones produce a unique spreading of activity across the auditory cortex.

The use of functional magnetic resonance imaging (fMRI) offers a clearer spatial resolution of the changes in blood oxygen in underlying brain tissue. However, since the full time-course for the blood-oxygen-level dependent (BOLD) contrast occurs on the order of seconds, fMRI is grossly incapable of investigating intensity modulation of N1. The acoustic noise of fMRI scanners is also a major methodological concern for studies attempting to evaluate psychophysiological processes related to specific auditory stimulus characteristics. Nonetheless, some studies have investigated the relationship of the fMRI BOLD response to auditory intensity in an attempt to map the amplitopicity of the auditory cortex, and have shown moderate correlations between tone intensity and levels of BOLD responses (e.g., Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002; Brechmann, Baumgart, & Scheich, 2002; Mulert, et al., 2005). While offering very little information about processes underlying N1/P2, these studies help confirm the recruitment of subdivisions of the auditory cortex implicated in ERP research (e.g., planum

temporale, Heschl's gyrus, etc.).

## 2.4 Neurophysiology, Neuropharmacology, and Clinical Utility of N1/P2 Intensity-Dependency

### 2.4.1 A Serotonin Modulated, Lateral-Inhibition Model of N1/P2 Intensity-Dependency.

The exogenous nature of N1 has commonly been exploited for research and clinical use in the field of objective audiometry (Coles & Mason, 1984; Hyde, 1997; Keidel & Spreng, 1965). Psychiatric research has focused on the clinical utility of N1/P2 as a measure for predicting treatment response to selective serotonin reuptake inhibitors (SSRIs) in patients with major depressive disorder. Hegerl and Juckel (1993) have suggested that abnormally large N1/P2 LDAEP effects observed in some depressed patients may be due to low levels of postsynaptic serotonergic (5HT) preactivation within the primary auditory cortex. According to this model, 5HT projections to the auditory cortex normally act to modulate sensory processing in the auditory cortex through helping maintain a competitive neuronal network similar to lateral inhibition (Hegerl & Jukel, 1993). For example, 5HT would help reduce the overall level of cortical activation by bolstering the activity of inhibitory interneurons that normally act to dampen (i.e., reduce resting membrane potentials) the excitability of cells surrounding those stimulated by incoming stimuli (e.g., loud tones). This adaptive process helps maintain an active modulation of sensory perception and discrimination. Since 5HT input is thought to act as an inhibitory neurotransmitter in this region, 5HT denervation (as seen in depressed patients) would lead to cellular preactivation levels closer to threshold and yield greater N1/P2 LDAEP effects.

### 2.4.2 Supporting Neurophysiological Evidence.

Neurophysiological evidence suggests that the 5HT system is well suited to influence auditory processing. The auditory N1 is generated by populations of neurons within the superior temporal plane of the auditory cortex, and histological assays have demonstrated dense 5HT innervation from dorsal raphé projections to the primary auditory cortex across species (Azmitia & Segal, 1978; Campbell, Lewis, Foote, & Morrison, 1987; DeFelipe, Hendry, Hashikawa, & Jones, 1991). Serotonergic fibers form atypical synapses predominantly on GABAergic interneurons, but also synapse directly on pyramidal neurons (cat auditory cortex, DeFilipe et al., 1991; primate prefrontal cortex, Smiley & Goldman-Rakic, 1996) indicating that 5HT enacts an inhibitory postsynaptic effect on projection cells through either direct synapses or indirectly through GABAergic interneurons (Sheldon & Aghajanian, 1990). Facilitation of acoustic startle behavior in serotonin-depleted animals (Davis, 1984) suggests that serotonin acts to stabilize signal processing by constraining the flow of information presumably by decreasing the signal amplitude (Spoont, 1992). Juckel, Hegerl, Molnar, Csepe, and Karmos (1999) found that activation of serotonergic neurons in the dorsal raphé nucleus using the $5HT_{1A}$ antagonist spipertone decreased the LDAEPs in cats. Therefore, recent research has been testing the hypothesis that low tonic 5HT preactivation levels associated with depression will show stronger LDAEP effects relative to healthy adults, which may in turn predict favorable response outcomes to SSRI therapy (Gallinat, et al., 2000; Paige, Fitzpatrick, Kline, Balogh, & Hendricks, 1994).

2.4.3 Electrophysiological Evidence in Humans.

Directly testing the intracranial neurochemical and physiological tenants of the LDAEP-5HT theory in humans is limited. Several studies have been conducted that

compare pretreatment to post-treatment LDAEP effects in depressed patients. In support of the LDAEP-5HT modulation, these studies have demonstrated that a subset of depressed patients who respond to SSRIs show enhanced N1/P2 LDAEPs at baseline, which later resolves to amplitudes comparable to healthy adults (e.g., Juckel, et al., 2007; Mulert, et al., 2007). Attempts to directly reduce central 5HT mechanisms in healthy adults through acute tryptophan depletion (ATD) have yielded mixed results (e.g., Debener, et al., 2002; Dierks, et al., 1999; O'Neill, et al., 2008). Many of the studies employing ATD do not show clear evidence of LDAEP modulation through acute reductions in 5HT. In light of these findings, some have suggested that LDAEP-5HT modulation may only occur in cases of chronic 5HT dysfunction, which is more likely the case in clinical depression (O'Neill, et al., 2008). In contrast to the enhancement of LDEAPs in depressed patients, attenuated LDAEPs among schizophrenic patients suggests that the higher levels of 5HT function (observed in this patient population) may dampen the normal afferent processes of the primary auditory cortex (Juckel, et al., 2003; Juckel, et al., 2008). This evidence is interesting as it suggests a double dissociation of LDAEP effects can be demonstrated between two clinical populations with overlapping neurochemical disorders.

2.4.4 Caveats to the LDAEP Paradigm.

A significant, often overlooked, concern for LDAEP-5HT investigations is controlling for the effects of arousal and/or temporally overlapping brain processes that may affect N1/P2 characteristics; (e.g., MMN, processing negativity; Hillyard, et al., 1973; Näätänen, 1975, 1990; Picton & Hillyard, 1974). Attempting to control for the level of arousal is necessarily important when examining the role of serotonergic

modulation on neuronal circuits. Serotonergic activity is highly dependent on the overall level of arousal and type of behavioral activity. In an awake state, serotonergic cells in the raphe nuclei display a consistent pattern of discharge, but as the level of arousal decreases to a sleep state the rate and regularity of firing decreases (for a review see Jacobs & Azmitia, 1992). Although other midbrain nuclei projecting to the auditory cortex behave in a similar manner across the sleep – wake cycle (e.g., norepinephrine), they differ distinctly in the following ways: a) Serotonergic cells do not habituate to repeated stimulus presentation whereas norepinephrine cells habituate rapidly; b) serotonergic cells demonstrate a linear relationship to the level of arousal whereas the activity of ascending midbrain nuclei decrease or do not change; c) whereas other cells types are activated during orientation, serotonergic cells are more strongly activated during sedentary or repetitive activities (Jacobs & Azmitia, 1992). While it has been argued that 5HT firing rates influence LDAEP (Hegerl, Gallinat, & Juckel, 2001), surprisingly few studies have discussed or controlled arousal states when examining the role of serotonergic modulation of LDAEPs.

Controlling for overlapping, endogenously-generated brain processes is another important, and often overlooked, consideration for LDAEP-5HT investigations. Discussed in detail later (Methods: Paradigm), measures of N1/P2 may be influenced by unbalanced stimulus probabilities, e.g., the level of intensity disparity between consecutive trials is usually unbalanced in standard LDAEP paradigms. Furthermore, the range and/or relative degrees of intensities regularly applied to LDAEP studies have not been systematically tested to rule out possible interactions of unrelated cognitive processes. For instance, it is possible loud stimuli may be perceived as painful or very

soft intensities perceived as stimulus omissions, which could potentially induce ERP components that overlap components of primary interest to these studies (i.e., N1/P2).

# CHAPTER 3: THE MISMATCH-NEGATIVITY (MMN)

## 3.1 Endogenous Mechanisms Attributed to MMN.

In contrast to N1/P2, endogenous or cognitive ERP components do not explicitly depend on the physical properties of stimuli (e.g., Donchin, Ritter, & McCallum, 1978). Although most ERP components that are considered to be endogenous occur at longer latencies (e.g., over 200 milliseconds), some overlap N1/P2 and contribute to the volume-conducted activity observed in the surface potential (Näätänen, 1990). For example, the mismatch negativity (MMN), observed as a relative difference between deviant and standard stimuli, partially overlaps and extends beyond N1/P2, and shares similar spatiotemporal characteristics with N1 (i.e., observed at the same electrode sites). MMN is widely considered an automatic preattentional (i.e., endogenous) mechanism that detects changes in established patterns of auditory stimulation (Kujala, Tervaniemi, & Schroger, 2007; Näätänen, Paavilainen, Rinne, & Alho, 2007). That is, MMN is thought to reflect the output of a memory-based process in the auditory cortex which constantly monitors the environment and provides signals of irregularities (Näätänen, et al., 1978). This interpretation suggests that MMN may be able to provide information about basic auditory perception, sensory memory representations of stimuli, and pre-attentional regulation of input to conscious perception (Näätänen, et al., 2007). However, this endogenously-mediated, memory-based interpretation of MMN has been recently challenged as discussed in section 3.2.2.

MMN is classically observed in a paradigm in which a stimulus is repeatedly presented at a high level of probability (establishing it as a ‘standard’) and periodically interrupted by a lower probability (‘deviant’) stimulus that deviates from the standard

stimulus in a specific physical dimension (e.g., intensity). The repetition of a standard stimulus is thought to produce a strong sensory trace, which is, presumably, mediated by processes related to N1. As a result, presenting a stimulus differing from the standard will produce a MMN response, which signals that a stimulus has deviated from the standard (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Näätänen & Winkler, 1999). A wealth of research has demonstrated that MMN is sensitive to many forms of stimulus deviation. For example, deviations in tonal frequency (Jacobsen & Schroger, 2001; Näätänen, et al., 1978), stimulus onset asynchrony (Sable, Gratton, & Fabiani, 2003), duration (Todd & Michie, 2000), and intensity all produce MMN when presented in context of standards. MMN amplitude and latency are usually associated with the magnitude of deviance, but not always (e.g., Horvath, et al., 2008). This effect has been observed for changes in frequency, spectral complexity, intensity, duration, spatial location, and SOA (for review see Näätänen, et al., 2007). MMN will be elicited if the feature of the lower probability stimulus deviates within a single dimension of the standard (e.g., high intensity deviant vs. low intensity standard) or deviates in multiple dimensions (e.g., high intensity & high frequency deviant vs. low intensity & low frequency deviant). Some evidence suggests MMN is additive when deviant features are compounded (e.g., Wolff & Schröger, 2001).

Several studies have demonstrated that MMN reflects more complex auditory processes than simply detecting deviations in static stimulus properties (Kujala, et al., 2007; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001a). For example, repeated presentations of tone pairs increasing in frequency do not elicit a MMN, but if a tone pair is presented in decreasing order MMN is elicited, although the actual stimulus

features have remained constant (Saarinen, Paavilainen, Schoger, Tervaniemi, & Näätänen, 1992). Moreover, departures from a 'standard' rule (e.g., the higher the frequency the higher the intensity) elicit MMN even when stimuli are continuously varied over a wide range of frequencies or intensities (Paavilainen, Simola, Jaramillo, Näätänen, & Winkler, 2001). Findings like these "suggest the auditory cortex does not only model the immediate auditory past but also forms extrapolatory traces on the basis of the regularities or trends detected in the auditory past" (Näätänen, et al., 2001a, p. 284). MMN has been implicated in cognitive phenomena such as, language development, perceptual learning, voice familiarity, audio-visual integration, stimulus grouping, and others (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001b; Paavilainen, Simola, Jaramillo, Naatanen, & Winkler, 2001; Winkler & Cowan, 2005).

### 3.2 Functional Interpretations of MMN.

#### 3.2.1 The Memory-Based Model.

Two plausible functional and physiological interpretations of MMN have been posited. The memory-based interpretation of MMN is the most commonly accepted and utilized theory. It assumes that neural activity contributing to MMN is both structurally and functionally independent of the neurophysiology underlying N1. A neurophysiological model advanced by proponents of the memory-based interpretation attempts to distinguish "mismatch detector cells" existing within the auditory cortex from topographically distinct, stimulus-specific afferent cells contributing to N1 (Sokolov, Spinks, Naatanen, & Lyytinen, 2002). According this model, stimulus-specific N1 cells project onto mismatch detector cells; each detector cell receives input from multiple N1 cells (i.e., cells responsive to characteristically similar and dissimilar stimuli).

Habituation of both detector cells and N1 cells occur with repeated presentations of identical stimuli (i.e., standards); however, dishabituation of the detector neuron occurs when other N1 cells responsive to stimuli dissimilar to the standard stimulus (i.e., deviants) stimulate the detector cell. Consequently, MMN represents the output of a discrimination process that is (at least partially) mediated by the dishabituation of detector neurons through inputs from N1, and represents a second-order process functionally distinct from primary sensory processes mediating N1. Näätänen (2007) sees MMN as providing "indirectly, a measure of the accuracy of the neural representation of the standard stimulus," which consequently, "opens a window to the perceptual and memory functions of the auditory cortex" (p. 2547). Therefore, this interpretation depicts MMN as an index of an endogenously generated comparative process that involves a highly accurate sensory-memory system able to detect slight deviations in stimulus parameters.

While many neurophysiological tenets of this model have not been adequately tested at the cellular level (i.e., evidence of "mismatch detector cells" has never been demonstrated), it is often cited and used to interpret experimental findings due to its elegance and relevance to various ecological, developmental, clinical, and psychophysiological theories.

3.2.2 The Adaptation Model.

Another interpretation of MMN, originally posited and rejected by Näätänen (1990), has been reemerging as a viable alternative- to the memory-based model as it offers a more simplistic interpretation of MMN based on known neurophysiological principles. This model suggests MMN is actually an index of the differential activity

between cells contributing to N1 (i.e., the same cells produce N1 and MMN); that is, neuronal populations repetitively activated by standard stimuli undergo adaptation and yield smaller N1 amplitude, whereas unadapted ("fresh") cells activated by deviant stimuli yield larger N1 amplitude (Jääskeläinen, et al., 2004; May & Tiitinen, 2001, 2004, 2009). According to this interpretation, a) standards and deviants activate overlapping neural populations, b) repeated presentations of standards leads to adaptation through lateral inhibition of cells tuned to the exact characteristic of the standard stimulus, whereas c) cells tuned to the deviant stimulus remain non-adapted or "fresh" (i.e., at or near normal threshold). Consequently, residual "negativity" observed in deviant-minus-standard difference waveforms (i.e., "mismatch negativity") is solely driven by normal or enhanced activation patterns of cells that are not in a state of refractoriness or hyperpolarization. In contrast to the memory-based model, MMN reflects a first-order modulation of N1 to deviant stimuli and not a second-order, memory-based, comparator mechanism. May and Tiitinen (2004, 2009) contest that the memory-based model of MMN relies on the existence of highly complex functionally-specific cell types in the auditory cortex, which is not supported by neurophysiological evidence. These authors argue that the adaptation model of MMN is consistent with known physiological and anatomical processes within the auditory cortex, citing well-documented evidence of the spatial and temporal organization of the primary auditory cortex, and adaptation and/or lateral inhibition mechanisms recorded from cells within this region.

Much of the evidence used to support the memory-based model can also be explained by the adaptation interpretation. For example, enhancements in MMN activity to disparities in tone frequency can be explained through a system of lateral inhibition in

the primary auditory cortex (similar to the process described in Section 2.4.1). That is, due to the tonotopic organization of the auditory cortex, tissue primarily responsive to deviant frequencies close to the standard may be affected by adaptation through the spreading of adjacent lateral inhibitory mechanisms; whereas tissue activated by very different frequencies are unaffected by adjacent inhibitory processes. In a critique of the adaptation hypothesis, Näätänen, Jacobsen, and Winkler (2005) have argued that the adaptation interpretation cannot explain why MMN activity is elicited by stimulus omissions within a temporally uniform series of stimuli (Oceák, Winkler, Sussman, & Alho, 2006; Raij, McEvoy, Makela, & Hari, 1997; Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997), or by omissions of a second tone within a standardized pair (Tervaniemi, Saarinen, Paavilainen, Danilova, & Näätänen, 1994). However, computational modeling and MEG evidence have demonstrated that N1-like activity within the auditory cortex can become synchronized to stimulation rate and persists after stimulation has ceased (May & Tiitinen, 2001). This evidence helps illustrate how the auditory cortex dynamically deconstructs the auditory environment into temporal and spectral components, and it provides a physiologically plausible means by which N1- or MMN-like activity may be observed to stimulus omissions.

The adaptation model suggests that the nature of electrical activity and spatial organization of N1 generators not only help detect and perceive basic features of auditory information (e.g., frequency, intensity, duration, etc.), but also provide the basic information for the detection of deviations within the environment. In contrast to the more structurally and functionally complex memory-based model, the adaptation model suggests that deviance detection arises from a relatively more efficient and elegantly

arranged neurophysiological system.

### 3.3 Inferring the Neuroanatomical Generators of MMN

#### 3.3.1 Evidence from Surface Potentials

It is commonly accepted that MMN activity is derived from two distinct cortical generators located in bilateral superior temporal cortex and right frontal cortex (Giard, et al., 1997; Kujala, et al., 2007; Näätänen, et al., 2007; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). While there is substantial evidence to support a contribution from bilateral temporal cortices, evidence supporting frontal involvement is not as extensive. Surface potential ERP measures of MMN using a nose-reference consistently reveal a frontocentral negativity (e.g., Fz and Cz) with a smaller polarity inversion over lateral inferior temporal sites (i.e., mastoid processes). Thus, the surface potentials of MMN and N1 not only overlap in time (although MMN temporally exceeds N1), but also share very similar scalp topographies.

#### 3.3.2 Evidence from Current Source Densities (CSDs)

There are relatively few published MMN studies utilizing CSD techniques; moreover, many of these studies do not conduct statistical analyses on the CSD waveforms, but rather use CSDs for illustration purposes (e.g., topographical maps). Nevertheless, CSD analyses of MMN have typically shown a bilateral frontal sink – temporoparietal source configuration indicative of a generator within the auditory cortex (e.g., Deouell, Bentin, & Giard, 1998; Giard, Perrin, Pernier, & Bouchet, 1990; Sato, et al., 2000). Deouell, Bentin, and Giard (1998) analyzed CSDs (32-channels) resulting from dichotically presented tones in which standard left/right frequency pairs (660/932 HZ, respectively) were periodically interrupted by a rare pitch change in either ear. Rare

tones were either 80 Hz increases in pitch (e.g., 740/932 deviant dichotic pair) or 100 Hz decreases in pitch (e.g., 660/830 deviant dichotic pair). Deviant-minus-standard CSDs showed enhanced MMN activity over auditory regions contralateral to the ear receiving the rare pitch and significantly larger MMN over the right hemisphere overall, which confirms previous findings by this group (Giard et al., 1990). Moreover, MMN was reportedly larger for rare decreases in pitch compared to increases in pitch.

### 3.3.3 Evidence from Equivalent Dipole Source Modeling

Equivalent dipole source analysis of MEG data show similar spatial overlap between the N1m and MMF (magnetic equivalent of MMN) source generators; however, source models suggest MMF generators are situated slightly anterior to N1m generators (Csépe, Pantev, Hoke, Hampson, & Ross, 1992). Other findings have shown an additional dipole source within right frontal regions (Giard, et al., 1997; Näätänen, Jacobsen, & Winkler, 2005). Dipoles models derived from MEG data have shown MMN generators differ as a function of the deviant stimulus feature; for example, the orientation of source dipoles located in the region of superior temporal cortex exhibit slightly different location and orientation for frequency, duration, intensity deviants (Frodl-Bauch, Kathmann, Moller, & Hegerl, 1997; Giard, et al., 1997; Rosburg, 2003). While findings such as those noted above seem to suggest MMN activity can detect and distinguish between specific anatomical portions of the cortex, again, such interpretations must be made cautiously (at best) in light of the amount of variability introduced by individual differences (e.g., brain anatomy).

### 3.3.4 Evidence from Intracranial Recordings

Human intracranial recordings corroborated much of the scalp-recorded electric

and magnetic findings and offer insight into specific subregions of the auditory cortex associated with processing deviant stimuli. Distinct cortical regions giving rise to N1 and MMN have been recorded in adults (Halgren, et al., 1995; Kropotov, et al., 2000) and children (Liasis, Towell, & Boyd, 1999, 2000). These studies have recorded activity in the timeframe of N1 and MMN within regions inferior to the Sylvian fissure on the lateral surface of the superior temporal gyrus that inverts in polarity over areas superior to the Sylvian fissure (i.e., implicating primary auditory cortex). Kropotov et al. (2000) was able to dissociate several subregions of the superior temporal gyrus related to standard (1000 Hz) and deviant (1300 Hz) tones, which involved primary (Brodmann's Area, BA 41), secondary (BA 42), and higher-order (BA 22) auditory cortices. Activity in primary auditory cortex (BA 41) revealed two temporally distinct negative deflections for the deviant-minus-standard difference. A relatively late deflection peaking at 150 ms significantly differed from baseline, while the earlier deflection at 80 ms did not. A comparison of equiprobable 1300 Hz and 1000 Hz tones revealed negative deflections only at 80 ms, which was significantly greater in amplitude for the higher frequency. Activity in the secondary auditory cortex (BA 42) also revealed significantly greater amplitude at 130 ms for the deviant tone. While activity in BA 42 did not differ between equiprobable frequencies (i.e., 1000 and 1300 Hz), significant differences in activity were related to stimulus presentation rate. That is, amplitude at the 130 ms latency was smaller for activity related to an independent block of 1000 Hz tones presented at a constant 850 ms interstimulus interval (ISI) compared to an independent block of the same tones presented at a constant 8500 ms ISI. Finally, activity in BA 22 revealed a significantly greater negative peak deflection at 140 ms for deviant tones. Activity in this region did

not differ between equiprobable tones of high and low frequency, nor were differences between interstimulus intervals found. Given this evidence, the authors suggest the likelihood that BA 22 underlies MMN in observed in humans.

Intracranial recordings in animals attempting to localize N1 and MMN generators have produced mixed results. For example, intracortical CSD recordings through the supergranular layers of primary auditory cortex (A1) in the monkey show MMN-like activity, but penetrations through regions anterior or medial to primary auditory cortex do not reveal MMN-like activity (Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994). However, recordings from electrode grids placed over primary and secondary auditory cortices in the cat suggest MMN-like activity is produced in regions anterior and ventral to the primary auditory cortices (i.e., secondary auditory cortex).

In summary, information gained from scalp and intracranial recordings do not clearly implicate separable brain regions for MMN and N1 activity. While differences in CSD, dipole moments, and intracranial recordings at times suggest that MMN generators are spatially distinct from N1 generators, these findings are not consistent, nor do they converge on a particular anatomical region. It is also possible that individual differences in brain anatomy could contribute to these mixed findings.

### 3.4 Intensity Modulation of MMN.

#### 3.4.1 Disparities in Intensity Produce MMN.

Relatively few studies have specifically investigated the effect of intenstity on MMN. Näätänen, Paavilainen, Alho et al. (1989) were one of the first to provide evidence that disparities in intensity between deviants and standards produce measurable changes in MMN. They demonstrated significantly greater MMN for deviant decrements of -23

dB and -10 dB, but not -3 dB tones compared to an 80 dB standard tone in separate blocks. Later, Schröger and Winkler (1995) reported significantly shorter MMN latencies for relatively larger intensity disparities (large disparity = -10 dB; small disparity = -4 dB; standard = 70 dB), but no significant differences in MMN amplitude. In another study, Pakarinen, Takegata, Rinne, Huotilainen, and Näätänen (2007) found significant MMN amplitude differences across six levels of intensity disparity randomized within a single block (successive decrements of 2.5 dB from the 60 dB standard); however, this study used a very complex paradigm in which intensity deviants were embedded within blocks containing three other deviant types (duration, frequency, and location). Each deviant condition had six levels; thus, one experimental block contained 24 unique deviant trials, which raises concerns about the specificity of these MMN findings to intensity deviance. In a less complex study, subjects were administered a forced-choice (2-button press) discrimination task between two equiprobable tones differing in frequency, and told to ignore changes in intensity (Rinne, Sarkka, Degerman, Schroger, & Alho, 2006). Tones were presented at 60 dB in 82% of the trials, while over the remaining 18% of trials intensity was increased (9%) or decreased (9%). Three levels of increments (+3, 6, 9 dB; $P = 0.03$ each) and three deviant decrements (-3, 6, 9 dB; $P = 0.03$ each) were presented equally within blocks. Results showed enhanced MMN for deviant increments and decrements; however, enhancement of frontocentral P3a was observed for increments, but not decrements. This finding is important as it suggests that loud deviants may be perceived and/or classified differently than soft deviants, as the P3a is thought to reflect automatic attentional orienting to novel or salient stimuli involving medial regions of the frontal lobe (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007;

Tenke, Kayser, Stewart, & Bruder, 2009). It is unclear, however, to what extent these findings were directly related to intensity deviance per se, or to what extent they were affected by the attentional demands of the discrimination task. For example, since participant's attention was directed toward correctly detecting rare frequency targets, louder (i.e., perceptually clearer) targets may have been more easily evaluated as salient or even novel thereby eliciting the P3a response. In contrast, perceptually muted (i.e., soft) tones did not facilitate target detection and did not elicit a P3a response.

While only a few published studies have specifically investigated intensity deviance using a MMN paradigm, together these studies suggest that a) MMN is elicited by intensity deviance, b) larger disparities produce enhanced MMN amplitude, and c) louder intensity deviants may recruit additional regions of brain activation thought to be related to the detection of novel or salient stimuli. These findings are important as they suggest that deviance-related mechanisms may contribute or interact with N1/P2 LDAEP effects.

### 3.4.2 MMN in the Context of a LDAEP Paradigm

To date, no published studies have investigated the intensity dependency of MMN in the context of a LDAEP paradigm; however, some aspects of the LDAEP paradigm could potentially elicit MMN. The standard LDAEP paradigm usually requires participants to listen to equiprobable, pseudorandomized presentations of tones differing in intensity. Although a "standard" intensity is not explicitly established in this paradigm, inevitably, disparity in intensity between consecutive presentations of tones may range from 10 to 40 dB depending on the study. Indeed, studies often report intensities that range from 60 to 100 dB. It is possible that an endogenous processes related to deviance-

detection (e.g., MMN) may be active in cases where the disparity between consecutive pairs of tones differs to a greater degree. Furthermore, large disparities will also occur less frequently when equiprobable intensities are randomly presented. For example, if 100 tones at five equiprobable intensities (60, 70, 80, 90, 100 dB; $p = 0.20$ respectively) are pseudorandomized so that no identical stimuli are presented consecutively then the probability of consecutive tones differing by 30 or 40 dB (20% and 10% respectively) is much lower than the probability of hearing 10 dB differences (40%). Thus, standard LDAEP paradigms may invoke overlapping endogenously-mediated brain activity related to detecting low-probability differences.

It may be possible to disentangle exogenously-related (N1/P2) and endogenously-related (MMN/P3a) mechanisms involved in processing intensity-specific information by employing a carefully constructed MMN paradigm. To this end, a mixed-deviant MMN paradigm may be applied where every level of intensity serves as a frequent standard or a rare deviant in separate blocks. This design would not only permit an analysis of N1/P2 LDAEP for standards and deviants, but it would also provide a means to analyze the intensity dependence of MMN and the effect of disparity in the context of a standard LDAEP paradigm. The current study will implement and test this experimental design.

3.4.3 Attentional Influences on MMN to intensity deviants.

Brain processes indexed by MMN were originally believed to be independent of attention, as dichotic listening studies revealed no differences in MMN to deviants presented in either relevant-attended or irrelevant-unattended channels (e.g., Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989; Näätänen, et al., 1978). However, a study published by Woldorff, Hackely, and Hillyard (1991) suggested that attention may

influence MMN processes. Their study used a dichotic listening paradigm in which participants were asked to respond (via button-press) to rare intensity decrements (ranging from -10 to -28 dB) in a standard 55 dB tone presented to one ear and ignore intensity decrements of a different frequency in the other ear. While MMN was observed in attended and unattended conditions, greater MMN amplitude was observed for deviants presented to the attended ear compared to the unattended ear, indicating an attentional modulation of MMN. The authors suggested that this attentional modulation resulted from suppression of sensory processing in the unattended channel. Näätänen (1991) disagreed with the interpretation of Woldorff and colleagues and contended that attentional modulation for intensity decrements was due to a dampening of a MMN amplification mechanism rather than basic sensory suppression. To test this hypothesis a study that used two types of deviants (frequency and intensity-decrements) in a dichotic listening task was designed (Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). Intensity for standards and both deviant types (80 dB and 70 dB respectively) were held constant across ears. Attentional load was manipulated in separate blocks by having participants 1) count frequency deviants in either the left or right ear, or 2) count intensity deviants in the left or right ear, or 3) ignore the stimuli altogether while reading a book. Differences in MMN amplitude were not observed between attended and unattended frequency deviants or attended intensity deviants, but MMN was significantly attenuated when intensity deviants were to be ignored (i.e., the reading condition). Näätänen argued that while the results show attentional modulation of MMN for intensity deviants, the attentional modulation of MMN cannot be due to generic processes of sensory suppression to irrelevant information. Näätänen rationale for this interpretation is that the

MMN to frequency deviants did not differ between attended and unattended ears.

Taken together, the studies reviewed here indicate that the detection of intensity deviance may be modulated by the level of attention paid to the auditory channel. However, attentional regulation of intensity deviance detection may be unique to decrements and not increments, as louder tones may carry greater environmental salience and, therefore, be harder to ignore. Unfortunately, no study has systematically tested whether MMN to increments or decrements is differentially affected by attentional demands.

Many have not controlled or accounted for attentional variation between subjects. That is, subjects instructed to simply listen to tones and visually fixate on some static point (e.g., fixation cross) may or may not rigorously attend to the stimuli. Furthermore, some subjects may passively attend/listen to tones whereas others may actively attend to them (e.g., count all tones, or perhaps only loud tones). Indeed, research has demonstrated that the level of attention or approach in attending to tones can affect N1/P2 responses. For example, the "attention" condition in Näätänen et al.'s (1993) study required participants to silently count intensity deviants, and in the "unattended" condition participants were asked to ignore tones and read a book. Hence, the two conditions differ in more ways than level of 'attention'. For one, the attended condition is actually a target-detection task requiring some active participation with the stimuli on the part of the subject, which can have a profound effect on the ERP (e.g., Kayser & Tenke, 2006). Furthermore, the reading condition not only lacks a response from the participant, but also lacks any behavioral measure that the participant was truly ignoring the stimuli (or even reading the book).

Muller-Gass, Stelmack, and Campbell (2005) noted the lack of consistency among published studies concerning the type of distracter task used for unattended conditions. They note many studies fail to clearly identify the extent of the participant's engagement, do not control for the content of distracter tasks between subjects (e.g., many studies have each participant bring his/her own reading material), and fail to verify if the participant was actually engaged in the task. Addressing these issues, Muller-Gass and colleagues (2005) varied the demands of a primary/diversion task commonly used in MMN studies (reading a book) and assessed the effect of this manipulation on MMN to frequency and intensity deviants. Specifically, participants were instructed to, 1) ignore tones and read a book *selected by the experimenter followed by a short quiz*, or 2) ignore tones and read a book *selected by the experimenter*, or 3) ignore tone and read a *self-selected book*, or 4) sit quietly (i.e., 'empty-control' condition). Results showed significantly greater MMN amplitude for participants queried about their reading following experimental blocks (1$^{st}$ condition). The authors note this finding is counter-intuitive to work showing reduced MMN when attentional demands for the primary tasks are increased; however they suggest their findings indicate that the nature of the diversion task (e.g., subject's a priori knowledge of a subsequent recall of reading material) can affect MMN. They also hypothesize that enhanced MMN amplitude observed in their study may reflect increased cortical excitability to the more demanding task. While difficult to assess by the information provided within the article, it is also possible that the significant difference in MMN observed for the reading – query condition was driven by less variability in the recorded ERPs due to a relatively more consistent level of attention needed for this condition with respect to the other conditions.

### 3.5 Neurophysiology, Neuropharmacology, and Clinical Utility of MMN

#### 3.5.1 A GABAergic and NMDA-Mediated, Lateral-Inhibition Model of MMN.

Javitt and colleagues (1996) have proposed that activity of N-methyl-D-aspartate (NMDA) receptors primarily mediate the cellular activity underlying MMN. These authors demonstrated that competitive and non-competitive NMDA antagonists block the generation of MMN without affecting early exogenous components in the awake monkey, which indicates that MMN acts through open and unblocked NMDA channels. Administration of bicuculline ($GABA_A$ antagonist) also enhanced the activity of cells within the supergranular layers of primary auditory cortex responsible for MMN. Based on these findings Javitt et al. have proposed a neurophysiological model to account for mechanisms underlying MMN, and deficits in MMN within particular psychiatric populations (e.g., schizophrenia). According to this model standard tones repeatedly activate stimulus-specific neurons within the supragranular layer, which leads to the inhibition of surrounding neurons sensitive to the same stimulus feature, which then disinhibits adjacent cells sensitive to other features. Lateral inhibition of cells responsive to the standard stimulus is thought to be mediated by GABAergic interneurons, which reduces the relative amount of current flow through voltage-mediated NMDA receptors. On the other hand, partially disinhibited cells (presumably due to less GABAergic activation) responsive to the deviant stimuli undergo relatively greater current flow through partially unblocked voltage-gated NMDA channels. Therefore, this model suggests electrophysiological differences observed for deviant-minus-standard trials represent greater current flow mediated by open NMDA channels.

#### 3.5.2 Supporting Neurophysiological Evidence

Supporting evidence for the GABAergic – NMDA mediated model of MMN is provided through pharmacological manipulations of the GABAergic and Glutaminergic systems in humans. For example, significant reductions in MMN amplitude but not other earlier components (e.g., N1) have been observed after infusion of the NMDA receptor antagonist ketamine (Heekeren, et al., 2008; Umbricht, et al., 2000). Heekeren et al (2008) demonstrated the specificity of NMDA receptor mechanisms by showing greater MMN reduction following ketamine administration compared to infusion of the $5HT_{2A}$ agonist dimethyltryptamine in healthy adults. Reduction in the MMN has also been observed after infusion of lorazepam ($GABA_A$ agonist) in healthy adults (Rosburg, Marinou, Haueisen, Smesny, & Sauer, 2004); however, small and large doses of diazepam ($GABA_A$ agonist) did not significantly affect MMN amplitude within a sample of schizophrenic patients (Kasai, et al., 2002).

### 3.5.3 MMN in Psychiatric Populations

Clinical applications of MMN within psychiatry have focused predominantly on the neurochemistry and psychophysiology of schizophrenic patients. Studies have revealed that deficits in MMN to duration and frequency deviants are related to abnormal auditory information processing in schizophrenia (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Javitt, Grochowski, Shelley, & Ritter, 1998; Michie, 2001; Shelley, et al., 1991). Umbricht et al. (2003) found that duration and frequency deviant MMN activity significantly differed between schizophrenic patients and healthy controls, whereas no difference was observed for comparisons between patients with affective disorders and healthy controls.

According to the LDAEP-5HT model previously discussed, serotonergic

innervation within auditory cortices may inhibit pyramidal cells directly or indirectly through activation of GABAergic interneurons. Since major depressive disorder is associated with reduced serotonergic function, it is possible that MMN may be influenced in the same subgroups as those showing enhanced LDAEP effects. However, MMN has not been investigated in depression nearly to the extent it has been evaluated in schizophrenia. Two studies have reported reduced MMN amplitude for frequency deviants in depressed subjects (el Massioui & Lesevre, 1988; Ogura, et al., 1993). However, two other studies have reported no differences in MMN to frequency deviants in depressed compared to healthy adults (el Massioui, Everett, Martin, Jouvent, & Widlocher, 1996) or in depressed children (Lepisto, et al., 2004). Studies attempting to manipulate the serotonergic system through pharmacological agents in healthy adults have been unclear. For example, tryptophan depletion has resulted in a reduction of MMN amplitude to frequency deviants (Ahveninen, et al., 2002) but has also been shown to increase MMN to frequency and duration deviants (Kahkonen, et al., 2005). An increase in MMN amplitude to frequency deviants was observed after healthy adults were given the SSRI Escitalopram (Oranje, Jensen, Wienberg, & Glenthoj, 2008). It is possible that the mixed findings in this literature may result from the acute changes in the serotonergic system via ATP administration or single doses of SSRIs in healthy adults, whereas the neurophysiological effects of chronic 5HT reduction in depression may more persistently affect MMN.

# CHAPTER 4: STUDY AIMS AND HYPOTHESES.

This study investigated a) the impact of varying levels of intensity disparity among consecutively presented tones on the loudness-dependency of N1/P2, and b) assessed the extent to which deviance-related processes (i.e., MMN) are affected by louder or softer tones of varying intensity disparity. A passive MMN-paradigm was employed using a range of intensities, common to loudness-dependence studies, as deviants and standards in order to isolate effects related to processing deviance (MMN) from stimulus specific N1/P2 effects.

## Aim 1: Characterize N1/P2 LDAEP for the Present Paradigm.

A CSD-PCA approach was used in order to adequately analyze the spatiotemporal characteristics of the ERP component structure underlying N1/P2 LDAEP elicited in the current study. Reference-free CSDs provide an unambiguous component polarity and a high spatial resolution, making this measure a superior choice for characterizing N1/P2 activity. The addition of unrestricted temporal PCA of CSD waveforms provides a means of obtaining data-driven, orthogonally-related measures of the component structure.

An important aspect to this study was to characterize N1/P2 LDAEP elicited by MMN paradigm and compare the effects to ERPs elicited by a standard LDAEP paradigm. The MMN paradigm used by the current study employed stimulus parameters (e.g., presentation rate) and task instructions (e.g., do not attend to tones) common to MMN paradigms; however, some of these parameters are quite different than those used in standard LDAEP paradigms. Because the MMN and standard LDAEP paradigms primarily differ with respect to stimulus probability (unequal probability in MMN, equal

in standard LDAEP), a block of equiprobable intensities was presented with the same presentation parameters as standard/deviant MMN blocks, so that only differences in presentation rate and instructions to attend/unattended to tones remained between paradigms. Specifically, the MMN paradigm was characterized by an unattended, fixed 500 ms SOA stimulus presentation, and the standard LDAEP paradigm used an attended, variable SOA (1600 –2100 ms) presentation. In this manner N1/P2 LDAEP elicited by the MMN paradigm could be compared to N1/P2 activity elicited by physically identical, equiprobable tones presented in a standard LDAEP paradigm. While it was assumed that the equiprobable intensities in the MMN paradigm would produce measurable N1/P2 activity that would vary with intensity, N1/P2 amplitude attenuation was expected for equiprobable trials in the MMN paradigm based on a) its relatively faster and constant presentation rate, and b) the fact that subjects were instructed to ignore tones (see sections 2.1.1, 2.1.2, and 2.3.1).

Aim 2: Investigate the Intensity Dependence of N1/P2 to Standard and Deviant Tones.

A convincingly large body of research has demonstrated a monotonic relationship between N1/P2 amplitude and tone intensity (i.e., N1/P2 LDAEP). However, it is unclear to what extent N1/P2 LDAEP may be affected by the context in which tones are cast (e.g., standard or deviant). Therefore, an important aim of this study was to examine potential differences in the intensity dependence of N1/P2 to standard and deviant tones. Theoretically, standard tones produce attenuated sensory-driven ERPs (e.g., N1/P2) as feature-specific cells within the auditory cortex adapt or habituate to the repetitive standard tone. However, studies have not systematically examined the extent to which N1/P2 adaptation is affected by intensity. It is possible that softer or louder tones are

affected differently by adaptation mechanisms and may affect the N1/P2 amplitude differently for loud or soft tones. Thus, the following hypotheses can be made concerning the intensity dependence of standard tones:

1) If a mechanism of sensory adaptation exists within the primary auditory cortex then CSD amplitude will be lower for standards than deviants or equiprobable intensities (an effect consistent with many MMN studies).

2) If sensory adaptation processes are uniquely applied to either loud or soft tones then N1/P2 reduction will be observed for only loud or soft intensities, but not both.

While the adaptation and memory-based MMN models differ in terms of the underlying neurophysiology, they offer virtually identical hypotheses about the behavior of N1/P2 to deviant intensities. According to the adaptation model, neural generators of N1 responsive to the deviant stimulus characteristics are non-adapted (i.e., not in a refractory state, in contrast to adapted/habituated cells responsive to standards); therefore, when these cells are activated by deviant tones they will produce larger N1 activity than standards. However, like standards, the frequency to which the deviant tone is presented will impact the refractory state of N1 generators such that they too may become partially adapted with faster presentation rates. Similarly, the memory-based model suggests that N1 generators tuned to the deviant tones are not in a state of refractoriness and should produce larger N1 activity relative to standards. Therefore, both models suggest that:

1) N1/P2 amplitude for deviants will be greater than standards, as well as equiprobable trials, suggesting that a) cells contributing to the deviant N1 do not undergo the same adaptation as cells contributing to standard N1, and b) N1/P2 amplitude to intensity varies with how often a tone is presented.

2) N1/P2 amplitude to deviants should covary with intensity level in a monotonic fashion, as the sources of N1/P2 activity elicited by deviant tones are not subjected to the same level of adaptation as N1/P2 to standards.

Aim 3: Investigate the Intensity Dependence of MMN.

Prior studies investigating intensity deviance using MMN paradigms have shown that a) MMN is elicited by intensity deviance, b) larger disparities produce enhanced MMN amplitude, and c) loud deviants may recruit activity related to detecting novel or salient stimuli. However, inconsistencies in paradigms and levels of intensity tested among these studies make it difficult to directly compare findings and/or appreciate the relationship between intensity disparity and MMN. In a separate, clinically-oriented body of literature, LDAEP paradigms are employed to investigate the intensity dependency of N1/P2. However, standard LDAEP paradigms used in these studies employ randomized presentations of widely varying levels of intensity, and thereby, necessarily (but unintentionally) produce unbalanced disparities in intensity between consecutive stimuli. Because large disparities (e.g., ±30 dB) occur much less frequently than small disparities (e.g., ± 10 dB) it is likely that large disparities are perceived differently than small disparities and thereby evoke additional brain activity related to novelty or salience (e.g., P3a).

The present study aimed to clarify the relationship between intensity disparity and MMN by investigating several levels of intensity as either standards or deviants while maintaining a fixed set of intensities across blocks. In this manner intensity dependency of MMN can also be assessed in terms of the direction of disparity (i.e., increments or decrements); that is, it is possible to assess whether MMN amplitude will covary with the

overall level of disparity regardless of the deviants being louder or softer, or whether MMN amplitude will be greater either louder or softer deviant tones. The following hypotheses about the intensity dependency of MMN can be tested with respect to this study's design:

1) MMN is expected to be elicited by disparities in intensity.

2) Increases in MMN amplitude are expected to covary with larger disparities, such that larger disparities will produce greater MMN. If this relationship is observed it would suggest either a) brain regions down-stream of N1 generators that mediate deviance detection (memory-based model) respond more rigorously to larger stimulus disparities, or b) larger regions of "fresh" N1-type cells are activated by greater differences in stimulus features (adaptation model).

3) The following two hypotheses concern the direction of disparity:

3a) If MMN reflects the activity of a deviant-detection mechanism that provides an endogenously-driven 'signal' of the degree of disparity between tones, and is unaffected by processes reflected by N1, then MMN amplitude should vary consistently across the level of disparity regardless of whether deviants were softer or louder (see Figure 1A).

3b) If mechanisms underlying MMN are related to those underlying N1, then MMN amplitude should also reflect the behavior of N1 activity in that the louder disparities will exceed softer disparities in amplitude (see Figure 1B).

Aim 4: Compare N1 and MMN Factor Score Topographies.

It is difficult to experimentally distinguish many of the theoretical differences between the memory-based and adaptation-based MMN models from scalp-recorded

data, as the theories both aim at explaining MMN from a cellular level (e.g., lateral inhibition or specific comparator cells). However, comparing PCA factor score topographies related to the N1 and MMN components derived from the CSD original CSDs and difference CSD waveforms (respectively) can help distinguish whether a) MMN reflects activity from a neural generator that is spatially-distinct from the N1, or b) whether the MMN and N1 generators spatially overlap. If MMN and N1generators overlap then their factor score (PCA factor weighting coefficients) topographies should highly correlate; whereas, if the MMN generator is spatially-distinct from the N1 generator then the factor score topographies should not be strongly correlated.

# CHAPTER 5: METHODS

## 5.1 Participants

Thirty-three paid healthy adults were recruited by advertisements. Written informed consent was obtained by all participants. All participants were physically healthy and between 18 to 65 years old. Hearing acuity was assessed using standard audiometric procedures, requiring all participants to have an ear difference of less than 10 dB and a hearing loss no greater than 25 dB at 500, 1000, or 2000 Hz. All participants were right-handed, as assessed with the Edinburgh Inventory (Oldfield, 1971). Participants were interviewed by a trained rater using the Schedule for Clinical Interview for DSM-IV Diagnoses, Patient Version (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 1996) and excluded from the project if psychopathology, alcoholism, drug abuse, history of seizure, significant brain trauma, or a known anatomical brain lesion was present.

## 5.2 Stimuli and Procedure

Presentation® stimulus delivery and experimental control software (Neurobehavioral Systems Inc., 2008) was used to deliver the experimental tones through a computer sound card. A 20 second 1000 Hz continuous sinusoidal tone presented by a matched pair of TDH-49 headphones was calibrated with a sound level meter at 100, 90, 80, and 70 dB sound pressure level (SPL). The calibrated tones were cut into segments of 40 ms duration (10 ms rise/fall time) and used in the intensity tasks. Video clips of underwater scenes were taken from the Discovery Channel—Planet Earth DVD and presented on a computer monitor. The video display was constrained to a visual angle of 14.2º X 9.5º in order to reduce extraocular activity.

The intensity MMN task was performed in a single session after the completion of

three EEG/ERP tasks required for a larger study. These tasks included (a) a resting EEG task, (b) an auditory novelty oddball task, and (c) an auditory intensity dependence task (LDAEP). These tasks are described in Appendix C. EEG/ERP tasks (including the intensity MMN task) lasted approximately two hours. Rest breaks (approximately 5 minutes) were given to participants between tasks.

5.3 The Design and Paradigm

All subjects were presented with four MMN blocks (standard/deviant) and one equiprobable intensity block. The four MMN blocks consisted of tones presented at four levels of intensity (70, 80, 90, 100 dB) and occurred at two levels of probability (70% = 'standard' and 10% = 'deviant'). For each MMN block, one intensity was presented as a standard and the three remaining intensities as deviants (each deviant = 10%; see Figure 2 – blocks A – D). The additional block of equiprobable intensities was intended to approximate those of the LDAEP paradigm, but using faster SOAs typical for MMN (see Figure 2, block E). Stimuli were presented at a constant 500 ms SOA and counterbalanced across blocks with block order counterbalanced across subjects.

As varying levels of attention can bias observations of LDAEP and MMN (c.f., sections 2.1.2 and 3.4.3) participants were given instructions to watch segments of a silent film and report its contents after each block. The accuracy of each participant's responses served as a manipulation check by providing a loose measure of their engagement in visual task. The silent video clips were displayed on a monitor directly in front of the participant while the tones were presented through headphones. Instructions were to carefully attend to the silent video while ignoring the tones and that a short quiz on the film's content will follow each experimental block. Two multiple choice questions

(e.g., “What type of animal was shown at the beginning of this clip? A) Turtle, B) Pelican, C) Crab) following each block served as a crude verification of attention to the video. No responses were required from participants during recordings.

5.4 EEG Data Recording and Artifact Correction

EEG was recorded from 72 expanded 10-20 system locations (Pivik et al 1993) with a Lycra stretch electrode cap (ActiveTwo EEG system; BioSemi 2001) using an active reference at sites PO1 (common mode sense) and PO2 (driven right leg). Along with 12 midline sites, the montage includes 30 homologous pairs over the left and right hemisphere (odd and even numbers), and extends laterally to include inferior and polar temporal lobes (Fig. 3). To allow reliable topographic analyses, the electrocap placement was optimized by precise measurements of electrode locations with respect to landmarks of the 10-20 system (nasion, inion, auditory meatus, and vertex). The scalp placements were prepared using a conventional water soluble electrolyte gel and the interface was verified by the acquisition software (ActiView; BioSemi 2001). Continuous EEG data, along with stimulus trigger codes and responses, were recorded at 256 samples/sec using the 72-channel, 24-bit Biosemi system. Data was exported into 16-bit Neuroscan format using Polyrex (Kayser 2003), a widely used conversion program that removes DC offsets, optimizes data scaling, and provides EEG re-referencing.

EEG artifact procedures included several proven screening and reduction routines successfully implemented at the Psychophysiology lab of the Division of Cognitive Neuroscience, New York State Psychiatric Institute. The EEG was screened offline for electrolyte bridges using an electrical distance measure (‘intrinsic Hjorth’). The intrinsic Hjorth procedure, discussed in detail by Tenke & Kayser (2001), determines the minimal

temporal variance of differences in potentials between recorded electrodes (i.e., electrical distance) to determine nearest electric neighbors. Electrical bridges are realized as zero-differences between electrical neighbors (i.e., flat lines). Bipolar vertical and horizontal EOG channels were computed from the available recording montage using spherical splines of all 72 recorded channels (Kayser, 2009; Perrin et al 1989; see Appendix D: 72-Channel Spherical Coordinates). Blink artifacts were removed from the raw EEG using a spatial singular value decomposition filter generated from identified blinks and artifact-free EEG periods (NeuroScan 2003).

Recording epochs (700 ms including a 200 ms prestimulus baseline) were extracted off-line, tagged for A/D saturation, and low-pass filtered at 20 Hz (-24 dB/octave). Volume-conducted horizontal eye activity was reduced through a regression-based correction procedure (Kayser et al., 2006) to maximize the number of artifact-free epochs. A reference-free approach was then used to identify EEG channels containing amplifier drift, residual eye activity, muscle or movement-related artifacts for any given trial (Kayser & Tenke, 2006d), and replaced by spherical spline interpolations (Perrin et al., 1989) using the data from artifact-free channels if possible (i.e., less than 25% of all channels contain an artifact).

5.5 ERP Averaging, and CSD Transformation Procedures

ERP waveforms were averaged from artifact-free trials. Visual inspection of the individual ERP waveforms was conducted to confirm a satisfactory signal-to-noise ratio for each participant. Averages were then low-pass filtered at 12.5 Hz (-24 dB/octave), and finally baseline-corrected using the 200 ms preceding stimulus onset. All artifacted and averaged ERP waveforms at each electrode were transformed into reference-free

current source density (CSD) estimates (μV/cm2 units; 10 cm head radius) using a spherical spline surface Laplacian (Perrin et al., 1989) with computation parameters (50 iterations; m = 4; smoothing constant λ = 10-5). CSDs were computed, artifactual channels were interpolated, and topographies were mapped with software (CSD Converter, Viewer, Mapper) developed by Jürgen Kayser for use in the NYSPI Psychophysiology Laboratory, which makes use of the 'CSD Toolbox' Matlab code published online (Kayser, 2009).

Artifact-free, averaged CSDs were obtained for standard and deviant tones individually at each level of intensity. Averaged CSDs were computed from a sufficient number of epoched sweeps for the standard (mean = 144.1 ± 8.3) and each deviant (mean = 36.2 ± 2.2) condition within blocks. As discussed above (section 2.9.2), deviant-minus-standard difference CSDs were computed for deviant trials in each block by subtracting the CSD waveform of standard trials (occurring in separate blocks) of the same intensity (*N* = 12; 3 difference waveforms per block). Difference CSDs were then averaged according to intensity (70, 80, 90, 100 dB) or level of disparity (+30, +20, +10, -10, -20, -30 dB).

5.5.1 Standard, Deviant, and Equiprobable CSDs.

A total of 24 averaged CSDs were computed per subject. Twenty averages were produced from the four MMN blocks, which included 4 standards (1 per block), 12 block deviants (three deviants per block), and 4 pooled deviants (4 levels of intensity deviants across 4 blocks). An additional 4 CSD averages were computed for each of the four intensities in the equiprobale block.

5.5.2 Deviant-minus-Standard Difference CSDs.

Difference waveforms were computed by subtracting standard intensities from each averaged deviant at the same intensity; for example, 100 dB standard subtracted from 100 dB deviant in a 70 dB standard block. This derivation is decidedly different from conventional approaches of computing MMN difference waveforms. Conventionally, activity elicited from standard tones is subtracted from activity elicited by physically deviant tones within the same block; however, this approach cannot account for exogenously-driven N1 differences between the standard and deviant conditions, which may potentially mask deviance related activity (Horváth et al., 2008). The alternative approach aimed to isolate intensity-deviance effects from stimulus-specific N1/P2 effects by comparing activity elicited by deviant and standard conditions for physically identical stimuli. Difference waveforms were computed for comparable levels of intensity within blocks (e.g., 100 dB deviant in 70 dB standard block-minus-100 dB standard; $n = 12$) and across blocks (e.g., 100 dB deviants across all blocks-minus-100 dB standard; $n = 4$), yielding 16 CSD difference waveforms.

3.5.3 Intensity-Disparity Difference CSDs.

Six disparity-specific difference CSD averages (-30, -20, -10, +10, +20, +30 dB) were computed from appropriate deviant-minus-standard difference CSDs across blocks (see Table 1 for index of each contributing average). Three additional pooled disparity-specific difference CSD averages were computed across direction (i.e., increment, decrement) yeilding waveforms for ±10, ±20, and ±30 dB.

5.6 Unrestricted Covariance-based PCA Analysis

Averaged CSD waveforms were submitted to temporal (waveforms) principal

components analysis (PCA) derived from the covariance matrix, followed by unrestricted Varimax rotation of the covariance loadings (Kayser & Tenke 2003, 2005, 2006a). Three separate PCAs were computed on individual averages depending on the particular hypothesis being tested.

5.6.1 Standard, Deviant, and Equiprobable CSDs.

Averaged CSD waveforms were submitted to a covariance-based PCA followed by unrestricted Varimax rotation of the loadings. Table 1 defines the cases and variables entered into each PCA employed by this study. The data matrix used to analyze intensity-dependent effects of N1/P2 for deviants and standards was comprised of 180 variables (timepoints, -200 to 500 ms) and 57,024 cases including 24 conditions, 33 subjects, and 72 sites (electrodes).

5.6.2 Intensity Disparity Difference CSDs.

Averaged Intensity-disparity difference CSDs were submitted to a covariance-based PCA (unrestricted Varimax rotation) consisting of 180 timepoints as variables and 14,256 cases that included the disparity 6 Conditions (see Table 1), 33 subjects, and 72 sites.

5.7 Statistical Analysis

PCA factors with the temporal and spatial characteristics that were unambiguously related to the CSD components (as indicated by factor loading peak latencies and factor score topographies) were selected for statistical analysis. For example, the derived PCA factor related to the N1 peak in the CSD waveform was used to test hypotheses related to N1, whereas the derived PCA factor related to the MMN peak in the CSD difference waveform (deviant minus standard) was used to test

hypotheses related to MMN. Recording sites were selected from areas most representative of the underlying activity of each derived PCA component (see Kayser & Tenke, 2006, for a discussion of this rationale). Depending on the observed component structure, these subsets of electrodes consisted of either midline sites or lateral, homologous recording sites over both hemispheres, thus adding either site, or site and hemisphere as within-subjects factors. For example, if a component has a temporal maximum over lateral sites that invert in polarity over lateral temporoparietal sites (e.g., N1 component) those sites will be selected for statistical analysis across all conditions.

To more fully appreciate interactions related to either intensity level (70, 80, 90, 100 dB) or disparity (±10 , ±20, ±30) between Disparity and Direction, additional ANOVAs were performed to simplify the model by restricting the Disparity factor to pairwise comparisons between each level of Disparity (i.e., ±10 to20 dB; ±20 to ±30 dB; ±10 to ±30 dB) while keeping all other statistical factors constant

Greenhouse-Geisser epsilon (ε) correction was used to compensate for violations of sphericity when appropriate. The sources of interactions and main effects were systematically examined through contrasts or simple effects, while focusing on condition effects and sites reflecting underlying cortical activity. Main effects and interactions were systematically examined through contrasts or simple main effects (BMDP-4V; Dixon, 1992). A conventional significance level ($p < .05$) will be applied for all effects.

Several repeated-measures ANOVAs were conducted depending on the hypothesis being tested. All ANOVAs are presented in the results below and Tables 2 – 8 list the factors and their corresponding levels along with the significant effects.

Time of Day (early, late) and Sex (male, female) between-group factors were

included as control variables in each statistical model; however, neither factor revealed main effects or interations, and were therefore not explicitly reported in the results.

Correlation coefficients for N1 and MMN factor score topographies were computed across the whole topography (72 electrodes) for each participant. N1 sink factor scores were compared to MMN sink factor scores at each level of Disparity (30, 20, 10 dB) and Direction (loud, soft). Correlation coefficients were computed across all electrodes for each participant each level of Disparity and Direction, normalized by a Fisher's Z transformation, then averaged across participants. The averaged Fisher's Z values for each condition were then transformed back to equivalent R values. Correlation coefficients were also computed for each of the ten electrodes used in the N1 and MMN ANOVA models (same sites were used in both ANOVAs) across subjects.

# CHAPTER 6: RESULTS

## 6.1 Characterization of CSD Waveforms and PCA Factor Loadings and Score Topographies.

Grand mean CSD waveforms for deviant and standard conditions, and equiprobable block trials (Fig. 4) showed a comprable and stable component structure characterized by a robust bilateral frontocentral N1 sink (C3/4; 113ms) with corresponding bilateral temporoparietal souce (TP9/10), bilateral temporal N1 sink (T7/8; 153 ms), and bilateral temporal P2 source (T7/8; 214 ms) coincident with a midline source (Cz). CSD amplitude for averaged deviant conditions was notably larger than standard and equiprobable conditions across most electrodes, but exhibited particularly greater activity over bilateral frontocentral sites and temporally corresponding bilateral temporoparietal sites, as well superior midline sites. Conversely, standards were characterized by a marked reduction in CSD amplitude across most sites relative to deviant and equiprobable conditions. CSD waveforms for equiprobable trials showed intermediate levels of amplitude.

Figure 5A shows the time courses of PCA factor loadings of the first four CSD factors extracted (71% explained variance after Varimax rotation). Three of the first four factors were within the time-range of N1/P2 and their corresponding factor score topographies (Fig. 5B) were highly consistent with identifiable peaks and troughs in the grand mean CSD waveforms. These three factors consisted of an N1 sink/source topography (peak latency 113 ms; 6% explained variance; sink maxima over bilateral central sites with tempoparietal sources) consistent with activation of primary auditory cortices (i.e., tangential N1); a temporal N1 sink (159 ms; 5%; sink maxima at sites T7/8)

consistent with activation of portions extending to the lateral surface of the temporal cortex (i.e., radial N1); and a complex P2 source topography (214 ms; 11%) characterized by bilateral frontotemporal maxima with an overlapping vertex source. In addition to the three N1/P2 factors of interest, a slow-building, high variance factor (50%; dotted line in Fig. 5A) attributable to background noise was extracted (i.e., successfully isolated from meaningful factors). Other factors (not shown) included an early P1 (66 ms; 3%) and a late, low amplitude parietal P3 (280 ms; 3%), which were not analyzed further. A significant main effect of intensity was observed for equiprobable intensities (see Table 2). Significant incremental increases in N1 sink and P2 source amplitudes were observed for 80, 90, and 100 dB tones, but CSD amplitude did not significantly differ between 70 and 80 dB.

Figure 6 visually compares the N1/P2 factors resulting from the equiprobable block in the current paradigm to like factors extracted from a standard LDAEP paradigm previoulsy analyzed by Tenke e al. (2009). Both paradigms produced highly similar factor score topographies (panel A) corresponding to a tangetially-oriented N1 sink, radially-oriented temporal N1 sink, and overlapping temporal and midline P2 sources. Both paradigms also yielded comparable amplitude/intensity slopes (panel B), but a marked reduction in CSD amplitude was observed for factors elicited by the unattended 500 ms SOA equiprobable block relative to activity elicited by the attended, longer-variable SOA LDAEP paradigm. The relative attenuation for the current equiprobable trials was particularly noticable for the tangential N1 sink and P2 source.

6.2 Intensity Dependence Effects for Standard and Deviant Tones.

To investigate the extent to which the intensity dependence of N1/P2 differs for

standards or deviants, statistics were conducted on each CSD-PCA factor of interest using a repeated-measures ANOVA model with Intensity (70, 80, 90, 100 dB), Condition (deviant vs. standard), and Hemisphere (left, right) as within-group factors, and Time of Day (early, late) as a between-group factor.

6.2.1 N1 Sink.

A sharply defined N1 sink factor loading waveform showed an increase in explained variance from approximately 50 ms to 180 ms, peaking at 113 ms (see Fig. 5A). Figure 7A shows N1 sink factor score topographies for deviants and standards by intensity. N1 sink topographies for both conditions were comparable at each level intensity, characterized by bilateral central sinks and temporoparietal sources (113 ms). Due to the sink/source (dipole) configuration of this well-known 'N1 sink' topography, statistics were performed on a composite measure for N1 amplitude, computed as the difference: mean temporoparietal sources (TP9/10, P9/10) minus mean bilateral central sinks (C1/2, C3/4, C5/6) seperately for left and right hemisphere. Comparable statistical results were observed for direct tests of sinks and sources (i.e., not composite measures), but are not shown. Significant ANOVA results are presented in Table 3 (means plotted in Figure 7B). Montonic increases in N1 amplitude to louder tones were apparent for deviants but not standards, and factor scores revealed significant main effects for Intensity (louder > softer) and Condtion (deviants > standards). A significant Intensity X Condition interaction revealed significant N1 sink enhancement for deviants compared to standards at 100 dB and 90 dB, while no significant differences were found between deviants and standards at 80 dB or 70 dB deviants. N1 amplitude paralleled increases in intensity from 80 to 90 dB and 90 to 100 dB for deviants but not standards. While

standard N1 activity was significantly greater at 80 dB compared to 70 dB, amplitudes were essentially identical from 80 to 100 dB.

6.2.2 Temporal N1 Sink.

Enhancements in temporal N1 sink paralleled increases in intensity at bilataral temporoparietal sites (T7/8, TP7/8, TP9/10; Fig. 8A). The loading for this factor ranged from approximately 120 ms to 230 ms, with a peak at 159 ms (see Fig. 5A). Table 4 shows significant main effects for Intensity(louder > softer) and Hemisphere(right > left), as well as a significant Intensity X Condition interaction. Pairwise comparisons revealed significant monotonic temporal N1 increases with intensities from 70 to 80 dB and 80 to 90 dB, but not for 90 to 100 dB (Fig. 8B) across conditions. A significant Intensity X Condition interaction showed that deviants were characterized by a markedly steeper rise in amplitude with increases in intensity as compared to standards.. A significant right-greater-than-left Hemisphere effect was observed for both standards and deviants.

6.2.3 P2 Source.

Factor score topographies (Fig. 9A) and statistical results (Table 5) for the P2 source suggest a strong intensity dependence at frontotemporal sites (FT7/8, FT9/10, T7/8). The loading for this factor showed a measurable change in explained variance between approximately 150 ms and 350 ms, with a peak latency at 214 ms. The main effect for Intensity at these bilateral frontotemporal sites was characterized by larger amplitude increases from 80 to 90 dB and 90 to 100 dB (Fig. 9B) across conditions. A significant Condition main effect and Intensity X Condition interaction revealed that the P2 source was greater for deviants at 100 dB, and marginally enhanced at 90 dB. P2 amplitude was significantly greater from 80 to 90 dB and 90 to 100 dB for deviants, but

no differences in amplitude were found between any standard intensity level.

Separate analyses were conducted on the vertex source overlapping the bilateral frontotemporal sources (statistics presented in Table 6). Similar to the frototemporal P2 sources, the effect of Intensity was due to increases in amplitude from 90 to 100 dB and 80 to 90 dB (Fig. 9C). A significant Condition effect and Intensity X Condition interaction revealed greater vertex source activity for deviant stimuli at 100 dB. While a significant amplitude differences were observed between 80 and 90 dB in both conditions, the greatest difference in amplitude was observed for deviants between 90 and 100 dB.

6.3 Intensity Deviance Effects for Deviant-minus-Standard CSD-PCA Factors.

Grand-mean CSD difference waveforms are shown in figure. 10. Differential activity peaking at approximately 130ms was most noticably seen at bilateral central (e.g., C3/4, C5/6) and frontocentral (e.g., FC3/4, AFz) sites with inversions in polarity at lateral temporoparietal sites (TP9/10). A large relative vertex source peaking at approximatly 230 ms was also evident in the CSD difference waveforms. Figure 11 displays time courses of the extracted CSD-PCA factor loadings (panel A) and corresponding factor score topograhies (panel B) for the first three factors (72% explained variance after Varimax rotation). Factors of interest included: 1) MMN sink (136 ms; 14% explianed variance) characterized by tangential bilateral-central sinks (eg., C3/4) with corresponding bilataral temporoparietal sources (e.g., TP9/10); 2) P3a-like Vertex Source (234 ms; 8% explained variance). Both factor score topographies were consistent with well-known MMN and P3a topographies and previously published intensity MMN findings (e.g., Deouell, Bentin, & Giard, 1998; Giard, Perrin, Pernier, &

Bouchet, 1990; Sato, et al., 2000; Tenke, et al., 2010).

6.3.1 MMN Sink.

MMN sink topographies exhibited enhancements with increasing disparities for intenity increments and decrements (Fig. 12A). The MMN sink factor loading showed an increase in variance from approximately 50 ms to 250 ms, and peak latency at 136 ms (Fig. 11A). MMN factor scores were tested via a repeated-measures ANOVA with Disparity (10, 20, 30 dB), Direction (increment, decrement), and Hemisphere (left, right) as within-subjects factors. ANOVA results (Table 7) revealed significant main effects for Disparity and Direction, as well as a significant Disparity X Direction interaction (see Fig. 12B). The main efect for Disparity showed that MMN amplitude significantly increased with greater intensity disparity for loud and soft deviants, and the main effect for Direction revealed that MMN was greater for increments compared to decrements. The Disparity X Direction interaction showed that there was a greater increase in amplitude (steeper rise) at each level of increasing disparity for louder deviants compared to softer deviants.

6.3.2 P3a Vertex Source.

P3a vertex source factor score topographies (Fig.13A) show monotonic increases in activity for louder disparity, but not softer disparities. The P3a source factor loading showed an increase in variance from approximately 180 ms to 300 ms, and peak latency at 234 ms (Fig. 11A). P3a factor scores were submitted to a repeated-measures ANOVA with Disparity (10, 20, 30 dB), and Direction (increment, decrement) as within-subjects factors. Results of this analysis (Table 8) revealed significant effects for Direction and Disparity, and a significant Direction X Disparity interaction (see Fig. 13B). P3a activity

was uniquely linked to increments, but not decrements in intensity disparity, and was characterized by monotonic increases in amplitude with increases in diparity. Pairwise comparisons between the levels of disparity revealed that the monotonic increases in P3a amplitude to increments significantly differed from decrements at each level of disparity except 10 dB, suggesting a relative absence of P3a for deviant increments of 10 dB.

6.4 Comparison of N1 and MMN sink Factor Score Topographies

Fig.14A shows averaged correlations for each electrode. 72 correlation values were obtained for each subject (variance accounted for by each correlation at a given site came from the subjects). All 72 correlation coefficients were normalized (Fisher's Z) for each subject, then averaged across subjects. The averaged Fisher's Z values (single vector of 72 values) was converted back to R values, then plotted. N1 and MMN factor score topographies were significantly correlated at each level of Disparity and Direction (see Table 9). Fig.14B shows averaged correlations for individual topographies. A single correlation coefficient was obtained for each subject (variance accounted for by each correlation came from the 72 sites). All 33 correlation coefficients were normalized, then averaged. The averaged Fisher's Z value (one value per condition) was converted back to an R value, then graphed. Correlations between factor score topographies highly corresponded to ANOVA findings for the MMN sink. That is, correlation between N1 and MMN sink topographies showed a) an increase in the strength of the relationship with increases in the level of disparity regardless of direction, and b) an overall greater correlation coefficients for louder than softer deviants. Table 10 shows the correlation coefficients for sites used in both N1 Sink and MMN sink ANOVA models (e.g., C1/2, C3/4, C5/6, P9/10, TP9/10). Correlations were consitently larger for left lateral-central

sites (e.g., C1 and C3); however, correlations between factors did not show a consistent pattern in relation to disparity and direction. For example, correlations for electrode C3 showed an increase in parallel with louder disparities, but higher correlations were found for lower levels of disparity (e.g., 10 > 20 > 30 dB) for softer conditions.

# CHAPTER 7: DISCUSSION

## 7.1 N1/P2 LDAEP Can Be Elicited by an Intensity MMN Paradigm

The intensity MMN paradigm yielded CSD waveforms that were consistent with well-known auditory N1/P2 topographies (e.g., Giard, et al., 1994; Kayser & Tenke, 2006; Näätänen & Picton, 1987; Scherg & Von Cramon, 1986; Tenke, et al., 2008; Vaughan & Ritter,1980). Three of the extracted CSD-PCA factors sufficiently characterized activity within the timeframe of the N1/P2 and exemplified the component structure of auditory ERPs. These factors included: 1) an N1 sink (113 ms peak latency) with a sink-source configuration consistent with a "field configuration expected from a dipole layer source lying in a plane perpendicular to the surface of the skull and parallel to the orientation of the primary auditory cortex…" (Vaughan & Ritter, 1970, p. 365), as well as other reported tangentially-oriented N1 activity (e.g., Godey et al., 2001; Hari et al., 1982; Scherg & Von Cramon, 1986; Tenke et al., 2010); 2) a temporal N1 sink (159 ms peak latency) that was characterized by bilateral current sinks, highly consistent with previously reported radially-oriented N1 generator patterns (e.g., Giard, et al., 1994; Kayser & Tenke, 2006; Tenke, et al., 2008), 2010); and 3) a P2 source (214 ms peak latency) characterized by current sources over frontotemporal sites coincident with a current source over the vertex, which was also consistent with published findings (e.g., Kayser et al., 2007, 2009; Tenke et al., 2008, 2010).

Grand mean CSD waveform amplitude in the timeframe of N1/P2 (approximately 100 to 300 ms) was notably larger for deviants compared to standards or equiprobable trials across most electrodes, especially at bilateral frontocentral, bilateral temporoparietal, and vertex sites. Conversely, standards produced markedly reduced CSD

amplitude in the N1/P2 timeframe at most sites relative to the deviant and equiprobable conditions, whereas CSD amplitude for equiprobable trials showed intermediate amplitude. While differences in amplitude were observed among conditions, the morphology of CSD waveforms and the topographies were highly comparable across all conditions. Moreover, the three CSD-PCA factors of interest were characterized by sharply defined factor score loading patterns (i.e., component waveforms). Together, these findings indicate that even though participants were instructed to ignore tones and attend to a silent video, the tones were still sufficiently detected and differentially processed according to their presentation characteristics (i.e., standard, deviant, or equiprobable contexts).

N1/P2 LDAEP has almost exclusively been investigated using attended tones separated by long, variable SOAs (e.g., Gallinat, et al., 2000; Hegerl, Gallinat, & Mrowinski, 1994; Keidel & Spreng, 1965; Näätänen & Picton, 1987; Rapin et al, 1966). Therefore, an important aim of this study was to verify whether N1/P2 LDAEP could be observed with tones that are to be ignored and presented with relatively faster and constant presentation rates (a common presentation protocol for MMN studies). To investigate the effect of the faster and constant SOA, a block of equiprobable intensities was designed to match the presentation parameters of the standard MMN blocks while maintaining aspects equal to most parameters used in a standard LDAEP paradigm (e.g., level of intensity, stimulus duration, number of stimulus presentations, etc.). Results showed a significant effect of intensity such that CSD amplitude for the N1 sink and P2 source incrementally increased with louder tones, thereby confirming that LDAEP effects

can be observed even when tones are presented at fast and constant SOAs and are ignored by participants.

Visual comparison of the component structure of equiprobable MMN N1/P2-related factors and analogous factor score topographies elicited by a standard LDAEP paradigm among the same participants (Tenke et al., 2009) shows the component structure (i.e., peak latencies of factor loadings and factor score topographies) between the two paradigms are highly comparable. Both paradigms yield a strong relationship between N1/P2 amplitude and stimulus intensity, but mean amplitudes for the equiprobable MMN block were remarkably reduced compared to the standard LDAEP paradigm. Attenuated amplitudes for equiprobable trials was not a surprising finding, however, as N1/P2 amplitude reductions are known to occur when stimuli are presented with a short and constant presentation rate (Cowan, et al., 1993; Ritter, et al., 1968); Sussman et al., 2008). Moreover, attenuated N1/P2 amplitudes were likely influenced by the attentional demands (or lack of auditory attention as it were) of the task. N1, in particular, is highly sensitive to the attentional state of the individual (for review see Näätänen, 1990). Early investigations noted that N1 amplitude increases in parallel with the attentional resources needed to successfully perform a task (e.g., Davis & Zerlin, 1966; Schwent & Hillyard, 1975), and N1/P2 is larger for attended tones than unattended tones (e.g., Hillyard, et al., 1973; Picton & Hillyard, 1974).

Interestingly, functional mechanisms that have been attributed to the attenuating effects of N1/P2 due to presentation rate and attention are dissimilar and had the potential to deleteriously impact observable LDAEP effects in the present study. It is believed that reduced N1/P2 to the fast presentations of tones is the result of neural habituation or

refractory processes (Budd, et al., 1998), which may result in reduced attention to the auditory stimuli (Cowan, 1997). Theoretically, reducing attention to the tones through habituation would have been compounded by participants explicitly ignoring the tones and focusing on the silent film. However, these paradigmatic manipulations resulted in measurable LDAEP N1/P2 in the equiprobable condition, and therefore, provided a basis on which N1/P2 intensity dependency could be investigated in the context of a MMN model (i.e., standards and deviants).

### 7.2 Intensity Modulation of Auditory N1/P2 Depends on the MMN Context

Intensity-dependent effects were compared for standard and deviant tones by the use of a mixed intensity MMN paradigm (Näätänen, Pakarinen, Rinne, & Takegata 2004). This paradigm is an extension of the classic MMN paradigm (i.e., single deviant stimulus) in that all classes of deviant intensities were included in each experimental block. By utilizing this modification each level of intensity could be compared in terms of its context as a standard or deviant, as well as in terms of its relative level of disparity from the standard intensity. Likewise, N1/P2 LDAEP of standards could be compared across blocks as each level of intensity served as a standard in separate blocks.

#### 7.2.1 N1/P2 LDAEP is Abolished by the MMN Standard Context

The tangentially-oriented N1 sink and P2 source, components classically implicated by LDAEP, elicited by standards did not differ in amplitude across most levels of intensity. N1 sink/P2 source amplitude was particularly asymptotic across 80, 90, and 100 dB; however, N1 sink was significantly greater at 80 dB than 70 dB. Amplitude of the temporal N1 sink for standards was greater for louder (90 and 100 dB) compared to softer tones (70 and 80 dB), but amplitude did not monotonically increase with intensity

(i.e., it did not show a stereotypical LDAEP response). These findings are consistent with several early studies examining N1/P2 intensity dependency (e.g., Adler & Adler, 1989; Davis & Zerlin, 1966; Moore & Rose, 1969; Picton, Woods, & Proulx, 1978; Rapin, et al., 1966; Snyder & Hillyard, 1976), where asymptotic intensity/amplitude slopes were commonly observed for intensities above 70-75 dB. It is likely that the fast presentation rate was responsible for the relative flattening of the amplitude/intensity slope because standard tones exceeding 75 dB have been shown to increase N1 when longer SOAs are employed (Näätänen & Picton, 1987). Furthermore, neural refractory processes may have also played a significant role in the brain responses to these highly repetitious and rapidly presented standard tones (Jääskeläinen, et al., 2004; May & Tiitinen, 2001, 2004, 2009; Näätänen, 1990; Sokolov et al., 2002). As previously discussed, the overall presentation rate of the MMN paradigm and instructions to ignore the auditory tones likely caused a general reduction in CSD amplitude (as compared to the standard LDAEP paradigm), where continuously presenting a standard intensity engaged neural refractory processes further and led to even greater amplitude reduction. However, this interpretation does not fully account for the asymptotic behavior of N1/P2 amplitude for tones louder than 70 dB. An alternative explanation is that normal mechanisms of auditory sensory adaptation were either enhanced by or overlapped by a top-down, executively-mediated, attentional mechanism that assisted in 'actively ignoring' tones and attending to the silent film. Theoretically, such a mechanism could act to down-regulate the auditory system while up-regulating the activity of brain regions needed to successfully complete the task (i.e., attend to the film for subsequent recollection of its content).

7.2.2 N1/P2 LDAEP Was Observed For Louder Deviant Intensities

Two hypotheses were posited about the intensity dependence of N1/P2 for deviants. It was predicted that deviant-related N1/P2 amplitude would exceed N1/P2 amplitude for standards for all intensities, and that deviant-related N1/P2 would monotonically covary with intensity (i.e., display N1/P2 LDAEP). Both hypotheses were based on the idea that the neural generators of the N1/P2 elicited by deviants would be a) relatively unadapted in comparison to standards as they were presented less frequently, and b) influenced by deviant-related brain mechanisms (i.e., overlapped by MMN processes).

Results did not support the hypothesis that deviant-related N1/P2 amplitude would exceed that of standards for all intensities. N1 sink/bilateral frontotemporal P2 sources did not yield a statistically significant difference between deviants and standards for the relatively softer tones (i.e., 70 and 80 dB) while deviants did yield larger amplitude for the relatively louder tones (i.e., 90 and 100 dB), consistent with the findings reported by Muller-Gass and colleagues (2005). This may suggest that deviant related brain mechanisms are only engaged for relatively louder tones because they are more salient stimuli. As hypothesized, deviant-related N1/P2 amplitude was found to monotonically covary with intensity. Stepwise increases in tangential N1 and bilateral frontotemporal P2 amplitude were observed between 80 to 90 dB and 90 to 100 dB, but not between 70 to 80 dB. Interestingly, these statistical results mirror those for stepwise comparisons of standard-related N1/P2 amplitudes. Whereas N1/P2 amplitude for standard tones differed only between the softest tones, amplitude for deviant tones differed only for the loudest tones. However, comparing the amplitude/intensity slopes of the tangential N1 sink and P2 source for deviants and standards reveals a very similar

response between conditions for the two softest tones and a marked divergence in amplitude for deviant tones at 90 and 100 dB. As the deviant tone intensity increases the CSD amplitude increases at an accelerated rate, whereas the standard CSD amplitude remains constant at levels at and above 80 dB. Thus, these data support the interpretation that, in contrast to adapted N1/P2 generators for standards, deviant stimuli remain unadapted and/or are influenced by overlapping deviance-related mechanisms (e.g., MMN). Furthermore, although all tones were to be ignored, as the stimulus intensity increased it may become more difficult to down-regulate the ecological importance of these loud stimuli which could indicate a potential threat within the environment.

### 7.3 MMN is Amplified by Loud Disparities in Intensity

Prior studies have shown that MMN is elicited by intensity deviance, where larger disparities produce greater MMN amplitude (e.g., Alho et al. 1989; Schröger and Winkler, 1995), and loud deviants recruit additional brain activity (i.e., P3a; Friedman, et al., 2001; Polich, 2007; Tenke, Kayser, Stewart, et al., 2009). These prior studies are highly relevant to a separate body of work analyzing the clinical utility of LDAEP paradigms in predicting successful 5HT treatment. However, the MMN and LDAEP literatures have remained disjointed because they are used to investigate specific clinical populations and test predictions derived from different physiological models. In addition, the standard LDAEP paradigm necessarily (but unintentionally) produces unbalanced disparities in intensity between consecutive stimuli which likely induce deviance related processes like MMN. The present study aimed to clarify the relationship between intensity disparity and MMN by investigating a range of intensities commonly used in LDAEP paradigms. It was predicted that large disparities in intensity would produce

greater MMN, but it was unclear whether softer or louder deviants would show the same relationship between MMN amplitude and relative disparity. Thus, the relationship between the level of disparity (10 to 30 dB) and direction (louder or softer) of intensity deviance was analyzed by maintaining a fixed range of intensities across experimental blocks, and systematically employing each intensity as either standards or deviants equally across blocks.

Two large temporal PCA factors were derived from difference CSDs and sufficiently characterized deviance-related processes overlapping N1/P2. A relative MMN sink was identified with a peak loading at 136 ms and a factor score topography particularly reminiscent of N1 sink. A relative P3a vertex source (230 ms peak loading) followed the MMN sink and resembled activity found at the vertex of the bilateral P2 topography. The spatiotemporal characteristics of MMN generally matched previous observations investigating intensity deviance and/or other deviant auditory characteristics (e.g., Deouell, Bentin, & Giard, 1998; Giard, Perrin, Pernier, & Bouchet, 1990; Sato et al., 2000). The CSD-PCA factor score topography for the MMN sink showed a similar pattern of activation as the tangentially-oriented N1 sink, and the MMN factor loading showed a temporal overlap with the tangential N1 sink; however, MMN sink activity extended for a longer duration than N1 activity (approximately 50 to 70 ms).The identification of the MMN sink and the P3a vertex source factors is important in two ways: 1) it confirms that MMN and P3a-like activity is elicited by intensity disparity; and 2) it suggests that the MMN and P3a-like activity not only overlap the N1 and P2, but also contribute to their scalp topographies, respectively.

MMN sink amplitude paralleled increases in intensity disparity regardless of whether deviants were louder or softer. However, louder disparities produced greater MMN sink amplitude for all levels of disparity compared to softer disparities and displayed a steeper rise in MMN amplitude at each successive level of disparity. The steeper rise in MMN amplitude for louder disparities is akin to the findings that the increases in N1/P2 amplitude for deviants were sharper over the relatively louder stimuli. As discussed above, the ecological importance of detecting meaningful changes within the environment affords the individual a mechanism to identify potential threats within the environment. While the detection of decrements in intensity may have particular advantages within a person's environment, the brain may have developed sensitivity to louder deviations within the environment. For example, as a potentially threatening stimulus approaches it is likely to emit louder auditory signals than one that is further away, thus it would be biologically imperative for an individual to detect disparities in intensity relative to the background context efficiently, particularly for louder disparities.

It should be noted that the tones in the current study were calibrated with a sound level meter at 100, 90, 80, and 70 dB sound pressure level (SPL), but the perceived loudness of each tone may have differed across participants. For this reason, some investigators opt to calibrate tones based on the particular hearing threshold level for each subject. Given that N1 amplitude has been shown to approximate a power law function (Keidel & Spreng, 1965), it may be that differences between intensities may not be perceived equally across the range used in this study. That is, larger, louder disparities may be easier to detect than smaller disparities as N1-related processes respond more vigorously for louder tones than softer tones. This could explain why the rise in the

amplitude/disparity slope for louder disparities is steeper than that of softer disparities. However, it is unlikely that this effect is solely due to perceptual processes (reflected by N1) because MMN amplitude increased monotonically to softer tones with larger disparity. If perceptual processes were responsible for the effect, softer deviants should produce less change in MMN amplitude as the disparity between softer tones increased. Thus, the increase in MMN amplitude is most likely due to deviance-related processes.

### 7.4 100 dB Deviants Are Processed Uniquely

The CSD-PCA for difference waveforms yielded a factor with spatiotemporal characteristics similar to the P3a reported in previous studies (Friedman, et al., 2001; Polich, 2007; Tenke, Kayser, Stewart, & Bruder, 2010). This P3a vertex source component was only observed in the loudest deviant conditions, i.e., for 100 dB deviants (see Fig. 15). The disproportionate enhancement of the vertex source for 100 dB stimulus may reflect automatic attentional processing uniquely for this stimulus, which suggests that 100 dB tones may be perceived as novel or salient stimuli (Friedman, et al., 2001; Polich, 2007). Enhanced MMN and the additional recruitment of P3a-like activity for loud but not soft tones are consistent with other findings in the literature. For example, Rinne and colleagues (2006) observed MMN for deviant increments and decrements, but monotonic increases in frontocentral P3a were only observed for deviant increments. Unlike the results reported by Rinne et al, the current findings show that P3a-like activity was primarily limited to 100 dB deviants. These contrasting findings are most likely due to differences in paradigms. Rinne et al employed a forced-choice frequency discrimination task and infrequently varied task-irrelevant tone intensities. Therefore, it is reasonable to assume P3a activity elicited by deviant increments in the forced-choice task

was due to the attentional and/or target-related demands of the task (i.e., participants attended to, detected, and responded to auditory targets). That is, a top-down, goal-oriented attentional facilitation (likely mediated by a frontal executive system) of sensory processes may have been relatively more engaged in the Rinne et al study as their paradigm required successful target detection. While spatiotemporal properties of the P3a are similar in the current study and the Rinne et al study, the P3a source reported here is sharply localized to the vertex, which is more posterior than the frontocentral region Rinne et al. reported. Interestingly, the vertex P3a elicited by the intensity MMN paradigm is highly reminiscent of a 'novelty vertex source' recently reported by Tenke et al. (2010), which was elicited by novel stimuli embedded within a target – detection task (novelty oddball task). The incidence of this vertex source was independent and characteristically different than the frontocentral source elicited by the targets (target P3a). Tenke et al suggests that:

"...the focal novelty vertex source suggests a more posterior generator (i.e., in or behind SMA), which is consistent with the localization of an equivalent dipole for go/no-go P3 in portions of cingulate cortex near motor areas, and is a location more consistent with processes related to response inhibition than with task-specific stimulus classification or error processing per se." (p. 142).

The correspondence between the vertex source observed in the present study and the novelty vertex source reported by Tenke et al suggests that they serve similar functional role. That is, participants in the current study were told to ignore auditory stimuli and attend to a silent film and report its content after each block. It is possible that participants were able to sufficiently ignore deviant intensities below 100 dB, but were

unable to ignore the loud 100 dB deviant tone particularly when the disparity was +20 dB or larger. In light of Tenke et al's interpretation, the 100 dB deviants may have evoked an automatic process similar to response inhibition. Indeed, P3a-like activity has been shown to accompany startle responses to loud stimuli in paired pulse paradigms (e.g., Sugawara, Sadeghpour, De Traversay, & Ornitz, 1994), it is also possible that the vertex response to the 100 dB tones was noxious to the participants and/or elicited a motor reflex. The current paradigm was not designed to address this possibility and such an interpretation is highly speculative. Moreover, the participants were not required to report their level of discomfort regarding loudness. The effect of a motor reflex could be examined in an additional study explicitly designed to examine this hypothesis.

### 7.5 MMN Findings Discussed in Terms of the Adaptation- and Memory-based MMN Models

Two functional interpretations of MMN were introduced: the memory-based model, and the adaptation-based model. The adaptation model assumes a first order process whereby the same cortical generators are responsible for N1 and MMN. In contrast, the memory based model assumes that neural activity contributing to MMN is both structurally and functionally independent of the neurophysiology underlying N1. While the models do not differ in their predictions, the models offer unique insights regarding the present findings.

#### 7.5.1 Adaptation-Based Model

The adaptation model suggests MMN indexes differential activity between neuronal ensembles that contribute to N1 and are, thus, derived from the same neuronal generators. The current findings provide support for this hypothesis as highly significant

correlations (up to 58% shared variance in some conditions) between overall factor score topographies for N1 and MMN sinks, which suggests that N1 and MMN share very similar generator patterns. Factor score correlations highly resemble MMN sink ANOVA findings (i.e., higher amplitude for greater disparities); however, lower correlations for smaller disparities is most likely driven by the reduction in MMN sink signal for those conditions.

The adaptation model posits that neurons uniquely activated by the standard tone undergo adaptation (i.e., neural refractory processes) leading to smaller N1 amplitude. In contrast, unadapted ("fresh") cells activated by deviant tones yield larger N1 amplitudes, especially when there is a greater physical discrepancy between the standard and the deviant (Jääskeläinen, et al., 2004; May & Tiitinen, 2001, 2004, 2009). Thus, any measurable activity resulting from a deviant-minus-standard difference within this timeframe actually reflects the residual activity of the unadapted cells. Due to a neural competitive network (e.g., lateral inhibition), large disparities in deviant tones produce greater activity because their afferents are not downregulated by nearby standard-specific cell adaptation. The current findings support this hypothesis as a) MMN amplitude significantly increased with greater disparities for both softer and louder deviants, and b) correlations between N1 and MMN factor score topographies increased with greater levels of disparity.

The finding that the monotonic relationship between MMN amplitude and level of disparity is greater for louder deviants can be explained in terms both an ampliotopographic neural representation on the auditory cortex (e.g., Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002; Brechmann, Baumgart, & Scheich, 2002; Mulert, et

al., 2005) and the correspondence of N1 amplitude to an exponential function (i.e., power law; Keidel & Spreng, 1965). That is, greater residual N1 activity (i.e., MMN) should occur for cases when relatively louder intensities deviate from lower intensity standards since a) loud intensities produce greater N1 amplitude and b) theoretically, high intensity N1 receptor cells are located (on primary cortex) further from lower intensity specific N1 cells that have become hyperpolarized due to high repetitions. In contrast, smaller residual N1 amplitude is expected to occur for softer intensity disparities as soft tones produce relatively lower amplitudes, but a slight rise in the MMN amplitude/disparity function is expected as the neural generators of the relatively softest tones spatially differ from those of the louder, adapted standards.

The plausibility of the adaptation model applied to the intensity MMN findings is supported by known physiological mechanisms such as lateral inhibition; however, it is limited by the lack of any consistent evidence for the ampliotopicity of the auditory cortex. Nevertheless, the adaptation model provides a parsimonious explanation of the current findings in terms of a physiologically plausible mechanism that reflects a first-order modulation of sensory processing within the primary auditory cortices (May & Tiitinen, 2004, 2009).

### 7.5.2 Memory-Based Model

The memory-based interpretation distinguishes “mismatch detector cells” from stimulus-specific N1 afferent cells both functionally and topographically (Sokolov et al., 2002). According to this model, the deviant-minus-standard subtraction would have cancelled out N1-related activity and preserved activity generated from mismatch detector cells (i.e., MMN activity). Thus, increases in MMN amplitude with greater

intensity disparities reflects a higher-order, informational output of a preattentional comparator mechanism, where greater activity of detectors cells denote greater deviance from the standard. However, the present findings only partially support the tenants of this model. Enhanced MMN amplitudes were observed for increasingly louder disparities, but less for softer disparities. Reporting a similar finding, Woldorff, Hackely, and Hillyard (1991; reviewed in section 3.4.3) had once challenged the validity of the memory-based model; yet Näätänen (1991) argued that MMN attenuation for deviant decrements was likely due to a dampening of the MMN amplification mechanism modulated by a higher-order attentional processes that uniquely affected softer deviants. However, the current findings do not support Näätänen's interpretation as MMN amplitude was found to increase with increasing levels of disparity even in the softest condition. Furthermore, the hypothesis that MMN is generated by topographically distinct 'mismatch-detector cells' is not supported by the current findings, as correlations between N1 and MMN factor score topographies were virtually identical for the greatest intensity disparities.

While the memory-based model is theoretically plausible, its neurophysiological tenants center on physiological activity of neural ensembles that have not been identified in the auditory cortex; which is in contrast to several published experimental findings of adaptive processes in auditory and other sensory regions (e.g., Brosch & Schreiner, 1997, 2000; Calford, 2002; Calford & Semple, 1995; Kohn, 2007). Although, the current findings cannot unambiguously support one MMN model over the other, comparatively, the adaptation model provides a much more concise and parsimonious explanation for the present results and more adequately explains the current findings.

## 7.6 Implications of the Current Findings for MMN Studies

This study systematically examined the intensity dependency of N1/P2 and MMN within the same paradigm. While other studies have investigated the effects of intensity deviance on MMN amplitude, none have utilized an experimental design that enabled the direct comparison of a specific range of intensities as either standards or deviants. By utilizing the mixed intensity MMN paradigm it was shown that intensity dependency of N1/P2 is eliminated by a high presentation rate of standards, while a sharp increase in N1/P2 amplitude is present for deviants. Furthermore, the mixed intensity MMN paradigm helped expose the interaction of intensity disparity and relative deviant direction. MMN amplitude was asymmetrically greater for louder disparities than for softer disparities at comparable levels. Moreover, since multiple deviants were presented in the same experimental block, the duration of recording sessions was much shorter than conventional MMN paradigms that utilize a single deviant per block.

An unconventional calculation of difference waves was used to measure MMN in this study. Rather than analyzing the conventional Deviant-minus-(within block) Standard waveform, a Deviant-minus-(comparable intensity) Standard waveform was computed. By doing so, deviance-related processes would not be confused with uncontrolled and unrelated activity specific to processing a different physical stimulus. Future MMN studies would be well served to evaluate comparable stimuli when examining questions about deviance-related brain activity.

The current findings are able to provide some information about the effect of attentional demands on a MMN task; however, since attentional demands were not experimentally manipulated the following observations are mainly speculative. The data seem to suggest that attention may have differently impacted MMN amplitude for louder

or softer tones. That is, MMN amplitude may be reduced if certain stimuli are more easily ignored than others. Presumably, this effect is not confined to intensity deviants, but would also apply to other stimulus properties (e.g., frequency, duration, etc.). A potential direction for future work would be to directly test this hypothesis by systematically manipulating attention toward or away from experimental tones.

Also of interest was the fact that a P3a-like vertex source was elicited solely by the 100 dB deviant condition. Although this activity was largest for the greatest disparity (+30 dB), it was also observed at every other level of disparity (+10 and +20 dB) for 100 dB. This finding suggests a) that the P3a reported by many MMN studies may not reflect a unitary process (i.e., classically thought of as attention to salience), and b) does not necessarily follow MMN activity, nor does it necessarily relate to deviance per se. Rather, P3a-like activity may reflect other activity such response inhibition or startle in cases where the intensity of stimuli exceed some subjective range of 'normalcy' or comfort (i.e., when intensity become noxious).

Lastly, the current findings did not unequivocally support one leading model of MMN over the other; however, the results were more parsimoniously described in terms of the adaptation model. Future work investigating the neurophysiological tenants of the memory-based model (i.e., second-order comparator neuronal ensembles) would help substantiate this model's theoretical assertions and potentially lead to new insights into sensory-perceptual processes. More significantly, researchers investing aspects of MMN within broad contexts would be well served to consider their findings in terms of the adaptation model, as new insights may be gleaned from this alternative perspective.

## 7.7 Implications of the Current Findings for Clinical LDAEP Studies

Insights gained from this study have direct implications for both clinical LDAEP and MMN research. With respect to clinical LDAEP studies, these findings suggest that the unbalanced probability of disparities between consecutively presented intensities may elicit overlapping endogenous responses (MMN) in the timeframe of N1. Additionally, very loud tones (e.g., 100 dB) may uniquely elicit activity overlapping the timeframe of P2 (i.e., P3a vertex source). Thus, the assumption that N1/P2 amplitude provides a purely "exogenous" and direct relationship between intensity and primary auditory cortical circuitry is questionable. This caveat is particularly germane to the investigations based on the LDAEP-5HT hypothesis as the model does not take into account that deviance-related processes reflected by MMN likely play a role in the derived amplitude/intensity slopes, and that other neurochemical or physiological mechanism may influence this measure (e.g., a GABAergic—NMDA mediated lateral inhibitory mechanism). Since LDAEP measures are being investigated as a potential clinical measure to predict SSRI treatment response, it is vital to gain a fuller understanding of the effects of 5HT on MMN since deviance related brain mechanisms are likely implicated in LDAEP paradigms. Very few studies have investigated the effect of 5HT on MMN, and most of these studies have used protocols that increase or decrease 5HT in an acute setting. Thus, more work is needed to fully appreciate the effect of chronic 5HT reduction (as implicated in major depression) on MMN, as well as the effects of SSRI therapy over extended periods.

An interesting insight gained by comparing the clinical LDAEP and MMN literatures was the observation that both areas implicate analogous neurochemical and physiological mechanisms. Whereas, the clinical LDAEP work is based on a competitive

neuronal network that features 5HT, the clinical MMN work bases its model on a competitive neuronal network that features the actions of Glutaminergic NMDA-receptor mechanisms or GABAergic activity. Future clinical work may benefit by integrating the two models and exploring how one mechanism may interact or impact the other.

# CHAPTER 8: CONCLUSIONS

MMN studies have provided insights about the brain's ability to perceive and/or detect deviations within established environmental patterns. Clinical LDAEP studies have provided insights about the relationship between the intensity of an external auditory stimulus and the activity of primary auditory cortex, as well as neurochemical processes affecting this relationship. Unfortunately, these two bodies of literature have remained somewhat disjointed. The present study integrates elements of each body of literature to investigate a) the impact of varying levels of intensity disparity among consecutively presented tones on the loudness-dependency of N1/P2, and b) assessed the extent to which deviance-related processes (i.e., MMN) are affected by louder or softer tones. A passive MMN-paradigm was employed using a range of intensities commonly used in clinical LDAEP studies as deviants and standards in order to isolate effects related to processing deviance (MMN) from stimulus specific N1/P2 effects. CSD-PCA approach was used to improve ERP component identification and source patterns of brain activity elicited by this paradigm. The main aims of this study were: 1) to characterize N1/P2 LDAEP within the constraints of the current paradigm (i.e., fast, constant SOA); 2) to compare the intensity-dependency of N1/P2 for standard and deviant tones; 3) to investigate the intensity-dependency of MMN; and 4) to compare the similarity between N1 and MMN topographies to test the hypothesis that neural generators of these components overlap.

The paradigm used in this study shared many characteristics common to MMN studies, but were markedly different than parameters characteristic of standard LDAEP paradigms. Differences between the current paradigm and the standard LDAEP paradigm

included the instructions to ignore tones and attend to a silent film, a much faster and constant presentation rate of tones for the current study, and the unequal frequency of intensities per block (i.e., high frequency standard, low frequency deviants). The paradigmatic differences were likely to affect N1/P2 LDAEP. In order to isolate the effect of presentation rate and instructions to ignore tones, ERPs from a block of equiprobable intensities were compared to those from the standard LDAEP paradigm. It was hypothesized that the equiprobable block in the current paradigm would yield overall attenuated N1/P2 due to its faster/constant presentation rate and its instructions to ignore the tones even though the stimuli were physically identical. Findings revealed that N1/P2 elicited by the equiprobable block in the current paradigm shared highly comparable temporal and spatial patterns with a standard LDAEP paradigm, and the CSD-PCA factor loadings and scores were highly comparable between the paradigms. Indeed, the equiprobable block produced an overall attenuation of CSD amplitude as compared to the standard LDAEP paradigm. These findings indicated that even though participants were instructed to ignore tones and attend to a silent video, the tones were still sufficiently detected and differentially processed in spite of their presentation characteristics.

As confirmed by the findings reported above, many studies have demonstrated a monotonic relationship between N1/P2 amplitude and tone intensity; however, no study has explicitly examined the extent to which N1/P2 LDAEP is affected within a MMN paradigm. In particular, it was unclear to what extent N1/P2 LDAEP would be affected by the context in which a given intensity was cast, i.e., standard or deviant. Since, it has been frequently shown that standard tones produce attenuated ‘exogenous’ components (e.g., N1/P2), which presumably result from neural adaptation, it was hypothesized that

standards would yield comparably smaller CSD amplitudes than deviants. However, it was also possible that adaptive processes may have been engaged unequally for louder or softer intensities, which would have produced an amplitude/intensity function that appeared less monotonically related. Interestingly, the current findings show that N1/P2 LDAEP was completely negated for the standard condition; that is, no statistical differences were observed between almost all levels of intensity (note that the difference between 70 and 80 dB did reach statistical significance). While it was predicted that the high repetition rate of standards would attenuate N1/P2 amplitude, the complete lack of N1/P2 intensity modulation was an unexpected finding. It is possible that this finding resulted from either basic neural adaptation (neural refractory responses due to the high frequency and fast/constant presentation rate), or through the interaction of a more complex attentional/executive process that enhanced/amplified neural adaptive process in the primary auditory cortex. Regardless of the actual neurophysiological mechanism, a significant dampening of the 'exogenously-related' components demonstrates the robustness of auditory perceptual system that dynamically adjusts to the 'standard' environmental context in order to detect meaningful changes.

In contrast to the standards, deviant intensities produced enhanced N1/P2, but only for the louder intensities; thus, the hypothesis that deviants would yield larger N1/P2 amplitude than standards at all intensities was not supported by the current findings. This finding is also inconsistent with many findings in the MMN literature, where generally, one expects to observe greater amplitudes for physically dissimilar deviant stimuli. This finding suggests that the attentional demands of the paradigm may have unequally influenced the exogenously-related processing of the tones where participants were

successfully able to suppress sensory-related process for softer intensities (70 and 80 dB) and they were not able to fully suppress processing of less probable, louder deviants (90 and 100 dB).

Another aim of this study was to investigate the intensity-dependency of MMN. A major rationale for conducting this study was that standard LDAEP paradigms employ an unbalanced presentation (unintentionally) of disparities between consecutively presented tones, which could potentially elicit deviance-related activity such as MMN and overlap N1/P2 activity and/or contribute to the scalp-recorded measures for the more extreme intensities (i.e., the loudest or softest tones). This study used an unconventional method for calculating difference waveforms, such that each difference was derived from ERPs evoked by physically identical tones which differed only in context (i.e., standard or deviant). As such, the residual variance was comprised mainly of deviance-related activity for each level of intensity. CSD-PCA results for difference waveforms revealed two large variance factors with spatiotemporal properties consistent with known MMN and P3a components. MMN was elicited by disparities in intensity and shown to increase in amplitude as a function of disparity such that larger disparities produced greater MMN amplitude, which supported two of the main hypotheses concerning MMN and intensity. The current findings also supported one of the alternative hypotheses regarding the direction of intensity disparity, where MMN was found to be larger for louder disparities in comparison to softer disparities (steeper slope for MMN amplitude/disparity function for louder disparities). Therefore, this finding suggests that MMN reflects and/or is impacted by the activity of N1/P2 to deviants rather than it reflecting the activity of a pure deviant-detection mechanism whereby MMN amplitude would increase with

disparity regardless of whether the tone was louder or softer. Given that MMN indexes a brain mechanism for the detection of deviances within the environment, the current finding suggests that this mechanism is biased for louder disparities in the 'standard' noise, which presumable corresponds to more salient or threatening stimuli in the real world. Alternatively, the fact that MMN responds more vigorously to louder disparities may simply be due the fact that louder disparities are more easily perceived than softer disparities.

Through this methodology, this study was not only able to confirm prior reports that increases in MMN amplitude vary with greater intensity disparities, but it successfully demonstrated that enhanced MMN can be seen for greater disparities in both softer and louder intensities within the same paradigm. In addition, a P3a-like vertex source was shown to be uniquely elicited by the loudest deviants (100 dB), which may represent either additional recruitment of attentional resources elicited by novel or salient stimuli, represent response inhibitory processes, and/or represent startle-related processes.

The final aim of this study was to compare PCA factor score topographies related to N1 and MMN components derived from the original CSD and CSD difference waveforms (respectively) to help distinguish whether a) MMN reflects activity from a neural generator that is spatially-distinct from the N1, or b) whether the MMN and N1 generators spatially overlap. To investigate this question, correlation coefficients for N1 and MMN topographies were analyzed from the reference-free, data-driven, orthogonally-derived factor score topographies (PCA factor weighting coefficients) extracted by the CSD-PCA. The findings strongly suggest that N1 and MMN activity

spatially overlap. Significant correlations between N1 and MMN topographies were observed at each deviant level of intensity and at each level of disparity regardless of the direction of disparity (i.e., louder or softer). Surprisingly, significant correlations at every site were observed between N1 and MMN at the greatest level of disparity, which suggests that N1 and MMN processes not only overlap at sites indicative of primary auditory cortex, but that the entire activation pattern is consistent across the scalp for each of these components. As such, these findings more strongly support hypotheses concerning the adaptation model over the memory-based/comparator model of MMN. In addition, these findings further support the hypothesis that MMN-related activity may contribute to the spatiotemporal characteristics of N1/P2 in standard LDAEP paradigms, especially in less-frequently presented cases where the disparity in loudness between consecutively presented stimuli greatly differ. Future work investigating differences in the disparity between consecutively presented intensities using a standard LDAEP paradigm would help elucidate whether N1-P2 components differ as a function of the level of disparity and/or loudness.

# APPENDIX

## A. TABLES

**Table 1.** *PCA Variables and Cases*

| Analysis | Variables | Cases | | |
|---|---|---|---|---|
| | | Conditions | Subjects | Sites |
| Deviant vs. Standard<br>(57,024 cases X 180 variables) | 180 Timepoints<br>(-200 to 500 ms) | *N*=24;<br>(4) Equiprobable<br>• 100 dB; 90 dB; 80 dB; 70 dB<br>(4) Standard<br>• 100std; 90std; 80std; 70std<br>(4) Pooled Deviants<br>• 100dev; 90dev; 80dev; 70dev<br>(3) 100 dB deviants in 3 standard blocks (dev/std)<br>• 100dev/90std; 100dev/80std; 100dev/70std<br>(3) 90 dB deviants in 3 standard blocks (dev/std)<br>• 90dev/100std; 90dev/80std; 90dev/70std<br>(3) 80 dB deviants in 3 standard blocks (dev/std)<br>• 80dev/100std; 80dev/90std; 80dev/70std<br>(3) 70 dB deviants in 3 standard blocks (dev/std)<br>• 70dev/100std; 70dev/90std; 70dev/80std | *N*=33 | *N* = 72 |
| Deviant-minus-Standard Difference<br>(38,016 cases X 180 variables) | 180 Timepoints<br>(-200 to 500 ms) | *N*=16;<br>(4) Pooled Intensities<br>• 100dev minus 100std<br>• 90dev minus 90std<br>• 80dev minus 80std<br>• 70dev minus 70std<br>(3) 100 dB differences<br>•100dev/90std minus 100std<br>•100dev/80std minus 100std<br>•100dev/70std minus 100std<br>(3) 90 dB differences<br>•90dev/100std minus 90std<br>•90dev/80std minus 90std<br>•90dev/70std minus 90std<br>(3) 80 dB differences<br>•80dev/100std minus 80std<br>•80dev/90std minus 80std<br>•80dev/70std minus 80std<br>(3) 70 dB differences<br>•70dev/100std minus 70std<br>•70dev/90std minus 70std<br>•70dev/80std minus 70std | *N*=33 | *N* = 72 |
| Deviance Disparity<br>(14,256 cases X 180 variables) | 180 Timepoints<br>(-200 to 500 ms) | *N*=6;<br>(1) 30 dB increment<br>(100dev/70std)<br>(1) 20 dB increment<br>(100dev/80std; 90dev/70std)<br>(1) 10 dB increment<br>(100dev/90std; 90dev/80std; 80dev/70std)<br>(1) 10 dB decrement<br>(90dev/100std; 80dev/90std; 70dev/80std)<br>(1) 20 dB decrement<br>(80dev/100std; 70dev/90std)<br>(1) 30 dB decrement<br>(70dev/100std) | *N*=33 | *N* = 72 |

**Table 2.** *Significant Repeated Measures ANOVA Effects forEquiprobable MMN Block*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| CSD-PCA Factor | Effect | *F* | *df* | *p* | *ε* |
| N1 sink: | Intensity | 48.7 | 3,27 | < 0.0001 | 0.63 |
| Bilateral Central/ | 90 dB to 100 dB | 47.0 | 1,32 | < 0.0001 | |
| Temporoparietal sites | 80 dB to 90 dB | 6.5 | 1,32 | 0.002 | |
| (C1/2, C3/4, C5/6 – TP9/10, P9/10) | | | | | |
| P2 source | Intensity | 13.8 | 3,27 | < 0.0001 | 0.85 |
| Frontotemporal sites | 90 dB to 100 dB | 10.8 | 1,32 | 0.002 | |
| (FT7/8, FT9/10, T7/8) | 80 dB to 90 dB | 6.9 | 1,32 | 0.01 | |

**Table 3.** *Significant Repeated Measures Anova Effects for N1 Sinks (113 ms)*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Bilateral Central Sink / | Condtion | 67.2 | 1,32 | < 0.0001 | |
| Temporoparietal | Intensity | 50.9 | 3,30 | < 0.0001 | 0.58 |
| Source | 90 dB to 100 dB | 38.6 | 1,32 | < 0.0001 | |
| (C1/2, C3/4, C5/6 – | 80 dB to 90 dB | 24.9 | 1,32 | < 0.0001 | |
| TP9/10, P9/10) | 70 dB to 80 dB | 11.1 | 1,32 | 0.002 | |
| | Condition X Intensity | 55.87 | 3,30 | < 0.0001 | 0.69 |
| | Condition at 100 dB | 100.9 | 1,32 | < 0.0001 | |
| | Condition at 90 dB | 36.0 | 1,32 | < 0.0001 | |
| | 90 dB to 100 dB at Deviant | 54.7 | 1,32 | < 0.0001 | |
| | 80 dB to 90 dB at Deviant | 45.5 | 1,32 | < 0.0001 | |
| | 70 dB to 80 dB at Deviant | 3.8 | 1,32 | 0.06 | |
| | 70 dB to 80 dB at Standard | 13.0 | 1,32 | 0.001 | |

**Table 4.** *Significant Repeated Measures ANOVA Effects for Temporal N1 (159 ms)*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Bilateral | Intensity | 14.3 | 3,30 | < 0.0001 | 0.54 |
| Temporoparietal | 80 dB to 90 dB | 13.4 | 1,32 | 0.0009 | |
| (T7/8,TP7/8, TP9/10) | 70 dB to 80 dB | 6.4 | 1,32 | 0.02 | |
| | Condition X Instensity | 3.3 | 3,30 | 0.3 | 0.92 |
| | Condition at 70 dB | 11.8 | 1,32 | 0.002 | |
| | 80 dB to 90 dB at Deviant | 17.0 | 1,32 | 0.003 | |
| | 70 dB to 80 dB at Deviant | 5.7 | 1,32 | 0.02 | |
| | 80 dB to 90 dB at Standard | 11.8 | 1,32 | 0.002 | |
| | Hemisphere | 12.7 | 1,32 | 0.001 | |

**Table 5.** *Significant Repeated Measures ANOVA Effects for P2 (214 ms) at Bilateral Frontotemporal Sites*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Frontotemporal | Condition | 19.3 | 1,32 | 0.0001 | |
| (FT7/8, FT9/10, T7/8) | Intensity | 20.3 | 3,30 | <0.0001 | 0.77 |
| | 90 dB to 100 dB | 17.6 | 1,32 | 0.0002 | |
| | 80 dB to 90 dB | 15.4 | 1,32 | 0.0004 | |
| | Condition X Intensity | 8.1 | 3,30 | 0.0002 | 0.89 |
| | Condition at 100 dB | 27.1 | 1,32 | <0.0001 | |
| | Condition at 90 dB | 4.5 | 1,32 | 0.04 | |
| | 90 dB to 100 dB at | 21.3 | 1,32 | 0.0001 | |
| | Deviant | 10.8 | 1,32 | 0.003 | |
| | 80 dB to 90 dB at Deviant | | | | |

**Table 6.** *Significant Repeated Measures ANOVA Effects for P2 (214 ms) at Vertex*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Vertex (Cz) | Condition | 15.6 | 1,32 | 0.0004 | |
| | Intensity | 15.5 | 3,30 | <0.0001 | 0.49 |
| | 90 dB to 100 dB | 14.7 | 1,32 | 0.0006 | |
| | 80 dB to 90 dB | 8.3 | 1,32 | 0.007 | |
| | Condition X Intensity | 22.4 | 3,30 | <0.0001 | 0.62 |
| | Condition at 100 dB | 29.0 | 1,32 | <0.0001 | |
| | 90 dB to 100 dB at Deviant | 27.2 | 1,32 | <0.0001 | |
| | 80 dB to 90 dB at Deviant | 4.7 | 1,32 | 0.04 | |
| | 80 dB to 90 dB at Standard | 5.7 | 1,32 | 0.02 | |

**Table** 7. *Significant Repeated Measures ANOVA Effects for MMN Sink (136 ms) to Intensity Disparity*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Bilateral Central Sink | Direction | 29.7 | 1,32 | <0.0001 | |
| /Temporoparietal | Disparity | 57.7 | 2,31 | <0.0001 | 0.79 |
| Source | ±10 dB to ±20 dB | 49.9 | 1,32 | <0.0001 | |
| (C1/2, C3/4, C5/6 – | ±20 dB to ±30 dB | 28.8 | 1,32 | <0.0001 | |
| TP9/10, P9/10) | Direction X Disparity | 7.4 | 2,31 | 0.005 | 0.67 |
| | Direction at ±10 dB | 19.7 | 1,32 | <0.0001 | |
| | Direction at ±20 dB | 30.3 | 1,32 | <0.0001 | |
| | Direction at ±30 dB | 9.2 | 1,32 | 0.0001 | |
| | ±10 dB to ±20 dB at Louder | 53.9 | 1,32 | <0.0001 | |
| | ±20 dB to ±30 dB at Louder | 36.9 | 1,32 | <0.0001 | |
| | ±10 dB to ±20 dB at Softer | 18.4 | 1,32 | 0.0002 | |
| | ±10 dB to ±30 dB at Softer | 18.0 | 1,32 | 0.0002 | |

**Table 8.** *Significant Repeated Measures ANOVA Effects for P3a Vertex Source (234 ms) to Intensity Disparity*

| | | ANOVA | | | |
|---|---|---|---|---|---|
| Region (sites) | Effect | *F* | *df* | *p* | ε |
| Vertex (Cz) | Direction | 29.2 | 1,32 | <0.0001 | |
| | Disparity | 37.9 | 2,31 | <0.0001 | 0.83 |
| | ±10 dB to ±20 dB | 18.5 | 1,32 | 0.0002 | |
| | ±20 dB to ±30 dB | 30.1 | 1,32 | <0.0001 | |
| | Direction X Disparity | 16.7 | 2,31 | <0.0001 | 0.87 |
| | Direction at ±20 dB | 14.2 | 1,32 | 0.0007 | |
| | Direction at ±30 dB | 31.2 | 1,32 | <0.0001 | |
| | ±10 dB to ±20 dB at Louder | 16.2 | 1,32 | 0.0003 | |
| | ±20 dB to ±30 dB at Louder | 31.8 | 1,32 | <0.0001 | |

**Table 9.** *Mean(SD) Correlation Values (Fisher's Z Transformed R values) for N1 and MMN Factor Score Topographies.*

| Condition | Mean(SD) | *t* | *df* | *p* |
|---|---|---|---|---|
| +30dB | 0.76(0.31) | 6.5 | 31 | <0.0001 |
| +20dB | 0.76(0.34) | 6.5 | 31 | <0.0001 |
| +10dB | 0.67(0.30) | 6.5 | 31 | <0.0001 |
| -10dB | 0.61(0.29) | 4.3 | 31 | <0.0001 |
| -20dB | 0.69(0.28) | 5.3 | 31 | <0.0001 |
| -30dB | 0.72(0.22) | 5.8 | 31 | <0.0001 |

**Table 10.** *Mean Correlation (R) value for N1 and MMN Factor Scores at Selected Sites (ANOVA model)*

| Condition | C1 | C3 | C5 | P9 | TP9 | C2 | C4 | C6 | P10 | TP10 |
|---|---|---|---|---|---|---|---|---|---|---|
| +30dB | 0.74 | 0.76 | 0.62 | 0.59 | 0.39 | 0.74 | 0.57 | 0.31 | 0.79 | 0.71 |
| +20dB | 0.70 | 0.82 | 0.45 | 0.75 | 0.54 | 0.60 | 0.76 | 0.56 | 0.82 | 0.76 |
| +10dB | 0.60 | 0.75 | 0.55 | 0.66 | 0.42 | 0.67 | 0.45 | 0.47 | 0.72 | 0.63 |
| -10dB | 0.58 | 0.79 | 0.67 | 0.79 | 0.84 | 0.87 | 0.72 | 0.50 | 0.81 | 0.82 |
| -20dB | 0.57 | 0.70 | 0.68 | 0.67 | 0.50 | 0.57 | 0.67 | 0.65 | 0.53 | 0.57 |
| -30dB | 0.55 | 0.65 | 0.57 | 0.64 | 0.56 | 0.65 | 0.55 | 0.61 | 0.55 | 0.49 |

## B. FIGURES

### Figure Captions

Figure 1. Theoretical Disparity X Direction MMN Effects. A) If MMN reflects the activity of a deviant-detection mechanism that provides an endogenously-driven 'signal' of the degree of disparity between tones, and is unaffected by processes reflected by N1, then MMN amplitude should vary consistently across the level of disparity regardless of whether deviants were softer or louder. B) If mechanisms underlying MMN are related to those underlying N1, then MMN amplitude should also reflect the behavior of N1 activity in that the louder disparities will exceed softer disparities in amplitude

Figure 2. Intensity MMN Design. Tones were presented at four levels of intensity (70, 80, 90, 100 dB) and occurred at two levels of probability in four experimental blocks. For each block, one intensity was presented as a standard (70%) and the three remaining intensities as deviants (each at 10% probability; see rows A – D). An additional block (row E) of equiprobable intensities served as a standard intensity-modulation paradigm to validate intensity effects on N1-P2. Example segments of each experimental block are shown to the right (rows 1 – 5). The level of disparity between each deviant and standard tone is shown as: green ± 10 dB; blue ± 20 dB; and red ± 30 dB. A total of 400 stimuli, consisting of 280 standards and 120 deviants (40 per deviant intensity), were counterbalanced and pseudorandomized across blocks (i.e. rows A – D). Block order was counterbalanced across subjects.

Figure 3. 72-Channel EEG Montage. 72 scalp sites with an active recording reference

composed of sites PO1 (common mode sense) and PO2 (driven right leg). Data were re-referenced to nose offline.

Figure 4: CSD Waveforms for MMN Conditions and Equiprobable Trials. A) Grand mean CSDs for deviant and standard conditions, and equiprobable block trials showed a stable component structure. Deviants (red) were notably larger across most electrodes, particularly at frontocentral, lateral posterior, and centrals sites. B) Representative sites depict a robust bilateral frontocentral N1 sink (C3/4; 113ms) with corresponding bilateral temporoparietal souce (TP9/10), bilateral temporal N1 sink (T7/8; 153 ms), and bilateral temporal P2 source (T7/8; 214 ms) coincident with a midline source (Cz).

Figure 5: PCA Factor Loadings and Factor Score Topographies for Standard, Deviant, and Equiprobable Trials. Time courses of PCA factor loadings of the first four CSD factors extracted (71% explained variance after Varimax rotation; panel A), and factor score topographies (panel B) for three of the first four factors characterized known components in the time-range of N1/P2. While factor score topographies are highy consistent across MMN conditions, deviants produced greater activity for N1 sink and P2 source, and standards yeiled the lowest scores on these two factors. The temporal N1 factor was relatively invariable across conditions.

Figure 6: Comparison of Equiprobable MMN and Standard LDAEP Trials. A qualitative comparison of N1/P2 CSD factor score topographies between a previously analyzed standard LDAEP paradigm (Tenke, Kayser, Gates, et al., 2009) and the current

equiprobable block across the same subjects showed that the paradigms produce similar spatiotemporal factors (panel A). However, factor score means (panel B) were much lower for the equiprobable MMN condition compared to the standard LDAEP trials.

Figure 7: N1 Sink Topographies and Mean Amplitudes of Standard and Deviant CSDs as a Function of Intensity. A) Factor score topographies show a similar spatial pattern of activation across standard and deviant conditions, but greater amplitude for louder deviant conditions. B) Mean amplitudes (SE) for N1 sink plotted at each level of intensity reveal that amplitude is significantly greater deviants at 90 and 100 dB, but comparable at 70 and 80 dB. An asymptotic amplitude-intensity function can be seen for standards at intensities above 80 dB, while significant increases occur for deviants from 80 to 90 dB, and 90 to 100 dB.

Figure 8: Temporal N1 Sink Topographies and Mean Amplitudes of Standard and Deviant CSDs as a Function of Intensity. A) Factor score topographies show a similar pattern of activation for standard and deviant conditions. B) Mean amplitude (SE) plotted at each level of intensity reveal relatively little change across standard intensities, while significant reductions in amplitude are observed for softer (70 and 80 dB) deviant intensities.

Figure 9: P2 Source Topographies and Mean Amplitudes of Standard and Deviant CSDs as a Function of Intensity. A) Factor score topographies show a consistent spatial pattern of activation for standards and deviants that is more pronounced in louder deviant

intensities compared to standards. B) Mean amplitudes (SE) for the bilateral, frontotemporal aspects of this factor reveal a relationship to intensity similar to that observed in N1 sink. Deviant intensities produce significantly greater amplitudes for louder tones, whereas, no differences between conditions are seen for softer intensities. C) Mean amplitudes (SE) for the corresponding vertex source reveal a significant increase in amplitude for the loudest (100 dB) condition.

Figure 10. Deviant-minus-Standard Difference CSD Waveforms. Grand-mean CSD difference waveforms show differential activity most noticably seen at a) bilateral central (e.g., C3/4, C5/6) and frontocentral (e.g., FC3/4, AFz) sites with inversions in polarity at lateral temporoparietal sites (TP9/10) peaking at approximately 130 ms, and b) at the vertex peaking at approximatly 230 ms

Figure 11. Deviant-minus-Standard Difference CSD-PCA Factor Loadings and Scores. Time courses of the extracted CSD-PCA factor loadings (panel A) and corresponding factor score topograhies (panel B) for the first three factors (72% explained variance after Varimax rotation). Factors of interest included: 1) MMN sink (136 ms; 14% explianed variance) characterized by tangential bilateral-central sinks (eg., C3/4) with corresponding bilataral temporoparietal sources (e.g., TP9/10); 2) P3a-like Vertex Source (234 ms; 8% explained variance). Both factor score topographies were consistent with well-known MMN and P3a topographies and previously published intensity MMN findings.

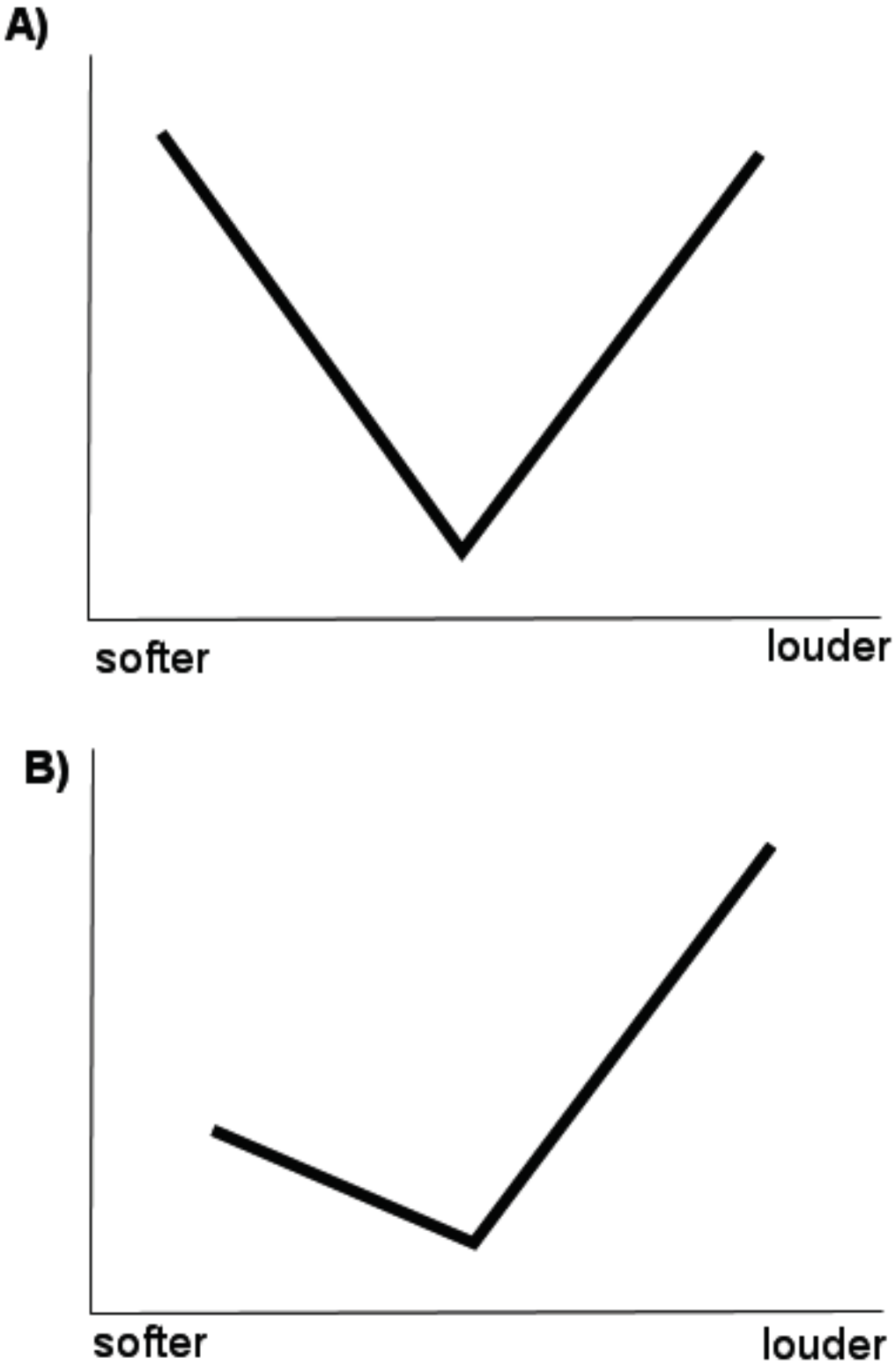
Figure 12. MMN Sink (136 ms) CSD Factor Score Topographies and Means. A) Factor score topographies are shown at three levels of disparity (10, 20, and 30 dB) for deviant increments and decrements. Increases in MMN sink can be observed at each successive level of disparity, but markedly greater in louder deviants. B) Means (SE) for the Disparity X Direction interaction reveal a significantly greater increase in MMN sink for increments than decrements at each level of disparity.

Figure 13. P3a Vertex Source (234 ms) CSD Factor Score Topographies and Means. A) Factor score topographies and shown at three levels of disparity (10, 20, and 30 dB) for deviant increments and decrements. Increases in P3a vertex source activity are observed at each incremental step in deviant disparity, while no activity is observed across decrements. B) Means (SE) for the Disparity X Direction interaction reveal a significant increase in activity at each level of disparity for loud deviants, whereas no change is observed at any level of disparity for softer deviants.

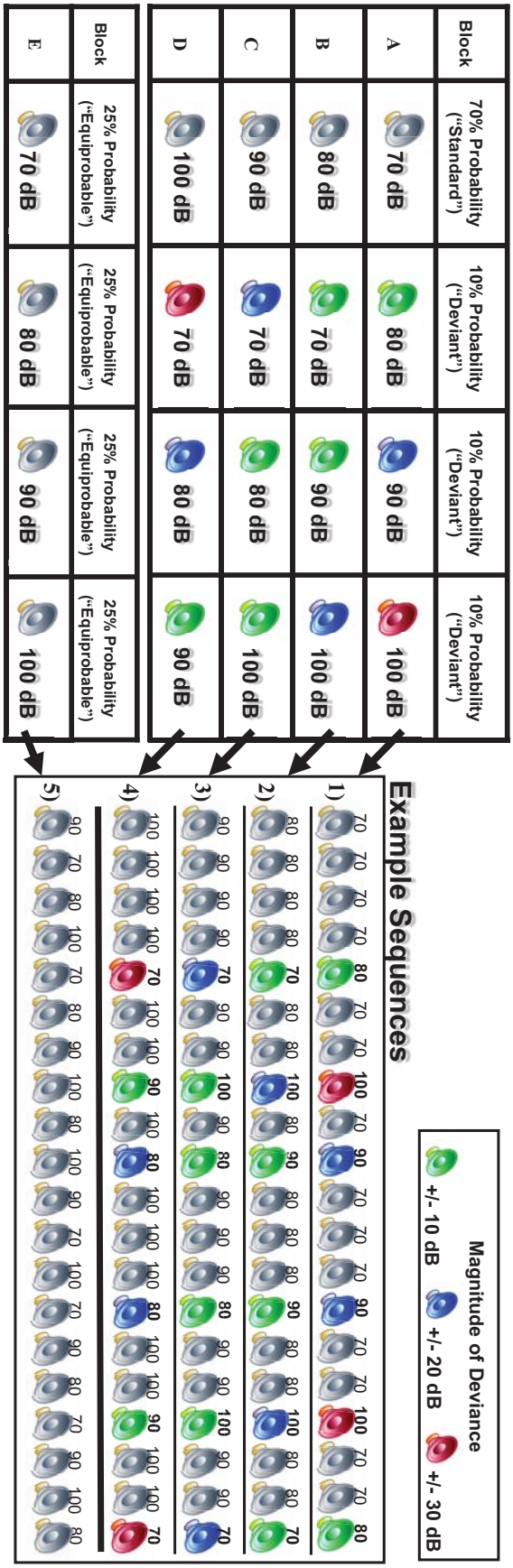
Figure 14. N1 & MMN Factor Scores Topography Correlations. A) N1 sink and MMN sink topographies for each level of Disparity and Direction show postive correlations across most sites, suggesting that these factors share highly comparable regions of activation. B) Mean normalized (Fisher's Z) correlation coefficients of complete topographies for soft and loud disparities show greater comparability at greater levels of disparity; however, louder disparities show the largest correspondance between factor scores.

Figure 15. P3a Vertex Source: Difference CSD Factor Score Topographies at Each Level of Intensity and Disparity. P3a vertex source activity is plotted at each intensity (70, 80, 90, 100 dB) by eachlevel of disparity (-30 to +30). Note that the P3a vertex source is only active in the 100 dB condition and virtually nonexistant in all other cells.

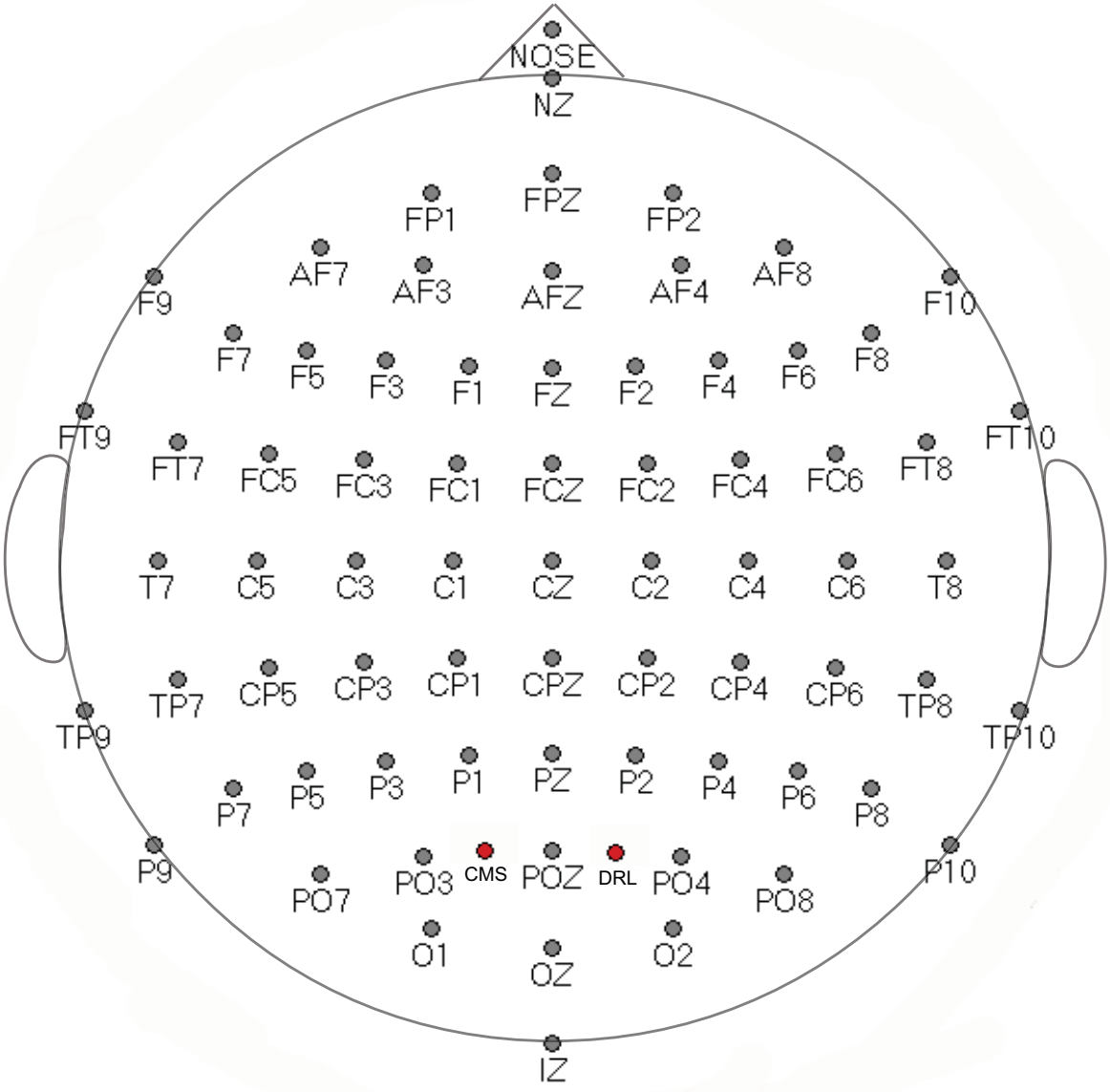
**Figure 1. Theoretical Disparity X Direction MMN Effects**



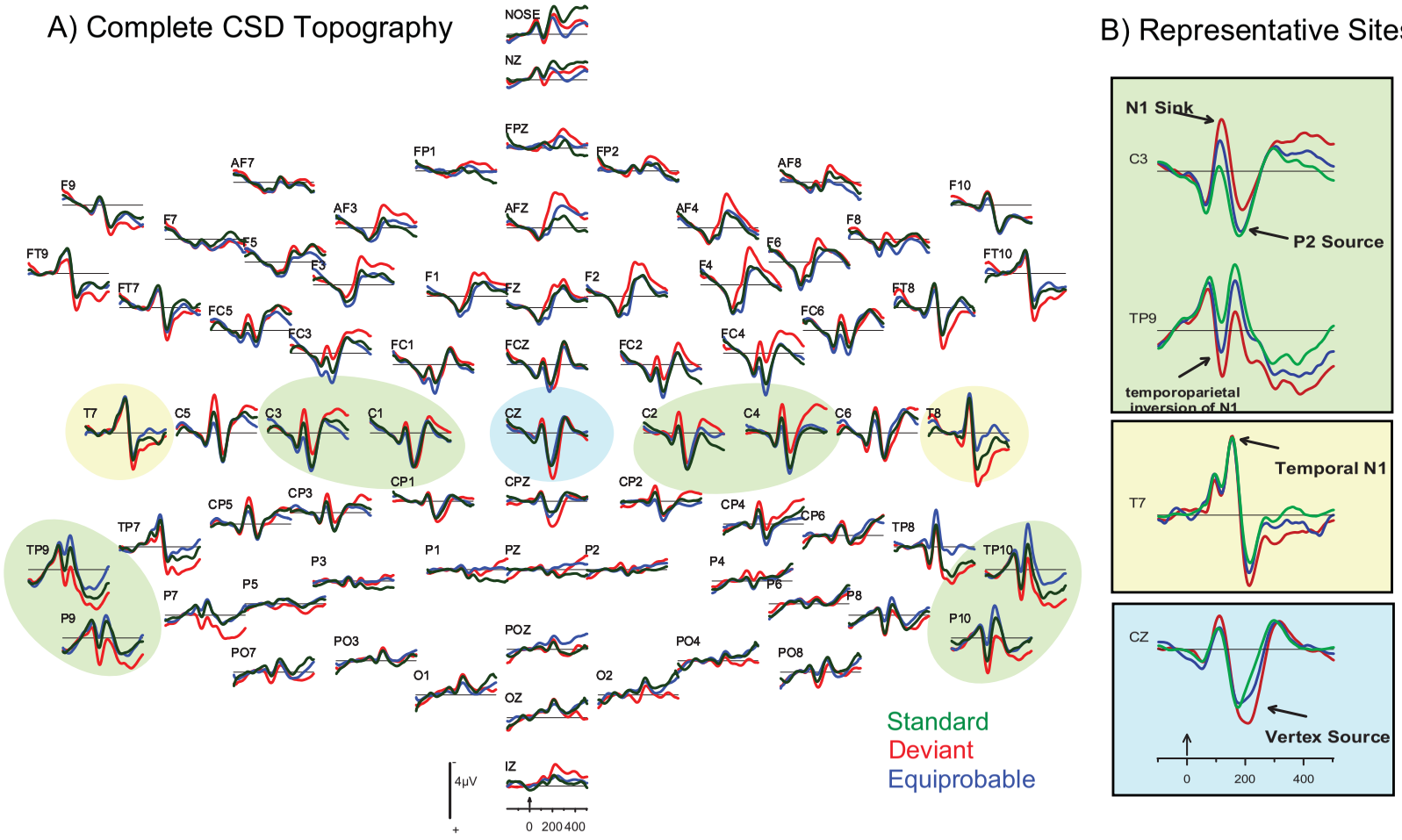
# Figure 2: Intensity MMN Design



## Figure 3: 72-Channel EEG Montage

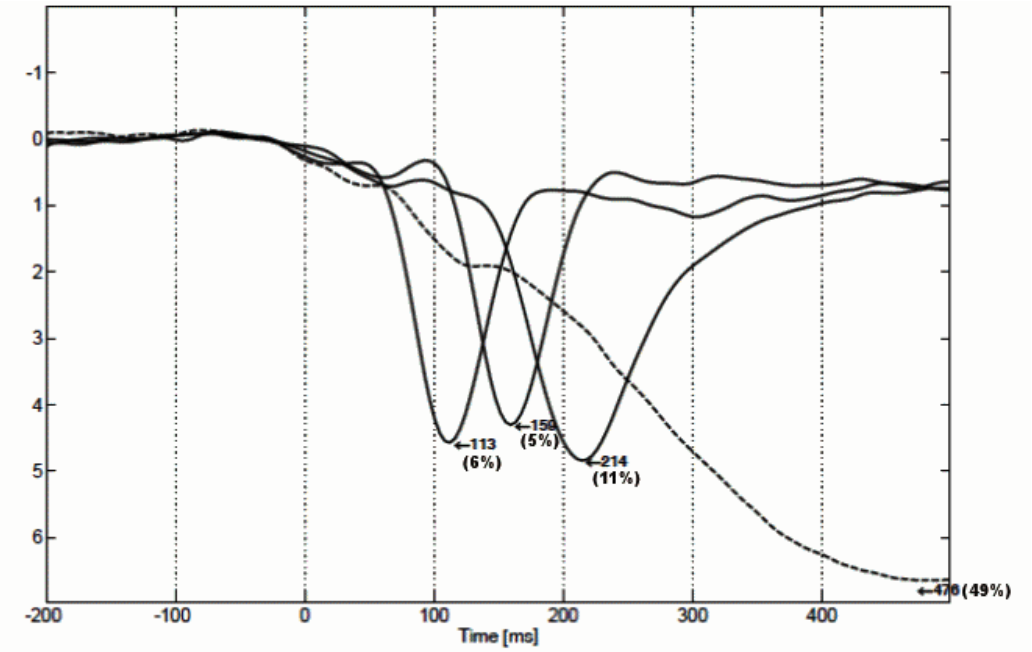


# Figure 4: CSD Waveforms for MMN Conditions and Equiprobable Trials

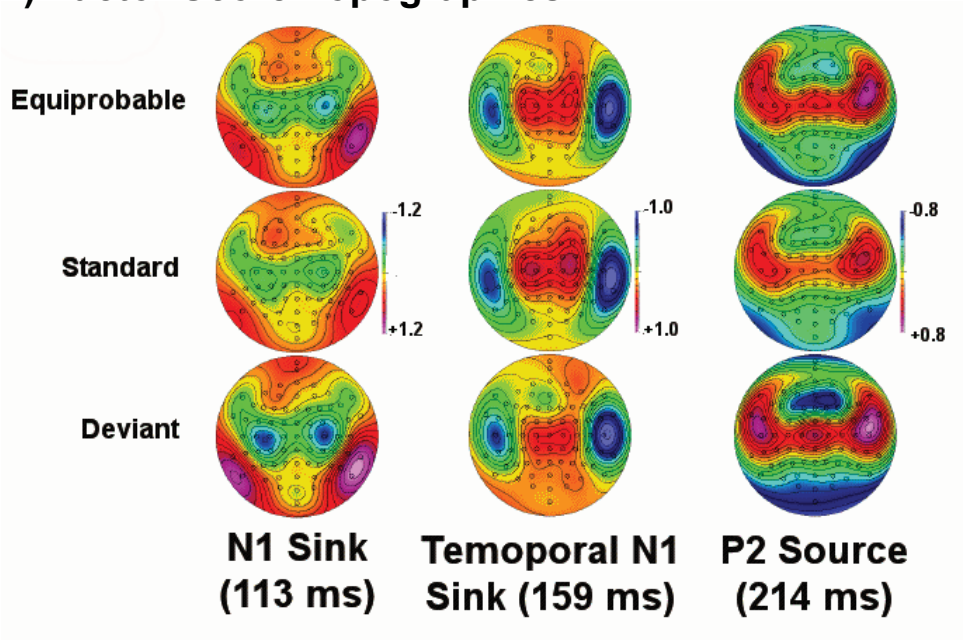


## Figure 5: PCA Factor Loadings & Factor Score Topographies for Standard, Deviant, and Equiprobable Trials

### A) Factor Loadings




### B) Factor Score Topographies



# Figure 6: Comparison of Equiprobable MMN and Standard LDAEP Trials

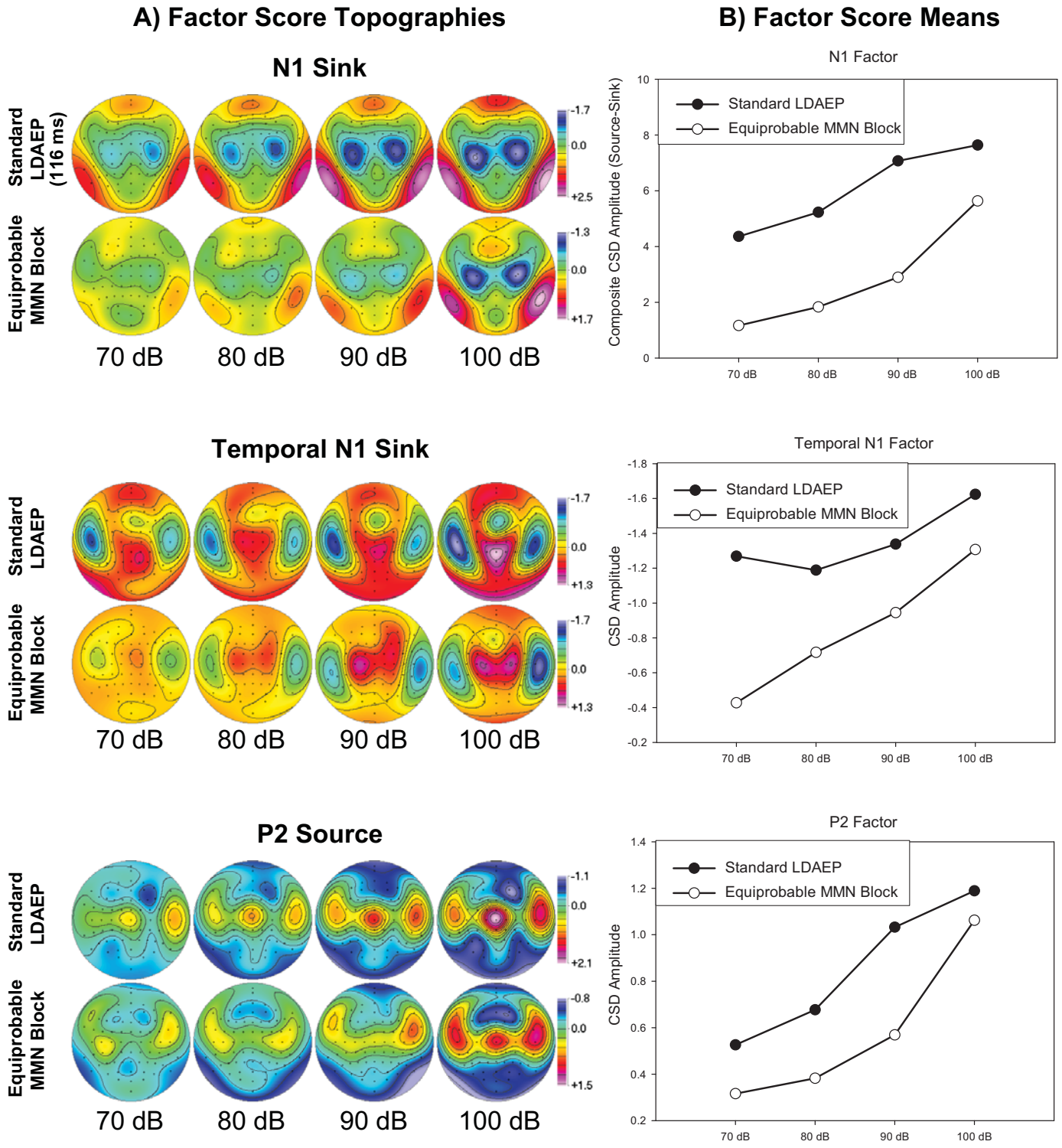


**Figure 7: N1 Sink Topographies and Mean Amplitudes of Standard and Deviant CSDs as a Function of Intensity**

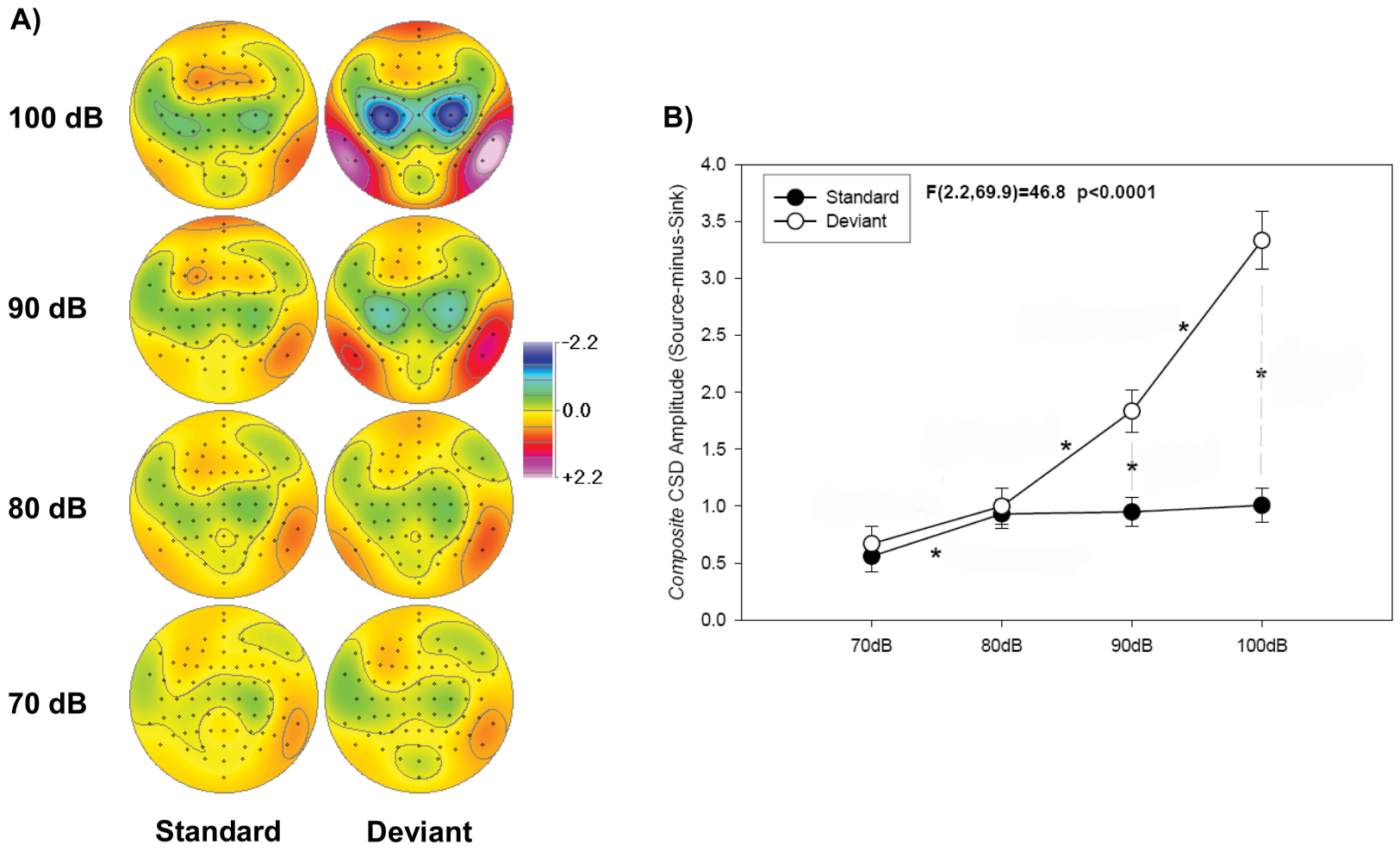
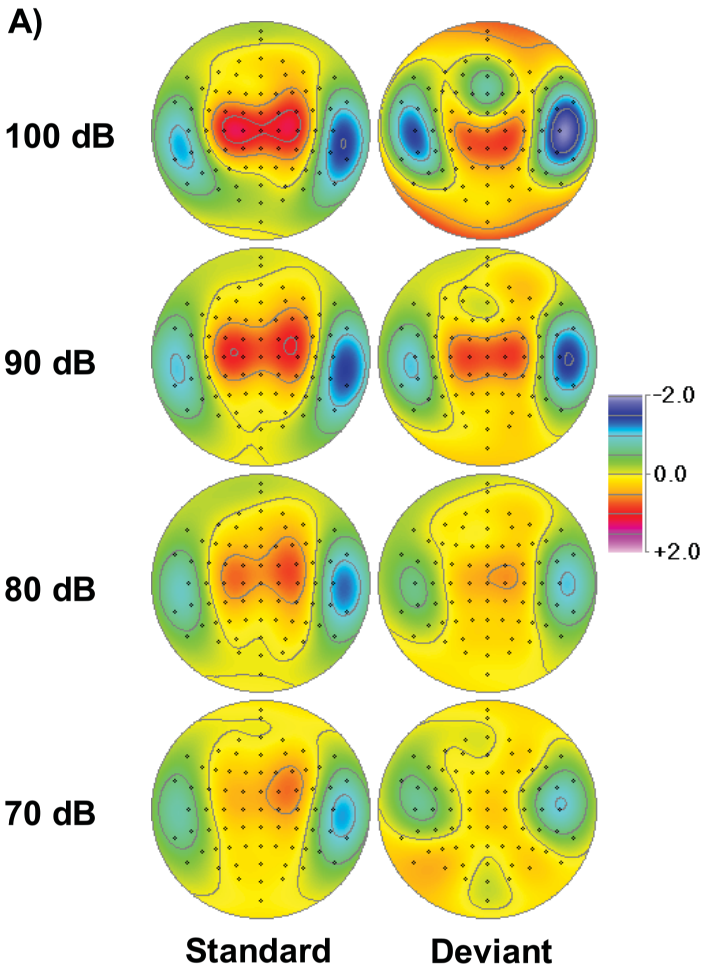


**Figure 8: Temporal N1 Sink Topographies and Mean Amplitudes of Standard and Deviant CSDs as a Function of Intensity**



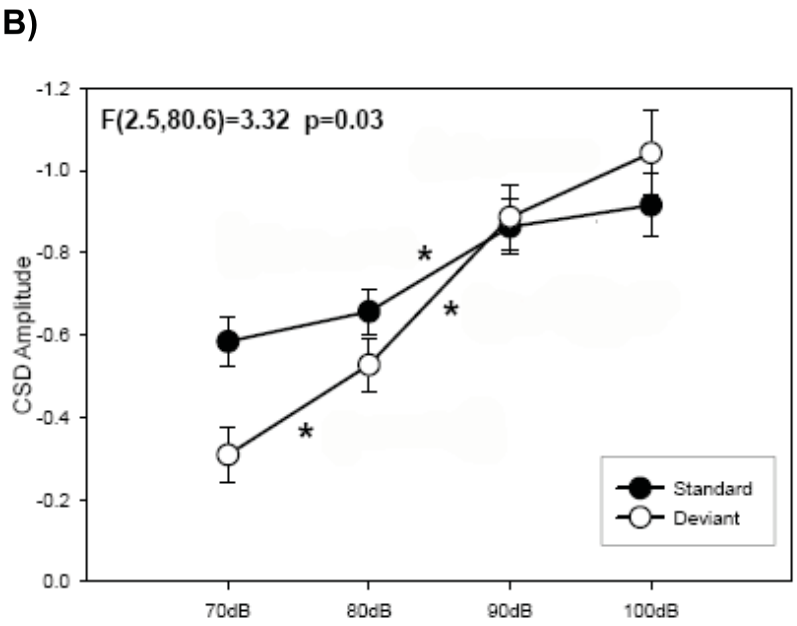
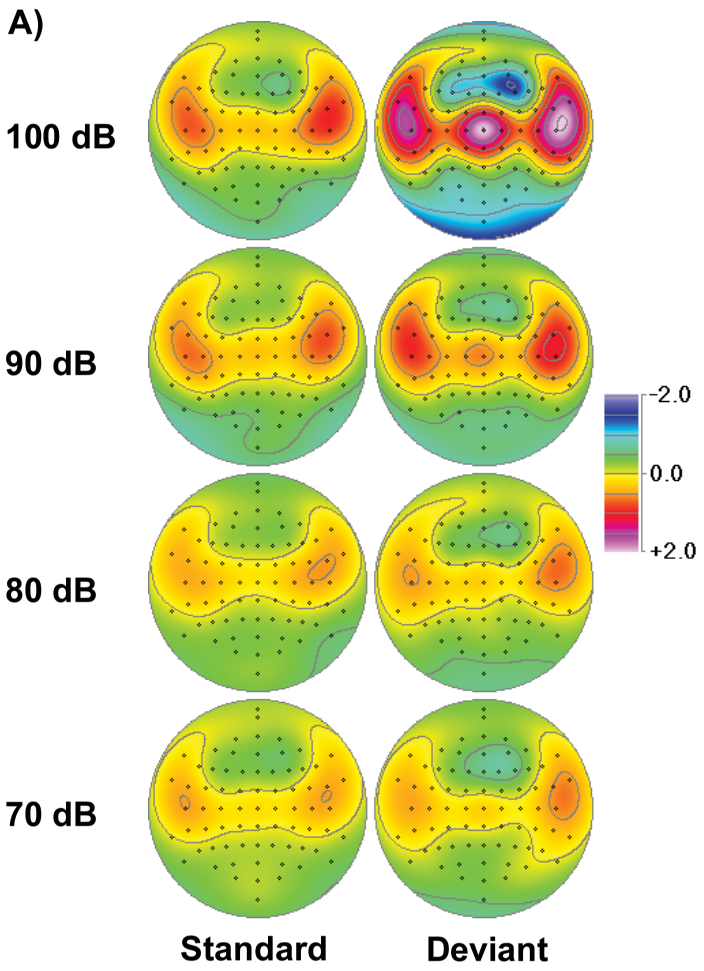
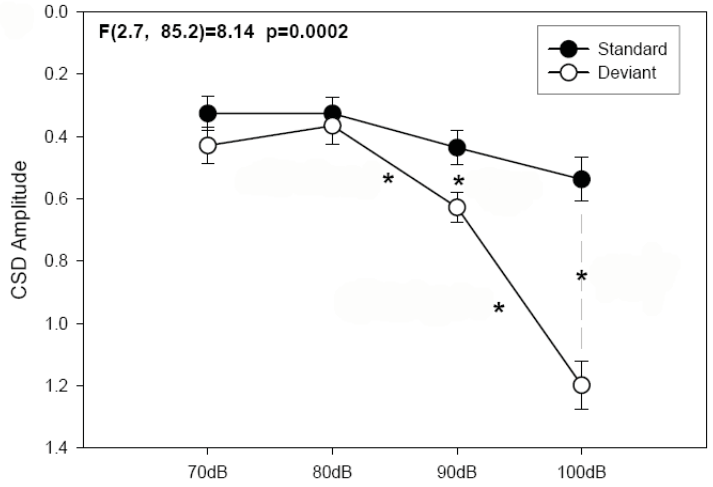



**Figure 9: P2 Source Topographies and Mean (SE) Amplitudes of Standard and Deviant CSDs as a Function of Intensity**



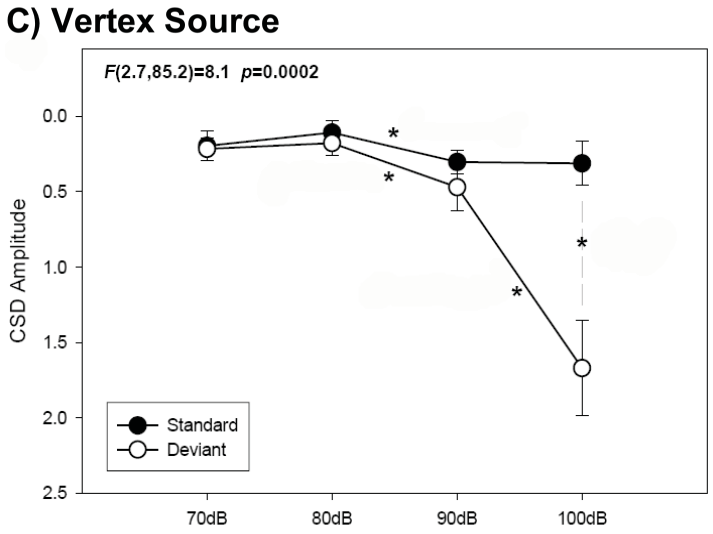
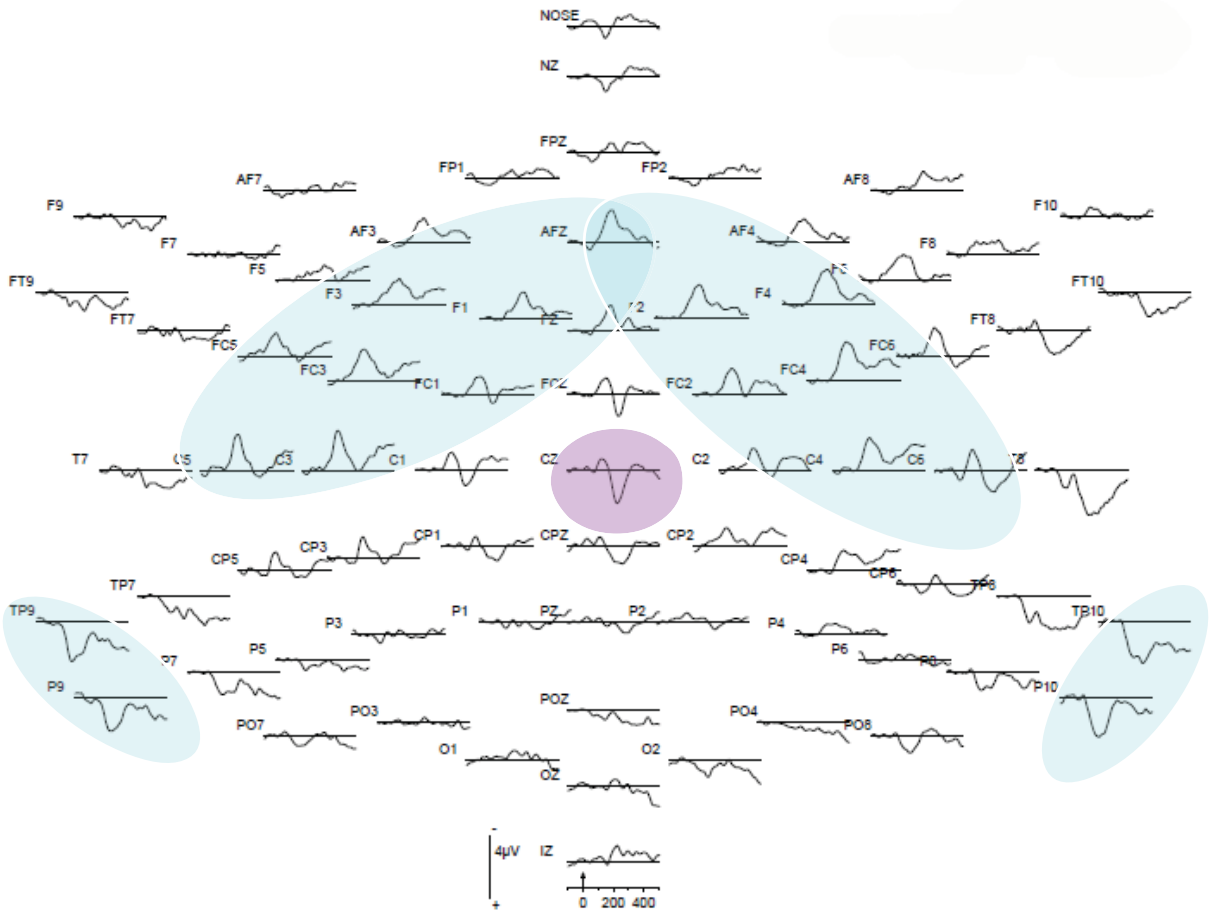
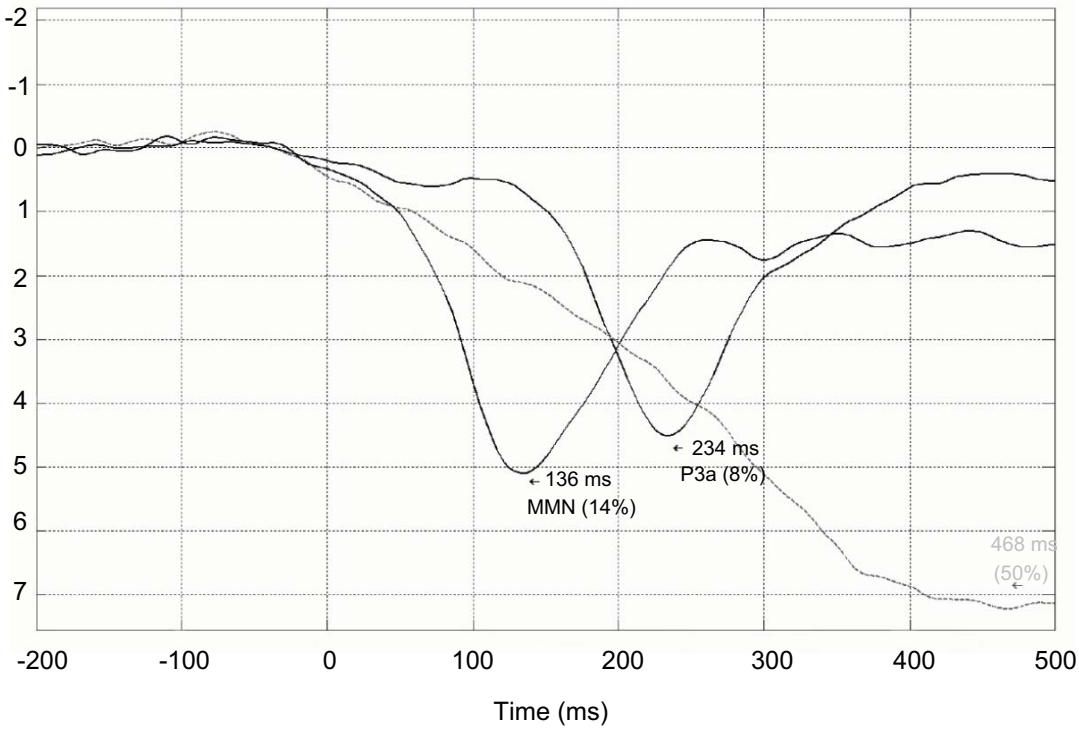



Figure 10. Deviant-minus-Standard Difference CSD Waveforms

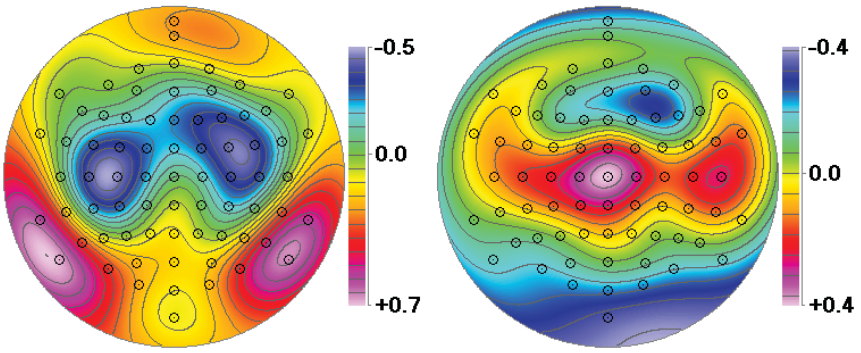


## Figure 11. Deviant-minus-Standard Difference CSD-PCA Factor Loadings & Scores

### A) Factor Loadings



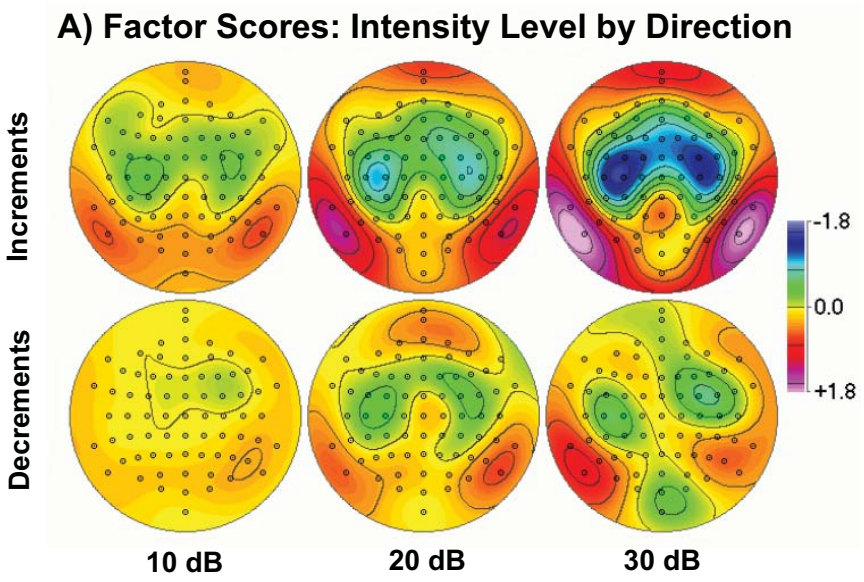

### B) Factor Scores

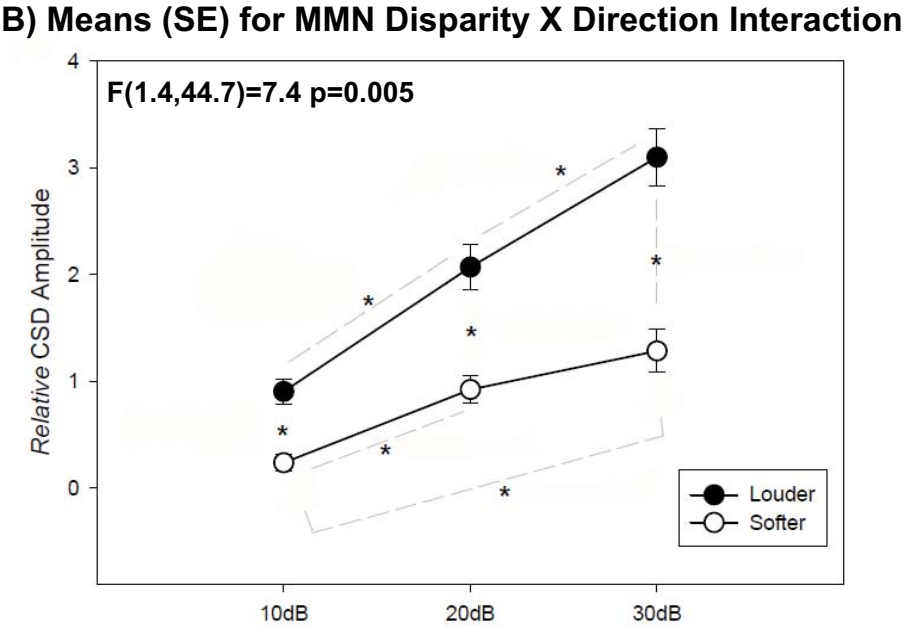



MMN Sink (136 ms)

P3a Source (234 ms)

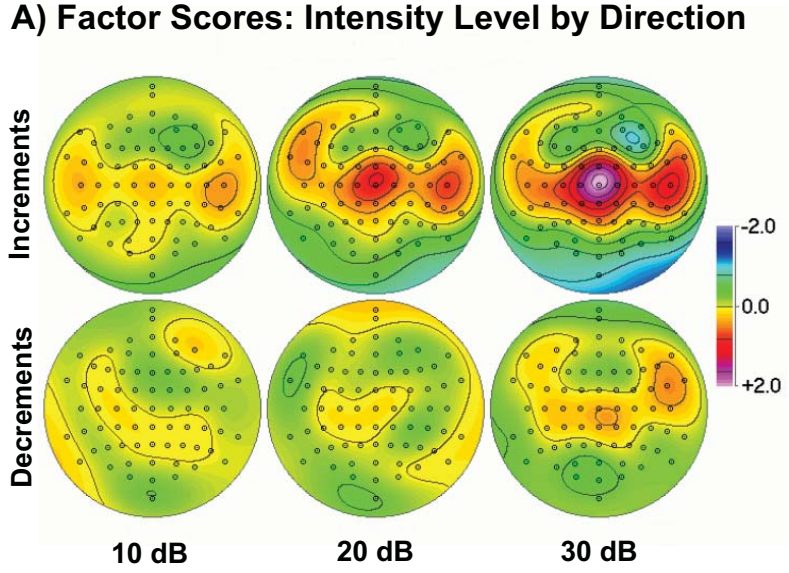
## Figure 12. MMN Sink (136 ms) CSD Factor Score Topographies & Means



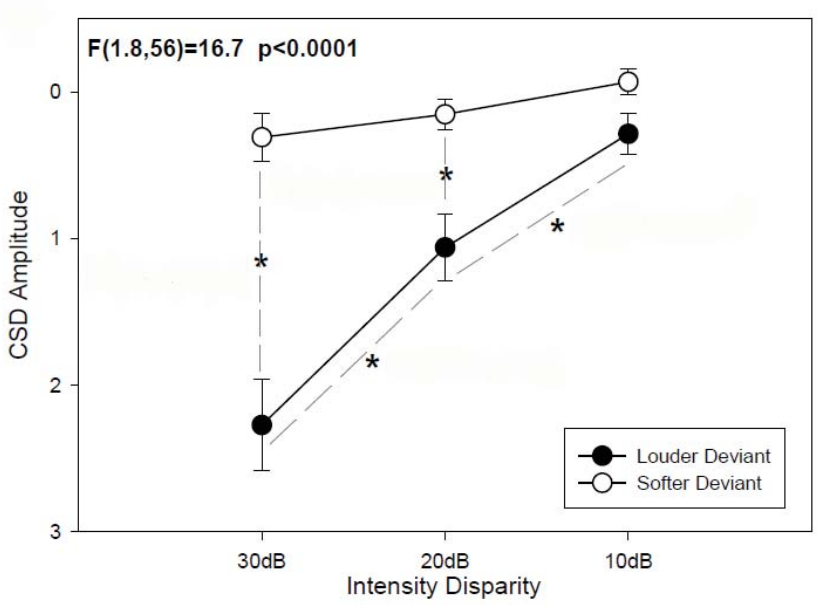



## Figure 13. P3a Vertex Source (234 ms) CSD Factor Score Topographies & Means

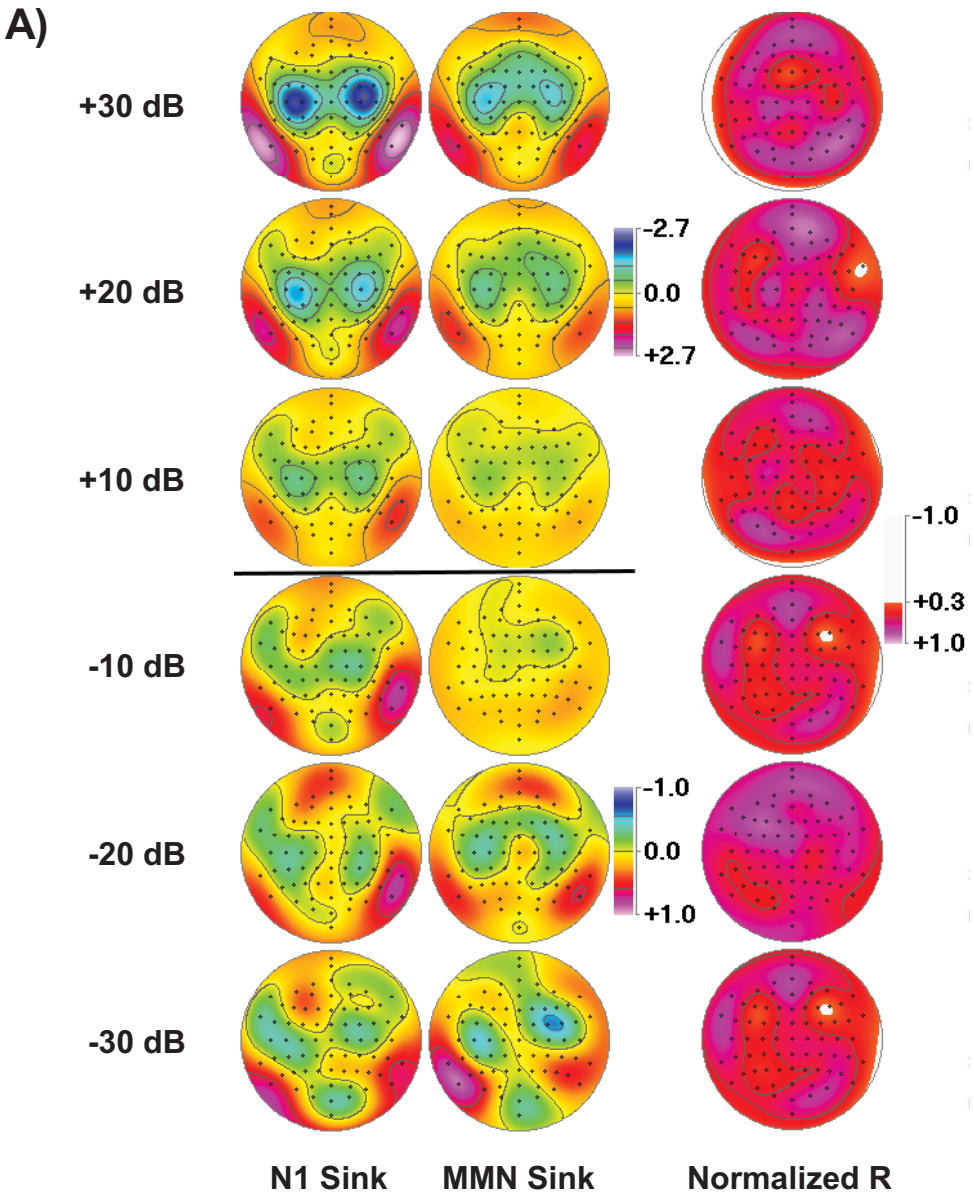
### A) Factor Scores: Intensity Level by Direction

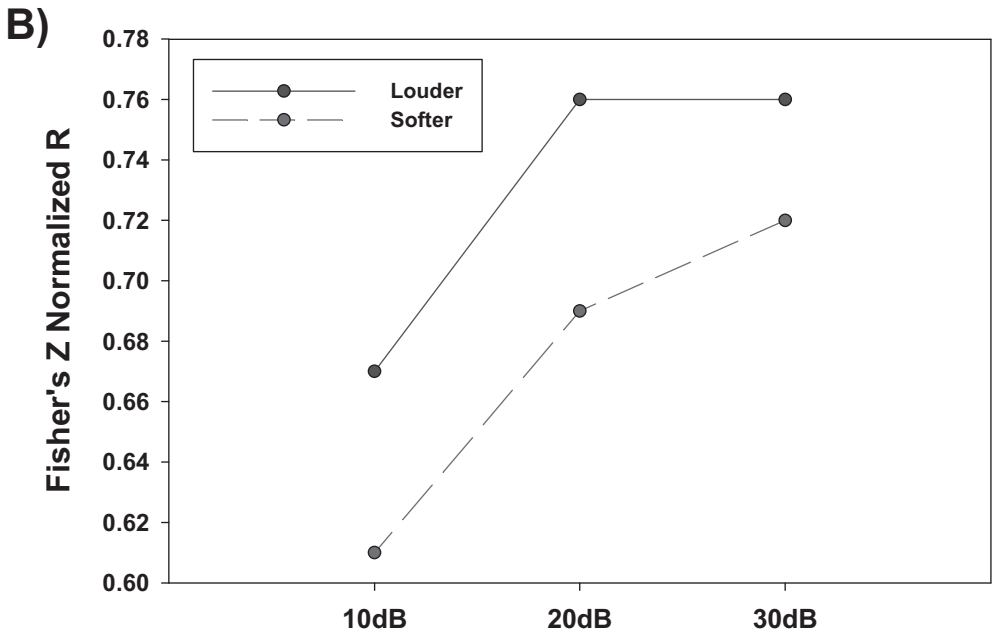



### B) Means (SE) for P3a Disparity X Direction Interaction



# Figure 14. N1 X MMN Factor Score Topography Correlations



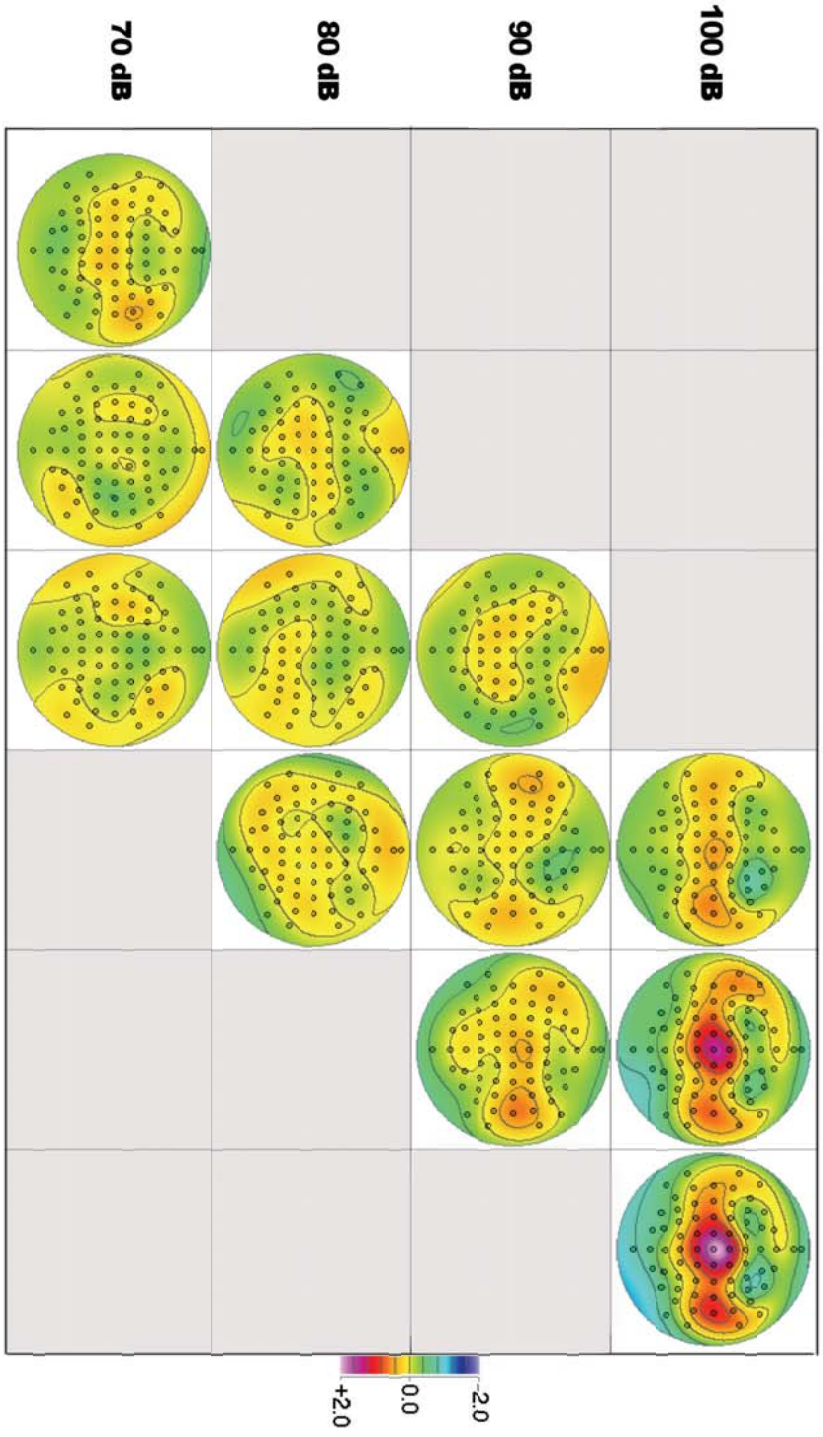


Figure 15. P3a Vertex Source
Difference CSD Factor Score Topographies at each Level of Intensity X Disparity
100 dB
90 dB
80 dB
70 dB
-30 dB
-20 dB
-10 dB
+10 dB
+20 dB
+30 dB
-2.0
0.0
+2.0

## C. SCHEDULE AND DESCRIPTION OF EEG OF TASKS PRECEDING THE MISMATCH NEGATIVITY TASK

*Resting EEG.* Resting EEG will be recorded during four 2-minute periods, half with eyes-closed (C) and half eyes-open (O) in a counterbalanced order (COOC or OCCO). During the eyes-open condition, the subject fixates on a central fixation mark and tries to avoid blinking. During the eyes-closed condition, subjects are instructed to avoid eye movements.

*Intensity Modulation/LDEAP.* The auditory ERP intensity-modulation paradigm requires subjects to sit quietly with their eyes opened and fixed on a cross while tones (1000 Hz, 40 ms duration with 10 ms rise and decay time) are presented at varying levels of intensity. Binaural tones are presented in a pseudorandomized order at five intensities (60, 70, 80, 90, 100 dB SPL) with interstimulus intervals ranging from 1600 – 2100 ms. Each stimulus intensity is repeated 100 times (i.e., 5 stimulus intensities = 500 trials).

*Novelty Oddball.* For each subject, 8 blocks of 50 trials consisting of two 300 ms tones are presented in pseudorandom order (stimulus onset asynchrony = 1000 ms). One nontarget tone of 350 Hz is presented to the subject frequently (p = .76) while the other is an infrequent 500 Hz target tone (p = .12). Novel sounds (e.g., animal sounds, musical instruments, environmental sounds) possessing durations of 100-400 ms are infrequently (p = .12) intermixed with the frequent tones and infrequent target tones. All stimuli are presented binaurally over headphones at 75 dB SPL. Subjects will be instructed to focus their eyes on a fixation cross displayed on a computer monitor and to respond with a button press as quickly as possible when, and only when, they hear the infrequent target tones.

## D. 72-CHANNEL SPHERICAL COORDINATES

| Channel | Theta | Phi | Radius | Cart. X | Cart. Y | Cart. Z |
|---|---|---|---|---|---|---|
| Nose | 90.00 | -33.75 | 1.00 | 0.00 | 0.83 | -0.56 |
| Nz | 90.00 | -22.50 | 1.00 | 0.00 | 0.92 | -0.38 |
| Fpz | 90.00 | 0.00 | 1.00 | 0.00 | 1.00 | 0.00 |
| AFz | 90.00 | 22.50 | 1.00 | 0.00 | 0.92 | 0.38 |
| Fz | 90.00 | 45.00 | 1.00 | 0.00 | 0.71 | 0.71 |
| FCz | 90.00 | 67.50 | 1.00 | 0.00 | 0.38 | 0.92 |
| Cz | 0.00 | 90.00 | 1.00 | 0.00 | 0.00 | 1.00 |
| CPz | -90.00 | 67.50 | 1.00 | 0.00 | -0.38 | 0.92 |
| Pz | -90.00 | 45.00 | 1.00 | 0.00 | -0.71 | 0.71 |
| POz | -90.00 | 22.50 | 1.00 | 0.00 | -0.92 | 0.38 |
| Oz | -90.00 | 0.00 | 1.00 | 0.00 | -1.00 | 0.00 |
| Iz | -90.00 | -22.50 | 1.00 | 0.00 | -0.92 | -0.38 |
| F9 | 144.00 | -22.50 | 1.00 | -0.75 | 0.54 | -0.38 |
| FT9 | 162.00 | -22.50 | 1.00 | -0.88 | 0.29 | -0.38 |
| TP9 | -162.00 | -22.50 | 1.00 | -0.88 | -0.29 | -0.38 |
| P9 | -144.00 | -22.50 | 1.00 | -0.75 | -0.54 | -0.38 |
| Fp1 | 108.00 | 0.00 | 1.00 | -0.31 | 0.95 | 0.00 |
| AF7 | 126.00 | 0.00 | 1.00 | -0.59 | 0.81 | 0.00 |
| F7 | 144.00 | 0.00 | 1.00 | -0.81 | 0.59 | 0.00 |
| FT7 | 162.00 | 0.00 | 1.00 | -0.95 | 0.31 | 0.00 |
| T7 | 180.00 | 0.00 | 1.00 | -1.00 | 0.00 | 0.00 |
| TP7 | -162.00 | 0.00 | 1.00 | -0.95 | -0.31 | 0.00 |
| P7 | -144.00 | 0.00 | 1.00 | -0.81 | -0.59 | 0.00 |
| PO7 | -126.00 | 0.00 | 1.00 | -0.59 | -0.81 | 0.00 |
| O1 | -108.00 | 0.00 | 1.00 | -0.31 | -0.95 | 0.00 |
| F10 | 36.00 | -22.50 | 1.00 | 0.75 | 0.54 | -0.38 |
| FT10 | 18.00 | -22.50 | 1.00 | 0.88 | 0.29 | -0.38 |
| TP10 | -18.00 | -22.50 | 1.00 | 0.88 | -0.29 | -0.38 |
| P10 | -36.00 | -22.50 | 1.00 | 0.75 | -0.54 | -0.38 |
| Fp2 | 72.00 | 0.00 | 1.00 | 0.31 | 0.95 | 0.00 |
| AF8 | 54.00 | 0.00 | 1.00 | 0.59 | 0.81 | 0.00 |
| F8 | 36.00 | 0.00 | 1.00 | 0.81 | 0.59 | 0.00 |
| FT8 | 18.00 | 0.00 | 1.00 | 0.95 | 0.31 | 0.00 |
| T8 | 0.00 | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 |
| TP8 | -18.00 | 0.00 | 1.00 | 0.95 | -0.31 | 0.00 |
| P8 | -36.00 | 0.00 | 1.00 | 0.81 | -0.59 | 0.00 |
| PO8 | -54.00 | 0.00 | 1.00 | 0.59 | -0.81 | 0.00 |
| O2 | -72.00 | 0.00 | 1.00 | 0.31 | -0.95 | 0.00 |
| C5 | 180.00 | 22.50 | 1.00 | -0.92 | 0.00 | 0.38 |
| C3 | 180.00 | 45.00 | 1.00 | -0.71 | 0.00 | 0.71 |
| C1 | 180.00 | 67.50 | 1.00 | -0.38 | 0.00 | 0.92 |

| | | | | | | |
|---|---|---|---|---|---|---|
| C6 | 0.00 | 22.50 | 1.00 | 0.92 | 0.00 | 0.38 |
| C4 | 0.00 | 45.00 | 1.00 | 0.71 | 0.00 | 0.71 |
| C2 | 0.00 | 67.50 | 1.00 | 0.38 | 0.00 | 0.92 |
| F3 | 129.25 | 29.83 | 1.00 | -0.55 | 0.67 | 0.50 |
| F4 | 50.75 | 29.83 | 1.00 | 0.55 | 0.67 | 0.50 |
| P3 | -129.25 | 29.83 | 1.00 | -0.55 | -0.67 | 0.50 |
| P4 | -50.75 | 29.83 | 1.00 | 0.55 | -0.67 | 0.50 |
| F5 | 138.89 | 15.62 | 1.00 | -0.73 | 0.63 | 0.27 |
| F6 | 41.11 | 15.62 | 1.00 | 0.73 | 0.63 | 0.27 |
| P5 | -138.89 | 15.62 | 1.00 | -0.73 | -0.63 | 0.27 |
| P6 | -41.11 | 15.62 | 1.00 | 0.73 | -0.63 | 0.27 |
| F1 | 112.95 | 40.72 | 1.00 | -0.30 | 0.70 | 0.65 |
| F2 | 67.05 | 40.72 | 1.00 | 0.30 | 0.70 | 0.65 |
| P1 | -112.95 | 40.72 | 1.00 | -0.30 | -0.70 | 0.65 |
| P2 | -67.05 | 40.72 | 1.00 | 0.30 | -0.70 | 0.65 |
| FC3 | 151.48 | 40.85 | 1.00 | -0.66 | 0.36 | 0.65 |
| FC4 | 28.52 | 40.85 | 1.00 | 0.66 | 0.36 | 0.65 |
| CP3 | -151.48 | 40.85 | 1.00 | -0.66 | -0.36 | 0.65 |
| CP4 | -28.52 | 40.85 | 1.00 | 0.66 | -0.36 | 0.65 |
| FC5 | 158.85 | 20.77 | 1.00 | -0.87 | 0.34 | 0.35 |
| FC6 | 21.15 | 20.77 | 1.00 | 0.87 | 0.34 | 0.35 |
| CP5 | -158.85 | 20.77 | 1.00 | -0.87 | -0.34 | 0.35 |
| CP6 | -21.15 | 20.77 | 1.00 | 0.87 | -0.34 | 0.35 |
| FC1 | 133.59 | 58.63 | 1.00 | -0.36 | 0.38 | 0.85 |
| FC2 | 46.41 | 58.63 | 1.00 | 0.36 | 0.38 | 0.85 |
| CP1 | -133.59 | 58.63 | 1.00 | -0.36 | -0.38 | 0.85 |
| CP2 | -46.41 | 58.63 | 1.00 | 0.36 | -0.38 | 0.85 |
| AF3 | 113.31 | 15.04 | 1.00 | -0.38 | 0.89 | 0.26 |
| AF4 | 66.69 | 15.04 | 1.00 | 0.38 | 0.89 | 0.26 |
| PO3 | -113.31 | 15.04 | 1.00 | -0.38 | -0.89 | 0.26 |
| PO4 | -66.69 | 15.04 | 1.00 | 0.38 | -0.89 | 0.26 |
| *LE* | *126.00* | *-22.50* | *1.00* | *-0.54* | *0.75* | *-0.38* |
| *RE* | *54.00* | *-22.50* | *1.00* | *0.54* | *0.75* | *-0.38* |
| *TE* | *90.00* | *-5.00* | *1.00* | *0.00* | *1.00* | *-0.09* |
| *BE* | *90.00* | *-40.00* | *1.00* | *0.00* | *0.77* | *-0.64* |
| *TE1* | *108.00* | *-11.25* | *1.00* | *-0.30* | *0.93* | *-0.20* |
| *BE1* | *108.00* | *-33.75* | *1.00* | *-0.26* | *0.79* | *-0.56* |
| *TE2* | *72.00* | *-11.25* | *1.00* | *0.30* | *0.93* | *-0.20* |
| *BE2* | *72.00* | *-33.75* | *1.00* | *0.26* | *0.79* | *-0.56* |
| *LE1* | *135.00* | *-22.50* | *1.00* | *-0.65* | *0.65* | *-0.38* |
| *RE1* | *45.00* | *-22.50* | *1.00* | *0.65* | *0.65* | *-0.38* |
| *TE3* | *72.00* | *-5.00* | *1.00* | *0.31* | *0.95* | *-0.09* |
| *BE3* | *72.00* | *-40.00* | *1.00* | *0.24* | *0.73* | *-0.64* |

*------ Virtual Eye Channels ------*

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