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The state of tranquility: Subjective perception is shaped by contextual modulation of auditory connectivity

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Abstract

In this study, we investigated brain mechanisms for the generation of subjective experience from objective sensory inputs. Our experimental construct was subjective tranquility. Tranquility is a mental state more likely to occur in the presence of objective sensory inputs that arise from natural features in the environment. We used functional magnetic resonance imaging to examine the neural response to scenes that were visually distinct (beach images vs. freeway images) and experienced as tranquil (beach) or non-tranquil (freeway). Both sets of scenes had the same auditory component because waves breaking on a beach and vehicles moving on a freeway can produce similar auditory spectral and temporal characteristics, perceived as a constant roar. Compared with scenes experienced as non-tranquil, we found that subjectively tranquil scenes were associated with significantly greater effective connectivity between the auditory cortex and medial prefrontal cortex, a region implicated in the evaluation of mental states. Similarly enhanced connectivity was also observed between the auditory cortex and posterior cingulate gyrus, temporoparietal cortex and thalamus. These findings demonstrate that visual context can modulate connectivity of the auditory cortex with regions implicated in the generation of subjective states. Importantly, this effect arises under conditions of identical auditory input. Hence, the same sound may be associated with different percepts reflecting varying connectivity between the auditory cortex and other brain regions. This suggests that subjective experience is more closely linked to the connectivity state of the auditory cortex than to its basic sensory inputs.

Introduction

Humans experience tranquility as a mental state characterized by calmness and self-reflection (Kaplan and Kaplan, 1989). Tranquility can be conceptualized as cognitive 'quiet' arising in contrast to the condition of effortful, sustained mental processing that is characteristic of day-to-day activity in the postmodern setting (Harvey, 1990). More specifically, tranquility can be thought of as a psychological state more likely to occur in the presence of environmental features that are associated with peace and quiet (Herzog and Barnes, 1999). Hence, subjective tranquil states can be reconciled with physically objective tranquil spaces (Lefebvre, 1991). Tranquil spaces are associated with the presence of open and natural landscapes, including natural water sources such as rivers and the sea. Conversely, tranquility is associated with the absence of overt human impact, urban development, roads and traffic noise (Pheasant et al., 2008). In psychological terms, a key characteristic of tranquil environments is that they generate subjective interest that is experienced as restorative in comparison with the subjectively fatiguing effect of sustained attention (Kaplan and Kaplan, 1989).

Although tranquility is an essentially subjective experience, most of the variance in its rating can be explained by quantification of visual and auditory features in the environment (Pheasant et al., 2008). Experimental control and manipulation of these environmental features might therefore be used to investigate mechanisms underlying the relationship between objective multimodal sensory inputs (Calvert et al., 2004) and subjective mental states. In terms of systems neuroscience, this implies identification of interactions between visual and auditory cortex that may be mediated by top-down influences (Gilbert and Sigman, 2007) of higher centres, including medial prefrontal

cortex. The rationale for focusing on medial prefrontal cortex in the current study is threefold. Firstly, the reflective component of subjective tranquility might draw upon the resources of the medial prefrontal cortex, which has been shown to be involved in self-reflection (Gusnard et al., 2001; Johnson et al., 2002) as well as related processes of theory of mind (Van Overwalle, 2009) and empathy (Farrow et al., 2001). Secondly, the psychological account of tranquility as cognitive 'quiet' and the absence of effortful mental activity (including sustained attention) resembles the definition of the resting state of the brain that has been probed in functional imaging experiments and also implicated medial prefrontal cortex, and other midline structures (Gusnard et al., 2001). Thirdly, medial prefrontal cortex has also been shown to respond to auditory cues for subjective mental states (e.g., evocation of memory by emotionally salient auditory stimuli; Janata, 2009). This paper reports the findings of a functional magnetic resonance imaging experiment designed to examine the modulating effect of environmental scenes associated with subjective tranquility upon effective connectivity between the auditory cortex and medial prefrontal cortex.

Although earlier studies have examined the effects of visual inputs on auditory activation (Calvert et al., 1997; Van Atteveldt et al., 2004; Pekkola et al., 2005a; Pekkola et al., 2005b; Van Wassenhove et al., 2005; Baier et al., 2006; Noesselt et al., 2007) a question remains about how these inputs might modulate the auditory cortex's effective connectivity with regions beyond sensory cortex. Effective connectivity is a measure of physiological influence between distinct brain areas and a marker of functional integration within the brain (Friston et al., 1997). Since the subjective entirety of perception includes sensory, cognitive and affective components (Kaplan and Kaplan,

1989), it is likely that connectivity of the auditory cortex with areas subserving these components is important in determining the overall perceptual experience. In the current study, we utilized different audiovisual environmental scenes (movies) that were visually distinct (beach images vs. freeway images) and experienced as tranquil (beach) or non-tranquil (freeway). Crucially, however, both sets of scenes had the same auditory component. This was possible because waves breaking at various distances from the shore on a shallow beach combine to create a near-constant sound that is very similar to the mainly rolling noise produced by heavy traffic on a freeway. Both sounds are subjectively experienced as a constant roar. Using an averaged spectrum from beach and freeway sources, this allowed, under conditions of identical auditory input, for examination of visually induced changes in the auditory cortex's connectivity with other brain regions. We hypothesized that scenes associated with subjective tranquility would also be associated with increased connectivity between the auditory cortex and medial prefrontal cortex.

Materials and Methods

Subjects and stimuli

Twelve healthy right-handed (mean ± SD right hand dominance = 90 ± 15%) males aged 22 ± 2 years were studied. Outside the scanner, subjects rated each of 6 unique beach and 6 unique freeway audiovisual scenes (movies) on a validated 0 to 10 tranquility rating scale (higher rating = more tranquil; Pheasant et al., 2008). Beach scenes were rated as significantly more tranquil than freeway scenes (mean ± SD beach vs. freeway tranquility rating = 6.64 ± 1.26 vs. 2.89 ± 1.59; t = 6.28; p < 0.001). Inside the MRI scanner, audiovisual scenes (movies) were presented according to a balanced 3 x 2 factorial design. The visual factor levels were: (1) tranquility-associated beach scene, (2) non-tranquility-associated freeway scene and (3) fixation cross. All visual stimuli were projected on a screen within the scanner room that filled the field-of-view when observed via a mirror inside the radiofrequency-receive head coil. The auditory factor levels were: (1) shaped broadband noise delivered over magnetic resonance compatible headphones at approximately 65 dB A-weighted sound pressure level and (2) silence. The broadband noise was produced by a Bruel & Kjaer Type 1405 noise generator, recorded on a PC using a Marc-8 soundcard operating at 44.1 kHz sampling rate and shaped to the logarithmically averaged spectrum of a freeway and beach using a custom Matlab 1024-th order finite impulse filter (Fig. 1). The freeway component of the average spectrum was based on predictions of the Harmonoise / Imagine traffic noise model (Watts, 2005) with an assumed flow of 2000 vehicles per hour and 15% heavy vehicles (3 or more axles) and 5% medium goods vehicles (2 axles) on a 2.5% gradient and a stone mastic

asphalt surface with a texture depth of 11mm. The receiver point was at a distance of 120m and flow resistivity of the intervening ground was 400 kPa s m^{-2}. The spectrum for the beach component was measured at Bantham, Devon (UK) using a sound level meter incorporating a one-third-octave analyser (CEL 593/1). The microphone was positioned approximately 20m from the shoreline. At these distances, the amplitude of predicted freeway and beach noise was approximately 65 dB sound pressure level and the spectra were adjusted to 65 dB (A-weighted) prior to logarithmic averaging. Figure 1 shows how frequency spectra from these 2 sources are similar, especially at mid-range frequencies. Sound files containing noise shaped to the 3 spectra shown in Figure 1 (freeway, beach, averaged) are available online.

Scanning paradigm

Each subject underwent 2 functional imaging runs on a 3T scanner (Achieva, Philips Medical Systems) at the University of Sheffield. There were 72 time-points per run. A single-shot, T2*-weighted, echo-planar imaging (EPI) sequence utilized a sparse technique (Hall et al., 1999) to acquire 43 contiguous 3mm-thick slices, covering the whole brain in a transaxial plane within the 3.5-s acquisition time that formed part of a 12.5-s repetition time between each of the successive 72 time-points per functional run (TE = 50ms; SENSE factor = 1.5). The data acquisition sequence setup yielded a voxel size of 1.8 x 1.8 x 3mm^3.

At each time point, subjects were presented with 3.5-s movies of either a beach scene or a freeway scene, or a fixation cross. Sparse scanning exploits the hemodynamic delay (6-7s) between auditory stimulus onset and maximum blood oxygenation-level-

dependent (BOLD) signal in order to separate responses to stimuli from responses evoked by MRI gradient noise. Using this technique, we presented stimuli with the gradients turned off, i.e., against the background of quiescent scanner room noise only. Following stimulus offset, the gradients were activated and the subsequent set of magnetic resonance images encoded the delayed BOLD response to each preceding scene or fixation cross. Utilizing a 12.5-s repetition time allowed for stimulus-evoked BOLD responses to decay to approximately pre-stimulation levels prior to delivery of the next stimulus.

Each scene or cross was played concurrently with the same shaped broadband noise or in silence. There were 6 unique beach scenes and 6 unique freeway scenes; each individual scene was played twice with and twice without accompanying sound in each functional run. The distinction between the 2 functional runs was that the presentation of scenes / crosses and sound / silence was in different pseudorandom orders.

Spatial preprocessing in SPM5

After quality control, we were able to analyse 21 of 24 functional runs obtained from 12 subjects. The EPI images for each run were corrected for head movement by affine registration using a two-pass procedure by which images were initially realigned to the first image and subsequently to the mean of the realigned images. After realignment, the mean EPI image for each run was spatially normalized to the Montreal Neurological Institute (MNI) single subject template using the unified segmentation approach (Ashburner and Friston, 2005). The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move the data into the space of the MNI

tissue probability maps, were then combined with the deformation field transforming between the latter and the MNI single subject template. The ensuing deformation was applied to the individual EPI volumes, which were thereby transformed into the MNI single-subject space and resampled at 2 x 2 x 2mm^3 voxel size. The normalized images were smoothed using a 6mm full-width at half-maximum Gaussian kernel to meet the statistical requirements of the General Linear Model and to compensate for residual macroanatomical variations.

Conventional fMRI analysis

Following spatial preprocessing, images were analysed using the General Linear Model in SPM5 (www.fil.ion.ucl.ac.uk/spm). For every included functional run, first-level parametric images were produced for each condition (cell) in the 3 x 2 factorial design. These were interrogated at the group level using a flexible factorial model with factors of subject, scanning session (to combine 2 functional runs per subject) and experimental condition. In this random-effects model, we allowed for violations of sphericity by modelling non-independence across images from the same subject and unequal variances between conditions and subjects as implemented in SPM5. We first identified the group average response maximum for the main effect of all sound vs. silence (i.e., irrespective of visual condition). We proceeded to use this focus to select session-specific seeds for subsequent auditory connectivity analyses (below). We also identified a volume-of-interest for statistical correction in the connectivity analyses by localising voxels where there were group-level [tranquil scene / non-tranquil scene] x [sound / silence] interaction effects at $p < 0.001$, uncorrected. At these interaction foci, we also examined contrast

estimates for the effect of sound vs. silence separately in the tranquility-associated condition compared with fixation baseline and non-tranquility-associated condition compared with fixation baseline. This allowed us to specify statistically significant interactions in terms of their underlying basic effects.

Connectivity analyses

For each included functional run (session), we identified the session-specific response maximum for the main effect of all sound vs. silence that was closest to the overall group maximum (i.e., left temporal cortex, see Results below). All included sessions revealed maxima in the same region as the group maximum. We extracted the time courses of the session-specific response maxima (i.e., the first eigenvariates of the time courses of all voxels contained within a sphere of 5mm radius centred on the session-specific response maxima). For each session we then had a 72-element vector representing the physiological time course of the left auditory cortex.

The session-specific psychophysiological interaction term (PPI; Friston et al., 1997) was produced by convolving the time course vectors with another 72-element paradigm vector describing the visual condition at each imaging time point: beach (+1), freeway (-1) or fixation (0). For each included session we entered the PPI term in the first-level design matrix as an effect of interest, along with the time course and paradigm vectors as effects of no interest. This approach amounts to a probe of effective connectivity and in this case identifies brain areas that demonstrate significantly enhanced connectivity with the auditory cortex under the tranquility-associated (beach) visual condition compared with the non-tranquility-associated (freeway) visual condition.

Using this method we produced parametric connectivity contrast images for the left auditory cortex for all included scans. These images were analysed at the group level in a flexible factorial model with factors of subject, scan session (i.e., first and second functional runs) and condition (i.e., PPI) with appropriate corrections for non-sphericity. We designated a main effect of condition (PPI) to produce a group average parametric brain map of t-statistics showing areas that demonstrated significantly enhanced connectivity with the auditory cortex under the tranquility-associated condition compared with the non-tranquility-associated condition. The voxel-level statistical threshold for reporting was $p < 0.05$, family-wise error corrected. By testing for the inverse contrast, we were also able to search for any brain areas that exhibited significantly enhanced connectivity with the auditory cortex under the non-tranquility-associated condition compared with the tranquility-associated condition.

In order to test for any effects of auditory seed laterality, we re-ran the first-level PPI analysis using time courses from session-specific maxima closest to the group maximum in the right temporal cortex (see Results, below). This produced parametric connectivity contrast images for the right auditory cortex for each included scan. At the group level, we used a flexible factorial model with factors of subject, scan session and condition (i.e., left auditory cortex PPI and right auditory cortex PPI) to test for differences in connectivity under the tranquility-associated condition compared with the non-tranquility-associated condition according to laterality of auditory time course.

Finally, in order to specify our main results we also ran versions of the auditory PPI analysis comparing the tranquility-associated and non-tranquility-associated conditions with fixation baseline. The PPI terms for these comparisons were produced by

convolving the corrected auditory time course vectors with 72-element paradigm vectors describing the visual condition at each imaging time point as: (a) beach [+1], freeway [0] or fixation [-1] and (b) beach [0], freeway [+1] or fixation [-1], respectively.

Results

Conventional fMRI analysis

In order to identify seed regions for our effective connectivity analyses (below) we first examined the main effect of auditory input (i.e., all sound vs. silence). The auditory evoked response followed the expected pattern of extensive and bilateral temporal lobe activation, maximal around left Heschl's and superior temporal gyri in Brodmann's area 41 / 42, which includes the location of the primary auditory cortex (left hemisphere: peak t = 21.71; p < 0.001, family-wise error [FWE] corrected in the whole brain; Montreal Neurological Institute [MNI] co-ordinates: -48, -22, 6; right hemisphere: peak t = 17.75; p < 0.001, FWE corrected in the whole brain; MNI co-ordinates: 54, -18, 4). We also examined the [visual condition] x [auditory condition] interaction in order to specify a brain volume-of-interest for the purpose of FWE correction for comparisons across multiple voxels in the subsequent effective connectivity analyses. Table 1 and Figure 2 show regions where [tranquility-associated scene / non-tranquility-associated scene] x [sound / silence] interaction effects were significant (p < 0.001, uncorrected).

Effective connectivity analyses

1) Auditory cortex connectivity:

Since the left temporal cortex was the site of the overall group maximum response to sound vs. silence, we used individual left temporal cortex time courses as seeds for effective connectivity analyses. Significantly enhanced connectivity with the auditory cortex under the tranquility-associated visual condition compared with the non-

tranquility-associated condition was observed in the medial prefrontal cortex, posterior cingulate gyrus, temporoparietal cortex and thalamus ($p < 0.05$, FWE corrected; Table 2; Fig. 3). No regions demonstrated significantly enhanced connectivity with the auditory cortex under the non-tranquility-associated condition compared with the tranquility-associated condition, even at the less conservative threshold of $p < 0.001$, uncorrected.

In an analysis of hemispheric differences, there was no significant effect of using time course seeds from the left vs. right auditory cortex (or vice versa) on connectivity under the tranquility-associated condition compared with the non-tranquility-associated condition (or vice versa) at any voxel within the volume-of-interest, even at the less conservative threshold of $p < 0.001$, uncorrected.

2) Accentuating effects on auditory cortex connectivity of tranquility-associated scenes vs. attenuating effects of non-tranquility-associated scenes:

At the 4 foci revealed in the main auditory connectivity analysis (Table 2; Fig. 3), we extracted connectivity parameter estimates from further effective connectivity analyses examining connectivity with the left auditory cortex under the fixation condition compared with the tranquility-associated and non-tranquility-associated visual conditions. This allowed us to specify whether the observed differences in connectivity between the tranquility-associated and non-tranquility-associated visual conditions were due to: (a) increased connectivity under the tranquility-associated condition compared with fixation baseline, (b) decreased connectivity under the non-tranquility-associated condition compared with baseline or (c) a combination of these effects. The medial prefrontal cortex, posterior cingulate gyrus and temporoparietal cortex showed the same pattern: (a)

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of significantly enhanced connectivity with the auditory cortex in the tranquility-associated condition compared with the fixation condition and (b) of no significant difference in connectivity with the auditory cortex between the non-tranquility-associated and fixation conditions (Fig. 4a-c). The thalamic focus showed a different pattern: significantly diminished connectivity with auditory cortex in the non-tranquility-associated condition compared with the fixation condition and no significant difference in connectivity between the tranquility-associated and fixation conditions (Fig. 4d).

Discussion

Our results demonstrate that visual inputs modulate effective connectivity between the auditory cortex and medial prefrontal cortex, posterior cingulate gyrus, temporoparietal cortex and thalamus. We used left-hemisphere seed regions in the main effective connectivity analyses because the group maximum auditory-evoked response in Heschl's gyrus (and adjacent areas) was left-lateralized. Such left-lateralization of neural response to a broadband noise stimulus is in accordance with work that has shown an early electrophysiological marker of primary auditory cortex activity (M50 response) to be strongly left-lateralized and greater for noise stimuli than for pure tones (Chait et al., 2004). It has been suggested that left-lateralization of response to basic stimuli in the primary auditory cortex reflects hemispheric dominance at a relatively early stage of processing, which may have been important in the evolution of left-hemispheric specialization for language function (Devlin et al., 2003). In the current study, an analysis of hemispheric differences showed that there was no significant effect of using left- vs.

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right-hemisphere seed regions on visual modulation of effective connectivity with the auditory cortex.

Using a novel 3 x 2 psychophysiological interaction design incorporating a fixation baseline condition, we observed two distinct patterns of modulation for auditory connectivity. Firstly, relative to fixation baseline, auditory cortico-cortical connectivity was enhanced under the tranquility-associated condition. Secondly, relative to baseline, auditory thalamo-cortical connectivity was diminished under the non-tranquility-associated condition. Importantly, these effects occurred under conditions of identical auditory input. Thus, the same sound may be associated with a subjectively tranquil or non-tranquil percept reflecting the auditory cortex's varying connectivity with other brain regions. This suggests that connectivity of sensory cortex may shape subjective percepts from multimodal sensory inputs.

Tranquility has been framed as a mental state emerging in a sensory context, i.e., a state of connection between sensory inputs and subjective experience (Kaplan and Kaplan, 1989; Herzog and Barnes, 1999). The current data suggest that this idea is mirrored at the neurobiological level by modulation of effective connectivity. Scenes associated with subjective tranquility are associated with strengthening of connectivity between the auditory cortex and medial prefrontal cortex. From our conventional fMRI analysis (Table 1) it is clear that interaction effects in medial prefrontal cortex were due to enhanced sound-evoked activation in the tranquility-associated condition vs. baseline. The current connectivity findings suggest that such enhanced activation was driven by increased connectivity between the auditory cortex and medial prefrontal cortex. In terms of interpretation, we postulate that these connectivity effects represent a form of

computational conjunction related to how different functions subserved by medial prefrontal cortex enable it to act as a hub linking sensory inputs and consequent mental states (Janata, 2009). From a cognitive / affective perspective, medial prefrontal cortex is implicated in self-reflection (Gusnard et al., 2001; Johnson et al., 2002), a function related to the evaluation of subjective mental state that is relevant to the subjective experience of tranquility (Kaplan and Kaplan, 1989). On the other hand, from a sensory perspective, medial prefrontal cortex is thought to be involved in processing auditory cues for subjective mental states (Janata, 2009), in processing affective dimensions of auditory perception (emotional response to music; Blood et al., 1999) and in the representation of perceptual templates more generally (Summerfield et al., 2006). Our current data suggest that medial prefrontal cortex has a role in auditory sensory evaluation, which may be facilitated in a context that also engages its cognitive / affective functions. Whilst speculative, it is possible that this might represent a form of feedforward gain enhancement to provide greater sensory information to support stability of the subjective state.

It is important to emphasize that effective connectivity is observed in the residual variance after the variance explained by the main effects of visual condition and auditory time series has been discounted (Friston et al., 1997). Hence, the observed differences in connectivity are not due to any trivial effect such as the low-level visual distinction between beach and freeway scenes. In the case of medial prefrontal cortex and other cortical foci this point is particularly emphasized by the similarity of connectivity parameter estimates in the non-tranquility-associated (freeway) and fixation cross conditions (Fig. 4). Furthermore, tranquility-associated scenes were significantly less

activating of visual cortex than non-tranquility-associated scenes, with the region of maximal difference located in the fusiform gyrus (peak t = 9.77; p < 0.001, FWE corrected in the whole brain; MNI co-ordinates: -36, -76, -20). The discrepancy between tranquility-associated scenes being more 'connecting' whilst less 'activating' emphasizes that effective connectivity is not simple co-activation and argues strongly against the connectivity effects being driven by attention to stimuli in one modality, which accentuates activation in the corresponding sensory cortex (Woodruff et al., 1996). Our findings also support the view (Gilbert and Sigman, 2007) that top-down influences amount to more than the 'spotlight' model of attention because, in the current study, we observed evidence for top-down influences that exert specific effects on connectivity and not activation. Conversely, in our conventional fMRI interaction analysis, we found foci in the left middle frontal gyrus and right inferior parietal lobule that exhibited increased sound-evoked activation in the non-tranquility-associated condition vs. baseline. This observation further speaks to the question of attentional effects and is compatible with increased attention in the non-tranquility-associated condition (vs. baseline) leading to cross-modal enhancement of sound-evoked responses (Busse et al., 2005). Again, we emphasize that any such effect of attention in the non-tranquility-associated condition did not impact upon *connectivity* with the auditory cortex because no regions exhibited increased auditory connectivity in the non-tranquility-associated condition.

Moreover, psychophysically speaking, the absence of directed attention is thought to be an important component in the overall experience of tranquility (Kaplan and Kaplan, 1989). In this context, it is interesting to note that medial prefrontal cortex and posterior cingulate gyrus are thought to be active in the default or resting state of the

human brain (Gusnard et al., 2001; Schilbach et al., 2008). Our conventional fMRI analysis (Table 1) revealed that interaction effects at foci located in medial prefrontal cortex and posterior cingulate gyrus were due to enhanced sound-evoked activation in the tranquility-associated condition vs. baseline. Hence, increased connectivity between the auditory cortex and these regions in the tranquility-associated condition could represent engagement of the resting state network by sensory systems, manifest as enhanced sound-evoked activation. There is considerable overlap between regions involved in the resting state and those implicated in the experience of mental states, leading to the hypothesis that self-referential processing of mental states is the major cognitive component of the functional resting state (Schilbach et al., 2008).

The auditory cortex also demonstrated increased connectivity in the tranquility-associated condition with the temporoparietal junction. In our conventional fMRI analysis (Table 1), it was apparent that interaction effects at this focus were due to enhanced sound-evoked activation in the tranquility-associated condition vs. baseline *and* diminished sound-evoked activation in the non-tranquility-associated condition vs. baseline. This suggests that enhanced sound-evoked activation in the tranquility-associated condition was driven by increased connectivity between the temporoparietal junction and auditory cortex. On the other hand, as we did not observe decreased connectivity between the temporoparietal junction and auditory cortex in the non-tranquility-associated condition vs. baseline, it is unlikely that diminished sound-evoked activation in the non-tranquility-associated condition arose as a direct consequence of attenuated connectivity between the temporoparietal junction and auditory cortex. However, it is striking that reduced temporoparietal junction sound-evoked activation in

the non-tranquility-associated condition mirrored the pattern of reduced auditory thalamo-cortical connectivity also observed in the non-tranquility-associated condition (we discuss the possible effects of thalamic filtering on attenuation of cortical activation below). Structures within the temporoparietal junction, notably the banks of the posterior superior temporal sulcus, are thought to be involved in multisensory processing including audiovisual integration in humans (Van Atteveldt et al., 2004; Beauchamp, 2005; Campanella and Belin, 2007; Noesselt et al., 2007) and non-human primates (Ghazanfar et al., 2005). The posterior and ventral aspect of the focus that we observed fell within the temporoparietal area believed to be part of a wider network for processing mental states (Van Overwalle, 2009). Hence, it is possible that connectivity with this region could represent sensory integration as a relatively early aspect of determining mental state (Van Overwalle and Baetens, 2009).

It is likely that effective connectivity between the auditory cortex and other cortical regions, which we observed using functional neuroimaging, is underpinned by anatomically distinct cortico-cortical backward projections. The key characteristic of such backward projections is their general termination in a bilaminar pattern of cortical layers III and V, and their avoidance of lamina IV (Rockland and Pandya, 1979; Felleman and Van Essen, 1991). This pattern has been observed for projections between the auditory cortex and prefrontal cortex (Romanski et al., 1999a; Romanski et al., 1999b), superior temporal polysensory area (Pandya et al., 1969; Hackett et al., 1998) and parietal cortex (Lewis and Van Essen, 2000). It has been suggested that these projections are likely conduits for visual backward modulation of the auditory cortex (Schroeder et al., 2003). Overall, this anatomical evidence points to effective connectivity between the

auditory cortex and other cortical regions being implemented through defined backward projections that, in functional terms, convey top-down influences.

Compared with non-tranquility-associated scenes, tranquility-associated scenes were related to enhanced connectivity between the auditory cortex and thalamus. However, unlike the cortico-cortical connectivity effects above, this was not due to accentuation of connectivity under the tranquility-associated condition. Rather, it was due to diminished connectivity in the non-tranquility-associated condition (relative to fixation baseline). This observation is in accordance with earlier work that suggests a filtering function for the thalamus in audiovisual integration (Baier et al., 2006). Our connectivity approach allows for mechanistic specification of this putative filtering effect. It appears that under a relatively non-preferred perceptual condition, the non-tranquility-associated freeway condition in our experiment, the thalamus reduces its connectivity with the auditory cortex. In our conventional fMRI analysis, interaction effects at foci in the middle temporal gyrus, inferior temporal gyrus, temporoparietal junction and cerebellum were wholly or partly due to diminished sound-evoked activation in the non-tranquility-associated condition vs. baseline. This raises the possibility that activation in these regions was attenuated by thalamic filtering of auditory signal in the non-tranquility-associated condition. In terms of implementation, such reduced connectivity / filtering could reflect stimulation of inhibitory thalamic interlaminar nuclei and consequent suspension of cross-modal thalamic gain enhancement, perhaps mediated by koniocellular projections (Jones, 1998; Schroeder et al., 2003).

From a statistical perspective, we acknowledge that the term used to derive the volume-of-interest for correction for multiple comparisons (from the conventional fMRI

interaction analysis) and the term used to derive the connectivity analyses were not orthogonal. This was because both terms contained the visual paradigm vector and, also, because the individual auditory time course vectors (used in the connectivity analyses) were necessarily related to the auditory paradigm vector (used in the conventional fMRI interaction analysis). Hence, our correction for multiple comparisons was likely to have been less conservative than under strictly orthogonal conditions. However, we emphasise that these terms were not co-linear; a point illustrated by the observation that the most significant focus in the connectivity analyses (thalamus, by an order of statistical magnitude) was not revealed in the conventional fMRI interaction analysis.

Overall, these findings demonstrate that visual context can modulate effective connectivity of the auditory cortex with cortical and sub-cortical regions beyond sensory cortex. Importantly, we have shown that this effect occurs under conditions of identical auditory input. Hence, the same sound may be associated with different percepts reflecting the auditory cortex's varying connectivity with other brain regions. From a neuroscientific perspective, this suggests that subjective experience is more closely linked to the connectivity state of the auditory cortex than to its basic sensory inputs.

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Table 1: Visual scene by auditory condition interactions.

Region (Brodmann's area) listed rostral to caudal	Peak t	MNI co-ordinates [x	y	z]	Voxels
Tranquility-associated / sound direction					
Medial frontal gyrus (9)	3.66[a]	[-10	52	36]	27
Inferior temporal gyrus (20)	4.01[b]	[44	-8	-32]	47
Middle temporal gyrus (21)	5.03[b]	[-58	-38	-10]	160
Posterior cingulate gyrus (31)	4.81[a]	[-16	-54	30]	225
Angular / supramarginal gyrus (39 / 40)	4.14[a]	[48	-54	34]	76
Temporoparietal cortex (22 / 39)	4.27[a+b]	[-56	-64	32]	221
Cerebellum	3.68[b]	[6	-58	-8]	50
	4.35[a+b]	[20	-42	-38]	60
	4.02[b]	[-18	-44	-36]	27

Non-tranquility-associated / sound direction

Inferior / middle frontal gyrus (45 / 46)	3.69[c]	[44	38	6]	20
Middle frontal gyrus (46)	3.72[c+d]	[-38	34	16]	32
Inferior parietal lobule (40)	4.19[c+d]	[62	-34	46]	51

Regions where [tranquility-associated scene / non-tranquility-associated scene] x [sound / silence] interaction effects were significant at voxel threshold $p < 0.001$, uncorrected and 20 voxels extent. Explanatory basic effects ($p < 0.05$) for interactions are codified as follows:

a = tranquility-associated condition > fixation / sound > silence

b = non-tranquility-associated condition > fixation / silence > sound

c = tranquility-associated condition > fixation / silence > sound

d = non-tranquility-associated condition > fixation / sound >silence

MNI = Montreal Neurological Institute.

Table 2: Effective connectivity of primary auditory cortex.

Region (Brodmann's area) listed rostral to caudal	Voxel-level statistics Peak t	FWE p	MNI co-ordinates [x	y	z]	Voxels
Tranquility-associated > non-tranquility-associated						
Medial frontal gyrus (9)	4.59	0.027	[-8	52	36]	345
Posterior cingulate gyrus (31)	5.03	0.011	[-18	-50	28]	289
Temporoparietal cortex (22 / 40)	4.78	0.019	[-46	-54	22]	499
Thalamus*	12.20	<0.001	[-14	-16	4]	220

Non-tranquility-associated > tranquility-associated

No regions

Regions that exhibited significant change in connectivity with auditory cortex between the tranquility-associated and non-tranquility-associated visual conditions. Statistical threshold is p < 0.05 for the peak voxel in each cluster, corrected in the conventional analysis

interaction volume (see Table 1), *except for the thalamic focus, which is outside the conventional analysis interaction volume but significant after correction for multiple comparisons in the entire brain volume. Voxels = cluster extent at voxel-level threshold p < 0.001, uncorrected (i.e., the visualisation threshold employed in Figure 3). MNI = Montreal Neurological Institute; FWE = family-wise error corrected.

Figure 1: Freeway and beach frequency spectra, and their logarithmic average.

The averaged spectrum was employed in the current experiment (see text for details). Photographic inserts are stills from typical movies used in the behavioural and scanning studies. SPL = sound pressure level.

Figure 2: Regions that exhibited significant [tranquility-associated scene / non-tranquility-associated scene] x [sound / silence] interaction effects.

 Voxel threshold p < 0.001, uncorrected and 20 voxels extent (see Table 1 for anatomical and statistical details). Data are rendered against the (a) left lateral surface, (b) right lateral surface and (c) medial surface of a high-resolution single-subject canonical brain. Composite data from two statistical parametric maps are shown: orange = tranquility-associated / sound direction; blue = non-tranquility-associated / sound direction.

Figure 3: Regions that exhibited significantly enhanced connectivity with the auditory cortex under the tranquility-associated visual condition compared with the non-tranquility-associated visual condition.

See Table 2 for anatomical and statistical details. For display purposes, the voxel threshold is $p < 0.001$, uncorrected. Data are rendered against the (a) left lateral surface, (b) right lateral surface and (c) medial surface of a high-resolution single-subject canonical brain. No areas demonstrated significantly enhanced connectivity with the auditory cortex under the non-tranquility-associated visual condition compared with the tranquility-associated visual condition.

Figure 4: Primary auditory cortex connectivity parameter estimates.

Parameter estimates for the foci shown in Table 2 and Figure 3 under the tranquility-associated and non-tranquility-associated visual conditions compared with fixation: (a) medial prefrontal cortex, (b) posterior cingulate gyrus, (c) temporoparietal cortex and (d) thalamus. Error bars are 90% confidence intervals, *p < 0.05