Published in final edited form as:

Am J Psychiatry. 2009 March ; 166(3): 354–360. doi:10.1176/appi.ajp.2008.08030411.

Increased hippocampal, thalamic, and prefrontal hemodynamic response to an urban noise stimulus in schizophrenia

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Abstract

Objectives—People with schizophrenia often have difficulty ignoring unimportant noises in the environment. While experimental measures of sensory gating have yielded insight into neurobiological mechanisms related to this deficit, the degree to which these measures reflect the experience of people with schizophrenia is unknown. The goal of this study was to develop a novel, clinically relevant sensory gating paradigm and to assess differences in brain hemodynamic responses during the task in schizophrenia.

Methods—Thirty-five subjects, including 18 outpatient subjects with schizophrenia and 17 healthy comparison subjects were scanned on a 3T MR system while passively listening to a mixture of common sounds simulating what a person may experience in a busy urban setting. The stimuli included multiple conversations and events recorded from a neighborhood gathering, music and conversations from the radio. P50 evoked responses from a typical paired-click sensory gating task also were measured.

Results—Listening to the “urban white noise” stimulus produced robust activation of the auditory pathway in all subjects. Activation was observed in the bilateral primary and secondary auditory cortices, medial geniculate nuclei, and inferior colliculus. Greater activation was observed in subjects with schizophrenia, relative to comparison subjects, in the hippocampus, thalamus and prefrontal cortex. Higher P50 test/conditioning ratios also were observed in subjects with schizophrenia. These evoked responses correlated with hemodynamic responses in both the hippocampus and prefrontal cortex.

Conclusions—The finding of greater activation of the hippocampus, thalamus and prefrontal cortex during a sensory gating task with high face-validity further supports the involvement of these brain regions in gating deficits in schizophrenia. This link is strengthened by the observed correlation between evoked responses in the paired-click paradigm and hemodynamic responses in fMRI sensory gating paradigm.

Keywords

Schizophrenia; Thalamus; Hippocampus; Prefrontal Cortex; fMRI; Sensory Gating

Introduction

The inability to ignore irrelevant noises in the environment is a common problem for people with schizophrenia. First described by Bleuler nearly 100 years ago, this flooding of sensory

information can substantially impact quality of life and may be related to disease pathology (1;2). To better understand this core problem in schizophrenia, investigators have developed physiologic and behavioral measures to study patients' responses to sounds.

One commonly studied physiologic measure is the P50 sensory gating paradigm, in which evoked responses to pairs of clicks are measured with electroencephalographic (EEG) techniques. In healthy subjects, responses to the second click in a pair of clicks are inhibited as part of a sensory gating or filtering mechanism (3). Subjects with schizophrenia fail to inhibit responses to this repeated stimulus, which is interpreted as an inhibitory failure in sensory gating (4). In a recent fMRI study, we identified greater activation of the hippocampus, thalamus and prefrontal cortex during a repeated-click sensory gating task in schizophrenia (5). Other paradigms, such as the pre-pulse inhibition task, in which a weak stimulus preceding a startling stimulus diminishes the startle effect, also have attempted to distill the sensory gating phenomenon into responses to pairs of stimuli (6;7). The simplicity of these measures, particularly the ability to translate the tasks into animal models, has revealed valuable information about the neurobiology underlying deficits in sensory gating.

A weakness of such measures, however, is the unknown degree to which repeated clicks or stimuli in other modalities reflects the experience of people with schizophrenia in daily life, i.e. an inundation by real noises in the environment. Previous studies using word stimuli or sounds from the environment have revealed behaviors that imply specific cortical deficits in schizophrenia. Since the late seventies, studies using dichotic listening paradigms have shown that subjects with schizophrenia are more distractible when trying to perform other tasks ranging from visual tracking (8) to speaking (9). Other listening studies, using dichotic speech tasks, digit pair tasks and monitoring tasks have differed in their findings, but consistently have demonstrated differences in the lateralization of auditory processing in schizophrenia (10).

Studies using more naturalistic or complex sounds have the advantage of higher face validity but have not been studied in the context of sensory gating. The present study sought to develop a new sensory gating task with higher face validity, e.g. one that more closely relates to real-life situations. The simple task involves passive listening to "urban white noise," a mixture of common sounds from the environment simulating what a person may experience in a busy urban setting, including multiple conversations and noises recorded from a party, music and conversations from the radio. The stimulus also includes items frequently reported to be noticed more often by people with schizophrenia such as traffic noise and a refrigerator motor randomly cycling on and off. This study tests the hypothesis that hemodynamic response in the hippocampus, thalamus and dorsolateral prefrontal cortex, regions previously identified as exhibiting greater response during a repeated-click gating task, will be more active in subjects with schizophrenia during the urban white noise sensory gating task. This study also evaluates the relationship between this new measure of sensory gating and typical P50 gating measures, and describes subjective responses to the novel gating task by participants.

Methods

Subjects

Thirty five subjects, including 18 outpatient subjects with schizophrenia (7 women/11 men, 36.6 SD 12.0 yrs old) and 17 healthy comparison subjects (6 women/11 men, 36.7 SD 12.5 yrs old), participated in this study. Two additional subjects were excluded due to excess head motion (> 1 mm) during scanning. Diagnoses were made with the Diagnostic Instrument for Genetic Studies (DIGS). No significant group difference in age was observed. Of the 18 subjects with schizophrenia, 16 were treated with atypical neuroleptics, one was treated with a typical neuroleptic and one was treated with both typical and atypical neuroleptics. All volunteers provided written, informed consent approved by the local IRB.

fMRI Methods

Following a hearing test (see below), a high-resolution, T1-weighted 3D anatomical scan was acquired for each subject (IR-SPGR, TR=9ms, TE=1.9ms, TI=500ms flip angle=10°, matrix = 256×256, FOV = 220mm², 124 1.7 mm thick coronal slices) for coregistration to functional data. Functional images were acquired with a gradient-echo T2* Blood Oxygenation Level Dependant (BOLD) contrast technique, with TR=14000ms (as a clustered volume acquisition of 2000 ms, plus an additional 12000 ms silent interval), TE=30ms, FOV=220mm², 64² matrix, 31 slices, 4mm thick, no gap, angled parallel to the planum sphenoidale. Additionally, one IR-EPI (TI=505ms) volume was acquired to improve coregistration between EPIs and the IR-SPGR.

Head motion was minimized with a VacFix head-conforming vacuum cushion (Par Scientific A/S, Odense, Denmark). Auditory stimuli were presented via MR-compatible headphones (Resonance Technology, Inc., CA, USA). MR-compatible goggles (Resonance Technology, Inc, CA, USA) were used for visual stimuli. Motor responses for the hearing test were collected via a fiber optic response pad (Cedrus Corp, USA).

fMRI Paradigm

Prior to scanning, subjects completed a hearing test in the scanner to set the task volume at 30dB above hearing threshold. In the scanning environment, this sound level resulted in a clearly audible, yet not overwhelming or startling volume. After the hearing test and structural scan, subjects performed the sensory gating task while undergoing fMRI. Subjects watched a silent movie during the scan while auditory stimuli were played in the background. The study used clustered volume acquisition, in which scans are not continuously acquired, but rather are spaced at long intervals, allowing stimuli to be presented in silence, while still capturing the peak hemodynamic response. This technique has been shown to substantially improve signal detection in auditory tasks (11). For consistency with our prior sensory gating study using repeated clicks, the paradigm used a total TR of 14s, which included an initial 2s of scan acquisition, followed by 11.5s of either 1) silence or 2) the “urban white noise” stimulus (described below) (Figure 1). Alternating 28s blocks of silence and auditory stimuli were presented to the subjects over two runs, totaling 15 minutes. Between runs, brief conversations were held with subjects to ensure that they were awake and responsive. After scanning, subjects were asked to describe their experience with an open-ended question of “what did you think about the task?”

The “urban white noise” stimulus consisted of a mixture of audio clips. Clips included segments from two talk radio shows, two classical musical pieces, sounds from a neighborhood block party, which included multiple background conversations and sounds from children playing, traffic sounds, a refrigerator motor cycling on and off, and frequent knocking sounds from glasses being set on countertops. Volumes of all of these elements were mixed so that no one element was readily identifiable. The subjective experience of the sound mixture was that of standing in a busy crowd of people, in which multiple conversations were occurring, with a low level of indistinguishable background music and other sounds. Supplemental Figure #1 shows a power spectrum characterizing the stimulus.

fMRI Data Analysis

Data were analyzed using SPM2 (Wellcome Dept. of Imaging Neuroscience, London). Data from each subject were realigned to the first volume, normalized to the Montreal Neurological Institute template, using a gray-matter-segmented IR-EPI as an intermediate to improve registration between the EPI and IR-SPGR, and smoothed with an 8 mm FWHM Gaussian kernel. Data were modeled with a HRF-convolved boxcar function, using the general linear model in SPM2. A 128s high pass filter was applied to remove low-frequency fluctuation in

the BOLD signal. The primary analysis modeled stimuli as 28s blocks of either silence or “urban white noise.” A secondary event-related analysis modeled each stimulus presentation separately to assess habituation effects within a block.

To account for both within-group and within-subject variance, a random effects analysis was implemented. Parameter estimates for each individual’s first level analysis (SPM contrast images) were entered into second-level t-tests for each contrast of interest. The contrast “urban white noise – silence” was evaluated. The main effect of task was evaluated with a whole-brain analysis, corrected for multiple comparisons using the FDR technique (12). For between-group comparisons, *a priori* hypotheses about activation in four regions, the superior temporal gyrus (STG), hippocampus, thalamus and dorsolateral prefrontal cortex (DLPFC) were evaluated using anatomically defined ROIs from the WFU Pickatlas (13). The hippocampal and thalamic ROIs included the entire anatomical structures. The DLPFC ROI consisted of Brodmann Areas 9 and 46 combined, excluding the superior frontal gyrus. These ROIs were identical to those used in our prior fMRI study of sensory gating using repeated clicks (5). The mean response for all voxels in each ROI was determined using the Marsbar toolbox (14) in SPM2. To improve statistical power, results were masked with a gray-matter mask, consisting of the average gray-matter from all subjects obtained from their segmented IR-EPIs. Functional results were overlaid onto the group average T1-weighted anatomical images and thresholded at a whole-brain $p < 0.01$ for visualization.

EEG Paradigm and Methods

Details of the paired-click recording paradigm have been described previously (15). The P50 potential was identified and measured by using a previously described computer algorithm (15). The amplitude of the P50 test wave was divided by the amplitude of the P50 conditioning wave, expressed as a percentage: the P50 ratio. Subjects were given no special instructions concerning the clicks they were hearing. Recordings were obtained from 31 of the 35 subjects who were scanned. One subject with schizophrenia and three control subjects were unavailable for EEG recording. Data from one additional subject with schizophrenia was excluded because the minimum number of recorded responses (three sets of averaged evoked responses to 16 pairs of stimuli) was not obtained due excessive eye blink and muscle artifact. (15)

Results

fMRI

Passive listening to the “urban white noise” stimulus produced robust activation of the auditory pathway in both subjects with schizophrenia and healthy comparison subjects. Figure 2 shows whole-brain responses to the stimulus across all subjects, thresholded at FDR $q < 0.05$.

Activation was observed in the bilateral primary and secondary auditory cortices and medial geniculate nuclei. Activation of the left inferior colliculus also was observed. MNI Coordinates for these regions are shown in Table 1.

Figure 3 shows greater responses during the task in subjects with schizophrenia, relative to healthy comparison subjects. Greater responses were observed in the hippocampus ($t=2.05$, $df=33$, $p=0.024$, left), thalamus ($t=1.95$, $df=33$, $p<0.030$, left; $t=1.68$, $df=33$, $p=0.051$, right) and dorsolateral prefrontal cortex ($t=1.80$, $df=33$, $p=0.040$, left). Differences in superior temporal gyri responses did not reach significance ($t=1.12$, $df=33$, $p=0.14$, right; $t=1.23$, $df=33$, $p=0.11$, left). Within the anatomically-based ROIs, local maxima were $t=3.43$ ($x=3$, $y=-12$, $z=12$), right thalamus, $t=3.49$ ($x=-33$, $y=-21$, $z=-18$), left hippocampus and $t=2.86$ ($x=-42$, $y=21$, $z=18$) left dorsolateral prefrontal cortex. Individual subject responses for local maxima, in terms of BOLD % signal change, relative to the global mean, are shown in Figure 3.

To evaluate differences in responses within a block, individual stimulus presentations also were evaluated as events, separating responses from the first and the second trials. In comparing the first stimuli to silence, no group differences were observed. In comparing the second stimuli to silence, greater responses in the hippocampus ($t=1.42$, $df=33$, $p<0.082$) and reduced responses in superior temporal gyri ($t=1.37$, $df=33$, $p=0.090$, right; $t=1.49$, $df=33$, $p=0.073$) were nearly significant in subjects with schizophrenia, relative to healthy controls. Responses in the dorsolateral prefrontal cortex were not significantly different. A nearly significant interaction between trial (presentation 1 vs. 2) and group was observed in the left hippocampus ($t=1.6$, $df=33$, $p=0.059$).

EEG

Subjects with schizophrenia had significantly higher P50 test/conditioning ratios than comparison subjects ($t=3.07$, $df=28$, $p=0.002$). Mean P50 ratios were 0.63 ± 0.16 for subjects with schizophrenia and 0.32 ± 0.13 for comparison subjects. P50 test/conditioning ratios were significantly correlated with the BOLD response in the fMRI sensory gating task in the left hippocampus ($R^2=0.32$, $df=29$, $p=0.001$), left dorsolateral prefrontal cortex ($R^2=0.19$, $df=29$, $p=0.015$) and nearly significant in the left thalamus ($R^2=0.11$, $df=29$, $p=0.067$).

SUBJECT SELF REPORTS

Subject reports of their experience during the task revealed that subjects with schizophrenia more often were distracted or bothered by the noise stimulus. None of the control subjects reported being bothered by the stimulus, though two complained that the scanner noise was loud. Nine of 18 subjects with schizophrenia reported being bothered or highly distracted by the stimulus. These reports ranged from descriptions of the stimulus as “a bit bothersome” to being “very hard to ignore.” One schizophrenia subject reported hearing a “phone noise” during the task, though no such noises were present in the stimulus. The most poignant comment came from a 44 year-old male subject with schizophrenia, who commented “I was trying to figure out where those little f*ckers were coming from.”

Discussion

Brain hemodynamic responses to the complex noises used in this study were robust, including activation of the primary and secondary auditory cortices, medial geniculate nuclei and the inferior colliculus. Responses in the brainstem auditory nuclei and the medial geniculate nuclei were not expected, as more sophisticated experimental designs using cardiac gating typically are required to detect responses in these small structures (16). Detecting responses in these low-level auditory structures seems reasonable, however, given the stimulus energy and broadband nature of the stimulus used.

Group differences in hemodynamic response during the sensory gating task included greater activation of the left hippocampus, bilateral thalamus and left prefrontal cortex in subjects with schizophrenia, relative to comparison subjects. This finding is similar to results from our previous fMRI study using repeated clicks to study sensory gating (5). The largest observed group difference in response was greater activation of the hippocampus in subjects with schizophrenia. The hippocampus is morphologically and neurochemically altered in schizophrenia (17). Involvement of the structure in sensory gating deficits in schizophrenia had been proposed previously (18). While our previous study is to date the only fMRI report of direct involvement of the hippocampus in gating deficits in schizophrenia, recent evidence from neurosurgical studies of patients undergoing invasive presurgical evaluation for epilepsy suggests its involvement in normal sensory gating (19–21). Animal studies have strongly implicated the involvement of the hippocampus in both normal sensory gating, and in animal models of deficient sensory gating (22–24).

Greater responses during the sensory gating task also were observed in the thalamus in subjects with schizophrenia, relative to healthy comparison subjects. The thalamus plays a key role in gating information to the cortex, mediated by the nucleus reticularis, a thin layer of GABAergic inhibitory neurons (25). Although early studies suggested involvement of the thalamus in auditory sensory gating, only recently has auditory gating been demonstrated in neurons in the nucleus reticularis of the thalamus (23).

Greater hemodynamic response in subjects with schizophrenia also was observed in the prefrontal cortex, consistent with our prior study using repeated clicks to assess gating (5). The prefrontal cortex has long been hypothesized to play a role in inhibitory processes such as sensory gating (26). Invasive recordings suggest the prefrontal cortex plays a role in the early stages of the gating response (19). Recent MEG studies further support prefrontal cortex involvement in gating responses, both in the auditory and somatosensory domains (27). The responses observed in the present study also may reflect differences in higher cognitive processes such as attention, which typically are not thought to play a dominant role in early sensory gating. Self reports in the present study indicating that many subjects with schizophrenia found the noises to be overtly distracting, suggest additional cognitive resources, which may include response of the prefrontal cortex, were engaged by these subjects. Future studies that modulate the level of distraction and control for attention are needed to further parse the role of the prefrontal cortex in sensory gating tasks.

Greater hemodynamic responses observed in the present study are consistent with physiological models of an altered balance between excitatory and inhibitory neurotransmission in schizophrenia. It is possible, for example, that the greater responses in subjects with schizophrenia reflect an inhibitory deficit stemming from abnormal GABA neurotransmission that has been proposed as a “final common pathway” for cortical dysfunction in schizophrenia (28). Such an inhibitory deficit may lead to the inappropriate excitation of a network of brain regions, as has been proposed previously (5). Alternately, the increased responses observed in the present study may stem from compensatory processes. Since no overt demands were made on subjects in the magnet, however, it is difficult to speculate about what deficit would be compensated for, if any, in the schizophrenia subjects.

The positive correlation between hemodynamic responses in the fMRI task and evoked responses during the paired-click sensory gating paradigm suggests that the “urban white noise” sensory gating paradigm may at least partially tap into neurobiological processes involved in gating mechanisms studied previously. It also is possible, however, that the correlation between the phenomena may be mediated by a common underlying biological factor not directly measured. The modest correlation coefficients observed are not unexpected given the substantial difference in both the paradigms used and the responses measured. Typical P50 auditory gating tasks, which are thought to be largely pre-attentive, record responses to discrete stimuli at a 50 ms latency. The “urban white noise” fMRI task 1) is not a discrete stimulus, lasting several seconds, and 2) incorporates both early responses, such as the P50, and later responses, which are known to be more dependent on additional cognitive processes.

There are several limitations to this study. All subjects with schizophrenia were treated with neuroleptics, which may alter their responses, or the measured BOLD signal. Braus et al (1999) has shown that neuroleptic treatment, particularly treatment with typical neuroleptics, may alter in the BOLD response in some brain regions (29). Recent studies have not, however, shown medication effects on the BOLD response in the context of bipolar disorder (30) or schizophrenia (31). Another limitation of this study is the use of silence as a baseline comparison. Because resting state activity may be altered in schizophrenia (32), future studies using graded auditory stimuli or other control conditions are necessary. An additional caveat

is that the open-ended question used to elicit the self reports described here lacked structure, and as such likely had low sensitivity to capture the salient aspects of subject's experiences.

Using a clinically meaningful sensory gating task, this study found hyper-activation of the hippocampus, thalamus and prefrontal cortex that was very similar to responses observed in our prior study using repeated clicks. Also, correlations were observed between responses to the "urban white noise" and P50 suppression as measured by EEG. Thus, our results suggest that patients' neuronal responses to simulated sensory overstimulation may share a common mechanism with responses to simple clicks as measured in a typical repeated-click paradigm. Results presented here also further support the notion of hyper-activity of the hippocampus, thalamus and prefrontal cortex as a pathological feature of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Reference List

1. Bleuler, E. Dementia praecox of the group of schizophrenias. International Universities Press; 1911.
2. Venables, PH. Input Dysfunction in Schizophrenia in Progress in Experimental Personality Research. Maher, BA., editor. Orlando, FL: Academic PRes; 1967.
3. Roth WT, Kopell BS. The auditory evoked response to repeated stimuli during a vigilance task. *Psychophysiology* 1969;6:301–309. [PubMed: 5353381]
4. Adler LE, Pachtman E, Franks RD, Peceovich M, Waldo MC, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry* 1982;17:639–654. [PubMed: 7104417]
5. Tregellas JR, Davalos DB, Rojas DC, Waldo MC, Gibson L, Wylie K, Du YP, Freedman R. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. *Schizophr Res* 2007;92:262–272. [PubMed: 17336502]
6. Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L. Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 1978;15:339–343. [PubMed: 693742]
7. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology (Berl)* 2001;156:234–258. [PubMed: 11549226]
8. Pass HL, Salzman LF, Klorman R, Kaskey GB, Klein RH. The effect of distraction on acute schizophrenics' visual tracking. *Biol Psychiatry* 1978;13:587–593. [PubMed: 728510]
9. Hotchkiss AP, Harvey PD. Effect of distraction on communication failures in schizophrenic patients. *Am J Psychiatry* 1990;147:513–515. [PubMed: 2316742]
10. McKay CM, Headlam DM, Copolov DL. Central auditory processing in patients with auditory hallucinations. *Am J Psychiatry* 2000;157:759–766. [PubMed: 10784469]
11. Edmister WB, Talavage TM, Ledden PJ, Weisskoff RM. Improved auditory cortex imaging using clustered volume acquisitions. *Hum Brain Mapp* 1999;7:89–97. [PubMed: 9950066]
12. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002;15:870–878. [PubMed: 11906227]
13. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003;19:1233–1239. [PubMed: 12880848]
14. Brett, M.; Anton, J.; Valabregue, R.; Poline, J. Region of interest analysis using an SPM toolbox. *NeuroImage*; Presented at the 8th International Conference on Functional Mapping of the Human Brain; June 2–6, 2002; Sendai, Japan. 2002. Available on CD-ROM
15. Adler LE, Olincy A, Cawthra EM, McRae KA, Harris JG, Nagamoto HT, Waldo MC, Hall MH, Bowles A, Woodward L, Ross RG, Freedman R. Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. *Am J Psychiatry* 2004;161:1822–1828. [PubMed: 15465979]

16. Guimaraes AR, Melcher JR, Talavage TM, Baker JR, Ledden P, Rosen BR, Kiang NY, Fullerton BC, Weisskoff RM. Imaging subcortical auditory activity in humans. *Hum Brain Mapp* 1998;6:33–41. [PubMed: 9673661]
17. Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus* 2001;11:520–528. [PubMed: 11732705]
18. Freedman R, Waldo M, Bickford-Wimer P, Nagamoto H. Elementary neuronal dysfunctions in schizophrenia. *Schizophr Res* 1991;4:233–243. [PubMed: 1645590]
19. Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernandez G, Schaller C, Elger CE. Neuronal substrates of sensory gating within the human brain. *Biol Psychiatry* 2003;53:511–519. [PubMed: 12644356]
20. Boutros NN, Trautner P, Rosburg T, Korzyukov O, Grunwald T, Schaller C, Elger CE, Kurthen M. Sensory gating in the human hippocampal and rhinal regions. *Clin Neurophysiol* 2005;116:1967–1974. [PubMed: 16000257]
21. Boutros NN, Mears R, Pflieger ME, Moxon KA, Ludowig E, Rosburg T. Sensory gating in the human hippocampal and rhinal regions: regional differences. *Hippocampus* 2008;18:310–316. [PubMed: 18064708]
22. Miller CL, Freedman R. The activity of hippocampal interneurons and pyramidal cells during the response of the hippocampus to repeated auditory stimuli. *Neuroscience* 1995;69:371–381. [PubMed: 8552235]
23. Krause M, Hoffmann WE, Hajos M. Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. *Biol Psychiatry* 2003;53:244–253. [PubMed: 12559658]
24. Zheng J, Yang Y, Tian S, Chen J, Wilson FA, Ma Y. The dynamics of hippocampal sensory gating during the development of morphine dependence and withdrawal in rats. *Neurosci Lett* 2005;382:164–168. [PubMed: 15911142]
25. Scheibel ME, Scheibel AB. The organization of the nucleus reticularis thalami: a Golgi study. *Brain Res* 1966;1:43–62. [PubMed: 4160184]
26. Knight RT, Scabini D, Woods DL. Prefrontal cortex gating of auditory transmission in humans. *Brain Res* 1989;504:338–342. [PubMed: 2598034]
27. Weiland BJ, Boutros NN, Moran JM, Tepley N, Bowyer SM. Evidence for a frontal cortex role in both auditory and somatosensory habituation: a MEG study. *Neuroimage* 2008;42:827–835. [PubMed: 18602839]
28. Lewis DA, Moghaddam B. Cognitive dysfunction in schizophrenia: convergence of gamma-aminobutyric acid and glutamate alterations. *Arch Neurol* 2006;63:1372–1376. [PubMed: 17030651]
29. Braus DF, Ende G, Weber-Fahr W, Sartorius A, Krier A, Hubrich-Ungureanu P, Ruf M, Stuck S, Henn FA. Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. *Schizophr Res* 1999;39:19–29. [PubMed: 10480664]
30. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 2008;165:313–320. [PubMed: 18245175]
31. Polli FE, Barton JJ, Thakkar KN, Greve DN, Goff DC, Rauch SL, Manoach DS. Reduced error-related activation in two anterior cingulate circuits is related to impaired performance in schizophrenia. *Brain* 2008;131:971–986. [PubMed: 18158315]
32. Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. Aberrant “default mode” functional connectivity in schizophrenia. *Am J Psychiatry* 2007;164:450–457. [PubMed: 17329470]

Figure 1. Schematic representation of experimental design

Two seconds of scanning was followed by 11.5 seconds of either silence or the “urban white noise” stimulus.

Figure 2. Activation of the auditory pathway in response to “urban white noise” in healthy subjects (N=35)

Activation is observed in the superior temporal gyri, bilateral medial geniculate nuclei and left inferior colliculus in a whole-brain, FDR corrected analysis. Statistical maps thresholded at FDR $q < 0.05$ and overlaid onto the group average anatomical image.

Figure 3. Greater activation of the thalamus and hippocampus in subjects with schizophrenia (N=18) relative to comparison subjects (N=17)

Individual subject responses in terms of percent signal change, relative to the global mean, are shown for the hippocampal, thalamic and prefrontal cortex local maxima. Statistical maps thresholded at $p < 0.01$ for visualization and overlaid onto the group average anatomical image.

Table 1

Brain regions showing response to auditory stimulus in all subjects.

Brain Region	t value	p-value	MNI coordinates
Superior temporal gyrus (R)	11.97	<0.001	57 -9 -6
Superior temporal gyrus (R)	9.27	<0.001	45 -30 6
Superior temporal gyrus (L)	11.27	<0.001	-48 -18 -3
Superior temporal gyrus (L)	10.79	<0.001	-60 -9 0
Superior temporal gyrus (L)	9.14	<0.001	-54 -3 -9
Middle temporal gyrus (R)	11.57	<0.001	60 -21 -9
Medial Geniculate nucleus (R)	4.54	<0.001	15 -27 -12
Medial Geniculate nucleus (L)	6.17	<0.001	-15 -27 -15
Inferior colliculus (L)	3.58	0.001	-9 -39 -12

Notes: All regions reported in table are significant at FDR $q < 0.05$.