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Sex differences in sensory gating of the thalamus during auditory interference of visual attention tasks

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Abstract

Men and women have different cognitive abilities that might reflect sex-specific neural organization. Here we studied sex effects on brain function using functional magnetic resonance imaging (fMRI) with variable acoustic noise (AN) to modulate the cognitive challenge and enhance the sensitivity for the detection of sex differences in brain activation. During the performance of a visual attention (VA) task that requires the tracking of multiple moving objects and has graded levels of difficulty, women (n=15) but not men (n=13) had shorter reaction times for “Loud” than for “Quiet” scans. Men activated more than women in the superior prefrontal and occipital cortices and the anterior thalamus. The latent connectivity of the PFC was higher with the anterior thalamus but lower with the auditory cortex for men than for women. Increases in activation with VA-load were larger for men than for women in the superior parietal and auditory cortices. Increased AN reduced brain activation in the parietal cortex and the anterior thalamus for men but not for women. Together, these sex-specific differences in brain activation during the VA task, at different cognitive and acoustic levels suggest differences in auditory gating of the thalamus for men and women.

Keywords

Acoustic noise; fMRI; Gender; Connectivity; thalamic; volumetric

Introduction

Men and women have different visuospatial skills (Geary D et al., 2000; Neave N et al., 1999; Postma A et al., 2004; Postma A et al., 1999), possibly due to the effects of sex hormones during brain development early in life (Kolata G, 1979). fMRI is a powerful tool to explore sex differences in brain function. Several fMRI studies showed that men have larger activation than women for sensory (Cowan R et al., 2000), cognitive and motor (Bell E et al., 2006; Gur R et al., 2000), and emotional (Schienle A et al., 2005; Shirao N et al., 2005) tasks. On the other hand, studies on working memory (Goldstein J et al., 2005; Piefke M et al., 2005),

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electrodermal stimulation (Butler T et al., 2005), and language (Baxter L et al., 2003) reported that women have larger activation than men. Sex-differences in the lateralization of brain function for language (Rossell S et al., 2002; Shaywitz B et al., 1995), verbal working memory (Speck O et al., 2000), and tactile discrimination (Sadato N et al., 2000) were also reported. These findings suggest differential recruitment on network resources for men and women during cognitive performance, and could reflect sex-specific differences in the organization of the brain.

However, sex differences in fMRI activation could also reflect different baseline activity for men and women due to different effects of physical stressors, such as the high sound pressure levels (*spl*) of AN produced by the scanner during the fMRI acquisition. As an example, for working memory tasks, we and others showed that increases in activation in the PFC and occipital cortices due to higher AN (Haller S et al., 2005; Tomasi D et al., 2005; Tomasi D et al., 2006) differed between men and women (Tomasi D *et al.*, 2005).

Therefore, we aimed to evaluate further potential sex differences in brain activity in response to variable AN (Tomasi D *et al.*, 2005) using a well-validated VA task that involves the tracking of multiple moving objects (Chang L et al., 2004; Tomasi D et al., 2004, 2006). This task is especially useful for detecting differential thalamic activation between men and women because it produces larger activation of the thalamus than many other cognitive tasks (Tomasi D *et al.*, 2006). We hypothesized that during the performance of this VA task, men will have larger thalamic and cortical activation than women because men have higher hematocrit, which would lead to greater BOLD signals (Levin J et al., 2001). Furthermore, we hypothesized that, even after co-variation for hematocrit differences, there would be significant sex by AN interactions in the thalamus, since it is the major structure for relaying and gating sensory afferents to the cortical regions (McCormick D and T Bal, 1994), and women were shown to have less suppression or gating of auditory evoked response than men (Hetrick W et al., 1996). The lower suppression in women suggests less neuronal response and might also explain why women perceive unexpected auditory noise as louder (Kimura D, 1999) and have larger startle responses (Kofler M et al., 2001) than men.

Experimental Procedures

Participants

Twenty-eight healthy, non-smoking, right-handed participants (13 men, age 32 ± 8 years, education: 16 ± 2 years; 15 women, age 28 ± 8 years, education: 16 ± 2 years) were enrolled in the study. Prior to the study, each participant signed a written consent, approved by the Institutional Review Board at Brookhaven National Laboratory. These participants were screened carefully with a detailed medical history, physical and neurological examination, blood tests (see below) and urine toxicology, to ensure they fulfilled all study criteria. Inclusion criteria were: 1) age 18 years or older, 2) normal vision and hearing (assessed by pure-tone audiometry in a soundproof room), 3) English as their first language, 4) healthy and on no medications (except for vitamins), and 5) ability to provide consent and willingness to participate in the study. Exclusion criteria were: 1) current or past drug abuse or dependence (including alcohol and nicotine) or positive urine toxicology (for amphetamines, benzodiazepines, cocaine, marijuana and opiates), 2) any past or current medical or neuropsychiatric illnesses, 3) significant abnormalities on screening blood tests, including a complete blood count, a chemistry panel, thyroid function tests, a positive HIV test or Hepatitis tests, 4) pregnancy (assessed by a urine test), during menstruation, or breast-feeding for female subjects, 5) history of head injury with loss of consciousness > 30 minutes, 6) any contraindications for MRI (e.g. metallic implants or claustrophobia).

VA paradigm

Subjects performed a set of non-verbal VA tasks with a blocked design, which involved mental tracking of two, three, or four out of ten moving balls (Chang L *et al.*, 2004; Culham JC *et al.*, 1998; Jovicich J *et al.*, 2001; Tomasi D *et al.*, 2004). The “task” blocks are composed of five “TRACK” and respond periods. In these periods, two, three, or four out of ten target balls were briefly highlighted, and then all balls started to move; the subjects’ task was to fixate on the center cross and track the target balls as they moved randomly across the display (12° of the central visual field) with instantaneous angular speed of $3^\circ/\text{second}$. The 10 balls moved in a simulated Brownian motion, and collided with, but did not penetrate, each other. At the end of “TRACK” periods, the balls stopped moving and a new set of balls was highlighted; the subjects’ task was to press a button if these balls were the same as the target set. Button press events were used to record performance accuracy and reaction times during the fMRI tasks. After a 0.5 second delay, the original target balls were then re-highlighted to re-focus the subjects’ attention on these balls. The “control” blocks are composed of five “DO NOT TRACK” periods. In these periods, all 10 balls moved and stopped in the same manner as during “TRACK” periods; however, no balls were highlighted, and subjects were instructed not to track the balls and view them passively; the use of this resting condition allowed us to control for the confounding effect of visual input activation. This task activates attention-related brain regions comprising prefrontal, parietal, and occipital cortices, thalamus, and the cerebellum. Similar activation patterns were observed in studies of sustained attention (Fassbender C *et al.*, 2004; Lawrence N *et al.*, 2003), selective attention (de Fockert J *et al.*, 2001; Le T *et al.*, 1998), visual search (Leonards U *et al.*, 2000), object recognition (Adler C *et al.*, 2001), attention to visual motion (Buchel C *et al.*, 1998), and orienting VA (Arrington C *et al.*, 2000).

The stimuli (movies in “Audio Video Interleave” format) were created using Matlab, and presented to the subjects on MRI-compatible goggles connected to a personal computer. The display software was synchronized precisely with the MR acquisition using an MRI trigger pulse. All response button events during stimulation were recorded using the Visual Basic and Visual C languages, to determine RT and performance accuracy. Subjects performed a brief training session (~10 minutes) of a shortened version of the paradigm outside of the scanner to ensure that they understood and were able to perform the tasks.

Data acquisition

Subjects underwent BOLD fMRI in a 4 Tesla whole-body Varian/Siemens MRI scanner using a T2*-weighted single-shot gradient-echo planar imaging sequence with ramp-sampling (TE/TR=25/3000 ms, 4 mm slice thickness, 1 mm gap, typically 33 coronal slices, 48×64 matrix size, 4.1×3.1 mm in-plane resolution, 90° -flip angle, 124 time points, bandwidth: 200.00 kHz for “Quiet”, and 219.78 kHz for “Loud” scans; readout gradient frequency: 1.16 kHz for “Quiet”, and 1.22 kHz for “Loud”) covering the whole brain. The resonant modes of vibration of our Sonata/Siemens gradient system provide a maximum 12 dBA *spl*-difference (a four-fold increase) between “Quiet” and “Loud” fMRI scans (Tomasi D *et al.*, 2005; Tomasi D and T Ernst, 2003). The entire set of VA tasks was performed twice under two different *spl*: 92 dBA (the equivalent to subway noise) for “Quiet” and 104 dBA (the equivalent to lawn mower noise) for “Loud”; thus, we used the maximum achievable *spl*-difference to maximize the effect of acoustic noise on brain activation. The acoustic noise produced by the “Quiet” and “Loud” protocols have very similar frequency distributions (Tomasi D *et al.*, 2005). Half the studies started with the “Quiet” session; the remaining studies started with the “Loud” session to control for practice effects (Tomasi D *et al.*, 2004). The order of VA-load conditions (2-, 3-, and 4-ball) was randomized for each subject to minimize any ordering effect. Padding was used to minimize motion. The *spl* at the subjects’ ears was reduced through the use of earplugs

(28dBA; Aearo Ear TaperFit 2; Aearo Company) and headphones (30dBA; Commander XG MRI Audio System, Resonance Technology, Inc.).

Anatomical images were collected using a T1-weighted 3D-MDEFT sequence (Lee JH et al., 1995) (TE/TR = 7/15ms, $0.94 \times 0.94 \times 3$ mm spatial resolution, axial orientation, 256 readout and 192×48 phase-encoding steps, 8 minutes scan time) and a modified T2-weighted Hyperecho sequence (Hennig J and K Scheffler, 2001) (TE/TR = 42/10000 ms, echo train length = 16, 256×256 matrix size, 30 coronal slices, 0.86×0.86 mm in-plane resolution, 5 mm thickness, 1 mm gap, 2 min scan time), which were reviewed to rule out gross morphological abnormalities in the brain.

Data processing

The first four volumes in the time series were discarded to avoid non-equilibrium effects in the fMRI signal. Subsequent analyses were performed with the statistical parametric mapping package SPM2 (Wellcome Department of Cognitive Neurology, London UK). A six-parameter rigid body transformation was used for image realignment, and to correct for head motion. Head motion was less than 1-mm translations and 1° -rotations for all scans. The realigned datasets were normalized to the standard brain (Talairach) using a 12-parameter affine transformation (Ashburner J et al., 1997), and a voxel size of $3 \times 3 \times 3$ mm³. An 8-mm full-width-half-maximum Gaussian kernel was used to smooth the data. A general linear model (Friston KJ et al., 1995) was used to calculate the activation maps for each condition (2-, 3-, and 4-balls) and each subject. We used blocked analysis based on a box-car design convolved with the canonical hemodynamic response function (HRF), and low-pass (HRF) and high-pass (cut-off frequency: 1/256Hz) filters.

Statistical analyses

The calculated BOLD maps (% signal change) for each trial and subject were included in a two-way repeated measures ANOVA model with two groups (men and women), six conditions (2-, 3-, and 4-balls; “Loud”, and “Quiet”), and the hematocrit (Hct) level as a nuisance covariate in SPM2. Brain activation and deactivation clusters with at least 15 voxels (400 mm³) and $p < 0.05$ (corrected for multiple comparisons) were considered significant in the group analysis (Friston KJ et al., 1994). Volumes-of-interest (VOI; 10 mm diameter spheres) were defined at the center of activations clusters that demonstrated sex or AN effects on brain activation.

Brain connectivity

The dynamic causal model (DCM) (Friston K et al., 2003), implemented in SPM5 (Wellcome Department of Cognitive Neurology, London UK), was used to estimate the latent (in absence of input) and induced (input-sensitive) connectivity. Specifically, to define the dynamic causal model we selected three brain regions of brain regions that demonstrated sex or sex $\times$ VA-load effects in fMRI activation: the medial frontal gyrus, Brodmann area (BA) 6 (MFG6), the anterior thalamus (ATHA), and the insula, BA13 (INS13). Functional time-series were extracted from these regions, using spherical (6 mm radius) volumes-of-interest (VOIs), and entered into a fully interconnected DCM model. Separate DCM analyses were carried out for each condition (AN: “Quiet”, “Loud”; VA-Load: 2-, 3-, and 4-balls) and for the left and right brain hemispheres (the left and right networks) using 156 time series (26 subjects $\times$ 6 conditions; DCM estimations did not converge for 2 subjects). We based the Bayesian probability estimation on the assumption that the coupling parameters have a half-life of 8 s or less (Friston K et al., 2003).

Coupling parameters (i.e. network connections) with a marginal posterior probability above 95% in the fixed-effect Bayesian DCM-analyses (2-, 3-, and 4-balls conditions) were averaged using the SPM5 function `spm_dcm_average.m`) were considered significant; paired t -tests

across subjects were used to determine whether latent connections were bi-directional (symmetric matrix coefficients) or unidirectional (asymmetric matrix coefficients). Latent and induced connections were evaluated with additional Bayesian random-effects DCM estimations (using the SPM5 function `spm_dcm_sessions.m`) to make inferences about the population; for these analyses, we constrained the coupling parameters to only those that were significant in the fixed-effects DCM estimation. To evaluate potential connectivity differences due to sex and VA-load for each VOI, the estimated coupling parameters for each subject and condition were included in a two-way repeated measures ANOVA model with two groups (males and females) and three conditions (2-, 3-, and 4-balls) using StatView (SAS Institute Inc. Cary, NC). Separate analyses were carried out for each AN condition (“Quiet” or “Loud”) and for the differential AN condition (“Loud” – “Quiet”).

Region-of-interest (ROI) analysis

Functional ROIs with an isotropic volume of 0.73 ml were defined at the cluster centers of brain activation to extract the average BOLD signal from these regions. A repeated measures ANOVA was conducted for each ROI to validate the voxel-by-voxel. Specifically, a 9 mm isotropic cubic mask was created and centered at the exact coordinates in Table 1 and kept fix across subjects and conditions. The average and standard deviation of BOLD responses in these regions were computed from the SPM2 contrast images using the mask and a custom program written in IDL (Research Systems, Boulder, CO). Linear regression analyses of load-related signal changes (from 2-balls to 4-balls) and AN-related signal changes (from “Quiet” to “Loud” scans) were computed to evaluate the dynamic range of hemodynamic responses in the ROIs. Additional regression analyses of behavioral measures (RT and performance accuracy) on BOLD responses in the brain were conducted to determine the significance of brain activation in relation to visuospatial performance. Statistical significance for ROI analyses was defined as $p = 0.05$ (uncorrected).

Segmentation-based volumetry of the thalamus

The thalamus was segmented and its volume was calculated to further determine whether the fMRI sex differences were associated with morphological differences. For this purpose, the T1-weighted structural images were corrected for inhomogeneous B1-sensitivity, and subsequently the images were normalized to the standard (Talairach) frame of reference, to account for differences in intra cranial volume between men and women, and segmented into gray- and white-matter, and cerebrospinal fluid in SPM2. The volume of the thalamus was calculated from the segmented gray matter using a customized mask of the extended thalamus; specifically, the volume of the normalized thalamus was computed as the volume of the segmented gray matter within the extended thalamic mask. This simple automated calculation minimizes human intervention and errors in the determination of thalamic volumes; differently to the voxel-based morphometry method that measures the gray/white matter density (Ashburner J and K Friston, 2000), our method measures the total gray matter volume within a volume-of-interest in stereotactic space. An operator that was blind to the sex of the subjects carefully ensured complete overlap between the mask and the thalamus and absence of overlap between the mask and other gray matter structures for all subjects. Six structural scans (2 in men and 4 in women) had poor quality due to excess motion and were excluded from further analysis.

Results

None of the participants had head injury

All women were premenopausal and primarily in the early luteal phase (mean $\pm$ SD; 15 ± 6 days in their menstrual cycles, based on the previous menstruation cycle) on the day of the study. As expected, blood hematocrit values were higher for men (46.0 ± 2.2) than for women

(38.4 ± 2.5 ; $p < 0.0001$; two sample t -test). The normalized thalamic volume also was larger for men (10.61 ± 0.84 ml; L&R) than for women (9.81 ± 0.72 ml; L&R; $p = 0.027$). Performance accuracy during the fMRI tasks did not differ between male and female subjects (Fig 1). For both groups, accuracy was significantly lower for the more demanding (4-ball) task as compared to the 2- and 3-ball tasks ($p < 0.0001$; two sample t -test), reflecting the increased difficulty of the tasks; however, it did not differ between “Loud” and “Quiet” scans, or between men and women (3-ways ANOVA: sex $\times$ VA-load $\times$ AN; $F < 3.1$; $DF = 26$). During “Loud” scans, women tended to perform better than men during the 4-ball tracking condition; this difference, however, was not statistically significant ($p = 0.07$). The reaction time (RT) also did not differ between men and women, or among the 2-, 3-, and 4-ball tracking tasks, in agreement with our previous studies (Chang L *et al.*, 2004; Tomasi D *et al.*, 2004, 2006). However, for the 3- and 4-ball tracking tasks, only women had shorter RT during “Loud” scans than during the “Quiet” scans (2-ways ANOVA: VA-load $\times$ AN; women: $p < 0.03$, $F = 3.78$, $DF = 27$; men: $p < 0.55$, $F = 0.36$, $DF = 27$).

Brain activation—The VA tasks activated a bilateral network (conjunctive analysis: 2-, 3-, and 4-balls combined; Table 1 and Fig 2, “Main”) that includes the PFC [anterior cingulate (Brodmann area 32, or ACG32), inferior (IFG47), middle (MFG6, MFG9, and MFG10), and superior (SFG8) frontal gyri], parietal [inferior (IPC40), and superior (SPC7), and the postcentral gyrus (PostCG7)], and occipital [fusiform gyrus (FusG37)] cortices, anterior (ATHA) and dorsal medial (DMTHA) thalamus, and the cerebellum, as reported in our prior studies (Chang L *et al.*, 2004; Tomasi D *et al.*, 2004, 2006). Conversely, the tasks deactivated the limbic lobe [ACG24, posterior cingulate gyrus (PCG31)], cuneus7 and precuneus (Precun7), and the posterior insula (Ins13).

Since the higher hematocrit in men than in women could alter BOLD signals (Levin J *et al.*, 2001), the group analyses included hematocrit as a covariate. However, sex differences persisted after co-variation for the hematocrit. Brain activation was larger for men than women bilaterally in the PFC (MFG6, MFG9, and SFG8), and the ATHA (Table 1 and Fig 2, “Sex”); women did not activate more than men in any brain region. However, brain deactivation in the Precun7 was larger for women than for men. Brain activation did not correlate with the normalized thalamic volume in any brain region (voxel-wise correlation analysis in SPM).

Increased VA-load from tracking 2-balls to 4-balls produced larger activation in the left MFG6, FusG37, and the DMTHA, and bilaterally in the SPC7, IPC40, and PostCG7 (Table 1 and Fig 2). The VA-load effect on activation was larger for men than for women in the right IFG47, while the VA-load effect on deactivation was larger for women than for men in the auditory cortex (Ins13) ($p_{\text{corr}} < 0.001$; Fig 2, VA-load $\times$ sex interaction).

“Loud” scans produced lower BOLD signals than “Quiet” scans in the left SPC7 and increased deactivation in the right Precun7. For men, increased AN reduced activation in the parietal cortices and ATHA ($p_{\text{corr}} < 0.001$; Fig 2), and did not increase activation in any brain region. For women, increased scanner noise did not change activation or deactivation in any brain region. The AN-related deactivation was significantly larger for men than for women in the left SPC7 and the ATHA ($p_{\text{corr}} < 0.002$; Fig 2, AN $\times$ Sex interaction).

ROI results—The ROI analyses demonstrated that BOLD signals were larger for men than for women in the superior PFC (MFG6, SFG8, and ACG32) and in the occipital cortex (Cuneus18 and Precun7), and that there were significant interactions between load and sex in cortical regions (SPL7, and Ins13), and between AN and sex in subcortical regions (ATHA) and the cerebellum (Fig 3). Across subjects, the VA-load responses (differential “4-balls” – “2-balls” BOLD signals for “Quiet” scans) and the AN responses (differential “Loud” – “Quiet” BOLD signals for the “4-balls” task) correlated negatively in the VA network ($p <$

0.001). Decreased performance accuracy from 2-balls to 4-balls was associated with VA-load activation of the DMTHA (Fig 4) and AN-deactivation of the SPC7 (not shown; $R = 0.39$, $p = 0.05$). Increased RT from “Quiet” to “Loud” was associated with differential AN-activation of the ATHA and differential AN-deactivation of the DMTHA (Fig 4).

Latent and Induced Connectivity—A DCM analysis was performed to study the interconnections among brain regions that showed significant effect of sex (MFG6, ATHA) or sex $\times$ VA-load (Ins13). The input stimulus was assumed to be located in the ATHA, and all coupling parameters were freely adjusted by SPM5. The DCM analysis demonstrated that Ins13, MFG6 and the ATHA have bi-directional latent (stimulus-free) connections (predominantly on the left side of the brain). The latent connectivity of the Ins13 with the MFG6 and the ATHA (left side only) was negative while the latent connectivity of the right ATHA and the right MFG6 was positive. The VA task induced connectivity between the left Ins13 and left MFG6. The task also induced self-connections in the MFG6.

Latent and Induced Connectivity vs. VA-load, sex, and AN—VA-load modulated both latent and induced connectivity. Increased VA-load increased the (bi-directional) latent connectivity between the MFG6 and the Ins13 ($p < 0.007$; two-way repeated measures ANOVA); this connection showed also an interaction between VA-load and sex ($p = 0.04$; right side only). During “Quiet” scans, men showed higher ATHA $\leftrightarrow$ MFG6 latent connectivity (left side and 4-balls only; $p = 0.02$) and lower Ins13 $\leftrightarrow$ MFG6 latent connectivity (right side and 4-balls only; $p = 0.005$). Increased AN during the more demanding 4-ball tracking task reduced the Ins13 $\leftrightarrow$ MFG6 latent connectivity for women ($p = 0.05$) but not for men; however, this differential connectivity decrease between the groups was not statistically significant ($p = 0.1$). The induced Ins13 $\leftrightarrow$ MFG6 connectivity increased with VA-load ($p = 0.003$) and exhibited an interaction between VA-load and sex ($p = 0.04$). The self-connectivity in the right MFG6 was modulated by VA-load ($p = 0.01$), and the self-connectivity of the left MFG6 had a VA-load $\times$ sex interaction effect ($p = 0.04$). During “Quiet” scans, women showed higher Ins13 $\leftrightarrow$ MFG6 induced connectivity (right side and 4-balls only; $p = 0.01$) and MFG6 self-induced connectivity (left side and 3-balls only; $p = 0.04$) than men.

Discussion

This is the first study that evaluated sex-differences in the influence of acoustic noise on brain activation associated with VA. The major findings are that for the VA task: 1) men have higher activation in the superior PFC, occipital cortices, and the ATHA and higher PFC $\leftrightarrow$ ATHA connectivity than women, while women have higher PFC $\leftrightarrow$ Ins13 connectivity than men; 2) for men, increased AN reduced brain activation in the SPC and the ATHA; 3) brain activation in women was less affected by increased cognitive load or increased AN compared to men; and 4) AN-modulation in the ATHA was positively related to RTs, while VA-load modulation in the DMTHA was inversely related to performance accuracy.

Men and women have different cognitive abilities that may reflect effects of sex hormones or differential brain development on the functional organization of the brain. Neuropsychological studies have shown that men tend to perform better than women on tasks to evaluate visuospatial skills (mental rotation) (Rilea S et al., 2004), motor function (Ruff R and S Parker, 1993), perceptual ability (Tirre W and K Raouf, 1994), and mathematical reasoning (Benbow C and J Stanley, 1983; Gallagher A et al., 2000). Women, on the other hand, tend to perform better than men on tests of verbal (Maitland S et al., 2004) and spatial (Duff S and E Hampson, 2001) working memory, precision manual tasks and fine motor coordination (Ruff R and S Parker, 1993), and mathematical calculation (Carr M et al., 1999) tests. In this study, women responded faster, without drop in accuracy, during “Loud” than during “Quiet” scans for the 3- and 4-ball tracking conditions (this effect was not statistically significant in men). This

suggests that periodic noise from the MRI scanner may be advantageous for visual tracking of moving objects. The larger AN effect on reaction times in women may reflect their larger startle responses (Kofler M *et al.*, 2001) compared to men. The women's perception of the "Loud" condition as being even louder could reflect lesser sensory gating (Hetrick W *et al.*, 1996) and hence lower BOLD responses in the thalamus for women than for men. Women tended to perform better than men during the more difficult condition (4-ball tracking), and especially during the "Loud" scan; this difference was not statistically significant, possibly due to the limited sample size and the relatively large variability of the behavioral responses.

The negative latent connectivity between the MFG6 and the Ins13 during "Quiet" scans was larger for women than for men, which probably contributes to the sex $\times$ VA-load interaction on the right latent connectivity of the MFG6 and the Ins13. Conversely, the positive latent connectivity between the MFG6 and the ATHA during "Quiet" was larger for men than for women. The significance of these connections is unclear; however, they might be related to the sensory gating function of the thalamus. Electrophysiological studies have shown that the thalamus controls the flow of sensory-motor information to and from the cortex (McCormick D and T Bal, 1994). This sensory gating function of thalamic neurons has been demonstrated experimentally in rodents (Krause M *et al.*, 2003) and other species (Ciancia F *et al.*, 1988; Schall U *et al.*, 1999). Sensory gating is modulated by a dopaminergic/glutamatergic mechanism (Schall U *et al.*, 1999) involving the brainstem, hypothalamus, and cerebral cortex. In sleeping or anesthetized animals, this mechanism generates the spontaneous spindle waves (0–15 Hz) of slow-wave sleep (Steriade M *et al.*, 1993) that disconnect the cerebral cortex from sensory input, probably to minimize sensory interference. Thus, it appears that the lesser auditory gating of the thalamus in the females might reduce the latent connectivity between the thalamus (ATHA) and the PFC (MFG6), but increase inhibitory connectivity between the PFC (MFG6) and auditory cortices (Ins13). This finding could also reflect a reduction in the flow of auditory information to the PFC.

The induced Ins13 $\leftrightarrow$ MFG6 connectivity was modulated by the VA-load and also exhibited a VA-load $\times$ sex interaction. This suggests that deactivation (defined as a negative BOLD response) of the Ins13 reflects inhibition (Tomasi D *et al.*, 2006) rather than a purely hemodynamic "blood stealing" mechanism (Raichle ME and DA Gusnard, 2002).

During the VA task, women also responded faster during louder conditions (Fig 1), and showed AN $\times$ Sex interactions in the ATHA (Fig 3), indicating that brain activation was less affected by acoustic noise in women than in men. The positive association between AN-modulation in the ATHA and increased RTs (Fig 4) further support our conclusion that men had to reduce activation in this hyperactive region (Figs 2 and 3) in order to keep their speed during the louder condition. Thus, it is possible that the lack of activation in the ATHA (Fig 3), or lesser sensory gating, may be advantageous for women to cope with the increased AN.

We recently evaluated the AN effect on working memory processing using the same precise and reproducible 12dBA *spl*-difference between "Loud" and "Quiet" scans used in this study, and found that for healthy volunteers, louder scanner noise increased activation in the occipital cortices, PFC, and the cerebellum (Tomasi D *et al.*, 2005). We further demonstrated that acoustic noise during working memory tasks has differential effects on brain activation in HIV patients compared to control subjects (Tomasi D *et al.*, 2006) and a right lateralization of AN-activation for female, but not for male subjects (Tomasi D *et al.*, 2005). In the present study on the VA task, increased AN led to reduced brain activation in the parietal cortices and the ATHA in men but not in women. We cannot determine whether the activation differences reflect differences during "task" or "rest" because the BOLD-fMRI signal only reflects relative changes between two conditions (e.g. from "rest" to "task"). However, this finding might reflect higher hemodynamic baseline ("rest") during louder conditions in these regions. During

the demanding sustained attention “TRACK” periods of this VA task, the hemodynamic response in these regions may have reached its maximum value for “Quiet” scans; therefore, additional AN-related hemodynamic increases were not possible. In contrast, during “rest” periods, the lower hemodynamic demands could have enabled a higher baseline for “Loud” than for “Quiet” scans. Therefore, the AN-related activation decreases might reflect lower hemodynamic bandwidth in parietal cortices and ATHA in men compared to women.

A model of limited dynamic range of hemodynamic responses in this study is supported by the negative correlations of VA-load and AN responses in the cortical and subcortical regions, which may reflect the limited capacity of the VA network (Tomasi D *et al.*, 2005; Tomasi D *et al.*, 2006). The larger VA-load effect on activation in the right DLPFC (IFG47) and the lower VA-load effect on deactivation in the insula for men than for women highlight sex-specific differences. Specifically, under increased VA-load conditions, men may shift attention to the balls to be tracked, causing larger parietal activation. In contrast, women may reduce attention to the AN, resulting in larger deactivation of auditory cortices (posterior insula), but allowing more focused attention to perform the task and having faster reaction times. This differential brain response could underlie the tendency to better performance accuracy during the more demanding 4-ball tracking task for women compared to men (Fig 1).

Some of the sex differences observed in other fMRI studies might be attributable to the higher hematocrit in men than in women, which could alter the BOLD responses (Levin J *et al.*, 2001). However, in our analysis, the higher hematocrit in men than in women cannot explain the larger activation in the former group because we co-varied for the hematocrit level. Therefore, the larger activation for men than for women in this study reflects sex-specific differences in the functional organization of the brain beyond that observed with hematocrit-related increased in BOLD signals in men than women.

Men also had larger thalamic volume than women, even after controlling for differences in intracranial volume. This finding is consistent with previous findings that showed larger thalamic volume for men than for women (Chang L *et al.*, 2005). Larger thalamic volume may be related to a larger number of neurons supporting greater neuronal activity in the thalamus and may partially explain the larger hemodynamic responses in the thalamus (Fig 3) for men than for women during the VA task. The lack of correlation between BOLD responses and the normalized thalamic volume suggests that higher thalamic activation in men does not simply reflect a larger thalamic volume. However, this preliminary finding could also reflect the small sample size and the large variability of the fMRI signals. Finally, the origin of behavioral and functional sex differences here reported could be partially attributed to cultural differences between men and women.

Conclusions

We evaluated the effects of sex on brain activation for VA tasks using high field (4 Tesla) BOLD-fMRI with variable levels of AN. This study demonstrates greater activation and AN-induced modulation of activation in the PFC and ATHA in men compared to women. Furthermore, men demonstrated higher connectivity between the PFC and the anterior thalamus than women. Women, on the other hand, showed higher connectivity between the PFC and the auditory cortex than men. With increased AN, women demonstrated faster RT but no changes in brain activation, whereas in men, increased AN did not change RT but reduced activation in the SPC7 and the ATHA. Differential load-effects in the DMTHA and deactivation of the ATHA with AN were associated with increased RT from “Quiet” to “Loud” scans. Compared to men, brain activation in women was less affected by increased cognitive load or increased AN, which might be related to the lower sensory suppression during these conditions. Together, these sex-specific differences in brain activation during the VA task, at

varying cognitive and acoustic levels, suggest differences in auditory gating of the thalamus for men and women.

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Glossary

ACG24 and 32

Anterior cingulate gyrus; Brodmann areas (BAs) 24 and 32

AN

Acoustic noise

ANOVA

Analysis of variance

ATHA

Anterior thalamus

BOLD

Blood oxygenation level dependent

Cuneus7

Cuneus; BA 7

DCM

Dynamic causal modeling

DMTHA

Dorsal medial thalamus

fMRI

Functional magnetic resonance imaging

FusG37

Fusiform gyrus; BA 37

Hct

Hematocrit

HIV

Human immunodeficiency virus

HRF

Hemodynamic response function

IFG47

Inferior frontal gyrus; BA 47

Ins13

Insula; BA 13

IPC40

Inferior parietal cortex; BA 40

L&R	left and right
MFG6	9, 10, Medial frontal gyrus; BAs: 6, 9, and 10
MRI	magnetic resonance imaging
PCG31	Posterior cingulate gyrus; BA 31
PFC	Prefrontal cortex
PostCG7	Postcentral gyrus; BA 7
Precun7	Precuneus; BA 7
ROI	Region-of-interest
RT	reaction time
SD	Standard deviation
SFG8	Superior frontal gyrus; BA 8
SPC7	Superior parietal cortex; BA 7
<i>spl</i>	sound pressure level
SPM2 and 5	Standard parametric mapping; versions 2 and 5
TE/TR	Echo time/Repetition time
VA	Visual attention
VOI	Volume-of-interest

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Fig 1.

Performance accuracy (top row) and reaction times (bottom row) for “Loud” (black) and “Quiet” (light-gray) scans in men and women, as a function of the number of tracked balls (VA-load). Note lower performance in men during the 4-ball task with the loud condition. Sample size: 13 healthy men and 15 healthy premenopausal women during the early luteal phase of the menstruation cycle.

Fig 2.

Statistical parametric maps of BOLD signals. VA: conjunctive analysis for all participants and conditions; Gender: Males > Females, conjunctive analysis for all conditions; Load: 4-balls > 2-balls, all participants and AN-conditions; AN: “Loud” – “Quiet”, all participants and load conditions; VA-Load × Gender: $[4\text{-balls} - 2\text{balls}]_{\text{Males}} > [4\text{-balls} - 2\text{balls}]_{\text{Females}}$; AN × Gender: $[\text{“Loud”} - \text{“Quiet”}]_{\text{Males}} > [\text{“Loud”} - \text{“Quiet”}]_{\text{Females}}$. Sample size: 13 healthy men and 15 healthy premenopausal women in the midcycle phase. Random-effects analyses (two-way repeated measures ANOVA); color bars show the *T*-score windows. Please also see Figure 3 for more detailed analyses of these regional changes in each group.

Fig 3.

Average BOLD specific signals in ROIs (Table 1). ROI-volume = 0.73 cc. Sample size: 13 healthy men and 15 healthy premenopausal women in the early luteal phase.

Fig 4. Statistical map of interaction ($-\text{AN} \times \text{Gender}$: [$[\text{"Loud"} - \text{"Quiet"}]_{\text{Females}} > [\text{"Loud"} - \text{"Quiet"}]_{\text{Males}}$) effects on BOLD signals (top left); the color bar is the t -score window. Average BOLD signals in specific ROIs (Table 1) as a function of behavioral data (top right, and bottom left and right). ROI-volume = 0.73 cc.

Table 1

Location of major areas of brain activation in the Talairach frame of reference, and statistical significance of BOLD responses in these regions.

Brain Region	Side	x	y [mm]	z	VA	Sex	T-scores	Load	AN
ACG32	C	-3	21	39	5.7*	6.0*	NS	NS	NS
ACG24	C	3	36	3	-7.8*	NS	NS	NS	NS
IFG9	L	-42	12	24	10.0*	NS	NS	NS	NS
	R	39	12	24	4.9*	4.4*	NS	NS	NS
IFG47	L	-30	21	-3	7.9*	NS	NS	NS	NS
	R	39	15	-6	6.9*	NS	NS	NS	NS
SFG8	R	21	15	45	4.1*	5.5*	NS	NS	NS
MFG6	L	-33	12	48	9.1*	4.4*	4.8*	4.8*	NS
	R	21	-3	48	11.7*	NS	2.9	NS	NS
MFG10	L	-30	42	18	9.5*	NS	NS	NS	NS
	R	33	48	18	6.7*	NS	6.7*	NS	NS
ATHA	L	-15	-9	9	6.1*	4.0*	NS	NS	NS
	R	9	-9	6	4.0*	3.8*	NS	NS	NS
DMTHA	L	-15	-24	-6	6.0*	NS	4.47	NS	NS
Ins13	L	-36	-15	15	-8.0*	NS	NS	NS	NS
	R	36	-18	15	-8.7*	NS	NS	NS	NS
Cuneus7	C	3	-66	30	-21*	NS	NS	NS	NS
Cuneus18	C	3	-78	9	NS	7.2*	NS	NS	NS
FusG37	L	-36	-57	-12	5.9*	NS	5.3*	NS	NS
	R	39	-54	-12	3.3*	NS	2.9	NS	NS
Precuneus7	L	-15	-69	39	-5.7*	7.1*	NS	NS	NS
	C	3	-48	48	-4.4*	NS	NS	NS	-3.37
CG24	C	0	-9	39	-5.5*	NS	NS	NS	NS
PCG31	L	-12	-54	21	-19.4*	NS	NS	NS	NS
	R	6	-54	18	-19.0*	NS	NS	NS	NS
IPC40	L	-36	-51	51	15.9*	3.0*	5.2*	5.2*	-4.0*
	R	27	-39	51	19.5*	4.6*	4.8*	4.8*	NS
SPC7	L	-30	-57	57	19.9*	NS	5.3*	5.3*	NS
	R	27	-48	63	22.0*	4.6*	4.8*	4.8*	NS
PostCG7	C	6	-48	69	11.1*	NS	4.8*	4.8*	NS
Cerebellum	C	3	-75	-12	9.4*	NS	NS	NS	NS

Sample size: 13 healthy men and 15 healthy women. VA: conjunctive analysis for all participants and conditions; Sex: Male > Female, conjunctive analysis for all conditions; Load: 4-balls > 2-balls, all participants and AN-conditions; AN: "Quiet" - "Quiet", all participants and load conditions. Bonferroni corrections: (*) Cluster-level corrected $p < 0.001$, (V) Cluster-level corrected $p < 0.05$.