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THE ROYAL SOCIETY

Towards a functional neuroanatomy of conscious perception and its modulation by volition: implications of human auditory neuroimaging studies

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Conscious sensory perception and its modulation by volition are integral to human mental life. Functional neuroimaging techniques provide a direct means of identifying and characterizing *in vivo* the systems-level patterns of brain activity associated with such mental functions. In a series of positron emission tomography activation experiments, we and our colleagues have examined a range of normal and abnormal auditory states that, when contrasted, provide dissociations relevant to the question of the neural substrates of sensory awareness. These dissociations include sensory awareness in the presence and absence of external sensory stimuli, the transition from sensory unawareness to awareness (or vice versa) in the presence of sensory stimuli, and sensory awareness with and without volition. The auditory states studied include hallucinations, mental imagery, cortical deafness modulated by attention, and hearing modulated by sedation. The results of these studies highlight the distributed nature of the functional neuroanatomy that is sufficient, if not necessary, for sensory awareness. The probable roles of unimodal association (as compared with primary) cortices, heteromodal cortices, limbic/paralimbic regions and subcortical structures (such as the thalamus) are discussed. In addition, interactions between pre- and post-rolandic regions are examined in the context of top-down, volitional modulation of sensory awareness.

Keywords: functional neuroimaging; positron emission tomography; audition; consciousness; volition

1. INTRODUCTION: HEARING WHAT IS NOT THERE AND NOT HEARING WHAT IS THERE

Although sensory information can be processed without awareness, the subjective experience of conscious perception is a central element of human mental life, and is important for explicit cognition and volitional behaviour. This chapter represents an inquiry into the systems-level, functional neuroanatomy that is sufficient, if not necessary, for human conscious sensory experience.

We and our colleagues have had a particular interest in the auditory sensory modality, which has received rather less scientific attention than the visual modality. We study this modality in the context of neuropsychiatric and neuropsychological states that can provide dissociations that are particularly conducive to a neurobiological examination of sensory awareness, and the effect of volition on conscious perception. These dissociations include sensory awareness in the presence and in the absence of external sensory stimuli, the transition from sensory unawareness to awareness (or vice versa) in the presence of sensory stimuli, and sensory awareness with and without volition.

These brain–mind states include: (1) hallucinations (involuntary auditory perceptions in the absence of sensory stimulation); (2) auditory imagery (voluntary auditory perceptions in the absence of sensory stimulation); (3) cortical deafness modulated by attention (lack of auditory perceptions in the presence of auditory stimulation, alternating with perception of the stimuli enabled only by volitionally attending to the auditory modality); and (4) hearing attenuated by anaesthesia (auditory perception in the presence of auditory stimulation, and the loss of this perception associated with a reduced level of consciousness).

The technique used to map the brain activity associated with these striking perceptual states was $H_2{}^{15}O$ positron emission tomography (PET). $H_2{}^{15}O$ PET provides an index of regional cerebral blood flow (rCBF), which is tightly coupled to neuronal activity (Raichle *et al.* 1983). Multiple rCBF measurements can be obtained during the performance of neuropsychological tasks to identify the brain regions underlying specific cognitive operations (Posner *et al.* 1988). We have developed methods of high-sensitivity $H_2{}^{15}O$ PET image acquisition and study design that allow the statistically significant identification of such brain activations in single subjects as well as groups (Silbersweig *et al.* 1993). These methods, followed by multiple steps of statistical parametric mapping (SPM) (Friston *et al.* 1995) image processing and analysis, were employed in the studies described below. Such methods and studies provide human, *in vivo*, systems-level information about normal and abnormal, conscious and unconscious brain states that is complementary to (and

can be integrated with) the neurophysiological and basic neuroscientific information described elsewhere in this issue.

2. FUNCTIONAL BRAIN IMAGING EXPERIMENTS ACROSS A SPECTRUM OF HUMAN AUDITORY PERCEPTUAL STATES: RATIONALE, METHODS AND FINDINGS

(a) *Auditory hallucinations in schizophrenia*

The prelude to Daniel Dennett's book *Consciousness explained* (Dennett 1991) is entitled 'How are hallucinations possible?' It is reasonable to begin an inquiry into consciousness by addressing the problem of hallucinations, because these phenomena represent a situation in which the brain creates its own reality. If one can be conscious of something that is not there, then the brain state underlying this mental state must be sufficient for a conscious percept, even in the absence of an external stimulus.

Hallucinations—involuntary perceptions in the absence of external stimuli—are not only of philosophical and neuropsychological interest. They are also of medical interest, given their prominence in neuropsychiatric diseases such as schizophrenia. In this common and devastating disorder the hallucinations have a number of defining characteristics. They are not simple sounds, but rather consist of voices talking to, or about, the patient. Complex hallucinations in other modalities, such as visual, also occur. These psychotic experiences have emotional or motivational relevance for the patient, who (unlike patients with hallucinations in the setting of other neurological disorders) often believes that they are real (DSM-IV 1994).

We studied six schizophrenic patients (Silbersweig *et al*. 1995): five medicated patients with classic auditory–verbal hallucinations, and one medication-naive patient with visual as well as auditory–verbal hallucinations. Each patient was instructed to press a button during each hallucination that occurred during 12 scanning periods. Each scan therefore contained a different number of hallucinations, each of a different duration. We then used a technique that we developed to determine the amount of radiotracer entering the brain per unit time during these events and to identify brain regions that, over many scans, had activity correlating with this hallucination-associated measure (Silbersweig *et al*. 1994).

In the patient with visual and auditory–verbal hallucinations, the following regions were activated: ventral visual association cortices (left greater than right Brodmann's areas (BAs) 18, 19 and 37), auditory–linguistic association cortices (left BA 22; posterior superior temporal gyrus), auditory association cortices (bilateral BA 21; middle temporal gyrus), post-rolandic heteromodal association cortices (left BA 39; angular gyrus), posterior cingulate gyrus (left BA 31), right parahippocampal gyrus and temporal pole, and right striatum (putamen).

In the group of patients with auditory–verbal hallucinations, the common areas of activation were: bilateral parahippocampal gyrus–hippocampus (extending toward the amygdala), bilateral thalamus, right ventral striatum and right anterior cingulate gyrus.

(b) *Auditory verbal imagery in normal subjects*

Mental imagery is a normal human function by which one voluntarily evokes a sensory experience in the absence of simultaneous corresponding external stimuli. This too allows one to address the issue of the central neural correlates of conscious sensory experience, dissociated from the perceptual apparatus. Mental imagery differs from pathological hallucinations in a number of regards, however, not the least of which is that it is under voluntary control. It therefore allows one to address volitional aspects of conscious sensory experience as well. Mental imagery (usually in the visual modality) has been the subject of much psychological, and more recently, some neuropsychological study (D'Esposito *et al*. 1997; Farah 1995; Kosslyn *et al*. 1995*a*, 1997). With our colleagues (especially Dr Philip McGuire and Professor Chris Frith), we studied auditory–verbal imagery, because it represents an important comparison condition for the auditory–verbal hallucinations of schizophrenia. For the purposes of this inquiry, however, we shall focus on the findings in normal subjects.

Six normal right-handed male subjects were studied (McGuire *et al*. 1995, 1996), with our slow-bolus $H_2{}^{15}O$ PET technique (Silbersweig *et al*. 1993), during an auditory–verbal imagery task, as well as during silent reading and inner speech control tasks (the cognitive psychological details of which are described by McGuire *et al*. (1996)). Auditory–verbal imagery shared the activation of Broca's area (left inferior frontal gyrus) with inner speech. Compared with inner speech, however, imagery was associated with the additional activation of bilateral rostral supplementary motor cortex, adjacent bilateral anterior cingulate gyrus, bilateral lateral premotor cortex, right dorsolateral prefrontal cortex and left posterior–superior temporal gyrus.

(c) *Attentionally modulated hearing in cortical deafness*

Unlike the above conditions in which a person hears something that is not there, cortical deafness is a condition in which a person, despite intact peripheral components of the auditory system, fails to hear something that is there (Bauer 1993). The neurological lesions associated with this condition can tell us about some of the brain regions that are necessary for conscious auditory perception. A rare patient with cortical deafness whom we studied with colleagues (Engelien *et al*. 1999) can tell us even more. Most of the time he could not detect sounds, but when he attended to the auditory modality he could identify simple acoustic attributes of the sounds. We could therefore study him in both the deaf and the attentionally modulated hearing states in the same study session. By using functional neuroimaging with neuropsychological probes to supplement the lesion analysis, we hoped to learn more about the neurobiology of conscious auditory perception and the role of top-down, volitional control.

S.B. is an unfortunate 24-year-old male with protein C deficiency who suffered two middle cerebral artery territory strokes (in 1990 and 1991). This left him with bilateral peri-sylvian lesions involving primary auditory cortex. He was able to detect the onset and offset of sounds and discriminate intensity levels only when

selectively attending to audition. He was unable to discriminate frequencies or complex patterns, and to localize or identify sounds or words. His brainstem auditory evoked potentials were normal, but he had irregular middle and long latency auditory evoked potential responses. He had electrodermal responses (skin conductance response) to auditory stimulation only when selectively attending to audition. Otherwise, he would not perceive or respond to sounds.

We and our colleagues (especially Dr Almut Engelien) examined S.B. with the slow-bolus $H_2{}^{15}O$ PET technique (Silbersweig *et al*. 1993) in three conditions: rest, unattended acoustic stimulation (environmental sounds, with stimulus and interstimulus intervals ranging from 6–15 s), and matched acoustic stimulation with focused attention to audition. SPM analysis revealed minor right posterior parietal and medial superior frontal activations with unattended auditory stimulation compared with rest. In the attended (conscious perception of simple acoustic attributes) compared with unattended condition, activation was noted in the following regions: bilateral prefrontal (BAs 6, 8, 9, 10, 11 and 46), spared superior and middle temporal (BAs 21 and 22), inferior temporal (BA 37), cerebellum; left frontal operculum, temporoparietal cortex (BA 39), posterior cingulate gyrus, head of caudate; and right putamen and thalamus. When normal subjects listened to environmental sounds (compared with rest), increased rCBF was seen in bilateral (right greater than left) primary and secondary auditory cortices and posterior thalamus, with extension on the right into the anterior insular–frontal opercular region and inferior parietal cortex (Engelien *et al*. 1995).

(d) *Pharmacologically modulated hearing*

With S.B. we had the opportunity of studying the presence and absence of conscious auditory perception, with auditory stimulation as a constant. We were involved in another study (Veselis *et al*. 1995, 1997), performed by our anaesthesiologist colleague Dr Bob Veselis, that provides complementary information. Here, too, we could examine the presence and absence of conscious auditory perception with auditory stimulation as a constant. In this study, however, it was pharmacology rather than attention that modulated the transformation into or out of the conscious perceptual state.

Fourteen normal male subjects were studied with $H_2{}^{15}O$ PET during passive listening to binaural tones at 1000 Hz (80 dB, 1.1 s interstimulus interval, eyes closed), without and with an intravenous infusion of the $GABA_A$ agonist midazolam. Electroencephalograph recordings were performed throughout the study sessions and analysed with spectral analysis techniques. A modified Rey auditory–verbal learning task (Lezak 1987) was performed twice between scans: once in the baseline state and once in the midazolam state. Seven subjects were scanned during low-midazolam effect and seven during high-midazolam effect. During low-midazolam effect (7.5 ± 1.7 mg, serum concentration 74 ± 24 ng ml^{-1}) high-frequency, low-amplitude beta (13–20 Hz) waves were noted. These subjects recognized 5 ± 4.5 out of 16 words at the end of the session. During high-midazolam effect (9.7 ± 1.3 mg, serum concentration 129 ± 48 ng ml^{-1}) 14 Hz spindle activity was noted. These subjects recognized 1.6 ± 1.7 out of 16 words at the end of the session. In addition to SPM analyses, quantitative analyses with arterial sampling were performed, all with a correction factor for changes in p_{CO_2}.

Midazolam was associated with a 12% decrease in global CBF. For the regional CBF changes, the low-midazolam effect results were a subset of the high-midazolam effect results. In the setting of constant auditory stimulation, reduced conscious perception resulting from midazolam sedation was associated with decreased activity in thalamus (the largest percentage change in rCBF), frontal (superior, middle and inferior) association cortices, anterior cingulate cortex, middle temporal association cortex, inferior parietal association cortex, and insula.

3. DISCUSSION

We have had the opportunity to examine the patterns of brain activity associated with normal and abnormal human auditory perceptual states: with and without external auditory stimulation, with and without awareness, and with and without volition. These dissociations within and across experiments, when considered individually and together, may permit us to make a few tentative observations about the systems-level functional neuroanatomy of human sensory awareness.

The results from the schizophrenic patient with visual and auditory–verbal hallucinations (when interpreted in light of the literature on primate electrophysiology, human lesions and normal human functional neuroimaging) show a striking correspondence between regional brain activation and the patient's report of his subjective experience. The patient reported seeing coloured, moving, objects while visual association cortices in the ventral (object processing) stream, including areas V4 (colour detection) and V5 (motion detection) (Zeki *et al*. 1991), were active. He also reported hearing voices while auditory–linguistic association cortices in left posterior–superior temporal regions (Haglund *et al*. 1994; Silbersweig *et al*. 1994) were active. These simultaneous visual and auditory hallucinations were also associated with activity in posterior heteromodal association cortices involved in the integration of perception across modalities (Mesulam 1985). The fact that activity was not detected in primary visual and auditory cortices is consistent with the complex nature of the reported sensory experiences, and with the fact that they did not arise from the processing of stimuli from the external world. This also supports the notion that primary cortices are not necessary for sensory experience (Barbur *et al*. 1993), and might explain the sometimes less than vivid nature of hallucinations in schizophrenia.

In contrast to these neocortical activations, the regions of common activation in the group of schizophrenic patients with auditory–verbal hallucinations were limbic/paralimbic and subcortical areas increasingly implicated in the pathophysiology of schizophrenia (Bogerts *et al*. 1990; Csernansky *et al*. 1991; Benes *et al*. 1992; Friston *et al*. 1992; Tamminga *et al*. 1992; Marsh *et al*. 1994; Andreasen *et al*. 1994). These deeper regions include: the thalamus, with an increasingly recognized role in the spatio-temporal binding of neuronal activity associated with

conscious representations (related or unrelated to the external world) (Llinás & Pare 1991); the hippocampus, with an increasingly recognized role in the retrieval (as well as acquisition) of representations and contextual information (Le Doux 1993; Schacter *et al*. 1996); and the ventral striatum, with an increasingly recognized role in emotional experience (and its integration with perception) (Heimer *et al*. 1997). These regions are therefore candidates for the generation of these complex, subjective, emotionally charged sensory representations, whereas the neocortical regions with which they are interconnected might supply the detailed sensory content. The paucity of activation in frontal executive regions (which are known to be dysfunctional in schizophrenia (Friston 1992; Frith 1992; Weinberger *et al*. 1994)) might relate to the lack of volition associated with these hallucinations, and such lack of top-down control might even contribute to the aberrant activation of these basal and post-rolandic regions. Additional experiments are currently being performed in our laboratory to examine these hypotheses.

In contrast to the pattern of activation associated with hallucinations in schizophrenic patients, the pattern associated with auditory–verbal mental imagery in normal subjects is notable for its preponderance of frontal activity. The executive and premotor regions active here are similar to those activated during the preparation of action (Deiber *et al*. 1991). The fact that this is the case for such a perceptual task might at first be surprising, but it most probably represents the volitional (at times effortful) control of imagery, and possibly reflects the evolution of cognitive systems from motor systems. Posterior superior temporal activation was noted as well, probably underlying the auditory–linguistic sensory component of the task. As with hallucinations, and as has been seen in some (D'Esposito *et al*. 1997)—but not all (Kosslyn *et al*. 1995*b*)—other imagery studies, primary sensory cortex was not necessary for the conscious sensory experience of imagery to occur.

In S.B., selective attention enabled conscious auditory perception (and autonomic responsivity) in an otherwise cortically deaf individual. Again, primary sensory cortex (here lesioned) was not necessary for this experience. This is consistent with imaging data from the visual and somatosensory modalities (Barbur *et al*. 1993; Bottini *et al*. 1995). Instead, there was activity in spared, peri-infarct middle and superior temporal cortices. Similar recruitment of spared cortices was seen in our study of a similar patient who partly recovered from auditory agnosia (Engelien *et al*. 1995); this phenomenon has also been noted in the setting of partial recovery from aphasia (Weiller *et al*. 1995). This can occur via belt auditory projections (Brugge & Reale 1982) (as opposed to core projections to primary cortices), which synapse in posterior thalamic nuclei, as well as via non-specific thalamic projections to polysensory cortices. Nevertheless, because of the extent of the gray and white matter lesions involving much of the auditory association cortex and its mesotemporal connections, semantic content was not accessible to the patient.

Such activation of post-rolandic sensory cortices occurred in the setting of bilateral frontal activation, as was seen in the study of normal mental imagery. Such volitional, attentional effects on perceptual functions represent a top-down modulation of activity in sensory cortices. Such attentional modulation has been noted in functional neuroimaging studies of normal subjects (Frith & Dolan 1997; Rees *et al*. 1997; Shulman *et al*. 1997). Known cortico-cortical connectivity (Pandya & Yeterian 1985) can underlie such effects. Interestingly, although we have been describing the patterns of increased activity noted in the studies on auditory hallucination, auditory imagery and auditory stimulation, they all share patterns of decreased activity in visual cortices. This finding of decreased activity in visual cortices accompanying increased activity in auditory cortices has been noted in other functional neuroimaging studies that we and others have performed (Engelien *et al*. 1995; Silbersweig *et al*. 1993). It may represent the reallocation of computational/energy resources and the reduced susceptibility to cross-modal interference associated with selective attention to the auditory modality.

The subcortical activations seen in S.B. are consistent with thalamic roles in sensory processing, gating and modulation (Guillery 1995; McCormick & Bal 1994) as well as with the newly emerging roles of the striatum (Alexander *et al*. 1986; Masterman & Cummings 1997; Parent & Hazrati 1995) and cerebellum (Jenkins & Frackowiak 1993; Leiner *et al*. 1993) in cognition. Much of the processing of these phylogenetically older regions is thought to be automatic (or unconscious) and not necessarily associated with awareness.

Just as attention enabled some conscious perception of the auditory stimuli in S.B., sedation disrupted it in the normal subjects of the midazolam study. The decreased level of consciousness and associated sensory awareness in these subjects was related in a dose-dependent manner with decreased activity in neural systems associated with arousal, attention and cognitive processing. Indeed, the bilaterally symmetric pattern of deactivation in this study is consistent with the lesion literature regarding the unconscious vegetative state (Plum & Posner 1982), and strikingly outlines the diencephalic and neocortical heteromodal association components of the oscillatory thalamo-cortical circuits postulated to underlie human awareness (Llinás & Pare 1991).

The studies described here demonstrate that functional neuroimaging can be an effective tool for the localization *in vivo* of systems-level brain function associated with human sensory awareness. They also demonstrate how the study of normal and abnormal (neuropsychiatric) mental states can be complementary and convergent with respect to this goal. In particular, such studies can increase our understanding of the brain states sufficient (if not necessary) for conscious perceptual experience and the volitional control of that experience.

The results of these studies highlight the distributed nature of the neural systems involved (Mesulam 1990) and (in the context of the behavioural neuroscientific literature) suggest specific roles for the sensory neocortical, prefrontal, limbic–paralimbic and subcortical nodes within these large-scale networks. The studies on hallucination and imagery support the role of unimodal sensory association cortices in providing detailed conscious sensory content, without the necessity of concomitant primary sensory cortex activity. They also suggest that the same brain regions that process higher-

order sensory information arriving from the outside world are capable of operating in concert with (or of being driven by) other regions to duplicate many aspects of external sensory experience. As discussed above, and as emphasized by Llinás (Llinás & Pare 1991), the role of the non-specific thalamic nuclei might be particularly important in this regard. The hallucination study suggests that such internally generated experience may have an emotional/motivational valence associated with limbic and ventral striatal activity, and might even be mistaken for reality, possibly owing to associated dysfunction in prefrontal executive systems (Frith 1992; Silbersweig & Stern 1996).

The imagery and attentional modulation of cortical deafness studies support a specific role for such prefrontal executive systems in the top-down, volitional control of conscious sensory experience. These two studies also demonstrate the centrality of pre-rolandic–post-rolandic (in this case fronto-temporal) interactions in this active perceptual process. Additionally, these studies highlight the link between intention and attention, and the importance of both for normal functioning or adaptation to injury.

Ultimately, controlled perception serves us all so seamlessly that it used to be thought that a homunculus, the ultimate subject of sensory awareness or source of volition, existed somewhere in the brain. Not suprisingly, in view of current thinking, our imaging studies do not support such a notion. Different types of normal or pathological sensory awareness appear to be associated with specific permutations of activity patterns in the distributed, modular, neural systems discussed above. Although these studies focused on the auditory system, one might expect analogous patterns for other sensory modalities such as vision.

It should be kept in mind that this inquiry represents an attempt to draw some tentative conclusions from a number of small studies that, although complementary, were not designed as a systematic set of experiments. Nevertheless, we hope to have shown the power of functional neuroimaging methods to provide *in vivo* maps of the brain states associated with human mental states. By combining these systems-level neuroimaging methods with methods (including those discussed in other papers in this issue) that offer greater temporal resolution and an understanding of cellular and molecular mechanisms, we can begin to piece together neurobiological models of at least one aspect of human consciousness. This is not a bad state of affairs as the 'decade of the brain' draws to a close because, not too long ago, consciousness was thought not to be amenable to scientific inquiry.

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