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# The Neural Networks Underlying Auditory Sensory Gating

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# Abstract

One of the most consistent electrophysiological deficits reported in the schizophrenia literature is a failure to inhibit, or properly gate, the neuronal response to the second stimulus of an identical pair (i.e., sensory gating). Although animal and invasive human studies have consistently implicated the auditory cortex, prefrontal cortex and hippocampus in mediating the sensory gating response, localized activation in these structures has not always been reported during non-invasive imaging modalities. In the current experiment, event-related FMRI and a variant of the traditional gating paradigm were utilized to examine how the gating network differentially responded to the processing of pairs of identical and non-identical tones. Two single-tone conditions were also presented so that they could be used to estimate the HRF for paired stimuli, reconstructed based on actual hemodynamic responses, to serve as a control non-gating condition. Results supported an emerging theory that the gating response for both paired-tones conditions was primarily mediated by auditory and prefrontal cortex, with potential contributions from the thalamus. Results also indicated that the left auditory cortex may play a preferential role in determining the stimuli that should be inhibited (gated) or receive further processing due to novelty of information. In contrast, there was no evidence of hippocampal involvement, suggesting that future work is needed to determine what role it may play in the gating response.

## Keywords

FMRI; sensory gating; auditory cortex; hippocampus

# INTRODUCTION

The ability to filter out irrelevant stimuli that are repeated in close temporal proximity is essential for the selection, processing, and storage of more salient information (Alho, 1992;

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Cadenhead et al., 2000; Cullum et al., 1993). Sensory gating, as measured by the paired-click paradigm, has been commonly used to measure these basic inhibitory processes in several clinical populations, including schizophrenia (Adler et al., 1982; Adler and Waldo, 1991; Boutros et al., 2004; Bramon et al., 2004; Hanlon et al., 2005; Huang et al., 2003; Thoma et al., 2003). Three recent meta-analyses suggest that the gating deficit is present in the majority of studies comparing schizophrenia patients with normal controls (de Wilde et al., 2007; Patterson et al., 2008) and others have suggested that the deficit may be an endophenotypical marker (Adler et al., 1999; Freedman et al., 2003). However, there is considerable heterogeneity in the magnitude of the effect across different studies and substantial debate remains regarding the underlying neuronal substrates. Specifically, both animal and invasive human neuroimaging techniques (Boutros et al., 2005; Freedman et al., 1996; Grunwald et al., 2003; Korzyukov et al., 2007) suggest that sensory gating is mediated by a network including the auditory cortex (AC), prefrontal cortex and hippocampus. In contrast, the majority of results from non-invasive electrophysiological studies have not implicated the prefrontal cortex and/ or hippocampus in gating.

In the standard paired-click paradigm (Adler et al., 1982), a gating ratio is derived from the proportion of the electrophysiological responses to the first (S1) and second (S2) of the paired stimuli (S2/S1\*100), which are typically separated by an inter-stimulus interval (ISI) of 500 ms. Although the superb temporal resolution of electrophysiological techniques permits for the disambiguation of S1 and S2 responses, these techniques are somewhat limited by their spatial resolution, such as their ability to image deep sources, radially oriented sources, or simultaneously occurring sources (Huang et al., 2003; Huotilainen et al., 1998; Korzyukov et al., 2007). Moreover, non-invasive electrophysiological studies have focused almost exclusively on earlier components of the gating response (EEG: P50 and N100; MEG: M50 and M100) instead of longer latencies (200–300 ms) where hippocampal involvement has been recorded with more invasive techniques (Boutros et al., 2005; Grunwald et al., 2003). Neuroimaging techniques with higher spatial resolution and the ability to independently evaluate activation on a voxel-wise basis, such as functional magnetic resonance imaging (FMRI), should therefore provide additional critical information on the role of the prefrontal cortex and hippocampus in sensory gating.

Numerous FMRI studies (Friston et al., 1998; Glover, 1999; Huettel and McCarthy, 2000; Inan et al., 2004) have demonstrated a non-linearity in the summation of the hemodynamic response function (HRF) for stimuli that occur in close temporal proximity (i.e., ISIs of less than 4 seconds). However, none have directly examined sensory gating using similar parameters commonly employed in the electrophysiological literature (i.e., two stimuli; 3–5 ms stimulus duration, 500 ms ISI; 7–10 s inter-trial interval (ITI)). One study compared two identical 1000 Hz tones (100 ms duration) separated by one, four or six second ISIs and reported both a reduced amplitude and delayed onset for the second stimulus at all ISIs (Inan et al., 2004). A more recent FMRI study attempted to compensate for the temporal sluggishness of the hemodynamic response by utilizing a click-train paradigm in which 9 clicks were presented over a 4 second interval (Tregellas et al., 2007). This study found increased dorsolateral prefrontal cortex, thalamic and hippocampal gating activity in patients with schizophrenia compared to normal controls.

A more complete understanding of the neural generators involved in *normal* sensory gating is critical for elucidating the pathological response that is often observed in clinical populations (Edgar et al., 2003; Patterson et al., 2008). In the current study, participants listened to pairs of identical and non-identical tones to examine the effects of distinct, compared to repeated, paired stimuli. Electrophysiological results from a similar paradigm indicate larger gating effects for the identical (P50 gating ratio = 44%) compared to non-identical tones condition (P50 gating ratio = 67%) in normal controls, with a reversal of effects in patients with

schizophrenia (Boutros et al., 1999). In addition, participants also listened to single, unpaired tones of the same two fundamental frequencies. The resultant HRFs for the single-tone conditions were then summed to obtain an estimation of the "true" hemodynamic response to pairs of identical (single 2000 Hz tone + single 2000 Hz tone) or non-identical (single 2000 Hz tone + single 3000 Hz tone) tones. In an ANOVA framework, the estimated HRFs could then be compared to the empirically determined (observed) HRFs to identify regions that exhibited a gating response for both non-identical and identical tones. In addition, a comparison between the *observed* HRF for identical compared to non-identical tones should directly replicate previous electrophysiological work indicating larger gating ratios for non-identical stimuli compared to identical stimuli (Boutros et al., 1999).

We predicted that the magnitude of the estimated HRF would be greater than the magnitude of observed HRF in the bilateral AC, prefrontal cortex and hippocampi for identical stimuli, indicative of sensory gating. In addition, we predicted that the magnitude of the observed HRF would be greater in these regions for the non-identical condition compared to the identical condition based on the assumption of a reduced gating response (i.e., increased S2) and subsequent increase in BOLD activity, for novel compared to repeated stimuli (see Figure 1).

## Methods

### Subjects

Twenty-one (11 female, 10 male) healthy adult volunteers participated in the current study. One female was identified as an outlier (above three standard deviations) on head motion parameters corresponding to image-to-image motion and was therefore excluded from further analyses (Mayer et al., 2007). All subjects (mean age = 26 + -5.8 years) were right-handed (mean Edinburgh Handedness Inventory score = 90.3% + -12.4%) and had no self-reported history of neurological disease, major psychiatric disturbance, substance abuse or psychoactive prescriptive medications usage. Written informed consent was obtained from all participants prior to data collection, according to institutional guidelines at the University of New Mexico.

# Task

Participants passively listened to a single auditory stimulus or a pair of stimuli (pure tones with 1 ms linear on and offset ramps) while undergoing FMRI on a 1.5 Tesla Siemens scanner. The current paradigm was a tone variant of the traditional paired-click paradigm and involved 4 different conditions. Participants were either presented with a pair of 5 ms binaural identical tones presented at 2000 Hz (identical tones condition; IT), a 5 ms binaural 2000 Hz tone followed by a 5 ms binaural 3000 Hz tone (non-identical tones condition; NT), a single 5 ms binaural 2000 Hz tone, or a single 5 ms binaural 3000 Hz tone. The frequency of tones was slightly higher than those adopted by Boutros and colleagues (1000 and 1500 Hz) so that they would be outside of the normal range of frequencies typically present during FMRI experiments (Seifritz et al., 2006). In the IT and NT conditions, the S1 and S2 stimuli were separated by an ISI of 500 ms. There were a total of 100 trials in each condition, and trial order was pseudo-randomized across the entire experiment.

A visual fixation cross (visual angle =  $2.63^{\circ}$ ) was present throughout the course of the experiment to minimize the likelihood of eye movements. The fixation cross changed to an asterisk to signal the start (2000 ms prior to the presentation of S1) and finish (1500 ms following the termination of S1) of a trial. Participants were instructed not to blink when the asterisk was present on the screen. This manipulation was added because we were interested in developing a paradigm that could be utilized in electrophysiological studies where artifact secondary to oculomotor activity (i.e., blinking) is a major concern. No other behavioral responses were required of the participants. An average ITI of 9 seconds (range 7–11 seconds)

was adopted to promote full recovery of the gating response (Patterson et al., 2008). In addition, by jittering the ITI at one-second intervals in relation to the two-second TR we were able to effectively achieve a 1 Hz sampling resolution of the hemodynamic response for each of the four conditions. Finally, this pseudo-randomized timing scheme permitted the establishment of a baseline state in the regression model (Burock et al., 1998).

Prior to the start of each experiment, the decibel (dB) level of auditory stimulation was determined separately for each participant by the limits method (Boutros et al., 2002; Thoma et al., 2003). Specifically, all auditory stimuli were first presented at 83 dBs via an Avotec SS-3100 audio system while the scanner was acquiring EPI data to simulate actual experimental conditions. Subjects then either attenuated or amplified the sound level with a MRI-compatible subject response device (MIND Input Device; Patent # 7,039,266). Sound levels were attenuated at increments of 5 dBs until the participant indicated that they could no longer hear the stimuli. Participants then amplified the dB level at increments of 1 dB until stimuli were again detected. The experimental stimuli were then delivered at 30 dBs above the individually determined threshold level (mean dB threshold for all participants = 64.9 + /-9.9). This sound level is consistent with a recent meta-analyses which reported larger effect sizes in controls at lower (70–75 dB) sound intensities (de Wilde et al., 2007). All participants were briefly exposed to the task in a separate session before proceeding to the scanner.

### **MR** Imaging

At the beginning of the scanning session, high resolution T1 [TE (echo time) = 4.76 ms, TR (repetition time) = 12 ms, 20° flip angle, number of excitations (NEX) = 1, slice thickness = 1.5 mm, FOV (field of view) = 256 mm, resolution =  $256 \times 256$ ] anatomic images were collected on a 1.5 Tesla Siemens Sonata scanner. For each imaging series, 156 echo-planar images were collected using a continuous (Seifritz et al., 2006) echo-planar pulse sequence [TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 256 mm; matrix size =  $64 \times 64$ ]. The first image of each run was eliminated to account for T1 equilibrium effects, leaving a total of 1550 images for the final analyses. Twenty-eight contiguous sagittal 5.5 mm thick slices were selected to provide whole-brain coverage (voxel size:  $4 \times 4 \times 5.5$  mm). A total of ten imaging series were collected for the experiment.

A continuous, rather than conventional, EPI sequence was chosen for the current experiment to maximize activation within auditory cortical areas. A clustered volume acquisition technique was not adopted for several reasons. First, it increases the total data acquisition time while decreasing the temporal sampling rate, which equates to fewer collected trials (i.e., reduced signal to noise and power) and decreased temporal resolution of the HRF (Seifritz et al., 2006). We were specifically interested in transient time-varying effects associated with gating (short stimulus duration), which requires an event-related paradigm with high sampling resolution. Secondly, clustered data acquisition techniques may result in functional activation associated with the abrupt onset of scanner noise, which could then potentially become confounded with the task-related hemodynamics given the low temporal resolution of FMRI.

### Image Processing and Statistical Analyses

Functional images were generated using Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Time series images were spatially registered in both two- and threedimensional space to the second EPI image to minimize effects of head motion, temporally interpolated to correct for slice-time acquisition differences and de-spiked. A deconvolution analysis was used to generate one HRF for each of the conditions on a voxel-wise basis. Each HRF was derived relative to the baseline state (fixation plus ambient noise) and based on the first eight images (16 seconds) post-stimulus onset (hereafter referred to as observed). In addition to the HRFs corresponding to each of the four experimental conditions, two simulated HRFs were created to estimate the true hemodynamic response to individual tones separated by a 500 ms interval (Glover, 1999). Specifically, the empirically derived HRFs for both the single 2000 and 3000 Hz tone conditions were first linearly interpolated to simulate a 500 ms temporal delay in the onset of the stimuli. The interpolated HRFs were then summed with the empirically derived HRF for the 2000 Hz single tone condition to estimate a "non-gated" hemodynamic response (hereafter referred to as estimated) for two identical tones (2000 Hz HRF + interpolated 2000 Hz HRF) and two non-identical tones (2000 Hz HRF + interpolated 3000 Hz HRF) conditions. These estimated HRFs should maximally simulate real hemodynamic data as if there were not an attenuated S2 response (Glover, 1999).

The peak percent signal change was calculated for each HRF by summing the beta coefficients for 7 to 10 seconds following the start of the trial (5–8 seconds following presentation of the tones) and dividing by the model intercept. The percent signal change maps were registered to the high resolution anatomical images, converted to a 1 mm<sup>3</sup> standard stereotaxic coordinate space (Talairach and Tournoux, 1988) and spatially blurred using a 6 mm Gaussian full-width half-maximum filter. A voxel-wise, 2 × 2 repeated-measures ANOVA [Condition (IT vs. NT)  $\times$  Method (Observed vs. Estimated)] was performed to identify regions that exhibited decreased activation (gating) for the empirically derived (observed) versus estimated (i.e., interpolated and summed) HRFs, and whether or not this varied for the identical compared to non-identical tones conditions. This analysis strategy permitted a hierarchical examination of gating responses within the whole brain. Specifically, a comparison of the estimated versus observed HRFs (main effect of method) could be used to determine the neuronal regions that exhibited sensory gating during both the identical and non-identical paired-tones conditions. A direct comparison of the observed HRFs for the non-identical and identical conditions (i.e., regions that exhibited a significant condition × method interaction) provides an indication of how the gating ratio varied as a function of whether repeated or novel information was presented during the two paired-tones conditions.

To minimize false positives, a parametric threshold corresponding to p < .005 and a minimum cluster size of 440 µl were adopted for all resultant ANOVA maps (Forman et al., 1995). These thresholds were determined based on 10,000 Monte Carlo simulations demonstrating that the chance probability of obtaining a significant activation cluster for an entire volume (Type I error) was less than p < .05.

# Results

Several frontal and temporal areas that have been previously implicated in sensory gating exceeded the two significance thresholds outlined above (p < .005; 440 µl) during the comparison of the estimated (non-gating) versus observed (gating) HRFs (Table 1; Figure 2). As predicted, the bilateral AC (insula and superior temporal gyrus (BAs 13/42) extending into the inferior parietal lobule (BA 40)) and dorsolateral prefrontal cortex (including anterior aspects of the insula, inferior frontal gyrus and precentral gyrus; BAs 9/13/44) both demonstrated gating effects (i.e, regions that exhibited gating during both the identical and non-identical tones conditions); however, the left AC also exhibited a significant interaction effect (see Table 2; Figure 3). Additional regions within the frontal and temporal lobes included the right superior and medial frontal gyrus (BAs 10/11), left superior and middle frontal gyrus (BAs 9/46), bilateral middle frontal and pre-central gyrus (BA 6/9), the anterior aspects of the right insula (BA 13), left inferior and middle temporal gyrus (BA 37) and bilateral parahippocampal and fusiform gyrus (BAs 19/37). An increased magnitude of response for estimated HRFs was also observed within the right posterior parietal lobule (precuneus, superior and inferior parietal lobule; BAs 7/40), left precuneus (BA 7), left precuneus/posterior cingulate gyrus (BA 7/31) and bilateral middle occipital gyrus (BA 18) extending into the cuneus and middle temporal gyrus (BA 37). Finally, the left putamen, right ventrolateral

nucleus of the thalamus, left culmen (lobules III–V) and left culmen/declive (lobule VI) of the cerebellum also demonstrated greater activation for the estimated HRFs. In contrast, there were no neuronal regions identified in the main effect contrasting identical and non-identical tones collapsed across observed and estimated HRFs.

The Condition  $\times$  Method interaction term (Table 2; Figure 3) was significant in the left AC (insula and superior temporal gyrus (BAs 13/42)) extending into the inferior parietal lobule (BA 40), the right parahippocampal gyrus (BA 36) extending into the hippocampus, and in the right precuneus (BA 7). Follow-up paired t-tests were then conducted in these functional regions of interest (ROIs) to determine which conditions were contributing to the variance. Specifically, we separately compared the magnitude of the percent signal change for identical and non-identical tone pairs for both observed (observed NT vs. observed IT) and estimated (estimated NT vs. estimated IT) HRFs. Results indicated that functional activity was significantly greater in the observed HRFs for the non-identical compared to identical tones condition in the left AC and right precuneus. This finding suggests that the left AC and right precuneus exhibit an increased gating ratio (less gating) for non-identical compared to the identical paired-tones as previously reported in the electrophysiological literature (Boutros et al., 1999). In contrast, functional activation was greater for the identical tones compared to the non-identical tones for all three ROIs in the estimated method.

### Supplementary ROI Analyses

Contrary to our predictions, neither the right nor the left hippocampus was directly implicated in sensory gating (estimated HRF > observed HRF or observed NT > observed IT) during any of the voxel-wise analyses. Specifically, the right hippocampus and parahippocampal gyrus only exhibited increased activation when the estimated activity was compared across the identical and non-identical conditions. We therefore conducted a ROI analysis comparing the average magnitude of the observed versus estimated trials and the magnitude of the observed non-identical and identical tones in manually traced (subject-by-subject basis) hippocampi (Figure 4). Although ROI analyses are typically more sensitive than voxel-wise analyses due to improved signal-to-noise ratio (signal averaging across voxels) and decreased variability (accounting for individual differences in neuroanatomy), the results from both of these analyses were not significant (p > .10).

# Discussion

To our knowledge, this was the first event-related FMRI study to examine both the cortical and deep neuronal sources that mediate the sensory gating response in a population of healthy controls during the processing of pairs of identical and non-identical tone pips. Current results indicated that a large network of cortical and subcortical structures, including both the bilateral dorsolateral prefrontal cortex and the AC, were implicated in auditory sensory gating during both non-identical and identical tone pairs (estimated HRF > observed HRF). In addition, the magnitude of the gating response in the left AC and the right precuneus was dependent on whether novel (i.e., non-identical tones) or repeated (i.e., identical tones) information was presented in the tone-pairs, with repeated information showing a larger gating effect. In contrast, there was no evidence of hippocampal involvement in sensory gating during any of the voxel-wise or ROI analyses.

Current results provide substantial support for the involvement of the bilateral superior temporal gyrus and surrounding auditory cortical areas in mediating the sensory gating response (estimated HRF > observed HRF). Previous evidence of AC's involvement in sensory gating has been reported in both invasive studies with surgically placed electrodes as well as from non-invasive imaging techniques such as FMRI and MEG. Specifically, source reconstructions of the P50 during intracranial recordings indicated that the main generators of

the gating response could be localized to the temporal lobes (Korzyukov et al., 2007). A previous FMRI study reported both reduced amplitude and a delayed onset (approximately 1 second) for the HRF of the second stimulus within the AC (BAs 41, 42 and part of 22) during paired stimuli (1000 Hz tones) that were separated by either a one, four or six second ISI (Inan et al., 2004). MEG studies have consistently localized the generators of M50 and M100 components to the superior temporal gyrus (Hanlon et al., 2005; Thoma et al., 2003) and other work suggests that a large portion of P50 variance (as measured by EEG) in healthy normal controls can be explained by source contributions (as measured with MEG) arising from within the temporal lobe (Huang et al., 2003). Finally, M50 gating differences between patients with schizophrenia and healthy controls have been reported for the left AC (Hanlon et al., 2005; Huang et al., 2003; Thoma et al., 2003; Thoma et al., 2005), although a FMRI study using a click-train paradigm was not able to replicate this result (Tregellas et al., 2007).

Interestingly, the left AC was only one of two structures to demonstrate increased activity in the non-identical compared to identical tones condition, suggestive of a reduced gating response for non-repeated stimuli. Previous MEG results indicate that the M50 component from the left AC is predictive of both psychophysical and neuropsychological measures of preattentional and attentional functioning and may be more useful at distinguishing between healthy and clinical populations. In these studies, the gating ratio derived from the left AC M50 component correlated with P50 EEG gating (Thoma et al., 2003), with neuropsychological measures of attentional functioning (Thoma et al., 2003), and with the left AC M100 component (Hanlon et al., 2005) in healthy controls. However, none of these correlational relationships existed for the right AC. Collectively, these results suggest that there may be an increased left hemispheric specialization for sensory gating processes.

Bilateral activation of the dorsolateral prefrontal and superior frontal gyrus was also present during a comparison of estimated versus observed HRFs. One model of sensory gating (Grunwald et al., 2003) proposes that the AC processes basic stimulus properties during the initial stages of auditory gating, whereas the prefrontal cortex acts to further inhibit the flow of sensory information within the cortex. In addition to current results, this model has received some empirical support from other research areas. For example, depth recordings during presurgical evaluations indicate that the prefrontal cortices are the main sources for reducing the amplitude of the S2 response (Korzyukov et al., 2007). In addition, gating deficits have been observed in patients with lateral prefrontal lesions (Knight et al., 1999) and the prefrontal cortex has been shown to be active during the processing of non-identical, but not identical, faces (Soon et al., 2003). Finally, the administration of haloperidol and ketamine disrupts sensory gating in healthy individuals, which was hypothesized to be the result of disruption in the prefrontal dopaminergic system (Oranje et al., 2002). In addition to prefrontal involvement, a portion of this sensory filtering process may also occur in other structures, such as the thalamus. Consistent with previous FMRI results (Tregellas et al., 2007) and animal models (Erwin and Buchwald, 1987), increased activity in the right ventral lateral nucleus of the thalamus was observed during the comparison of estimated to observed HRFs.

Contrary to our predictions, an increased magnitude of the HRF for the non-identical compared to identical tones condition was not observed in the right AC or bilateral prefrontal cortex. Previous electrophysiological results (Boutros et al., 1999) demonstrated an increased amplitude for the P50 and N100 S2 response during the non-identical compared to identical tone conditions in healthy subjects, suggesting that the summation of resultant hemodynamic response might produce a similar result (see Figure 1). One important difference between the current study and that of Boutros et al. (1999) was the order in which different conditions were presented. Specifically, the current experiment used a pseudorandom event-related design for the presentation of non-identical and identical tone pips whereas Boutros et al. presented the tone pips in separate blocks that were then counter-balanced. The use of the event-related

design in the current experiment may have resulted in a more generalized sensitization to tone pairs so that gating was equally evident for both non-identical and identical tone pairs. Alternatively, the small electrophysiological differences between the identical and non-identical tone conditions may have been limited to certain time epochs (e.g., P50 and N100), which may not have necessarily generalized to the hemodynamic response (see limitations section).

Finally, greater activation for the estimated compared to the observed HRFs was also found within the extra-striate cortex, cuneus, the ventral and dorsal visual streams, and the bilateral middle frontal and pre-central gyrus, corresponding to the frontal eye fields (Paus, 1996). Activity in the dorsal visual stream could be directly related to the gating response as temporal-parietal activity has been reported during intracranial recordings of auditory sensory gating (Grunwald et al., 2003). Alternatively, activation of these visual and frontal oculomotor regions may have resulted from the other key requirement of the task, which was to inhibit blinking during the presence of the asterisk. The asterisk was displayed 2000 ms before, during, and 1000 ms after the presentation of the single- or paired-tone conditions and was used to both warn participants of the upcoming auditory stimulus presentation and to remind participants not to blink. The latter constraint was added to potentially reduce the amount of discarded trials due to eye-movement artifact during future electrophysiological data collection efforts.

In contrast to the above positive findings, a null finding for hippocampal involvement in sensory gating was consistently observed in all voxel-wise analyses (estimated vs. observed; non-identical vs. identical) and during ROI analyses in which the hippocampi were manually traced on a subject-by-subject basis. Findings of hippocampal involvement in the sensory gating response have also not been reported during MEG studies of healthy and clinical populations (Hanlon et al., 2005; Huang et al., 2003; Thoma et al., 2003) although these studies typically examined earlier time epochs (M50 and M100) rather than the time epoch (200-300 ms) associated with hippocampal activity during invasive studies. For example, previous evidence of hippocampal involvement in sensory gating has been reported in animal studies of single-cell recordings (Freedman et al., 1996), during pre-surgical mesial-temporal lobectomy human evaluations (Boutros et al., 2005; Boutros et al., 2008; Grunwald et al., 2003), and in pharmacological stimulation of the hippocampal interneurons with nicotinic acetylcholine-mediated neurotransmission (Adler et al., 2001). A recent FMRI study also reported hyperactivation of the hippocampus in patients with schizophrenia compared to normal controls using a click-train paradigm (Tregellas et al., 2007). Importantly, hippocampal activity was not present in the normal controls.

Some potential limitations with studies reporting hippocampal involvement in sensory gating include species related differences in the gating response and the use of human populations with known neurological dysfunction. For example, human intracortical recordings are typically performed in patients with intractable epilepsy and associated neurological dysfunction (Boutros et al., 2005; Boutros et al., 2008; Grunwald et al., 2003). Similarly, Tregellas et al.'s (2007) finding of increased hippocampal activation was based on differences between patients with schizophrenia and normal controls, rendering it likely that their findings may be secondary to disease-related neuronal pathology, neuronal pathology resulting from secondary disease characteristics (e.g., increased smoking in schizophrenia patients), medication effects, group differences in levels of cerebral blood volume (Brambilla et al., 2007) due to population differences in the basic parameters of the HRF (Ford et al., 2005; Fox et al., 2006), or a combination of all of the above factors.

It is unlikely that our negative finding of hippocampal involvement in sensory gating was the result of poor spatial resolution, inability to image measure deep structures (e.g., other deep structures, such as the right thalamus and left putamen, did show evidence of gating-like

activity), or the result of poor signal-to-noise ratio (e.g., 100 trials were used for each condition average). A potential explanation for the null finding is that the hippocampus might have also been active during the baseline fixation period, which would have then reduced the magnitude of activity during the single- and paired-tone conditions. Specifically, previous FMRI research on memory functioning indicates that the magnitude of hippocampal activation is increased when visual fixation is used as a baseline rather than a more cognitively activating task (unrelated to memory) such as counting dots (Stark and Squire, 2001). Increased activity in the medial temporal lobes during passive mental activity may be a result of the random episodic and autobiographical memory processes that occur when participants are not otherwise occupied (Greicius and Menon, 2004). Although this explanation potentially accounts for the null effect for estimated versus observed HRFs, the direct contrasting of non-identical and identical tones conditions should have resulted in relatively greater hippocampal activation. Specifically, one putative role for the hippocampus in sensory gating is to generate a memory trace comparing S1 and S2 for novelty of information which should have been greater in the non-identical tones condition (Grunwald et al., 2003). Therefore, additional work is necessary to elucidate the nature of the hippocampal signal that has been frequently recorded in invasive animal and human studies of sensory gating.

Several limitations of the current study should be considered. First, previous research has demonstrated a non-linear summing of the HRF for stimuli with inter-trial intervals of three seconds or less (Glover, 1999). The basis for this non-linear summing could be a gating-like neuronal refractory period (i.e., as measured electrophysiologically), or could be secondary to differences in other factors which compromise the hemodynamic response such as non-linearities in neurovascular coupling, cerebral blood flow, volume, and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) ratios (Friston et al., 1998; Inan et al., 2004). Obviously it is not possible to delineate these potential contributions to the reduced response observed in the current experiment.

Second, the continuous ambient noise resulting from the switching of the gradient coils during FMRI data collection may have reduced the magnitude of the gating response in both paired-tones conditions. However, there have been several reports of sensory gating in the presence of white noise (Blumenfeld and Clementz, 1999; Clementz et al., 1997; Clementz and Blumenfeld, 2001) and the current EPI sequence was specifically adopted due to its continuous noise properties, which have been shown to reduce obligatory AC activity (Seifritz et al., 2006). Collectively, these results suggest that it is unlikely that gradient noise adversely affected current results.

Third, our paradigm differed from previous research in that participants were asked to refrain from blinking while an asterisk presented itself on the screen during tone presentation. This manipulation was added as we were interested in developing a paradigm that could be utilized in electrophysiological studies where artifact secondary to oculomotor activity (i.e., blinking) is a major concern. However, the fixed temporal interval between the asterisk (indicating to the subject to not blink) and the tones may have generated a contingent negative variation (Walter et al., 1964), which then affected the gating response. However, other studies have demonstrated that only attentional manipulations that are directly relevant to the task (e.g., attending to certain physical characteristics of the stimulus such as frequency, timing, intensity, and laterality) affect the sensory gating response in normals (Guterman et al., 1992; Staines et al., 2002; Sutton et al., 1967). In contrast, task-irrelevant activity, such as performing serial subtraction, active or passive movements (Waldo and Freedman, 1986), and attending to stimulus characteristics not pertinent to the primary gating task (Staines et al., 2002; Sutton et al., 1967) do not generally produce a significant effect. In addition, if a contingent negative variation was present, it would likely be generated for all conditions and therefore subtracted out for all condition comparisons.

Finally, perhaps the biggest potential limitation of the current experiment is the limited temporal resolution of the hemodynamic response. The vast majority of previous electrophysiological studies (Adler et al., 1982; Boutros et al., 1999; Boutros et al., 2004; Freedman et al., 1996; Huang et al., 2003; Thoma et al., 2003) have investigated differences in sensory gating during very specific time epochs (i.e., P50, N100, M50 and M100). If the differences between non-identical and identical tone pairs are limited to these restricted epochs of time they may not translate to the evoked HRF response, which likely represents an integration of these individual electrophysiological responses (i.e., 0– 500 ms) for *both* S1 and S2 stimuli. However, recent data indicates a reduced S2 response for N100 and P200 components as well as P50 response (Rentzsch et al., 2008), suggesting that it is more likely that gating effects will be present throughout the entire electrophysiological response.

In summary, one of the most consistent electrophysiological deficits reported in the schizophrenia literature is a failure to inhibit, or properly gate, the neuronal response to the second stimulus of an identical pair (Adler et al., 1982; Cullum et al., 1993; Freedman et al., 1996; Huang et al., 2003; Thoma et al., 2003). The methodology employed in the current experiment provides a mechanism for investigating sensory gating deficits using identical experimental parameters during both non-invasive electrophysiological and hemodynamic studies. This collective information will respectively maximize our understanding of the temporal and spatial properties of the sensory gating response, providing a more thorough characterization of what has been described to be a potential endophenotypical marker of schizophrenia (Adler et al., 1999; Freedman et al., 2003). Current results support an emerging theory that the gating response is primarily mediated by the AC and prefrontal cortex (Korzyukov et al., 2007) with additional potential contributions from the thalamus. In addition, the left AC may play a preferential role in determining which stimuli should be gated or receive additional processing. In contrast, there was no evidence of hippocampal involvement, suggesting that future work is needed to determine what role it may play in the gating response.

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### Figure 1.

Panel A depicts a cartoon representation of the basic event order of the two main conditions in the current experiment. A binaurally presented, 2000 Hz tone (S1) was first presented followed by another tone (S2) of either 2000 (identical tones condition; IT) or 3000 (non-identical tones condition; NT) Hz frequency. The ISI between the tone pairs was always 500 ms, and an ITI of 7 to 11 seconds followed each condition. Panel B presents a cartoon depiction of the underlying electrophysiological response for pairs of identical and non-identical tones. Both S1 (solid line) and S2 (short dash) are presented for the P50, N100 and P200 responses in microvolts ( $\mu$ V) as a function of time (ms). Based on previous electrophysiological results (Boutros et al., 1999), we predicted a smaller reduction in amplitude for S2 in the non-identical compared to identical conditions. Panel C represents the magnitude of a theoretical HRF in percent signal change (PSC) as a function of time (seconds). We predicted that the S1 response (solid line) would be the same for both conditions, but that the resultant S2 (short dash) response would be greater for the non-identical tones condition. This should result in a greater PSC for the overall HRF (long dash), which is a non-linear summation of the underlying response to both S1 and S2.



### Figure 2.

Selected brain regions that exhibited greater activity during the estimated (warm coloring) compared to observed condition are displayed. Key areas of activation include the 1) bilateral auditory cortex, 2) and 4) bilateral dorsolateral prefrontal cortex and 3) right ventral lateral nucleus of the thalamus. Below these brain slices, the graphs display the percent signal change (PSC) for the estimated (red) and observed (blue) hemodynamic response functions for the: 1) right auditory cortex; 2) right prefrontal cortex; 3) right thalamus; and 4) left prefrontal cortex. Error bars represent standard deviations across the sample of subjects. All hemodynamic response functions were derived for the first 16 seconds past the onset of the asterisk. The first and third slices correspond to both the right and left hemisphere 50 mm lateral to the origin of Talairach space, whereas the second slice is 14 mm superior to the origin of Talairach space.



### Figure 3.

A display of the regions that were significantly active (warm coloring) during the Condition  $\times$  Method interaction. Areas of activation included the 1) right parahippocampal gyrus and hippocampus, 2) left auditory cortex, and 3) right precuneus. The graphs to the right of these brain slices display the percent signal change (PSC; range adjusted for each ROI) for each of the four conditions based on the first 16 seconds post the onset of the asterisk. Error bars represent standard deviations across the sample of subjects. The hemodynamic response function for the estimated (pink) and observed (orange) identical tones conditions and the estimated (cyan) and observed (green) non-identical tones condition are presented. The position of axial slices is given according to distance from the origin of Talairach space.



### Figure 4.

Examples from the ROI analyses in which the hippocampi were manually traced on a subjectby-subject basis. Panel A displays the manually traced ROIs from two subjects. The graphs in panel B display the percent signal change (PSC) data from the hippocampi for the both the estimated (red) and observed (blue) HRFs and for the observed identical (orange) and nonidentical (green) tones condition.

Areas demonstrating greater activation during the estimated compared to observed hemodynamic response functions. Table 1

Region	Side			Activatio	u	
		BA	X	Υ	Z	Vol
Frontal Lobe						
Superior and Medial Frontal Gyrus	Я	10/11	22	52	-10	1.220
Superior and Middle Frontal Gyrus	Т	9/46	-39	37	26	1.039
	Ч	6/9	37	1	42	4.564
Middle Frontal and Pre-central Gyrus	Г	6/9	-37	-3	38	0.640
	R	9/13/44	41	13	22	9.272
Dorsolateral Fretrontal Cortex	L	44	-47	4	13	1.151
Insula	Я	13/47	32	17	4	1.311
Temporal Lobe						
Auditory Cortex and Inferior Parietal Lobule	Я	13/42/40	46	-36	20	8.825
Inferior and Middle Temporal Gyrus	Т	37	-20	-63	5	1.358
: - - -	Я	19/37	67	-53	-3	3.579
Farahippocampal and Fusilorm Gyrus	L	19/37	-26	-50	8	2.587
Parietal Lobe						
Posterior Parietal Lobule	R	7/40	28	-46	40	6.344
Precuneus	Г	7	-22	-45	41	1.570
Precuneus/Posterior Cingulate Gyrus	Г	7/31	-19	-63	24	0.783
Occipital Lobe						
	R	18/37	29	-80	11	11.404
ivitadie Occipital Gyrus, Cuffeus and Middle Temporal Gyrus	L	18/37	-28	-85	13	4.006
Subcortical						
Putamen	Г		-29	-10	2	0.922
Ventral Lateral Nucleus of Thalamus	R		14	-14	10	2.281
Cerebellum						
Culmen (Lobules III–V)	L		-12	-36	-18	2.499
Culmen/Declive (Lobule VI)	Г		-12	-58	-12	3.248

Note: Side refers to the hemisphere showing activation, where L = left, and R = right hemisphere. The Brodmann area (BA), the center of mass in Talairach coordinates (X, Y, Z) and volume (Vol) in milliliters are specified for each area of activation. All regions showed greater activation when cues were uninformative.

# Table 2 Regions that demonstrated a significant Condition X Method interaction effect.

Kegion     Side     BA       Temporal Lobe     Side     BA       Auditory Cortex and Inferior Parietal Lobule     L     13/40/42       Parahippocampal Gyrus and Hippocampus     R     36	X	Y	z	Vol	OBS NT vs. IT	EST NT vs. IT
Temporal Lobe     L       Auditory Cortex and Inferior Parietal Lobule     L     13/40/42       Parahippocampal Gyrus and Hippocampus     R     36	1					
Auditory Cortex and Inferior Parietal Lobule     L     13/40/42       Parahippocampal Gyrus and Hippocampus     R     36	12					
Parahippocampal Gyrus and Hippocampus R 36	10-	-30	21	2.174	NT > IT	IT > NT
	33	-24	-18	0.903		$\mathbf{IT} > \mathbf{NT}$
Parietal Lobe						
Precuneus R 7	15	-42	51	1.135	NT > IT	IT > NT

milliliters are specified for each area of activation. The results of follow-up tests are reported on the right side of the table. Follow-up analyses comparing non-identical tones (NT) versus identical tones (IT) were conducted separately for both observed (OBS) and estimated (EST) hemodynamic response functions. Note: Side refers to the hemisphere showing activation, where L = left, and R = right hemisphere. The Brodmann area (BA), the center of mass in Talairach coordinates (X, Y, Z) and volume (Vol) in