Using fMRI to investigate speech-stream segregation and auditory attention in healthy adults and patients with memory complaints

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Statement of publications

The two studies presented in Chapter 3 of this thesis have been published in Cerebral Cortex (Kamourieh *et al.*, 2015). The data presented in Chapters 4 and 5 has been submitted to Lancet Neurology.

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Declaration of originality

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Synopsis

Poor memory for recent conversations is the commonest presenting symptom in patients attending a cognitive neurology clinic. They also frequently have greater difficulty following and remembering conversations in the presence of background noise and/or unattended speech. While the ability to participate in and recall conversations depends on several cognitive functions (language-processing, attention, episodic and working memory), without the ability to perform auditory scene analysis, and more specifically speech-stream segregation, recall of verbal information will be impaired as a consequence of poor initial registration, over and above impaired encoding and subsequent retrieval.

This thesis investigated auditory attention and speech-stream segregation in healthy participants (‘controls’) and patients presenting with ‘poor memory’, particularly a complaint of difficulty remembering recent verbal information. Although this resulted in the recruitment of many patients with possible or probable Alzheimer’s disease, it also included patients with mild cognitive impairment (MCI) of uncertain aetiology and a few with depression.

Functional MRI data revealed brain activity involved in attention, working memory and speech-stream segregation as participants attended to a speaker in the absence and presence of background speech. The study on controls demonstrated that the right anterior insula, adjacent frontal operculum, left planum temporale and precuneus were more active when the attended speaker was partially masked by unattended speech. Analyses also

revealed a central role for a right hemisphere system for successful attentive listening, a system that was not modulated by administration of a central cholinesterase inhibitor.

Therefore, this study identified non-auditory higher-order regions in speech-stream segregation, and the demands on a right hemisphere system during attentive listening. Administration of a central cholinesterase inhibitor did not identify any benefit in the present patient group. However, my research has identified systems that might be therapeutic targets when attempting to modulate auditory attention and speech-stream segregation in patients with neurodegenerative disease.

Abbreviations

ACC	anterior cingulate cortex
ACh	acetylcholine
AChE	acetylcholinesterase
ACE-R	Addenbrookes Cognitive Examination - Revised
AD	Alzheimer's disease
AI	anterior insula
aI/FOp	anterior insula and adjacent frontal operculum
aMCI	amnestic mild cognitive impairment
ASA	auditory scene analysis
BBR	Boundary-Based Registration
BOLD	blood-oxygen level dependent
BET	Brain Extraction Tool
CChEI	central cholinesterase inhibitor
CBF	cerebral blood flow
ChI	cholinesterase inhibitors
CingOper	cingulo-opercular network
COPE	contrasts of parameter estimates
CSF	cerebrospinal fluid
CVR	cerebrovascular reactivity

dACC	dorsal anterior cingulate
DAN	Dorsal Attention Network
deoxyHb	deoxygenated haemoglobin
DLB	dementia with Lewy bodies
DLPFC	dorsal lateral prefrontal cortex
DTI	diffusion tensor imaging
EPI	echo-planar imaging
ERPs	event-related potentials
EV	explanatory variable
FEAT	FMRI Expert Analysis Tool
FLAME	FMRIB Local Analysis of Mixed Effects
FLIRT	FMRIB Linear Image Registration Tool
fMRI	functional magnetic resonance imaging
FEF	frontal eye fields
FOp	frontal operculum
FSL	FMRIB Software Library
FTD	frontotemporal dementia
F_0	fundamental frequency
FWHM	full-width half-maximum
GDS	Geriatric Depression Scale
GLM	general linear model
HC	healthy controls

HRF	haemodynamic response function
HRTF	head-related transfer functions
HG	Heschl's gyrus
ICA	independent component analysis
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
IPL	inferior parietal lobe
IPS	intraparietal sulcus
ISSS	interleaved silent steady state
MCI	mild cognitive impairment
MDD	major depressive disorder
MEG	magnetoencephalography
MFG	middle frontal gyrus
MELODIC	Multivariate Exploratory Linear Decomposition into Independent Components
M0	net magnetisation of spinning protons
MNI	Montreal Neurological Institute
NFT	neurofibrillary tangles
oxyHb	oxygenated haemoglobin
PAL	Paired Associate Learning
PET	positron emission tomography
PFC	prefrontal cortex
PT	plana temporale

RTI	Reaction Time
RF	radiofrequency
ROI	region of interest
RVP	Rapid Visual Information Processing
SFG	superior frontal gyrus
SMG	supramarginal gyrus
SNR	signal-to-noise ratio
SPL	superior parietal lobe
STG	superior temporal gyrus
stROI	superior temporal lobe region of interest
STS	superior temporal sulcus
SWM	Spatial Working Memory
TE	echo time
TR	repetition time
TROG	Test for reception of grammar
VAN	Ventral Attention Network
WM	working memory

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1 Introduction

1.1 The ‘cocktail-party’ effect

Conversations often take place in noisy environments, which often includes the presence of unattended speakers. Segregating the attended speech from others is a remarkable human skill, and has been the subject of much research since the publication of an influential article by Miller in 1947. Successful perception of what an attended speaker has said depends on both ‘bottom-up’ (stimulus-driven) and ‘top-down’ (goal-directed) processing of the speech signal. Once the auditory signal has been segregated from any background noise or unattended speech, it can then be further processed by systems that realise meaning and that encode the verbal message in episodic memory (Zion Golumbic *et al.*, 2013). Successful registration of what a speaker is saying may be confounded at many levels, from low-level, modality-specific (auditory) impairment through to disorders of high-order, domain-general attention and working memory; but even if a listener has normal hearing and an absence of brain pathology, partial masking of the attended speech and a low level of interest in, and hence attention to, what a speaker is saying influence the ability to participate in a conversation.

Speech-in-speech masking has become known as the ‘cocktail-party effect’ (Cherry, 1953). Masking places demands on both focused and sustained attention, which in turn depend on the context. For example, listening to a lecture requires a lengthy period of attention and the ability to encode the semantic content as enduring memories, whereas turn-taking in a conversation requires brief periods of attention, and is more reliant on working memory.

Separating speech and sounds

Recent research on speech-in-speech masking has mainly been directed at the auditory cues that listeners use to overcome the peripheral (energetic, at the level of the cochlea) and central (informational) masking (Brungart, 2001). These include differences in voice pitch and prosody, spatial information, and the asynchrony of the onset and offset of speech sounds (Bregman, 1990; Carlyon, 2004; Darwin, 2008; Darwin and Hukin, 2000a, b; Feng and Ratnam, 2000; Snyder and Alain, 2007). Ease at segregating speech streams will depend on acoustic differences between the attended and unattended speech (Bregman, 1990). Unattended speech is more problematic when it conveys pre-lexical, lexical and semantic information, as this informational masking presents an additional challenge, over and above any peripheral masking that may originate from, say, multi-speaker babble. Listening to a speaker when there is an unattended speaker in the near vicinity of the same sex, speaking in the same language and talking on a similar topic presents the greatest challenge (Brungart *et al.*, 2001), and places increased demands on attention.

Carlyon (2004) has reviewed current knowledge about 'how the brain separates sounds'. An important phenomenon is the effect of 'auditory streaming', or the perceptual organisation of sounds over time, which has important implications for how music is perceived. This can be demonstrated using even very simple stimuli, such as when investigating the perceptual experience for a listener of manipulating both the frequency differences between two pure tones and the rates at which regular bursts of these two pure tones are heard. Differences in the onset and, to a lesser extent, offset times of sounds (Darwin and Carlyon, 1995) assist in the separate grouping of sounds (see Figure 1.1A). Spatial cues, conveyed by interaural level differences (and to a lesser extent interaural time differences) are particularly helpful to the

listener (see Figure 1.1B) (Culling and Summerfield 1995; Darwin, 1997; Darwin and Carlyon, 1995; Gockel and Carlyon 1998; Licklider, 1948), as are binaural phase differences and monaural cues such as head related transfer function (HRTF). For speech, in particular, there is benefit if the fundamental frequency (F_0) of the individual voices is very different. Further, the quasi-periodic nature of speech, with the rapidly fluctuating intensities in the speech signal, permit 'glimpses' of the attended speech through the masking unattended speech (McDermott, 2009).

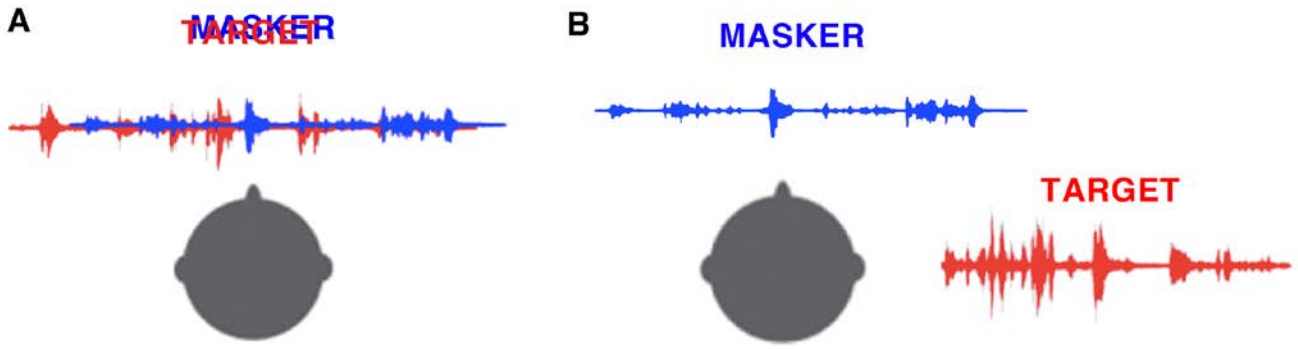


Figure 1.1: Segregation of speech

***A**. Schematic diagram of a listener with two speakers talking at the same time. Cues used to aid the listener include: differences in onset and offset of speech and also differences in fundamental frequencies (F_0). This is demonstrated by the difference in obscuration of the 'target' and 'masker' lables. **B**. One speaker positioned in front (masker) and one to the right (target). Cues used to aid the listener in following the target speech include interaural level differences and interaural time differences.*

Although auditory cues were employed in conditions used in my functional imaging studies of attentive listening to a speaker (such as employing attended and unattended speakers of different sex, and therefore with different F_0, and with simulated spatial cues in some listening conditions), they were not the subject of investigation – not least because much of the

information encoded by these cues occurs within the subcortical auditory pathways, and therefore largely below the resolution of the brain imaging technique I employed, namely functional magnetic resonance imaging (fMRI). My interest was primarily in the top-down processes engaged during attentive listening, and the modulation of primary and association auditory cortices under their influence.

1.2 Auditory attention: top-down control

According to Broadbent's (1958) 'selective filter' theory, presenting two speakers using a dichotic listening condition would result in processing of the unattended speech stream only as far as analysis of its basic auditory properties. Whilst it has been confirmed that when the two ears are used as separate channels for an attended and unattended speaker the listener remains largely unaware of the content of the unattended speech, nevertheless it would appear that the 'filter' attenuates rather than completely blocks the unattended speech stream (Treisman, 1964). In contrast, Kahneman (1973) argued that attention could be allocated to multiple sensory inputs until it reached a processing limit, whilst Allport (1989) argued against both the bottleneck and the limited capacity models and suggested that the so-called limits on attention were related to preserving an output related to the goal rather than being driven by every input. These theories raise the question of how early in the processing stream attention modulates the input, and how deeply the non-attended stimuli are processed. It is known that the salience of unattended speech can capture attention, a typical example being when a listener suddenly becomes aware that his or her name has been spoken by an unattended speaker, 'Cocktail party effect'.

The role of attention in auditory scene analysis (ASA) remains controversial. Some have proposed that attention isn't required to segregate one auditory sequence from others (Sussman *et al.*, 2007), that is, it is pre-attentive, but once segregation has occurred one single source of sound becomes the object of attention. Others have proposed that auditory stream segregation is dependent on attention (Cusack *et al.*, 2004). The likelihood is that the ability to segregate one speech stream from a complex auditory environment involves several stages that rely on both 'bottom-up' and 'top-down' processes (Alain, 2007; Xiang *et al.*, 2007). This implicates a distributed network of auditory cortical and subcortical structures, functionally and anatomically connected with a more domain-general attentional network that includes parietal, frontal and anterior cingulate cortical regions (Bidet-Caulet and Bertrand, 2005; Foxe *et al.*, 2005; Peers *et al.*, 2005; Raz and Buhle, 2006; Serences and Yantis, 2007). This interconnected network separates one source of sound sequences from others so that, in the case of speech, it can then be processed further for meaning, encoded as a memory (briefly, in working memory, or as a more enduring episodic memory if of sufficient importance to be retained for later retrieval) and a response prepared, such as formulating an appropriate answer to a question.

Therefore, although 'bottom-up' processing of salient acoustic features is important, attention is key to highlight foreground over background and to switch attention between objects and streams of interest (Alain and Arnott, 2000; Fritz *et al.*, 2003; Fritz *et al.*, 2005). Pre-attentive segregation of speech streams is augmented by spatial, temporal and vocal differences (Bregman, 1990; Brungart *et al.*, 2001), but overcoming informational masking is more

dependent on top-down control. This is enhanced by the listener's familiarity with the speaker's voice (Brungart *et al.*, 2001; Newman and Evers, 2007).

Limitations of fMRI and auditory attention

MRI scanners require strong magnetic fields and rapidly switching magnetic gradients in order to achieve good spatial and temporal resolution (see Methods 2.1 for more detail), which generates noise that can exceed 110dB sound pressure level in intensity (Moelker and Pattynama, 2003). Although protective headphones reduce the intensity, scanner noise is part of the auditory scene for listeners in fMRI experiments (Mathiak *et al.*, 2002) with continuous data acquisition, and brain activity in response to auditory stimuli will also include a response to scanner noise (Hall *et al.*, 1999; Hall *et al.*, 2000; Shah *et al.*, 1999). To reduce this confound, the listening conditions in my studies depended on sparse sampling and interleaved sparse sampling or ISS (Hall *et al.*, 1999; Schwarzbauer *et al.*, 2006), in which the auditory stimuli were presented during periods of silence or much reduced scanner noise respectively (see Methods 2.3.5). An unavoidable limitation with this method of data acquisition is a reduced number of image volumes, lowering the signal-to-noise ratio in comparison with continuous scanning protocols (Huang *et al.*, 2012).

The majority of research on attention, both neuropsychological and functional neuroimaging, has depended on visual stimuli (Corbetta and Shulman, 2002). Functional neuroimaging studies on auditory attention have often used designs derived from those that have used visual stimuli. One such design investigates cerebral activity when attention is cued towards and away from the target location, and is based on the Posner visual cueing paradigm

(Posner, 1980). Variants of this design have been used in auditory attention studies using simple and more complex stimuli to investigate attention based on acoustic features such as pitch and location (Hill and Miller, 2010; Lee *et al.*, 2012; Mayer *et al.*, 2006). However, this does not capture the complexity of normal auditory environments. In order to investigate and understand the processes involved in auditory attention as usually experienced, the system needs to be placed under 'high load' conditions (Hill and Miller, 2010). My studies were based on attentive listening to an attended speaker in the absence or presence of an unattended speaker, which closely approximates everyday listening experiences.

Attentional modulation of auditory cortex

Before imaging studies were available, understanding the mechanisms involved in the processing of speech was dependent on behavioural studies on patients with lesions (lesion-deficit analyses). The best-known example is the original study by Wernicke on aphasic patients, which associated the posterior left superior temporal gyrus with speech perception. A more recent example was a study on patients after either a left or right temporal lobe resection, performed to control frequent epileptic seizures, which demonstrated hemisphere differences in the ability to process changes in pitch direction (Johnsrude *et al.*, 2000). Despite the importance of these clinical observations, the obvious advantage of functional neuroimaging is to localise function in normal participants, in whom pathology has not altered brain organisation, and without the need to find patients with critically placed lesions.

It has been proposed that segregating sounds from background noise is dependent on matching the temporal and spectral structure of those sounds with stored auditory 'templates',

with a central role played in this process by the plana temporale, (Griffiths and Warren, 2002). However, fMRI has identified attention-related modulation of the auditory cortex (Langner *et al.*, 2012; Petkov *et al.*, 2004). There is a general increase in activity within the auditory cortex during attentive compared to passive listening (Paltoglou *et al.*, 2009, 2011), and with dichotic listening trials there is increased activity in the Heschl's gyrus (HG) and planum polare in the hemisphere contralateral to the attended side of the auditory source (Jäncke and Shah, 2002; Rinne, 2010; Rinne *et al.*, 2008; Yang and Mayer, 2014). In animal studies, it has been demonstrated that neurons within the auditory cortex alter their response characteristics to allow better discrimination of target sounds (Fritz *et al.*, 2003). Further, these changes in responses are dependent on task context, changing if the task-dependent goal is determined by, for example, the location or pitch of a sound, even in the presence of background noise (Fritz *et al.*, 2007). In these studies, although the authors did not determine their origin, the rapid plasticity of auditory cortex may be in response to attentional signals.

A number of functional neuroimaging studies have investigated the processing of masked speech in the absence of spatial cues. Hwang and colleagues (2006) required participants to listen to a story in their native language (Chinese), presented in the absence or presence of continuous white noise. The authors reported reduced activity in the left superior temporal sulcus (STS) during the speech-in-noise condition, but this may have been an incidental effect of the reduced intelligibility of the masked speech, particularly as continuous data acquisition imposed scanner noise in addition to the white noise masker. This interpretation is supported by studies that have demonstrated activity in the left STS that is dependent on the intelligibility of the speech stimuli (McGettigan *et al.*, 2012; Rosen *et al.*, 2011; Scott *et al.*, 2000). Wong and colleagues (2009) used 'sparse' sampling (Hall *et al.*, 1999), so that the stimuli were heard without background scanner noise. The authors required participants of

varying ages to listen to single words in the absence or presence of multi-talker babble. At certain signal-to-noise ratios (SNR), the performance of older participants declined relative to that of younger participants, and this was associated with declining activity in auditory cortex. However, activity increased in frontal and midline posterior (precuneus) regions, and the activity in these higher-order, non-auditory regions correlated with performance on the word detection task. The authors describe this phenomenon as the 'decline-compensation hypothesis' associated with ageing, but put another way this suggests that greater difficulty with the task for the older participants resulted in increased top-down control to accomplish the task. However, components of this network have also been seen with passive listening 'cocktail party' tasks (Golden et al., 2015 neuroimage). Increased attention and cognitive control will also help compensate for the almost inevitable high tone hearing impairment experienced by participants over 50 years. Hearing loss in the higher tones reduces the intelligibility of speech, mainly conveyed by consonants, many of which lie in the frequency range 1000–8000Hz, with vowels in the frequency range 250–500Hz (see 1.4.1 for more information).

Attention and auditory tasks

The observation of Wong and colleagues (2009) on the involvement of non-auditory regions during attentive listening has been replicated in other fMRI studies on normal participants. A dorsally directed cortical network, including the plana temporale (PT) and posterior superior temporal gyri (STG), supramarginal gyri (SMG), intraparietal sulci (IPS) and their reciprocal prefrontal connections have been observed (Hill and Miller, 2010; Kong *et al.*, 2014; Overath *et al.*, 2010). It is known that the frontal cortex participates in top-down attentional processes (Hill and Miller, 2010; Obleser *et al.*, 2007; Schönwiesner *et al.*, 2007), although the role of

parietal cortex has been less certain. It has been suggested that it may be involved in primary labelling of salient signals (Cohen, 2009; Downar *et al.*, 2000) or attentional modulation (Hill and Miller, 2010). However, these attempts to assign specific processing functions to higher-order non-sensorimotor cortical regions are often speculative, as the functions they perform are dependent on systems encompassing a distributed network of cortical regions.

The influence of spatial and non-spatial features on auditory attention has been the subject of a number of studies. Activity within left and right premotor and inferior parietal regions has been demonstrated in sound localisation tasks (Degerman *et al.*, 2006; Mayer *et al.*, 2006). A recent study by Hill and Miller (2010) determined the regions that became active as listeners prepared to attend to location or pitch. There was increased activity in bilateral premotor and parietal regions for location trials, the left inferior frontal gyrus during the preparation to attend to pitch and bilateral superior temporal sulci (STS) during the stimulus period when the listeners were attending to pitch compared to location (Hill and Miller, 2010). Therefore, attention to specific features may involve control from different higher-order neural systems.

It does seem, however, that the ability to switch attention from one auditory stimulus to another involves a fronto-parietal network, similar to that seen in visual attention tasks (Shomstein and Yantis, 2006). In particular, posterior parietal cortex appears to be involved in both non-spatial and spatial attention in both the auditory and visual modalities (Serences *et al.*, 2004; Shomstein and Yantis, 2006; Yantis *et al.*, 2002).

With regards to orienting attention, later studies which separated cued attention shifting from

target identification determined that both voluntary attention switching and target discrimination activated a fronto-insular-cingular system (including the anterior insula, medial frontal and inferior frontal cortex) (Huang *et al.*, 2012[1]; Salmi *et al.*, 2009). However, it is important to note that the results of many auditory attention studies may have been affected by the noise of the scanner, as studies using sparse sampling design are limited.

Nakai and colleagues (2005) performed a speech-in-speech masking study that required participants to follow a story periodically masked by two different forms of speech, either speech recorded by the same talker (SV) or a talker of different sex (DV). Masking by the same speaker was predictably the more difficult of the two masking conditions (Brungart, 2001). The authors identified bilateral STG activation in the contrast of DV with unmasked speech, but when the same speaker masked single speech there was increased activity in both posterior temporal cortex and non-auditory regions. Of particular note, activity in the SV condition was increased in a cingulo-opercular network that has since become associated with domain-general cognitive control (Dosenbach et al., 2008).

1.3 Task-related cognitive control and attentional networks

Much of our understanding of these networks is based both on functional neuroimaging studies on normal participants and lesion-deficit analyses on patients with focal lesions (for example: Aron *et al.*, 2014; Corbetta *et al.*, 2008; Corbetta and Shulman, 2011; Dosenbach *et al.*, 2007, 2008; Duncan, 2010, 2013; Hampshire *et al.*, 2010, 2012; Menon and Uddin, 2010;

[1] This study used sparse sampling design.

Roca *et al.*, 2010; Shallice *et al.*, 2008; Singh-Curry and Husain, 2009; Vincent *et al.*, 2008; Woolgar *et al.*, 2011, 2013). Early neuropsychological studies often attempted to associate impairments of specific cognitive functions with focal lesions, on an assumption that specific functions are localised to specific cytoarchitectonic regions of cortex.

Lesion studies

Stuss and colleagues investigated the cognitive function of patients with frontal lesions (Shallice *et al.*, 2007; Stuss *et al.*, 2001; Stuss and Alexander, 2007). The authors associated lesions in left dorsolateral prefrontal cortex (PFC) with what they termed task setting and those in right dorsolateral PFC with performance self-monitoring, while lesions to superior medial frontal structures impaired cognitive effort or 'energization' (Shallice *et al.*, 2008; Stuss and Alexander, 2007). Other studies have associated deficits in sustained attention (Rueckert and Grafman, 1996; Wilkins *et al.*, 1987) and inhibitory control (Aron *et al.*, 2004; Dimitrov *et al.*, 2003; Floden and Stuss, 2006) with right frontal lesions.

As the distribution of lesions rarely conforms to functional cortical boundaries, single case studies that directly relate anatomy to function are rare. Therefore, in order to establish a direct causal relationship between location and cognitive function, lesions studies have often relied on patient groups with differently distributed focal lesions but with common overlap within one brain region. Computerised methods to overlap differently distributed strokes have become popular (Bates *et al.*, 2003), but the precision of these techniques has been questioned (Mah *et al.*, 2014). Furthermore, although lesion-deficit analyses implicate both 'necessary and sufficient' functions of brain regions specialised for sensorimotor or domain-

specific cognitive functions, they are less able to determine the distribution of functional systems involved in domain-general cognitive control and attention. Although regional increases in brain activity observed in functional neuroimaging studies cannot of themselves determine that a particular brain region is both 'necessary and sufficient' for a particular function, nevertheless they are particularly suited to reveal widely distributed brain systems.

Domain-general networks revealed with functional neuroimaging

A number of distributed systems, identified over the last two decades with functional neuroimaging, have been implicated in domain-general cognitive control, working memory and attention: two dorsal fronto-parietal systems, which are symmetrically distributed between the hemispheres; a third, more ventral, fronto-parietal system usually considered to be predominantly right-lateralised; and lastly a fourth network distributed between dorsal midline frontal cortex and bilateral anterior insular and adjacent frontal opercular cortex. The exact processes mediated by sub-components of these networks are not yet clearly defined.

Research into the demands made on these domain-general systems that enable us to understand and remember what a speaker has said, either when speaking alone or in the presence of masking noise or background speech, is limited. This contrasts with the abundant research on more domain-specific sensory, language and memory (semantic and episodic) systems involved in speech comprehension. However, any task-dependent processing of sensory stimuli engages domain-general systems, and listening to speech during the normal conversational use of language is never 'passive'.

In vision, a fronto-parietal network has been shown to activate the endogenous orienting of attention (Corbetta and Shulman, 2002; Shulman *et al.*, 2002), and studies in auditory attention have generally agreed that similar neural substrates are involved (Mayer *et al.*, 2006; Shomstein and Yantis, 2004, 2006; Wu *et al.*, 2007). Others have observed a 'fronto-parietal' network that incorporates the left and right anterior and dorsolateral prefrontal cortices and the intraparietal sulci/adjacent dorsal inferior parietal cortices (Dosenbach *et al.*, 2007, 2008; Power *et al.*, 2011; Power and Petersen, 2013), which they have tentatively related to the initiation of task performance and task-by-task adjustment of cognitive control (Figure 1.2). Although task-related activity results most often in symmetrical bilateral activity, multivariate analyses of fMRI data to reveal so-called resting state networks have indicated that the left and right lateralised components may be functionally separable (Smith *et al.*, 2009, 2012).

A more dorsal fronto-parietal network, or 'Dorsal Attention Network' (DAN) has been observed in studies of visual attention (Corbetta *et al.*, 2008; Kincade *et al.*, 2005). It has been suggested that the function of the DAN is to maintain goal-directed, top-down selection of neural signals that bias processing of specific target properties and cortical location (Corbetta *et al.*, 2008). Regions included are the intraparietal sulcus (IPS) and superior parietal lobe (SPL), dorsal regions of the frontal lobe at or near the frontal eye fields (FEF), and the middle frontal gyrus (MFG) (Figure 1.2). Although activity within the DAN has been observed when participants orient attention to auditory stimuli (Downar *et al.*, 2000; Driver and Spence, 1998; Langner *et al.*, 2012; Mayer *et al.*, 2006; Shomstein and Yantis, 2006; Sridharan *et al.*, 2007; Wu *et al.*, 2007), studies on the processing of speech have rarely resulted in increased activity within this system. An empirical review and meta-analysis of 128 language studies (Cabeza and Nyberg, 2000; Vigneau *et al.*, 2011) showed no activation of the SPL or FEF

during the processing of speech. Focal parietal lesions with visuospatial neglect (Malhotra *et al.*, 2009) are not often accompanied by difficulty identifying sounds (Marshall, 2001), although auditory sustained attention (Robertson *et al.*, 1997) and spatial localisation (Pavani *et al.*, 2002) have been reported. With the majority of evidence for a dorsal fronto-parietal network based on visual studies (Corbetta *et al.*, 2008 for review), its involvement in auditory attention remains inconclusive.

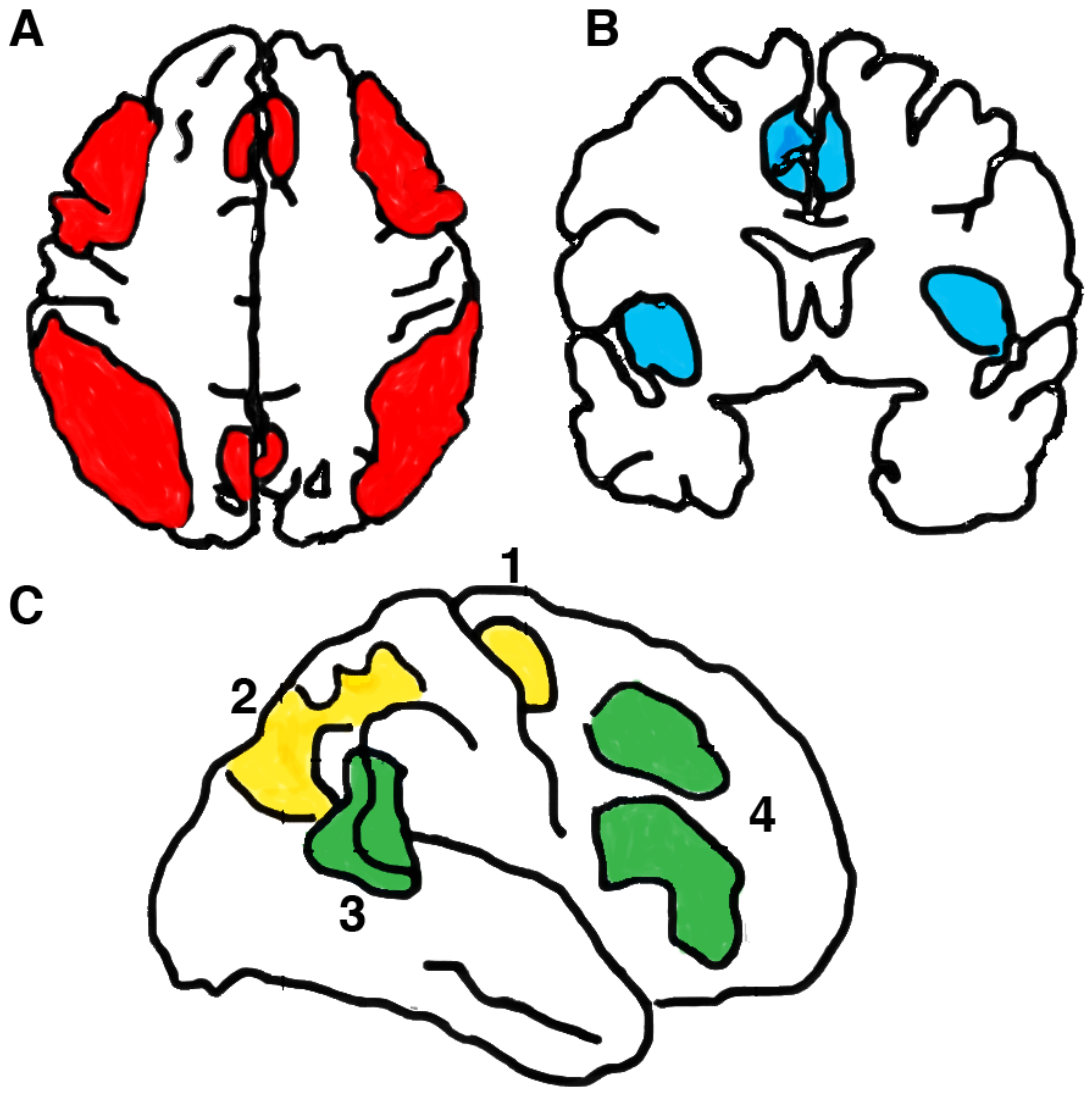


Figure 1.2: A schematic drawing of the spatial distribution of domain-general networks engaged in top-down control of attention

*(**A**) Fronto-parietal control network (**B**) cingulo-opercular network. Although separable, the cingulo-opercular and fronto-parietal control networks involved in attentional and executive control, decision-making and monitoring and correcting for errors, are often co-activate. (**C**) 'Top-down' task-driven attentional system, the Dorsal Attentional Network, bilateral, in yellow. 1. Frontal eye fields. 2. Intraparietal sulcus/superior parietal lobe. 'Bottom-up' attentional system, stimulus driven, known as the Ventral Attention Network, is largely right lateralised, in green. 3. Temporo-parietal junction; inferior parietal lobe/superior temporal gyrus. 4. Inferior/middle frontal gyrus.*

The DAN is distinct from a ventral fronto-parietal network, the 'Ventral Attention Network' (VAN), which includes the junction of the inferior parietal lobe with the posterior temporal lobe. This network is predominantly right lateralised and has been associated with the 'bottom-up' capture of attention by behaviourally relevant stimuli (Corbetta and Shulman, 2000, 2002; Corbetta *et al.*, 2008; Mayer *et al.*, 2006; Singh-Curry and Husain, 2009) (Figure 1.2). However, several fMRI studies have identified overlap between the dorsal and ventral regions in visual attention (Rosen *et al.*, 1999; Serences and Yantis, 2007). Although important in auditory processing, fewer studies investigating voluntary attention shifting in auditory modality exist and the results are not consistent (Huang *et al.*, 2012).

A further system, the cingulo-opercular network, comprises the dorsal anterior cingulate cortex and adjacent medial superior frontal gyrus (dACC/SFG) and bilateral anterior insulae and adjacent inferior frontal gyri (AI/IFG) (Dosenbach *et al.*, 2007, 2008; Power *et al.*, 2011; Power and Petersen, 2013). These regions often coactivate with fronto-parietal networks across a wide range of tasks (Vincent *et al.*, 2008), and it is not usually apparent what distinct processes are being subserved by these different systems. Based on a limited number of experiments, it has been suggested that the fronto-parietal system initiates and adjusts control whereas the cingulo-opercular system provides a stable 'set-maintenance' throughout the task (Dosenbach *et al.*, 2008), but this can only be considered speculative on present evidence.

Another network, which is found to deactivate when particiapnts are engaged in a task, is called the Default Mode Network (DMN) (Buckner *et al.,* 2008; Raichle *et al.,* 2001). Its distribution includes the ventral anterior posterior cingulate cortex, rostral dorsolateral prefrontal cortex, the angular gyri, the medial temporal lobes and the precuneus. Although this is commonly described as a 'resting state' network, part of this network overlaps with those of the fronto-parietal networks. An anticorrelated relationship between the DMN and top-down networks has been identified (Fox *et al.,* 2005), with a disruption of this noted in normal aging (Andrews-Hanna *et al.,* 2007) and dementia (Zhou *et al.,* 2010). Although I will not be discussing this network in detail in this thesis, it is important to identify it with regards to linking between stimulus-independent and stimulus-directed processing (Leech and Sharp, 2014).

1.4 Ageing, neurodegenerative disease and difficulties in cognitive control and in speech-stream segregation

It is evident that impaired function of fronto-parietal and cingulo-opercular domain-general networks will have a major impact on task performance, including attentive listening, particularly when the attended speech is masked by noise or unattended speech. Patients with Alzheimer's disease (AD) are known to have impaired attention early in the course of the disease (Perry and Hodges, 1999; Perry *et al.*, 2000). In everyday conversational situations, a reduction in these functions, and the inability to segregate attended from unattended speech, will result in impaired registration of the attended speech. The consequences will be difficulty following conversational themes, and a subsequent inability to remember what was said. This 'poor memory' will be as much a problem of initial registration as an impairment of episodic encoding.

1.4.1 Age- and hearing-related decline in central auditory processing

Age-related decline

Older adults often have difficulty in following conversation in the presence of background sound, especially unattended speech (Pichora-Fuller *et al.*, 1995; Tun *et al.*, 2002). This may be secondary to peripheral or central auditory dysfunction (or both) and can occur at four levels: (i) detection of the target (attended) speech; (ii) separation of target speech from maskers; (iii) suppression of interference from competing speech; and (iv) impaired processing of target speech, including selective attention and working memory (Figure 1.3). Impairment at one level would be sufficient to impair a person's ability to understand speech in a noisy environment.

Studies have identified impairments in tasks involving both executive functions, such as working memory, and attention in older individuals (Gazzaley and Nobre, 2012). Further, ageing is associated with increasing difficulty in suppressing distracting information (Gazzaley *et al.*, 2005), with functional neuroimaging studies demonstrating activity related to the processing of irrelevant stimuli (Fabiani *et al.*, 2006; Gazzaley *et al.*, 2005; Stevens *et al.*, 2008). This may be explained by the loss of activity and coherence within the fronto-parietal network, normally involved in reducing interference from distractors (Campbell *et al.*, 2012).

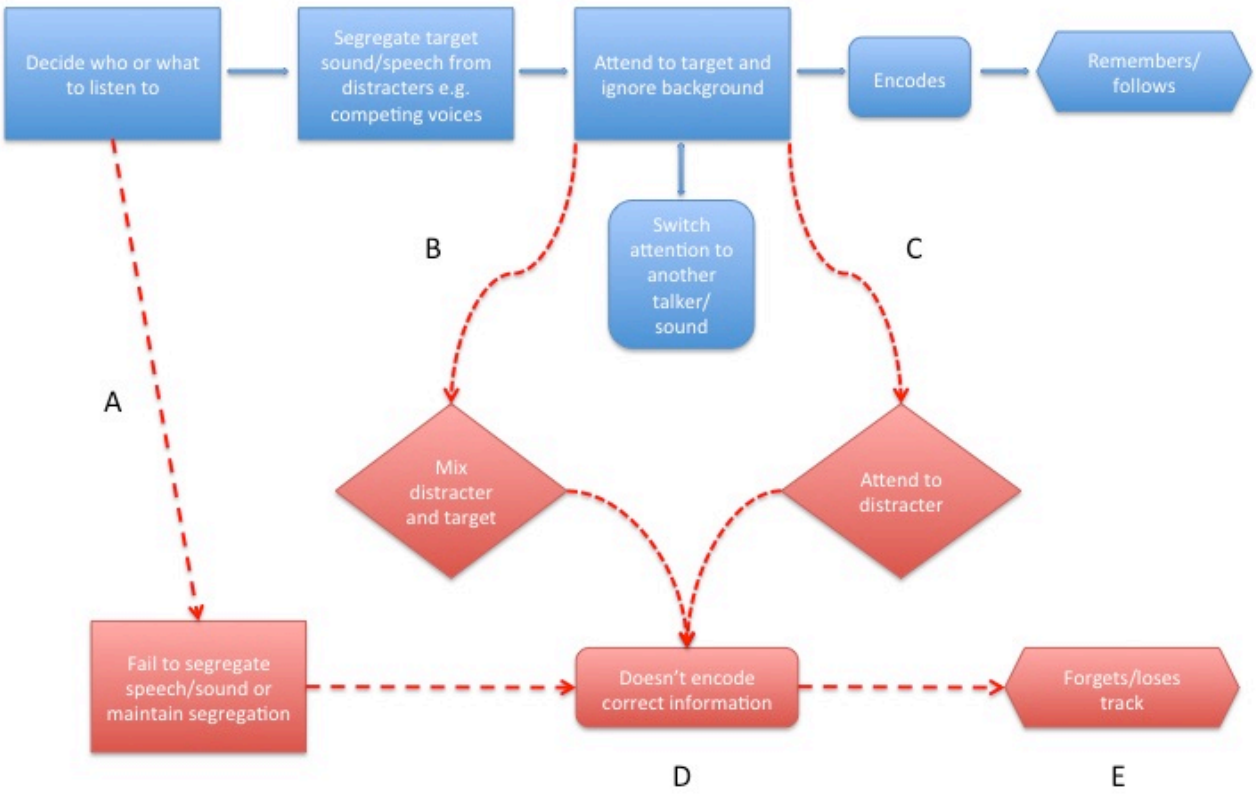


Figure 1.3: Schematic representation of following a conversation and where problems can occur

Red dotted arrows highlight areas where problems can occur. ***A****. Failing to segregate the speech;* ***B****. inability to attend to the target speech and avoid being distracted;* ***C****. inability to switch between speakers;* ***D****. failing to register the information resulting in failure of encoding;* ***E****. failure to retrieve the verbal information and participate successfully in the conversation.*

Hearing loss

Age-related hearing loss, across all frequencies but especially higher ones, is common, and at least some hearing impairment exists in most adults over the age of 70 years (Gates and Mills, 2005) (Figure 1.4). It is associated with sensory loss (loss of outer hair cells), metabolic changes within the cochlea and neural loss (loss of ganglion-nerve cells) (Aydelott *et al.*, 2010).

Conversational speech is dynamic and time-varying, and the acoustic composition of speech sounds is shaped by the preceding and following sounds. Consonants contribute more to the intelligibility of speech than vowels, and their perception is more vulnerable to reduced hearing in the higher frequencies (Ross, 2004). Loss at 4–8KHz may affect consonant discrimination in the presence of masking noise (Abel *et al.*, 2000), and while modest hearing loss at frequencies above 2KHz may have only limited effect on speech perception in quiet environments or in the presence of low levels of background noise, speech perception is severely affected with higher levels of background noise (Pekkarinen *et al.*, 1990) (Figure 1.4).

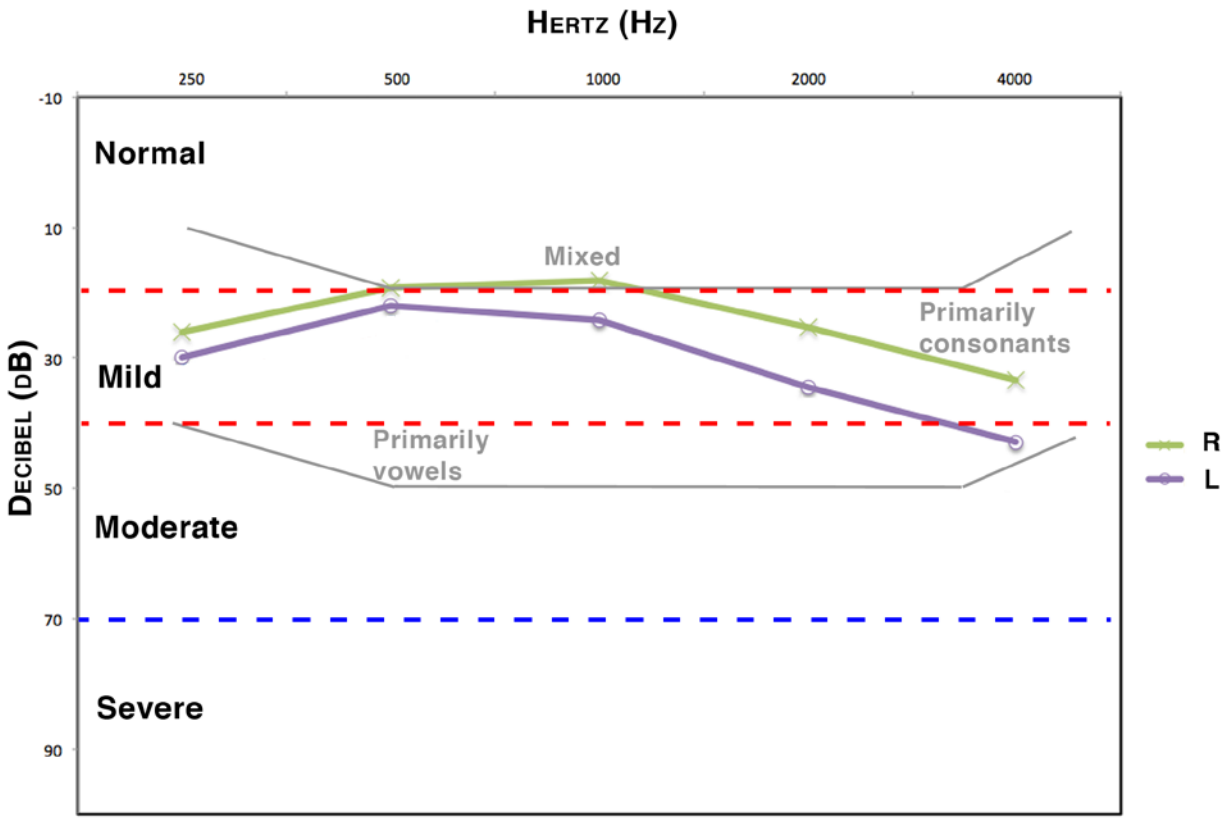


Figure 1.4: Audiogram

Figure of an audiogram (frequency in Hz and hearing loss in dB). The right ear (R) is shown as Xs and the left ear (L) is represented as 0s. Thresholds for normal/mild/moderate and severe hearing impairment are shown. The area between the grey lines demonstrates the frequency levels and decibels where speech sounds are generally perceived. Primarily vowels around 40–50dB at 500Hz; mixed vowels and consonants at 20–30dB at 1000–2000Hz and primarily consonants at 30–40dB at 4000Hz.

1.4.2 Anxiety- and depression-related decline in attention and executive control

Depression and cognitive decline

Depression is a risk factor for cognitive decline (Jorm, 2000), with neuropsychological deficits that involve frontal functions and memory occurring in association with major depression

(Zakzanis *et al.*, 1998). In elderly people with major depression, the chief complaint is of memory disturbance and this may be mistaken for dementia, and is known as pseudodementia (Marazziti *et al.*, 2010). Depression is biologically heterogeneous, and there are inconsistent findings with regard to the involvement of frontal impairment and executive deficits, which may depend on age and the severity of the disease (Goodwin, 1997). Studies have identified problems in selective attention (Lemelin *et al.*, 1996), working memory (Austin *et al.*, 1999; Harvey *et al.*, 2004; Hugdahl *et al.*, 2004; Zakzanis *et al.*, 1998) and executive processes (Lockwood *et al.*, 2002; Harvey *et al.*, 2004).

Anxiety disorders and cognitive decline

Anxiety affects task performance and may increase in the novel environment associated with MRI, and when required to do a task under experimental observation. Anxiety disorders have been associated with impairments in episodic memory and executive functioning (Airaksinen *et al.*, 2005). Functional neuroimaging studies on patients with anxiety have demonstrated increased activity in the cingulo-opercular and ventral fronto-parietal systems and decreased function in the more dorsal fronto-parietal system and in the default mode networks (Sylvester *et al.*, 2012). It has been proposed that these changes reflect maladaptively low thresholds to alterations in cognitive control and inappropriate directing of attention to distractors (Hajcak *et al.*, 2003; Paulus *et al.*, 2004; Sylvester *et al.*, 2012). Further, the distributed functional changes may result in deficits in implementing cognitive control (Bishop, 2009; Sylvester *et al.*, 2012). Although the existence of changes in the function of fronto-parietal networks in anxiety is controversial (Sylvester *et al.*, 2012), they may be a factor affecting in-scanner performance.

1.4.3 Memory impairment and speech-stream segregation

Patients with memory complaints often find that attending to speakers over long periods or when they are distracted by background speech is particularly problematic. As a result, the additional impairment in registering verbal information will aggravate any deficit in the encoding of verbal information. As attention and cognitive control are potential targets for symptom-modifying pharmacotherapy (for example, Klinkenberg *et al.*, 2011; Robertson, 2014), improved understanding of the function of these systems in early cortical neurodegenerative disease may inform improved symptom-modifying treatment in mild-to-moderate dementia.

Mild cognitive impairment

Mild cognitive impairment (MCI) is defined as cognitive decline without impaired ability to carry out the activities of daily living. It has a prevalence of 29% in those over 85 years and 19% in those over 75 years (Lopez *et al.*, 2003). Over a three-year period, approximately 20% of patients with MCI were subsequently diagnosed with dementia, and of those 78% were Alzheimer's disease (AD) (Palmer *et al.*, 2008). At the time of diagnosis, patients with MCI have subjective memory problems, greater then expected for age and education (Petersen, 2004), and objective cognitive decline, which may include executive function (Crowell *et al.*, 2002) and attention (Dannhauser *et al.*, 2005; Perry and Hodges, 2003). Impaired speech-stream segregation/central auditory dysfunction have also been described in patients with MCI (Gates *et al.*, 1996; Idrizbegovic *et al.*, 2011).

Studies have identified neuropathological and executive difference between MCI and normal ageing (Markesbery, 2010; Dannhauser *et al.*, 2005), and neuropathological similarities between MCI and AD (Price and Morris, 1999). This would support the idea that similar distributions of degenerative pathology may result in functionally similar impairments in attention in patients with established AD and those with MCI.

Alzheimer's disease

The global prevalence of dementia is estimated to be approximately 35 million, with the prediction that this figure will double every 20 years (Prince *et al.*, 2013). AD is one of the commonest forms of cognitive decline in the Western world. It may have a variable clinical presentation (Stopford *et al.*, 2008), but the onset most typically commences with symptoms of poor memory (Perry *et al.*, 2000; Welsh *et al.*, 1991), followed by more global cognitive decline and an impaired ability to carry out activities of daily living.

Initially, episodic (autobiographical) memory (Petersen *et al.*, 1994; Perry *et al.*, 2000), linking occurrences to a particular time and location (e.g., what was had for breakfast that morning) is affected. Semantic (knowledge-based) memory (e.g., what is "bacon"), not linked to a specific time or place, can also be affected in AD, but usually at a later stage (Hodges and Patterson, 1995; Lambon Ralph *et al.*, 2003; Perry *et al.*, 2000). Attention and its executive control are also impaired early in the course of the disease (Baddeley *et al.*, 2001; Belleville *et al.*, 2007; Perry *et al.*, 2000). Patients are often described by their carers as being easily distractible, unable to concentrate, and when asked, find it difficult to follow a conversation when several are occurring at the same time. Examples of executive problems include:

difficulty carrying out two tasks concurrently (Baddeley *et al.*, 1991, 2001; Belleville *et al.*, 2007; Logie *et al.*, 2004); poor function in task-switching (Perry *et al.*, 2000); poor selective attention (Baddeley *et al.*, 2001; Calderon *et al.*, 2001; Perry *et al.*, 2000); impaired working memory (Baddeley *et al.*, 1991; Becker, 1988; Belleville *et al.*, 2007; Morris and Baddeley, 1988); and impaired inhibitory control (Calderon *et al.*, 2001; Perry *et al.*, 2000).

In AD there is reduced basal forebrain cholinergic system input to neocortical areas involved in attention (prefrontal, parietal and thalamus) (Mesulam and Geula, 1988; Perry and Hodges, 1999). This is due to degeneration of the nucleus basalis of Meynert and adjacent structures that are the sole source of cholinergic innervation of the cortex (Arnold *et al.*, 1991). Attentional impairments are also associated with disruption of the corticocortical pathways, e.g. longitudinal fasciculi connecting frontal and parietal cortices.

Diagnosis

AD is diagnosed based on clinical history and the pattern of cognitive impairment detected on standard neuropsychometric assessments (e.g., Addenbrooke's Cognitive Examination) (Mathuranath *et al.*, 2000). Neuroimaging, specifically brain MRI scans, also shows characteristic patterns of atrophy in medial temporal and posterior cortical regions early on (Buckner *et al.*, 2005). Alongside these assessments, blood tests to exclude other causes of cognitive decline, including metabolic abnormalities, are performed alongside electroencephalography and cerebrospinal fluid (CSF) examination (Dubois *et al.*, 2007). In particular, CSF examination may demonstrate a reduction in CSF $A\beta_{1-42}$ and increase in levels of both p- (phosphorylated) and t-tau (total-tau) in patients with AD (Blennow *et al.*,

2010). An elevated CSF p-tau is relatively specific to AD, but a high t-tau can be found in several neurological disorders including stroke, encephalitis, trauma and other neurodegenerative disorders.

Auditory scene analysis

Along with the cognitive and executive changes detected in AD, deficits in central auditory processing and auditory scene analysis (ASA) have also been demonstrated early in the disease course (Gates *et al.*, 1996, 2008, 2011; Golden *et al.*, 2015a, c; Goll *et al.*, 2011, 2012; Golob *et al.*, 2007; Strouse *et al.*, 1995). Performance in ASA is influenced by working memory, attention and other cognitive control processes including inhibitory processes (Goll *et al.*, 2011).

Damage in areas implicated in ASA, including the temporal and parietal lobes, is likely to overlap with regions involved in working memory and attention (Buckner *et al.*, 2009; Conway *et al.*, 2001; Goll *et al.*, 2012; Stopford *et al.*, 2012). Studies investigating selective and divided attention using speech or dichotic tasks found AD patients unable to perform this task easily (Gates *et al.*, 2002, 2008, 2011; Goll *et al.*, 2011; Idrizbegovic, 2011; Krishnamurti, 2013). This was initially thought to be due to temporal lobe atrophy in the AD group (Goll *et al.*, 2011); however, more other Studies have postulated the involvement of the posterior cingulate cortex (Goll *et al.*, 2011), and parietal and frontal lobes in attention and planning (Duchek and Balota, 2005; Jäncke and Shah, 2002).

Pathophysiology

The extracellular deposition of amyloid (Aβ) plaques and intracellular tau neurofibrillary tangles (NFT) described by Alzheimer comprise the main pathological features of the disease (Ballatore et al, 2007; Braak and Braak 1997; LaFerla et al, 2007). Studies have suggested that tau is prominent early in the course of the disease in the medial temporal lobes (MTL) and progresses into the neocortex, particularly association cortices rather than primary sensory and motor cortices; whilst amyloid has a wider cortical distribution including the MTL (Braak and Braak, 1991, 1997; Price *et al.*, 1991) and frontal cortex (Buckner *et al.*, 2005) (Figure 1.5). These pathological findings are regarded as either the cause or the consequence of cellular dysfunction in AD, including excitotoxicity, reduced metabolism and oxidative stress (Bamberger and Landreth, 2002; Eckert *et al.*, 2003). Studies looking at volumetric MRI in AD have shown bilateral thinning in limbic regions and in heteromodal association regions, including the inferior temporal, temporal pole, precuneus, inferior parietal (supramarginal and angular gyri), superior parietal, inferior frontal and superior frontal cortices (Buckner *et al.*, 2005; Chételat *et al.*, 2008) (Figure 1.5).

Grey matter atrophy, β-amyloid plaques and glucose hypometabolism are all well-described hallmarks of pathology in AD (Figure 1.5). They have been demonstrated with neuroimaging techniques (Herholz and Ebmeier, 2011; Frisoni *et al.*, 2010), and have proved useful in the early detection of AD, but also in understanding the pathological mechanisms (Rabinovici and Roberson, 2010).

Although the brunt of the pathological changes in AD are found in higher-order association cortices of the frontal, parietal and temporal lobes, reports also describe pathology in brainstem nuclei, the hippocampus and the auditory cortex.

The presence of neurofibrillary tangles and neuritic plaques has been found to affect primary auditory cortex to only a mild degree, but association auditory cortex within the superior temporal gyrus (Brodmann's area 22) becomes severely affected over time (Arnold *et al.*, 1991; Esiri *et al.*, 1986; Sinha *et al.*, 1993). Also, the nucleus basalis of Meynert, the source of all cholinergic projections to the cerebral cortex, is affected early in the course of the disease (Francis *et al.*, 1999; Salehi *et al.*, 1994), and the cholinergic innervation of primary auditory cortex is relatively greater than that of surrounding association cortex. Therefore, lack of histopathological damage to the primary auditory cortex does not mean that the primary auditory synaptic function is normal.

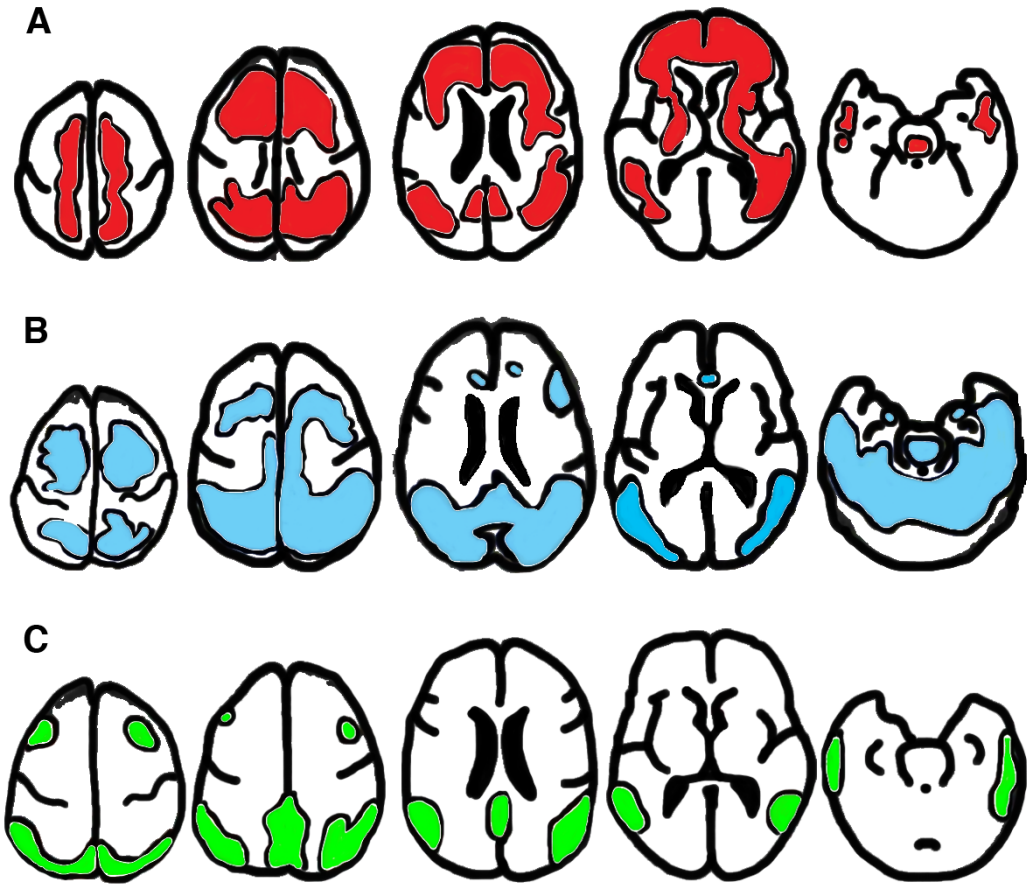


Figure 1.5: A schematic drawing demonstrating areas of amyloid deposition and atrophy in AD

Source: Consent obtained to modify figures from Buckner et al., 2005 (Fig 2, 3, 5). ***A****. Amyloid deposition measured by [11C]PIB. Regions in red = percentage of uptake. Uptake can be seen in the medial and lateral posterior parietal regions, extending into posterior cingulate, precuneus and retrosplenial cortex, as well as in frontal cortex along the midline. It can be seen that medial temporal amyloid deposition is minimal.* ***B****. Longitudinal atrophy regions in mild AD. Marked atrophy in medial temporal cortex, and cortical regions including precuneus, posterior cingulate, retrosplenial and lateral posterior parietal regions.* ***C****. Regions of decreasing glucose metabolism. Prominent reductions in precuneus extending into posterior cingulate and retrosplenial cortex and lateral posterior parietal regions. (Frontal regions were identified in Buckner et al., 2005 at lower thresholds.)*

Brainstem nuclei are also affected by AD pathology, and a number of publications have discussed the pathological changes in components of both the inferior colliculi and, to a lesser degree, the medial geniculate bodies (ventral nuclei) (Sinha *et al.*, 1993). The inferior colliculi are important structures in the localisation of sound sources, and it is known that patients with AD are impaired at sound-source localisation (Kurylo *et al.*, 1993; Golden *et al.,* 2015a). However, the cochlear nuclei and auditory nerve were not affected (Sinha *et al.*, 1993). The distribution of degenerative changes would suggest that all frequency ranges would be affected in patients with AD. In contrast, high-frequency presbycusis, seen in the ageing population, is more likely explained by lesions in the auditory nerves or cochlear, and not the central auditory nuclei (Sinha *et al.*, 1993). Studies with event-related potentials (ERPs) and magnetoencephalography (MEG) have also demonstrated altered neurophysiology in the auditory pathways of patients with AD (Golob *et al.*, 2009; Golob and Starr, 2000; Pekkonen *et al.*, 1996).

1.5 Central cholinesterase inhibitors

The development of effective treatment for AD and related dementias is important both for the individual patients and for societies with ageing populations. Several treatment strategies are under investigation, and advances in detection and diagnosis have been made (Doody *et al.*, 2001*;* Knopman *et al.*, 2001; Petersen *et al.*, 2001). Current approved treatments focus on increasing the availability of acetylcholine (Gauthier, 2002). Although these treatments were initially developed to target the cholinergic system and memory, they have also been shown

to modulate other cognitive functions, including attention, working memory and behavioural disturbances – including apathy and anxiety (Cummings, 2000, 2003; McAllister *et al.*, 2004; Soreq and Seidman, 2001; Svensson and Giacobini, 2000).

1.5.1 Cholinergic hypothesis and central cholinesterase inhibitors in AD

At the biochemical level, deficits in cholinergic neurotransmission and loss of cholinergic neurons within the nucleus basalis of Meynert have been identified as important features in the pathology of AD. Based on this finding, the cholinergic hypothesis of AD was developed (for a review, see Francis *et al.*, 1999). This proposed that knowing the role of the cholinergic system in cognition, and in particular memory, the loss of cholinergic neurotransmission in the cortex caused by the degeneration of nerve cells in the basal forebrain may contribute to the progressive loss of cognitive abilities seen in patients with AD.

The aim of current symptom-modifying treatments is to maximise available acetylcholine (ACh) through inhibiting its breakdown by synaptic cholinesterase (acetylcholinesterase, AChE). Mesulam (1995) identified the origin of the major cholinergic innervation to the hippocampal formation, cingulate cortex, hypothalamus and olfactory bulb to be the medical septal nucleus and vertical nucleus of the diagonal band, while the nucleus basalis of Meynert provides the main innervation to the amygdala and cerebral cortex (Mesulam, 1995). In AD the cholinergic deficit is most marked in the hippocampus, temporal cortex and in the parietal and frontal cortices (Geula, 1998).

Examples of central cholinesterase inhibitors (CChEIs) selective for AChE include donepezil, rivastigmine and galantamine. In the UK, the practice guidelines were changed in 2010 to permit their use in mild-to-moderate AD (NICE, 2010). They have shown modest levels of efficacy. However, not all treated patients show benefit, and the amount of benefit is variable (Venneri, 2007). A review by Cummings (2000) suggested that the variability in behavioural symptoms and responsiveness to therapy may reflect the dynamic interactions between the cholinergic and other transmitter systems (Cummings, 2000; Cummings *et al.*, 1998; Cummings and Kaufer, 1996).

Despite the increasing use of CChEIs in patients with AD, concerns remain over the efficacy of this class of drugs and the minimal evidence to support their use later on in the disease course (Mount and Downton, 2006). In order to be approved for use, centrally acting ChEIs must show a significant drug–placebo difference. It is important to note that 30–40% of patients do not respond to treatment with central cholinesterase inhibitors, and 29% of those treated leave clinical trials due to side effects (Birks, 2006; Mount and Downton, 2006).

However, results from clinical trials need to be interpreted carefully, due to differences in trial patients and the patients encountered in routine clinical practice (Cummings, 2003). Participants enrolled in clinical trials tend to have fewer physical illnesses, less behavioural disturbance, and to deteriorate more slowly and experience lower mortality rates than the general population (Cummings, 2003). The care patients receive in clinical trials is different from that in community clinics, and the clinicians are highly motivated to ensure patients continue the trial (Cummings, 2003). Therefore it is likely that efficacy in clinical-trial populations may not be matched by the population of patients with memory impairments seen in routine clinics (Cummings, 2003).

For the studies in this thesis, the participants in the treatment group were prescribed galantamine long-acting (4mg once a day for one week, then 4mg twice a day for one week, then 8mg twice a day from then on). Galantamine was chosen due to its more rapid effects on attention than donepezil (Galvin *et al.*, 2008).

1.5.2 Imaging studies of effects of cholinergic modulation of cognition in AD

The use of fMRI to detect changes in the brain's response to pharmacological agents may assist in understanding the modulation of brain activity by approved or trial drugs. In AD, the research has mainly focused on pharmacological agents that enhance cholinergic neurotransmission. Information on the effect of central cholinesterase inhibitors on auditory attention is limited. Preliminary results suggest that cholinesterase inhibitors act at least by partly upregulating activity in frontal systems (for a review see Thiel, 2003). However, cholinergic innervation is widespread, and therefore more global alterations in brain activity are likely (Levin and Simon, 1998).

Activation of the cholinergic system is associated with increased attention and improved working memory (Furey *et al.*, 2000, 2008; Klinkenberg *et al.*, 2011) (Figure 1.6). Correlations have been shown between the level of ACh inhibition and the degree of improvement in attentional and executive functions in AD treated with donepezil (Bohnen *et al.*, 2005). A one-year longitudinal study was carried out on patients with mild AD treated with donepezil, which identified an attenuated decline in tests assessing executive function and attention (Bracco *et al.*, 2014). This can be compared to studies investigating attention in untreated AD, where

there was deterioration at six weeks (Yaguez *et al.*, 2011) and 12 weeks (Viola *et al.*, 2011). Other fMRI studies looking at working memory for faces, in which patients with MCI and AD were given galantamine, demonstrated changes in brain activity in both patient groups after five days of treatment (Goekoop *et al.*, 2004). However, results in later studies were not consistent, (Goekoop *et al.*, 2006; Gron *et al.*, 2006; Miettinen *et al.*, 2011), highlighting the problems that arise in interpreting results, given the heterogeneity of response amongst patients (Venneri, 2007).

Studies suggest that cholinesterase inhibitors improve global cognitive measures by acting primarily on attention (Dumas and Newhouse, 2011). Verbal memory recall is associated with activity in frontal and fronto-parietal control networks, including a left lateralised fronto-parietal and the cingulo-opercular regions (Dhanjal and Wise, 2014). These regions have been shown to be impaired in patients with AD, but there may be a partial normalisation of activity in these systems following treatment with donepezil (Dhanjal and Wise, 2014).

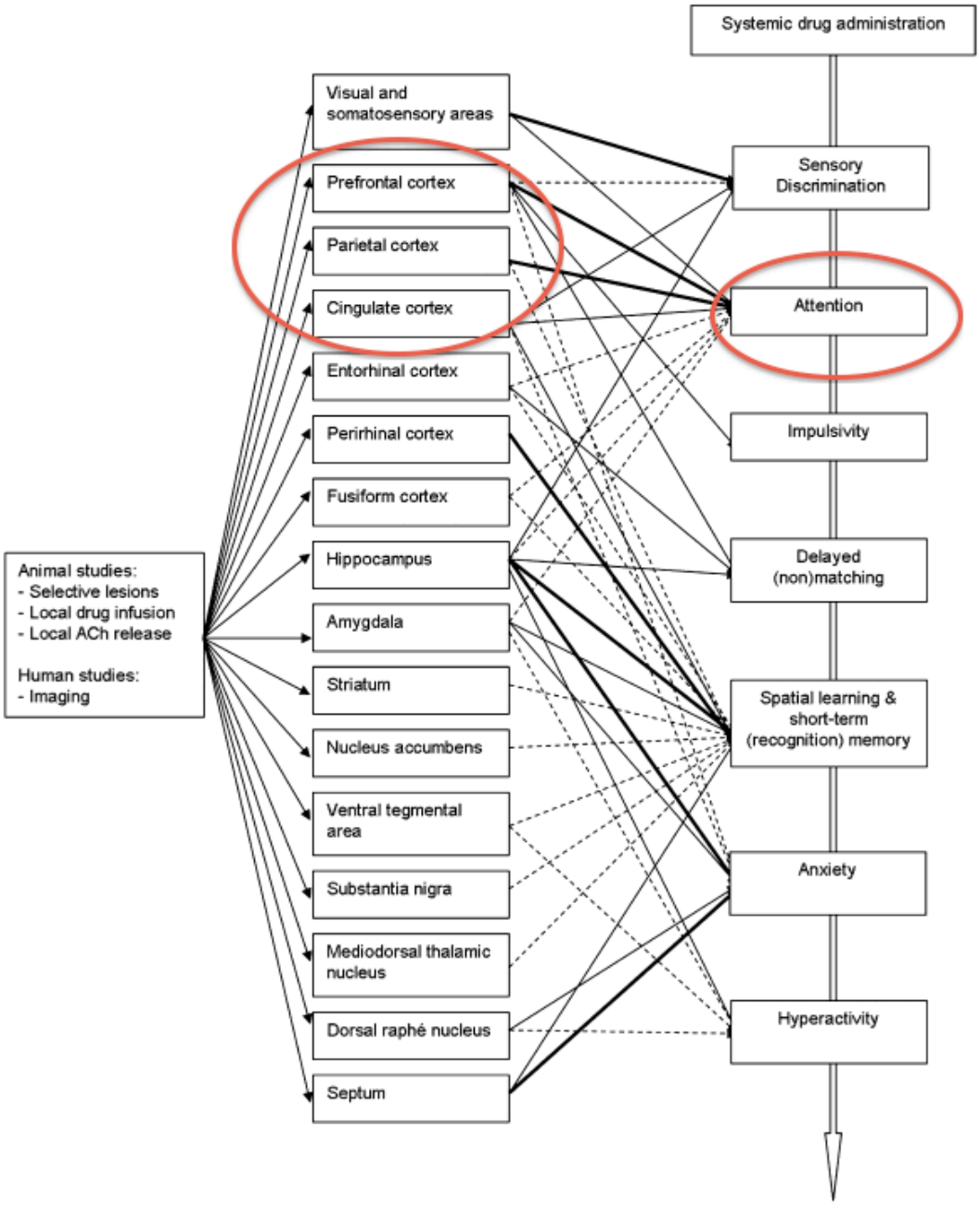


Figure 1.6: Cholinergic neurotransmission

Source: Figure from Klinkenberg et al., 2011. Permission to reproduce from Elsevier. The role of the cholinergic neurotransmission in particular brain areas on cognition and behaviour (based on animal and human studies) Strong evidence and/or involvement is indicated by bold lines, normal lines indicate average involvement and/or mixed findings and dotted lines suggest small involvement or inconclusive results.

The improvement in attention compared to memory in patients with mild–moderate AD treated with CChEIs (Sahakian *et al.*, 1993) can be explained by the activity in the forebrain cholinergic system (Klinkenberg *et al.*, 2011; Sarter *et al.*, 2006; Sarter and Paolone, 2011). Earlier studies identified an influence of CChEIs on frontal regions (Miettinen *et al.*, 2011), and this may be explained by the dense representation of cholinergic fibres in that region (Kaasinen *et al.*, 2002; Nobili *et al.*, 2002*)*, or from secondary upregulation of dopaminergic systems (Saykin *et al.*, 2004), or due to a drug-induced increased density of frontal nicotinic receptors (Barnes *et al.*, 2000*)*.

fMRI studies have not yet addressed the variability in patients' responses to CChEIs, or the heterogeneity of patient groups and neurodegeneration; for example an MCI group may contain patients with brain changes associated with normal cognitive ageing through to those with Alzheimer's pathology. In addition, day-to-day variability in attention and working memory, may be more pronounced in patient groups compared to normal participants.

1.6 Main aims and hypothesis of this thesis

This thesis used fMRI to investigate speech-stream segregation and auditory attention in healthy adults and patients with a primary complaint of memory impairment. Summaries of each chapter are discussed below (Section 1.5).

The three experimental chapters were motivated by three main aims:

1- Investigate the participation of networks involved in domain-general attention and cognitive control when listening to speech, both unmasked and when masked with unattended babble/speech.

Although it is accepted that domain-general networks are involved in top-down control across a broad range of task contexts, and there is consensus about their anatomical distribution, their functional dissociations and precise nature of their processing roles are the subject of continuing research in humans (Aron *et al.*, 2014; Corbetta *et al.*, 2008; Corbetta and Shulman, 2011; Dosenbach *et al.*, 2007, 2008; Duncan, 2010, 2013; Hampshire *et al.*, 2010, 2012; Menon and Uddin, 2010; Roca *et al.*, 2010; Shallice *et al.*, 2008; Singh-Curry and Husain, 2009; Vincent *et al.*, 2008; Woolgar *et al.*, 2011, 2013). The present studies were designed to investigate activity across these networks during attentive listening to speech, in preparation for a subsequent response to what had been heard, either delayed or immediate. My main hypothesis was that higher-order control networks would be important in speech-stream segregation, and that activity within these systems would be demonstrated in both the

control and patient groups. A further prediction was that the impaired activity within these systems might relate to the stimulus type. Thus, normal subjects would be expected to increase activity within the domain-general systems when speech was partially masked by another speaker.

2- Investigate the functional integrity of the domain-general networks in patients presenting with memory problems, and correlate the imaging data with behavioural measures of attention, memory and executive function.

Higher-order language- and domain-general systems interact to assist in the tracking of attended speech in the presence of unattended speech by modulating the response of auditory cortex (Ding and Simon, 2012a, 2012b; Kerlin et al*.,* 2010; Zion Golumbic et al*.,* 2013). Therefore, it is generally accepted that the pre-attentive perception of several speech sources is modulated by working memory and attentive processes that group auditory 'events', with only the attended speech stream processed as auditory 'objects' (words, phrases and sentences) (Alain and Arnott, 2000). My first hypothesis was that patients would be impaired at attentive listening, when compared to normal participants. My second hypothesis was that higher-order control networks would be would be demonstrated in both the control and patient groups. The prediction was that activity within these systems might be reduced in the patiet group, and that this would be most evident in those most affected; that is, those patients with the worst in-scanner performance would show the most evident failure to activate some or all components of their domain-general systems. The increase response within the domain-general systems to stimuli requiring speech stream segeregation would not be evident in the patient group.

3- Determine whether the function of fronto-parietal systems is modulated by a CChEI (galantamine).

CChEIs are used for symptom control in AD. Donepezil (Whitehead *et al.*, 2004; Winblad *et al.*, 2001), and galantamine (Aronson *et al.*, 2009; Raskind et al 2000, 2004; Tariot *et al.*, 2000; Wilcock *et al.*, 2003) (and a third CChEI, rivastigmine) have shown benefit in improving behavioural and cognitive measures. Studies in which AD and MCI groups were administered galantamine have shown increased activity in anterior cingulate and lateral prefrontal regions respectively (Mega *et al.*, 2005; Goekoop *et al.*, 2004). I wished to observe whether there were behavioural improvements in speech-stream segregation with galantamine, and whether these improvements were mirrored by a corresponding change in task-dependent activity within cingulo-opercular fronto-parietal systems.

1.7 Thesis overview

1.7.1 Chapter 2: Methods

In Chapter 2, the techniques used for functional neuroimaging and the behavioural assessments are presented. The imaging preprocessing steps and the statistical analyses of the functional imaging data, using FSL (FMRIB Software Library), are outlined.

1.7.2 Chapter 3: Auditory attention, speech-stream segregation and the role of task manipulation in healthy controls

The ability of a person to remember what a speaker has said depends on attention. During conversational speech, the emphasis is on brief periods of attention, and encoding what has just been heard within working memory. By contrast, listening to a lecture encourages episodic memory encoding, and attention sustained over many minutes. Where there is simultaneous interference from background speech, the need for attention increases. I recreated these context-dependent demands on auditory attention within the scanner in two ways. The first was to require participants to attend to one speaker in either the absence or presence of a distracting background speaker. The second was to alter the task demand by requiring either an immediate or delayed recall of the content of the attended speech. Across two fMRI studies, common activated regions associated with segregating attended from unattended speech were the right anterior insula and adjacent frontal operculum (aI/FOp), the left planum temporale and the precuneus. In contrast, activity in a ventral right fronto-parietal system was dependent on both the task demand and the presence of a competing speaker. These results make predictions about impairments in attentive listening in different communicative contexts following focal or diffuse brain pathology.

1.7.3 Chapter 4: Impaired speech-stream segregation in patients with memory impairment

Segregating attended from unattended speech depends on pre-attentive auditory processes and increased attention and cognitive control, functions affected by cortical neurodegenerative disease. This chapter compared attentive listening in the 22 normal participants (presented in Chapter 3) with results from 31 patients presenting with a prominent

symptom of poor memory for recent conversations. All participants underwent fMRI (see Chapter 2 section 3.2). The data acquired during fMRI related to epochs of attentive listening. Each listening trial was followed by a response trial, during which the success of the normal participant or patient at processing the attended speech and holding it in working memory was assessed. This design provided in-scanner behavioural scores that could be related to brain activity during the listening trials. Behaviourally, the patients were impaired at attentive listening compared to the normal participants, when hearing unmasked speech but more so when the attended speech was masked by background babble or an unattended speaker. The patients activated the same systems as the control group, but the overall activity throughout these systems correlated with their in-scanner behavioural scores on response trials, which in turn correlated with their scores on a standard clinical assessment battery for dementia. A multivariate analysis demonstrated the functional connectivity of the left posterior temporal region with left fronto-parietal cortex, incorporating regions associated with verbal working memory and controlled access to meaning, and with the cingulo-opercular network. There was reduced activity throughout these systems in the patient group compared to the normal participants. Therefore, this chapter concluded that a complaint of poor recent verbal memory, while often attributed to hippocampal pathology and impaired encoding, will also have its origins in poor registration. This was a consequence of impaired function in several distributed high-order systems that are frequently affected by cortical neurodegenerative diseases.

1.7.4 Chapter 5: The effects of a central cholinesterase inhibitor on the behavioural and functional imaging results in the patient group

In the previous chapters I demonstrated in normal participants the distributed neural systems involved in attentive listening in the absence or presence of an unattended speaker. In Chapter 4 I extended this study to a group of patients who presented with a history of impaired verbal memory. This identified reduced connectivity in top-down control networks. This chapter reports on the same group of patients, approximately two-thirds of whom had possible or probable AD based on clinical and routine diagnostic assessments. Within the total group, 17 patients, randomly selected, were prescribed a central cholinesterase inhibitor (CChEI), galantamine, after their first scan. This chapter describes the behavioural and functional neuroimaging consequences of treatment with galantamine on attentive listening, but also on the effects of inter-individual between-sessions in-scanner behavioural scores. There was wide inter-individual variability in performance between the two scanning sessions, but this did not correlate with subjects' ACE-R, and nor was it modulated by the CChEI. Therefore, changes in performance over this timeframe must relate to variability in attention at the time of scanning. I identified a right hemisphere system, distributed between dorsolateral prefrontal cortex and the posterior temporal lobe, when correlating the between-scan behavioural variability and brain activity.

1.7.4 Chapter 6: Thesis summary and future directions

In this chapter, I review and discuss the main findings of this thesis and explore future studies. In particular I discuss two hypotheses raised by my findings from Chapter 5, and their potential clinical implications.

2 Methods

This chapter outlines the recruitment of normal participants and patients, the behavioural assessments of the patients (out-of-scanner and in-scanner), the functional neuroimaging and its analyses. It highlights the processes involved in patient identification and recruitment and a classification of the severity of their memory complaint. It explains the battery of neuropsychological testing used to assess participants' cognitive function and reviews the behavioural paradigms used for the functional imaging studies. The chapter begins with a consideration of the general principles of magnetic resonance imaging (MRI), and a description of functional MRI (fMRI). The last section details the scanning protocols and parameters used in the studies presented in this thesis.

2.1 MRI

Summary of the principles of MRI

MRI is an imaging technique that utilises a strong magnetic field to produce images of biological tissue. These images are produced through a series of changing magnetic gradients alongside pulse sequences to produce electromagnetic fields. Different tissue types are identified depending on the pulse sequences used, e.g., fluid versus tissue, low- versus high-proton density, and white versus grey matter. The physics behind MRI is explained in the following sections, together with the various levels of imaging, the different fields and assortment of coils.

Principles of nuclear magnetic resonance

Nuclear magnetic resonance (NMR) relies on the understanding of the spin properties of the atom. Within the nucleus of an atom are two particles, protons and neutrons. These normally spin randomly about their axis, producing an angular momentum. A magnetic momentum, a small magnetic field, is created by the spin of the proton, which is positively charged. The constant, known as the gyromagnetic ratio (y), is the ratio between the magnetic and angular momentum, and is specific to each magnetically active nucleus. As the majority of human tissue is composed of water, which is high in hydrogen, and hydrogen's nuclei produce a significant amount of magnetic momentum, it is not surprising that MRI scanners are generally configured to detect this.

The magnetic fields B_0 and B_1

The proton within the nucleus of the hydrogen atom behaves like a bar magnet. Owing to its ability to spin, when placed in a strong magnetic field (B_0) it aligns itself, either parallel or anti-parallel, with the direction of the field (Figure 2.1), which is known as the Z-plane (e.g., head to toe of the participant placed in the MRI scanner). The low-energy state is when the proton is parallel in orientation and a high-energy state when it is anti-parallel. In general, the greater the B_0, the larger the number of particles that align parallel with the magnetic field. In order to achieve a measurable signal, the protons must be excited. Once stopped, the spin precesses around the magnetic field, with similarities to a spinning top around its axis.

The radiofrequency (RF) transmitter coil generates the magnetic field B_1, which is at an angle to B_0. Once the B_1 field is generated, it flips the hydrogen protons down from the B_0 direction.

They begin to precess and align to the sum of B_0 and B_1. When the field is turned off they 'relax' and gradually return to their original orientation at B_0. The RF receiver coil then detects the emitted signal from this 'relaxation'. As mentioned previously, the frequency of the spin precession is determined by the strength of the magnet. Changes in frequency allow the identification of the proton spin locations through the use of X, Y and Z gradient coils.

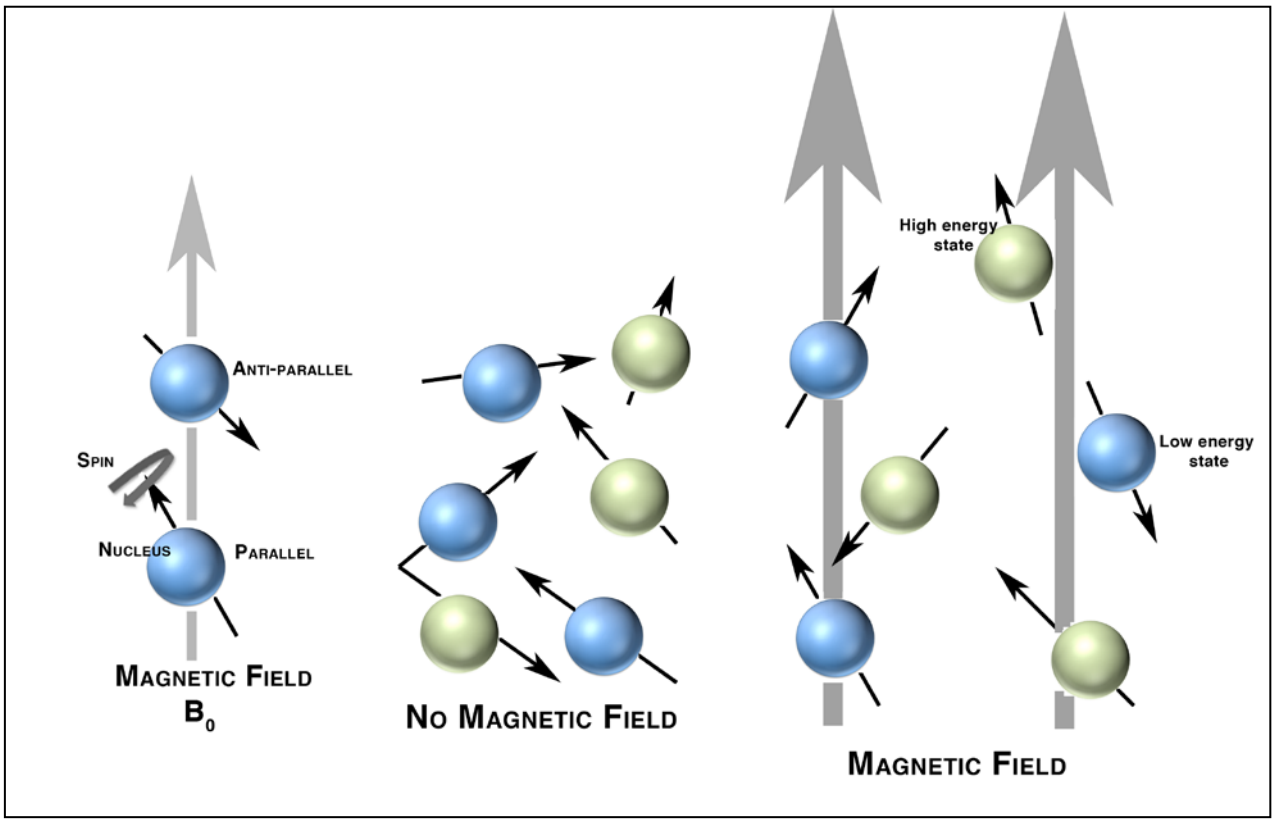


Figure 2.1: Properties of nuclear protons, which adopt a parallel and anti-parallel configuration in the application of an external magnetic field B_0

Shimming coil

In order to avoid image artefacts, including signal dropout and distortions, a homogeneous magnetic field is needed. This is provided by shimming, where an additional magnetic field is added on top of the existing magnetic field. To ensure this remains constant throughout, it is applied before scanning starts.

RF coils

RF pulses are transmitted to excite the spins, and when received, to measure the signal by coils. They are found perpendicular to the B_0 and transmit the RF energy at the same frequency as the pulsating proton, thus permitting absorption of the energy by the tissue protons. Following the pulse, the energy is then re-emitted by the tissue and this is received by the coil. When the energy is re-emitted by the protons, they return to a low-energy state. The time taken for this is known as the T1 relaxation time.

Gradient coils X, Y, Z

The detection of hydrogen atoms by the RF coils is a function of time not space. Thus, gradient coils detecting frequency responses identify the location of the spins. There are three gradient directions. The first (X) is horizontal (left to right), Z is horizontal (head to toe) and Y is vertical. A magnetic field is produced by each coil, and increases in strength along one spatial direction. At the centre the field is zero, meaning the B_0 is at normal strength. The use of these coils allows the reconstruction of three-dimensional images, through determining the frequency of the MR signal at different spatial locations.

2.2 The MRI scan

MRI parameters

Two factors determine the time at which MR images are collected. The first is known as the repetition time (TR), which is the interval between excitation pulses. The second is the echo time (TE), which is the interval between excitation and relaxation. By modifying these two parameters, variations in signal intensities with T1, T2 and T2* relaxation occurs. Two other terminologies are used. First, T1 recovery is when an increase in energy occurs along the longitudinal (Z) plane as precession moves back towards B_0. Second, T2 decay occurs due to the loss of phase coherence in the spins, leading to energy reduction in the transverse (X) plane.

T1-weighted MR imaging

T1-weighted imaging is most commonly used for structural anatomical images of the brain. These images rely on T1 relaxation time, which is the time taken for the excited spin to return to its low-energy state and align itself along the Z-plane in the direction of the main magnetic field. With this image, the signal intensity of individual voxels is reliant on the T1 value of the tissue. Voxels with long T1 values are dark, for example fluid and grey matter, while short T1 values are light, for example white matter.

T2-weighted MR imaging

T2 images are particularly useful for clinical structural imaging in the diagnosis of pathological conditions, for example detecting tumours. In contrast to T1 relaxation, T2 relaxation relies on the random and temporary 'spin–spin' interaction between protons in various tissue types, resulting in a loss of signal. To obtain good images, the TR must be long, to ensure the T1 contrast is minimal, which allows for almost complete recovery in all tissue types. Once more, whereas T1 dictates the longitudinal relaxation, T2 governs transverse relaxation (the X–Y plane). In T2-weighted images, grey and white matter appears dark, whilst fluid appears as white.

Finally, a third image is the T2*-weighted image, which is similar to the T2-weighted image. This image takes into account the inhomogeneous nature of the magnetic field, due to the presence of a human body in the scanner, something not considered with T2 images. T2* relaxation is also quicker than that of the T2 and this makes it useful for functional imaging. T2* is also sensitive to the amount of deoxygenated haemoglobin (deoxyHb) within the blood (see 2. 3 below).

2.3 Functional MRI

Functional MRI (fMRI) is used to investigate changes in neuronal activity in response to cognitive tasks (for example, to test memory, reasoning and attention), such as those used in the studies in this thesis. This neuronal activity relies on a metabolic response in particular

brain regions, involving the consumption of glucose and oxygen and a haemodynamic response. The haemodynamic response is evident in a rise in cerebral blood flow (CBF), blood oxygenation and blood volume. This physiological basis is described further in the following sections.

Blood-oxygen level dependent response

The difference in magnetisation between oxy- and deoxyhaemoglobin is measured by fMRI though blood-oxygen level dependent (BOLD) imaging. Deoxygenated haemoglobin that occurs following the transfer of oxygen to active neurons is paramagnetic. Oxygenated haemoglobin (oxyHb) is diamagnetic. This difference in magnetic susceptibility allows the scanner to detect the change in the proportions of oxy- and deoxyhaemoglobin. During neuronal activation and firing, oxygen consumption increases along with the CBF to that area. With a greater amount of oxygenated blood delivered than is required for that activity, this increase in local oxyHb is evident.

The neurovascular/haemodynamic response

The haemodynamic response function (HRF) is the time taken for the change in the local ratio of oxyHb to haemoglobin (Hb). There is a delay in temporal sensitivity using BOLD-fMRI, to the underlying neural activity. In order to allow for the correct identification of changes in BOLD in relation to specific cognitive tasks, this is modelled when analysing the data. Because the time course of neural activity is rapid in comparison with the vascular response, an initial dip is seen, followed by an increase in BOLD, with a peak of approximately 6 seconds after the stimulus onset. For the studies in this thesis, a canonical HRF (from FMRIB

Software Library, FSL) is used in the analysis, which is an assumed profile of the sum of local neuronal activity and the vascular response.

Echo-planar imaging for fast fMRI acquisition

In order to acquire images of brain function, typically echo-planar imaging (EPI) is used. It is a T2*-weighted sequence that is able to collect data from an entire image slice by sending one RF pulse from the transmitter coil. It then introduces rapidly changing magnetic field gradients during the recording of the signal. Although this reduces the time needed to acquire the images, its high speed results in lower spatial resolution than in conventional scans, and thus predisposes it to distortion and artefacts. In order to analyse EPI images, a T1-weighted image is typically acquired to aid registration because T1-weighted images have better resolution.

Model-based fMRI analysis

The identification of brain regions, and specifically voxels that respond to changes in cognitive task demands, is the main aim of model-based fMRI analysis. It typically compares brain activity, measured by the BOLD signal, between two different conditions. By comparing the difference in BOLD responses between two tasks, it becomes possible to identify the brain regions associated with a specific task. This technique is known as a subtractive method and it cannot give an absolute measurement, merely a measure of activity in one task compared with another. For the model-based fMRI analyses presented in this thesis, the FMRI Expert Analysis Tool (FEAT) is used (the version used is mentioned in the individual chapters), which is part of the FSL (FMRIB Software Library; www.fmrib.ox.ac.uk/fsl) (Smith *et al.*, 2004).

‘Sparse’ and ISSS scanning

The acoustic scanner noise generated in the MRI by rapid gradient switching in EPI is a crucial confounding factor in auditory studies. Acoustic scanner noise of up to 120dB can make it very difficult for subjects to hear auditory stimuli and may also alter the task by making it perceptually difficult, and therefore influence the activations obtained in simple contrasts during continuous acquisition (Figure 2.2) (Davis and Johnsrude, 2003). ‘Sparse’ imaging designs overcome this confound through the acquisition of a single brain volume after a silent period (Figure 2.2). This minimises the interference from the scanner noise (Hall *et al.*, 1999), and is particularly useful with auditory stimuli such as those used in this thesis. This technique was used in Study 1 of this thesis and was an effective way of avoiding the gradient noise. However, fewer EPI data are acquired, reducing statistical power, and assumptions have to be made about the time-to-peak of the evoked haemodynamic response. A new sparse imaging method was later developed, called ‘interleaved silent steady state’ (ISSS) sampling. This allowed rapid acquisition of EPI volumes following every silent period. It avoided signal decay during the acquisition through the maintenance of steady-state longitudinal magnetisation, with a train of slice-selective excitation pulses during the silent period during which the audio stimulus was delivered (Schwarzbauer *et al.*, 2006). This ensured that the signal contrast remained constant across successive scans (Schwarzbauer *et al.*, 2006).

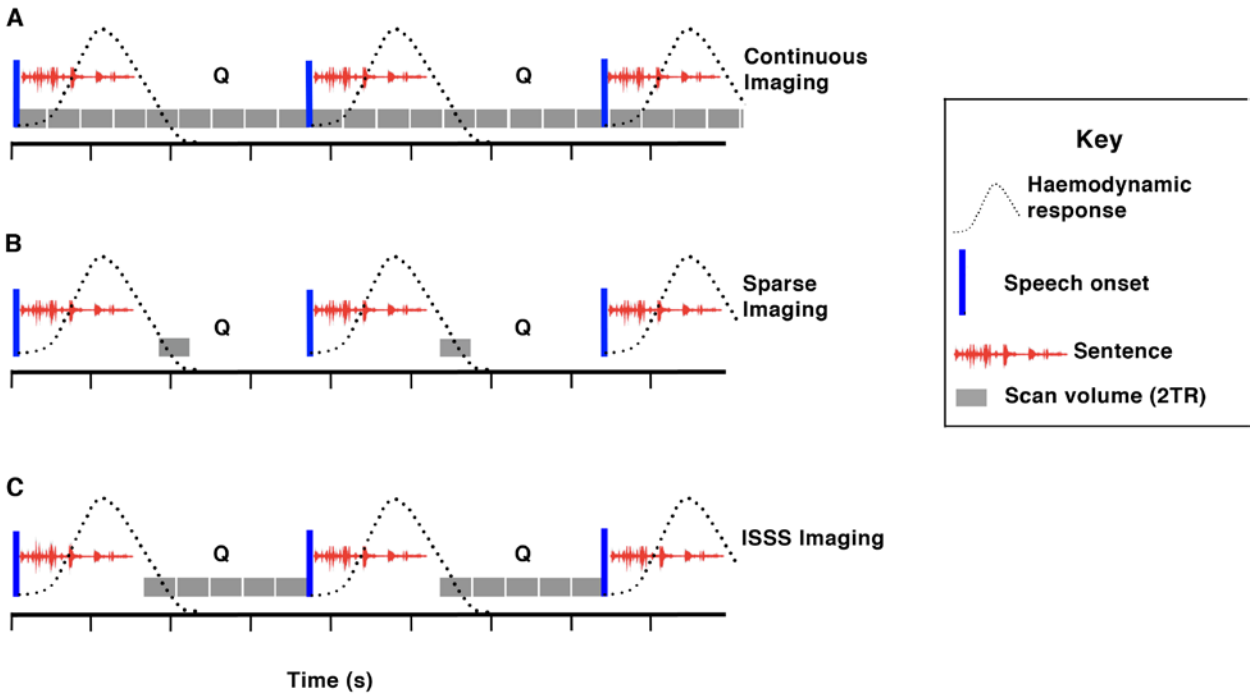


Figure 2.2: Schematic diagram of imaging protocols

***A** = Continuous imaging; **B** = Sparse imaging; **C**= ISSS imaging. Q = visual questions appear on the screen and patient responds during the scan; (s) = seconds (modified from Schwarzbauer et al., 2006, Fig 3).*

2.4 Analysis of fMRI data

Data pre-processing

fMRI data analysis requires registration and pre-processing. The data in this thesis were pre-processed using a publicly available software from FMRIB (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) Software Library (FSL; Smith *et al.*, 2004). Pre-processing steps carried out automatically using FSL toolboxes include brain extraction, registration, motion correction, spatial smoothing, high-pass filtering and physiological signal

regression. The stages involved in the analysis of studies presented in this thesis are described in the following sections and within the individual results sections.

Brain extraction

Before fMRI data can be analysed, the non-brain tissue contained in T1-weighted structural images needs to be removed. This is performed using the Brain Extraction Tool (BET) in FSL. It identifies the optimal solution to separate brain tissue from the rest (Smith, 2002) (Figure 2.3). EPI images were extracted automatically as part of the process in FEAT.

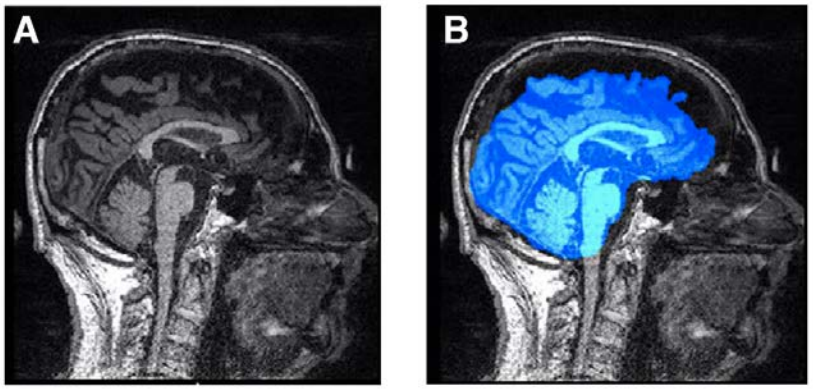


Figure 2.3: Diagrammatic example of brain extraction

A = T1 image; B = Blue overlay of extracted brain

Temporal filtering

This process allows the signal-to-noise ratio to increase by removing noise from the EPI data. Low-frequency noise generated by minor instabilities in the scanning process can be removed by high-pass filtering. In the analysis of the data for this thesis, temporal high-pass filtering was used to correct for this drift as an automated process in FEAT analyses.

Motion correction

In order to accurately analyse the data, the anatomical location of single voxels must remain constant throughout the scan. However, with scans lasting on average 1 hour, it is impossible for participants to remain completely still for that length of time. The addition of artefacts manifesting as apparent 'activations' and the reduction in signal-to-noise ratio can occur with head movements. I used FSL's Motion Correction FMRIB Linear Registration Tool (MCFLIRT) to correct for motion in the analysis. This aligns all the images to a specific reference volume. FEAT reports a summary output of the amount of relative and absolute movement in each direction, which needs to be carefully reviewed (see Figure 2.4 for an example). FEAT can also enter the motion parameters into the design matrix to model head movement with changes in signal intensity. In addition, through the use of the motion outlier tool, time points with large signal changes probably related to motion are used to create a matrix of outliers, which is then added to the FEAT analysis.

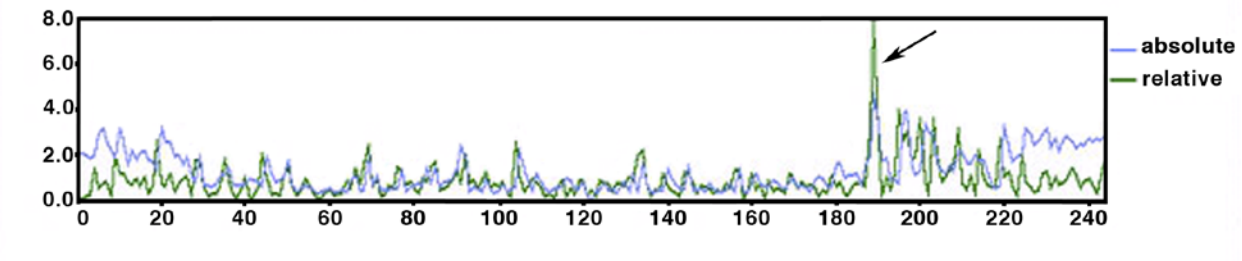


Figure 2.4: Diagrammatic representation of motion correction (arrow represents a motion artefact)

Spatial smoothing

By filtering out high-spatial frequency, spatial smoothing acts to improve the signal-to-noise ratio. In cognitive tasks, relatively large areas of brain are activated, which encompass several voxels in an EPI image. Biologically plausible sources are assumed to produce signals that typically take the form of spatially smooth areas of activity, approximately 5mm–8mm in diameter. It assumes any areas of smaller activity to be noise and filters out signals that are not shared by the adjacent voxels and enhances those that are. A Gaussian kernel (normal distribution curve) is used to convolve the data, with a full width at half maximum (FWHM) specified by assuming an anticipated cluster size. In the analyses of the studies presented here, an 8mm FWHM Gaussian kernel was used, as interest was mainly in the process occurring in larger areas of the brain.

2.5 Statistical analysis of fMRI data

Statistical software packages, for example FSL, are used to identify true physiological changes. The software uses a multilevel approach. A general linear model (GLM) produces summary statistics at each level, which are then moved on to the next level (Beckmann *et al.*, 2003). The GLM ($y=B_0 + X_1B_1 + X_2B_2 + \ldots + e$) describes the response (y, the dependent variable), for example a voxel's BOLD response, in relation to all the contributing factors (XB, where X is the design matrix and B is the matrix of parameter estimates for each EV) in a linear combination and accounting for the contribution of errors (E). With multiple responses (**γ**) taken during functional imaging, the above equates to a matrix. Each predictor (X), through an expected signal time course, contributes to the dependent variable **y** (Figure 2.5). To use the GLM, a design matrix containing the onsets and duration of each condition, or explanatory variable (EV), is created. These individual EVs are then convolved with a 'double-gamma'-shaped canonical HRF and the resulting timeseries are entered into the equation as the variable (X_a). Other factors such as temporal derivatives are included in the model, which account for variability of the shape of the HRF. In general, a first-level analysis is run for each individual participant's session. This is combined into runs within participants through fixed effects during the intermediate level. This is then used to make comparisons (e.g., comparing different groups of participants) at the higher level using random effects analysis.

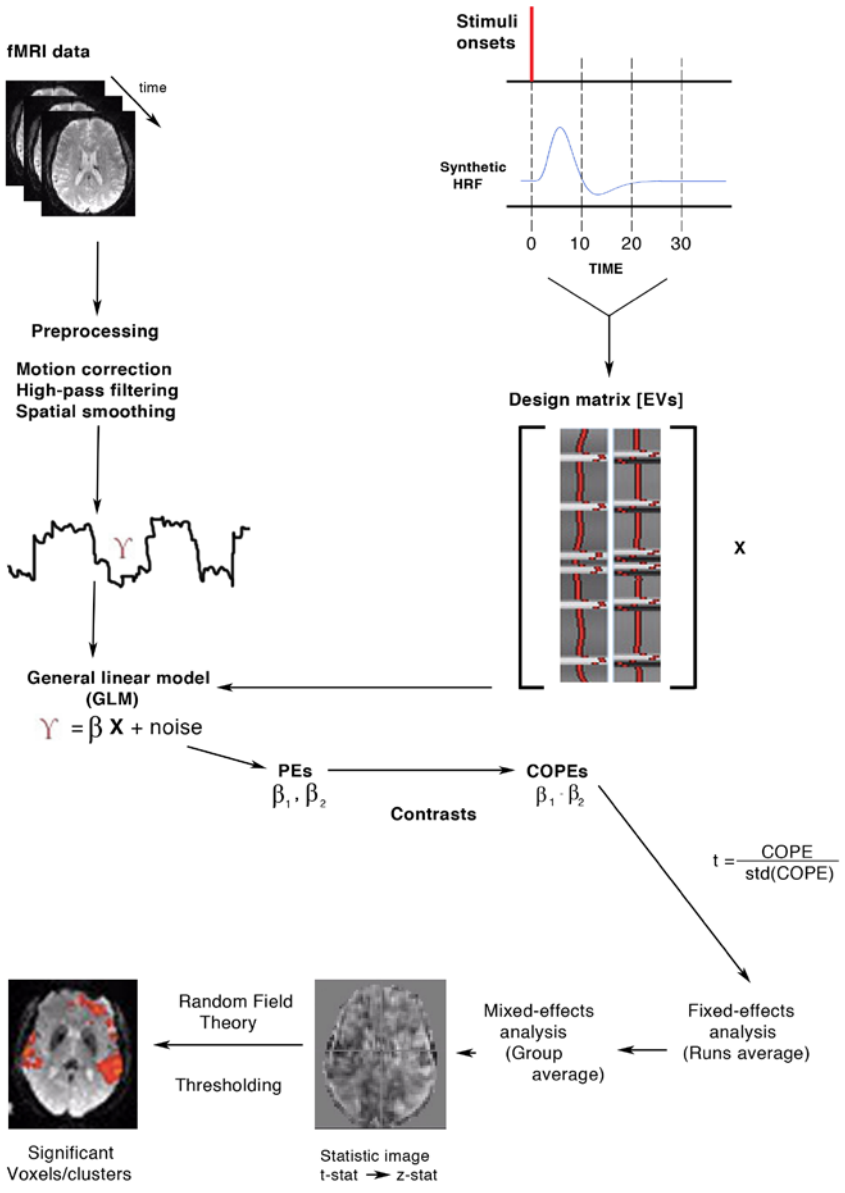


Figure 2.5: Schematic representation of fMRI data analysis

*Note: The GLM takes the individual time courses of the experimental conditions, and convolves them with a synthetic HRF (X). The parameter estimates (B) display how well each explanatory variable (EV) (X) fits the data (**γ**) at every voxel. Through subtracting one parameter estimate from another, contrasts of parameter estimates (COPEs) are generated. These are then converted into t-statistic images by dividing the COPE by its standard error. This image is then transformed into a z-statistic image, which is then thresholded using voxel interference or Gaussian random field-based cluster. The runs are averaged using fixed-effect analysis within participants and mixed-effect analysis is used for higher level multi-participant group averages.*

Thresholding and correction for multiple comparisons

The z-statistic image created by the initial tests is then thresholded to identify clusters or voxels activated at specific significance levels. With a large number of data points, even at the standard statistical threshold $p < 0.01$ ($z > 2.3$), there is a risk of falsely rejecting the null hypothesis (type II error). Therefore, a correction for multiple comparisons is performed. If all the voxels are considered to be independent, a Bonferroni correction method can be used. However, with the very high number of data points, this method could be too conservative to apply to fMRI data (Nichols and Hayasaka, 2003). In fMRI datasets, the z-scores from one voxel are correlated with values from neighbouring voxels, so a better method of correction would account for the number of possible independent observations in biologically plausible regions of activity, i.e. from the spatially smoothed data.

Within FSL, a cluster-based correction for multiple comparisons is carried out applying the Gaussian random field theory. As explained previously, images with a z-statistic for each voxel are produced from the data analysis. The threshold (used typically in the analysis in this thesis) of $z > 2.3$ is applied, resulting in any voxels with a z-statistic of lower then 2.3 being set to 0, and therefore allowing for the identification of contiguous clusters. These significant clusters are then used to mask the original z-statistic image with inference based on cluster size. In the studies within this thesis, Gaussian random field-based cluster inference was used with a standard height threshold of $z > 2.3$ and a cluster significance threshold of $p < 0.05$.

2.6 Registration

Although optimised for temporal resolution, the fMRI sequence has relatively low spatial resolution and can be affected by spatial distortions. In addition, the variability in the size and shape of individual brains among subjects means it is important that the images are in an identical 'standard space' before inferences can be made about the regions of activity devoted to a given task. This is carried out using the FMRIB Linear Image Registration Tool (FLIRT) (Jenkinson *et al.*, 2002). Two stages are involved: first, registration of the EPI functional data to the higher resolution and T1-weighted structural image, after brain extraction (Figure 2.6A). This process uses six degrees of freedom transformations (translation and rotation in each of the three dimensions).

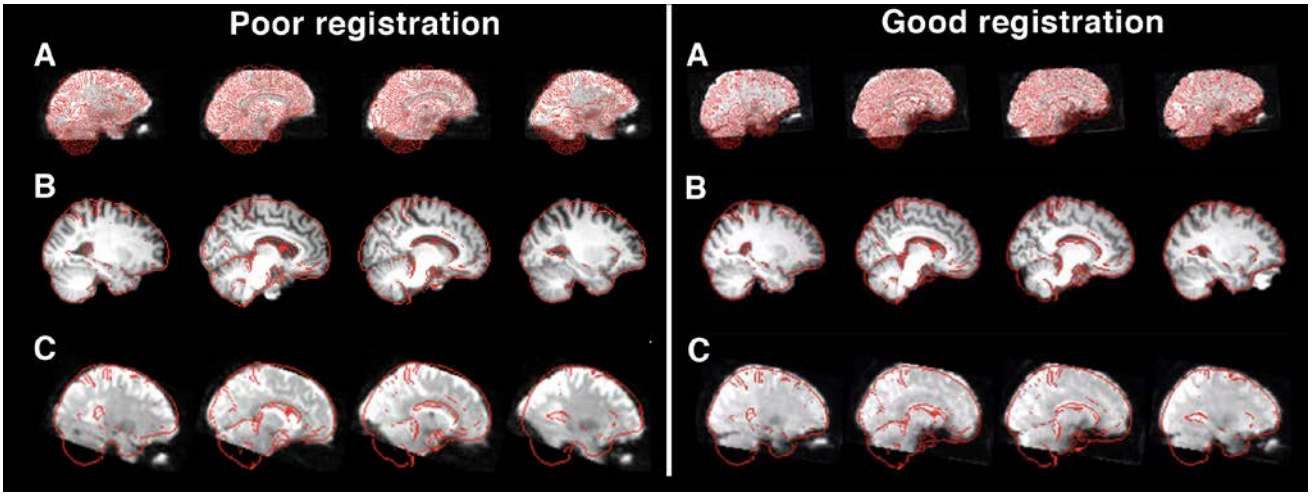


Figure 2.6: Example of good and poor registration

***A** = Registration of EPI functional data to the high-resolution T1-weighted image; **B** = Registration of the high-resolution image to a standard structural brain template; **C** = Registration the fMRI image to the standard space image.*

The second stage involved registering the high-resolution brain onto a brain template using 12 degrees of freedom transformations (Figure 2.6B). For the analyses in this thesis, the MNI-152 (Montreal Neurological Institute) template was used, based on the T1 MRI scans of 152 normal participants. That there is a lot of variation across individual T1-weighted images was evident, especially given the age and clinical population included in this thesis. As a result, the FSL tool Boundary-Based Registration (BBR) was used to improve registration and the accuracy of the results. BBR is a new tool where white matter boundaries are mapped to the EPI image to get a best fit (Greve and Fischl, 2009). This was felt to be a better registration method than the alternatives available with FLIRT. Further details of the specific techniques used are discussed in Chapters 3 and 4.

2.7 Region of interest analysis

To increase statistical power, and in the presence of a clear hypothesis about a specific brain region, a region of interest (ROI) analysis was used. ROI analysis reduces the problem of multiple comparisons and increases the signal-to-noise ratio. ROIs can be identified from anatomical boundaries or from higher-level analysis using independent data. The analyses in this thesis used 8mm-radius spheres and the FSL tool Featquery, which examined the FEAT results and then extracted the mean percentage of BOLD signal change within an ROI.

2.8 Functional connectivity analysis

If there is a correlation of BOLD signal over time at two voxels, it is said that those voxels are functionally connected to each other. To investigate whether two regions are functionally connected, a correlation or regression coefficient is calculated between pairs of regions in the simplest case (Friston, 1994). Confounds such as motion and physiological signal (e.g. from white matter) are regressed out of the data to reduce the chance that the dependency is due to physiological factors or scanner artefacts that may also correlate across voxels.

ICA principles

Independent component analysis (ICA) is a data-driven technique, which does not require prior knowledge about a region's involvement in specific tasks. It can be followed by a 'dual-regression' analysis to explore the relationship between performance and functional connectivity, as presented in Chapter 4.

Applied to fMRI data, ICA can identify independently distributed spatial patterns with similar activity over time (McKeown and Sejnowski, 1998). Each independent component (IC) displays a different portion of the variability that exists in the data. Since it is data-driven, the neural signals identified can be explored without prior knowledge of their nature. In this thesis, the Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC version 3.10, part of FSL (Beckmann and Smith, 2004) tool was used, as detailed below.

MELODIC

MELODIC is used in FSL to perform ICA (Beckmann and Smith, 2004). Datasets are broken down into various spatial components. In-group analysis uses either a tensor ICA, where data are decomposed into spatial maps, subject/session modes and time courses, or simpler temporal concatenation was used. The latter is preferred when investigating common spatial patterns where the associated temporal response may not be consistent between sessions/subjects (e.g., as in experiments with randomised presentation of stimuli). An ICA can also be used to 'clean up' data by compartmentalising the noise sources into components, therefore improving SNR (Beckmann and Smith, 2004). This technique also allows for multiple signals to be present in the data, whilst for univariate analyses only the average signal is considered and more subtle signals may be hidden (Leech *et al.*, 2012). Although the signals are data-driven, by using cross-correlations of the signal timeseries and the task timeseries, they can still be assessed for their relationship to the design model (McKeown *et al.*, 2003), as in the GLM.

In the analyses in this thesis, both temporal concatenation and tensor-ICA approaches were used with the group ICAs. In temporal concatenation, data from each subject and run are concatenated in time, and therefore components do not necessarily have temporal similarity across subjects (Beckmann and Smith, 2004). In tensor-ICA, the data from each subject and run are aligned in time, and therefore only activation patterns that share temporal covariance are identified (Beckmann *et al.*, 2005). This approach is more suited for task-based fMRI analyses, where we expect the activation to follow similar temporal profiles to the task timings. Pre-processing steps similar to those described above for FEAT analysis are carried out along with some automated steps consisting of voxelwise variance normalisation

('whitening') and data de-meaning. Through default, MELODIC produces an automatic number of components; however, various ICs were specified depending on the study. For example, in Chapter 3, 20 ICs were used. This number was considered high enough to distinguish between distinct functional networks such as the saliency and default mode network and low enough to prevent them being split into sub-systems.

Dual regression analysis

One limitation of the above method, ICA, is the difficulty in obtaining the same ICs across different subjects or different groups of subjects, due to its unconstrained nature. Therefore dual regression was proposed to compare functional connectivity measures of the same ICs between subjects (Beckmann *et al.*, 2009). This produced subject-specific approximations to the unthresholded spatial ICs in the group ICA output (Zuo *et al.*, 2010).

Dual regression is carried out in two main steps. The group ICA spatial maps are entered as EVs in a regression of each individual's pre-processed data (first regression). This produces a timeseries with the weightings at each time point for every ICA map that best explains the activation pattern seen in the data. There may be subtle differences to the group-averages timeseries in these subject-specific ones, but they retain the within-subject variance associated with this timeseries. Once each subject-specific timeseries is derived, a second regression is carried out on them, which produces a subject-specific spatial map that identifies regions with activity relating to those timeseries. These subject-specific spatial maps are similar to the group-ICA spatial maps, but will differ for each subject. Group difference in the spatial map distribution or temporal variation in the timeseries can then be compared

using a group-level GLM, for example comparing the healthy controls and the patients. This technique is explored further in Chapter 4 (see 4.2).

2.9 Participants, behavioural measures and methods

This section outlines information about the participants included in the studies in this thesis and the behavioural measures used (see Appendix 1). Further demographic detail and information regarding the specific tasks are presented separately in each chapter.

All participants had normal or corrected-to-normal vision. Although none reported significant hearing loss, the loudness of the stimuli was adjusted for each participant to a level that they reported they could hear clearly during scanning. The local research ethics committee approved the studies and written consent was obtained from all participants.

Participants

Two separate control groups were used for the experiments in this thesis. For Study 2, where participants were used for comparison with the patient group, they were all age- and gender matched as closely as possible to the patient group. Healthy controls in the studies presented in this thesis had no history of neurological or psychiatric disorders.

Study 1 involved 29 healthy participants (11 females, two left-handed) with a mean age of 44 years (range 23–71). Twenty-five age-matched healthy controls were included in Study 2 (13 females, one left-handed) with a mean age of 66 years (range 51–83). Controls had a range of performance on the Addenbrooke's Cognitive Examination - Revised (ACE-R) of 80–100. Only two had an ACE-R score below 88, a cut-off score with high sensitivity but low specificity for the presence of dementia. Neither participant had symptoms of memory or other cognitive impairment. Some participants were relatives of patients recruited for study.

Study 3 had a total of 31 patients aged between 59 and 87 years (see Appendix 2). They were referred from their local memory clinics at Charing Cross Hospital, The Royal Free Hospital and Brentford Lodge, where they were undergoing investigation for memory and, in many cases, other cognitive symptoms. They had all received a provisional diagnosis of Alzheimer's disease (AD) or amnestic mild cognitive impairment (aMCI) based on accepted criteria by a consultant neurologist with an interest in dementia. Patients had an ACE-R range of 50–98. Patients, especially those with lower ACE-R scores, were only recruited if they were able to understand the task, and it was felt (an intuitive judgement) that they would be able to co-operate with the study once they were in the scanner. Exclusion criteria for the patients were an absence of other major co-morbid neurological, psychiatric or systemic medical conditions, or the presence of metallic implants precluding scanning.

Within the patient group, participants were randomly allocated into one of two groups: a treatment group, who received galantamine, and an untreated group. Seventeen patients completed the study on galantamine and 14 completed it on no treatment.

Problems with patient recruitment

Although 50 patients were initially invited to join the study, data were eventually only available on 31. This was due to several factors. Seven patients changed their minds after leaving the clinic and chose not to take part. Six were unable to complete the first scan, either finding it too difficult once they were in the scanner to remember the task or feeling so anxious about the procedure that scanning had to be stopped. One patient started the galantamine before the first scan and therefore those data were unable to be used[2]. Another patient with relatively mild symptoms was excluded after returning an exceptionally low score on the ACE-R of only 33, for reasons that were not apparent. Four patients were lost to follow-up either due to deterioration in their condition, becoming unwell, forgetting appointments or other commitments that would result in a significant delay between the two scans. Patients and relatives were contacted several times before and between scans to try and avoid loss of follow-up. The final experimental analyses included 31 patients.

Within the control group, three participants were excluded from the analyses in Chapters 4 and 5 when comparing their results with the patients. Those excluded were the two participants with ACE-R <88, the published cut-off score for the ACE-R, and one participant who returned an in-scanner behavioural performance >2.5 standard deviations below the other normal participants.

[2] Following this case, patients allocated into the treatment arm were not provided with the galantamine until after their first scan.

Behavioural measures for Study 2

In Study 2, behavioural and cognitive tests were carried out on all participants, control and patients, within seven days of each scanning session. They consisted of the following:

Addenbrooke's Cognitive Examination – revised

The ACE was designed in 2000 to provide a simple cognitive battery for use in a clinical setting. It includes the mini mental state examination (MMSE) and encompasses other areas of cognition, including executive function and visuospatial skills (Mathuranath *et al.*, 2000). The revised version (ACE-R) was issued in 2006 and consists of 26 tasks divided into five domains: attention and orientation, memory, verbal fluency, language, and visuospatial skills (Mioshi *et al.*, 2006). The cut-off score is 88 with 94% sensitivity for dementia and 89% specificity; the sensitivity is probably close to 100%, but with a lower specificity (Larner, 2007).

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a self-rated depression scale for the older population, used in both clinical and research settings (Sheikh *et al.*, 1991; Yesavage *et al.*, 1982; Yesavage and Tinklenberg, 1983). GDS scores were collected on all participants to ensure depression was not a major contributing factor to account for their cognitive impairment.

Digit span

Participants were asked to listen to a series of random numbers, presented at a rate of one per second. In the digit span forwards, they were asked to repeat the numbers in the forward sequence as presented, and in the digit span backwards they needed to recall the numbers in reverse order. Normal scores are 7 +/- 2 digits forwards and 6 +/- 2 backwards.

CANTAB

CANTAB (Cambridge Neuropsychological Test Automated Battery) was used to investigate memory, executive function and attention. Participants were asked to perform a selection of five computerised neuropsychological assessments used to assess cognitive function in a diverse group of neurological and psychiatric conditions, including dementia, depression and Parkinson's disease (de Jager and Budge, 2005; Foltynie *et al.*, 2004; Robbins *et al.*, 1994; Weiland-Fiedler *et al.*, 2004). CANTAB has been standardised in a large elderly normal control population study (Robbins *et al.*, 1994).

Once the initial simple 'motor screening task' was completed (the CANTAB uses a touchscreen computer), patients were given the remainder of the tasks in the following order:

- Rapid Visual Information Processing (RVP), a continuous visual performance task that tests sustained visual attention and also requires selective attention and working memory to be executed successfully;
- Paired Associate Learning (PAL), a visuo-spatial associative learning task that has been shown to be impaired in patients with AD, probable AD or MCI (Egerhazi *et al.*, 2007; Sahakian *et al.*, 1990; Gould *et al.*, 2005);

- Reaction Time (RTI), which measures the speed of response to a visual target; and
- Spatial Working Memory (SWM), which tests the participant's ability to retain spatial information and to manipulate it in working memory.

The individual breakdown of the results appears in Appendix 1.

Test for reception of grammar

The test for reception of grammar (TROG) [3] was carried out to assess participants' understanding of grammatical contrasts, and hence sentence-level comprehension (Bishop, 1989). Participants are required to identify the target picture from a choice of four to match the spoken sentence. In total there are 52 items. All healthy controls successfully completed this test and all patients bar one completed the TROG. The one who failed the test did so only on the last set of four pictures.

Peripheral hearing test

To assess any peripheral hearing loss that may have affected performance on the experimental tasks, all participants underwent pure-tone audiometry. This was administered using a screening audiometer (AS608/AS608e from PCWerth and TDH 39 headphones) in a quiet room. Five frequency levels were assessed (0.25, 0.5, 1, 2, and 4 KHz). Participants heard a continuous tone that slowly increased in intensity at each frequency and were asked to raise a hand when the tone was heard. The lowest intensity for each frequency was recorded. For a breakdown of the results, see Chapter 4.

[3] TROG – 2 was used in this thesis

Training

Each participant undertook two short practice runs on the auditory attention task. They were talked through the instructions and given the opportunity to ask questions at the end of each trial, to ensure they understood the task before entering the MRI scanner. Each practice run consisted of one set of four sentences from each condition. They were instructed to listen to the female voice throughout and then answer the written questions that followed the auditory sentences. The questions related to the factual content of the attended spoken female sentences or the unattended spoken male sentences. The response was a simple button-press, yes or no, to a visual question, which was presented on the screen after the auditory stimuli (see scanning design in Chapter 3 (3.2) for more detailed information).

2.10 Scanning protocol Study 1

2.10.1 Description of scanning sessions

Participants underwent one structural brain T1-weighted scan, two fMRI scans (described below), and a resting-state fMRI scan, acquired over 10 minutes during which they were instructed to relax and close their eyes. A senior consultant neuroradiologist reviewed all the structural MRI scans.

2.10.2 Scanning parameters

Scanning parameters for the specific studies were kept constant. Due to access difficulty, the scanner used for Study 1 was not available for Study 2, hence a change in parameters. MRI data for Study 1 were obtained from a Phillips (Best, The Netherlands) Intera 3.0 Tesla MRI scanner using Nova Dual gradients, a phased-array head coil and sensitivity encoding with an undersampling factor of 2.

2.10.3 Structural T1

High-resolution ($1mm^3$) T1-weighted structural images were acquired for each subject. The following acquisition parameters were used: matrix size 208 x 208; slice thickness = 1.2mm, 0.94mm x 0.94mm in plane resolution, 150 slices; TR = 9.6ms; TE = 4.5ms; flip angle 8^0.

2.10.4 fMRI

Functional magnetic resonance images were obtained using a T2*-weighted gradient-echo, echo-planar imaging (EPI) sequence (repetition time 8s; acquisition time 2s; echo-time 30ms; flip angle 90^o). Thirty-two axial slices with a slice thickness of 3.25mm and an interslice gap of 0.75mm were acquired in ascending order (resolution 2.19 x 2.19 x 4mm; field of view 280 x 224 x 128mm). To correct for magnetic field inhomogeneities, a quadratic shim gradient was used. T1-weighted images were acquired for structural reference.

Stimuli were delivered through ear-defending MR-compatible headphones (MR Confon, www.mr-confon.de/en/). The trials were programmed using E-prime software (Psychology Software Tools) and then presented on an IFIS-SA system (In Vivo Corporation).

2.11 Scanning protocol Study 2

2.11.1 Description of scanning sessions

Normal participants underwent one fMRI scanning session while the patients underwent two sessions, separated by at least six weeks. The sessions consisted of a structural brain T1 scan, two task-based fMRI scans (described below), a resting-state fMRI scan, acquired over five minutes during which patients were instructed to relax and close their eyes, and finally a 10-minute diffusion tensor imaging (DTI) scan, when 64 non-collinear directions are acquired. The resting state data and DTI data are still undergoing analysis, and do not form part of this thesis. The age- and gender-matched normal participants only underwent one of these scanning sessions. A senior consultant neuroradiologist reviewed all the structural MRI scans. A six-week interval between the first and second scan was planned; however, due to last-minute changes, scanning room closures, lack of slots, problems with the MRI machine requiring repair and service, holidays and other studies, 13 participants had longer intervals; seven had seven weeks; three had eight weeks; one had nine weeks; one had 10 weeks and one had 11 weeks. In those patients who received it, the galantamine was continued throughout the inter-scan interval. To avoid a loss of follow-up, patients were booked into the next available slot.

2.11.2 Scanner parameters

Data were acquired on a 3T Siemens Tim Trio scanner with the 12-channel phased-array head coil.

2.11.3 Structural T1

High-resolution T1-weighted images were acquired with slice thickness of 1mm and ADNI-GO recommended parameters (Jack, 2008) with a parallel imaging factor of 2.

2.11.4 fMRI

Functional magnetic resonance images were obtained using a T2*-weighted gradient-echo, echo-planar imaging (EPI) sequence. Thirty-five contiguous axial slices at each of two echo times (13ms and 31ms) with a slice thickness of 3mm were acquired in interleaved order (resolution, 3 x 3 x 3mm; field of view 192 x 192 x 105mm), with a repetition time of 2s, and 242 volumes were acquired in 14m:42s. To correct for magnetic field inhomogeneities, the manufacturer-provided higher order shim procedure was used.

Stimuli were presented using the Psychophysics Toolbox (Brainard, 1997) under MATLAB (Mathworks, Natick MA). Sounds were delivered through MR-compatible headphones and a two-button-press was used to record responses.

3 Auditory attention, speech-stream segregation and the role of task manipulation in healthy controls

Listening to a speaker so that what was said is understood and remembered requires attention. This is influenced by context. For example, taking turns during conversations depends on periods of brief attentive listening, with the emphasis on working memory. In contrast, attendance at a lecture requires the listener to maintain attention over time while encoding details of the semantic content of the lecture as enduring memories.

The majority of research into speech-in-speech masking has focused on auditory cues used to overcome the peripheral (energetic, at the level of the cochlea) and central (informational) masking (Brungart, 2001), with less research on the demands made on domain-general systems for attention that contribute to understanding and remembering what a speaker has said. This study explored attentive listening under different communicative contexts, to investigate changes in whole-brain function in response to listening to a speaker in the presence of background speech. This study has been previously published (Kamourieh *et al.*, 2015). The normal participants attended to the verbal message conveyed by a speaker, either in the presence or absence of background speech, with or without spatial cues. An alteration in task demand also allowed investigation into the influence of the task on these systems.

3.1 Aims and hypotheses

The aims were:

1. To investigate the systems involved in domain-general attention and cognitive control as participants attended to a speaker in the absence or presence of unattended speech.
2. To investigate task-dependent modulation of activity within these systems.

The participation of widely distributed, domain-general attention and cognitive control networks has been demonstrated in a wide range of functional neuroimaging studies. Although it is clear that these systems are involved in top-down control across very diverse tasks, it remains uncertain whether the components are truly divisible in terms of functional dissociations. Therefore, the precise nature of the processing roles of the cortical components, and the contribution of anatomically and functionally connected subcortical structures, are the subject of continuing research.

I will focus on four systems, using anatomical labels: two dorsal fronto-parietal systems, symmetrically distributed between the hemispheres; a third, more ventral, fronto-parietal system that is usually considered to be predominantly right-lateralised; and a fourth that is distributed between dorsal midline frontal cortex and bilateral anterior insular and adjacent frontal opercular cortex.

The two hypotheses were:

1. Common regions would be activated when segregating speech from unattended speech, irrespective of task demand, with previous publications placing an emphasis on the role of posterior auditory association cortex (the plana temporale).
2. Task demand would modulate the activity observed in domain-general fronto-parietal systems, as a consequence of differing demands on working memory and attention sustained over time.

Therefore, the studies in this chapter were designed to investigate brain activity during attentive speech comprehension, as measured with fMRI, and the modulation of this activity by different contexts encountered in everyday life. A better understanding of the normal systems involved in everyday communicative contexts will inform the problems encountered by patients with diverse common pathologies, such as stroke, neurodegenerative disease or traumatic brain injury.

3.2 Materials and methods

3.2.1 Subjects

Two experiments were carried out. One involved 29 healthy participants (11 females, two left-handed) with a mean age of 44 years (range 23–71). The second experiment involved 25 healthy participants (13 females, one left-handed) with a mean age of 66 years (range 51–83). Participants were recruited from the community through personal contacts and advertisements. None had a history of neurological or psychiatric disorders. Even though none reported difficulty with hearing, the loudness of the stimuli was adjusted for each participant to a level at which they reported they could hear the stimuli clearly during scanning. All had normal or corrected-to-normal vision. All participants gave their written consent, with prior approval from the North West Thames ethics committee.

3.2.2 Study 1

Auditory stimuli

There were two auditory speech conditions, with equal numbers of stimuli in each condition. In the first, only a male speaker was heard by the participants. In the second, participants heard the simultaneous voices of a male and female speaker, with the separate voices mixed into the same channel; that is, diotic presentation with no spatial cues (Figure 3.1). Those taking part were informed before the start of scanning that they would be asked questions about what the male speaker had said at the completion of scanning. They did not know in advance the form these questions would take.

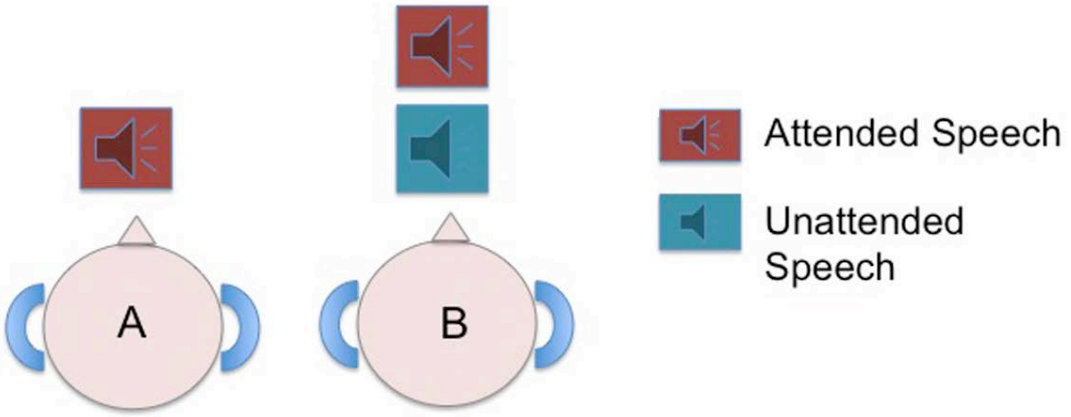


Figure 3.1: Diagrammatic representation of the auditory conditions heard during Study 1

Study 1 included listening conditions A and C. Figure depicts the delivery of stimuli. A. The attended speaker alone (Male); B. Simultaneous voices of a male and female speaker delivered with the attended speaker through the same channel (diotic presentation.

All sentences, spoken by the male or female, were recorded in an anechoic chamber and adjusted to 2s duration, using Sound Studio 2.2.4 (Felt Tip software www.felttip.com). The participants were required to attend to the sentences spoken by the native English male speaker. These sentences were taken from the Speech Intelligibility in Noise (SPIN) test (Kalikow *et al.*, 1977). These sentences have previously been used in an fMRI study on language comprehension (Obleser *et al.*, 2007). Sixty-four sentences were randomly chosen from SPIN. All sentences ended in a noun, and these final nouns were reallocated to produce an equal number of sentences, each with a semantically incongruous noun ending. This resulted in a total of 128 sentences. The addition of an incongruous ending to half the sentences spoken by the male speaker was intended to determine whether breeching an anticipated sentence ending modulated activity within the higher-order networks regulating attention and cognitive control during speech comprehension. The expectation was that the unexpected ending would result in a transient increase in arousal, followed by a brief, if

unsuccessful, attempt to integrate the anomalous ending into the meaning conveyed by the rest of the sentence.

Previously, sentence-ending semantic relatedness has been much studied using event-related potentials (ERPs), specifically the effects on the N400 (Kutas and Federmeier, 2000), and there have been a few studies on the influences of age or dementia on the N400 (Iragui *et al.*, 1996; Olichney *et al.*, 2008).

The recorded sentences were adjusted using Praat (www.fon.hum.uva.nl/praat/) to have the same root-mean squared average intensity. The sentences spoken by the native English female speaker were recorded and adjusted in the same manner as those spoken by the male speaker. The female speaker read aloud sentences from a variety of sources, including subsections of contemporary news stories, Wikipedia and a children's book. During the diotic presentation of two speakers, sentences spoken by a male and a female voice were mixed together equally, with a 0dB signal-to-noise ratio. In addition, there were two low-level baseline conditions: one with bursts of a continuous pure tone at 400Hz, without any task demand (Tones), and one with no auditory stimuli (Silence). The 400Hz tone bursts were adjusted to have the same duration and equivalent root-mean squared intensity as the sentences.

Study design

The study relied on 'sparse sampling' (Hall *et al.*, 1999) during functional image acquisition, so that all stimuli were heard without masking by background scanner noise. For each trial,

the stimuli were presented during a period of 8s when there was no data acquisition (and hence no scanner noise). Data were then acquired during the ensuing 2s. As soon as one epoch of data acquisition was complete, a visual cue, '*listen to the male voice*', appeared and remained for 8s when the sentences were presented. When the pure tones were presented, the visual cue was '*listen to the sounds'*. During a sixth condition, without the presentation of stimuli or any task demand (Silence), the participants saw the single word '*relax*'. During each trial, the participants listened through ear-defending headphones (MR Confon, www.mr-confon.de/en/) to three different sentences spoken consecutively by the male speaker, masked by the female speaker on half the trials, or three consecutive identical pure tones. The first sentence or tone commenced 0.5s after the onset of the visual cue, and there were 0.5s separating each of the three consecutive stimuli delivered during each trial. The presentation of the stimuli, with intervening periods, was complete within 8s. After this, the scanner was triggered to acquire data. Each participant underwent two runs of functional imaging data acquisition, a run consisting of each of the four conditions presented six times. This required the presentation of 144 sentences with either the male speaking alone with sentence endings that were either predictable ($M_{ALONE/PRED}$) or unpredictable ($M_{ALONE/NON-PRED}$), or in the presence of the female speaker ($MF_{DIOTIC/PRED}$ and $MF_{DIOTIC/NON-PRED}$). As the database only contained 128 sentences, 16 sentences were presented a second time. The order of conditions during each run was pseudo-randomised within subjects. The two runs were separated by the acquisition of a high-resolution T1-weighted anatomical MR scan.

Following the scanning session, the participants were presented with a forced-choice sentence recognition task on a list of 120 written sentences (See Appendix 3). Eighty of these sentences were those spoken by the male speaker during the scanning session. Of these, half were of the male speaker alone and half with his voice partially masked by the female

speaker. An equal number was chosen from those with and without a semantically predictable ending. None of the sentences was drawn from the 16 that had been presented twice. Of the remaining 40 sentences, 20 were those spoken by the female speaker and 20 had not been presented during the scanning session. The subjects were required to indicate which sentences they recognised as having been spoken by the male speaker during the scanning session. Subjects were familiarised with the experiment, both with the prompts and with examples of the stimuli. During the scanning session, the example stimuli were not used.

Data acquisition

Data acquisitions for Study 1 were the same as described in Chapter 2 (2.10). There were two runs, each of 109 volumes, TR = 8s.

3.2.3 Study 2

Auditory stimuli

Five speech auditory conditions were used (Figure 3.2A). The first auditory condition was a female speaker alone (F_{ALONE}). The second was the female speaker in the presence of background babble (F_{BABBLE}), with the voice and babble mixed into the same channel to remove spatial cues (diotic presentation). The third was the female speaker in the presence of a male speaker, again with diotic presentation (FM_{DIOTIC}). The fourth and fifth conditions had a female and a male speaker competing for attention, as in the third condition, but in these a simulated azimuth spatial cue was added (dichotic presentation). This was either with the female speaker at 30^{o} to the left and the male speaker at 30^{o} to the right ($F_{LEFT}M_{RIGHT}$) of the

midline, or vice versa ($M_{LEFT}F_{RIGHT}$). Each subject included in this study was rehearsed to ensure that they perceived the intended directionality of the fourth and fifth auditory conditions.

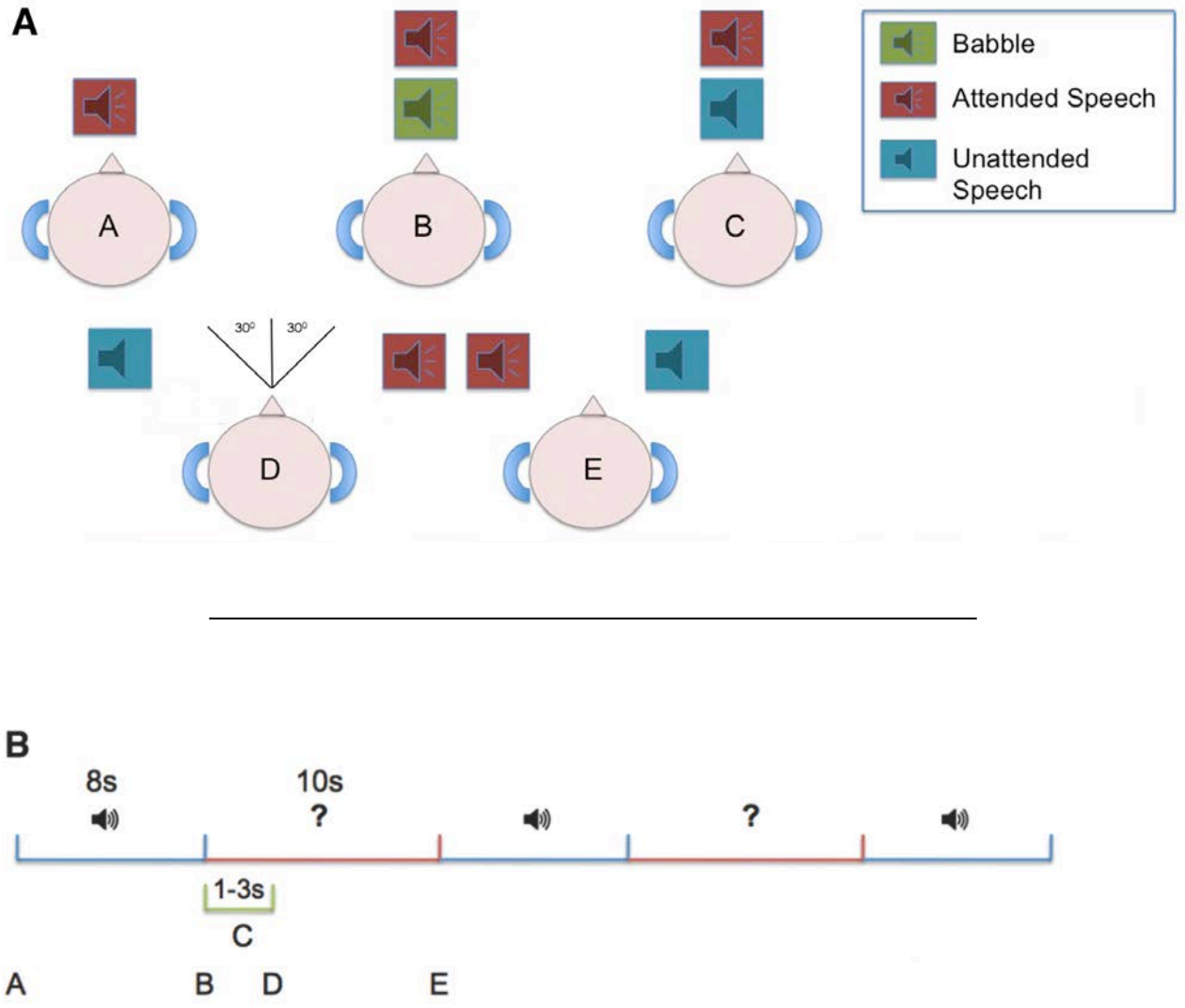


Figure 3.2: Diagrammatic representation of the auditory conditions heard during Study 2

*Study 2 has five auditory conditions. Upper panel (**A**) depicts the delivery of stimuli. A. The attended speaker alone (Female); B. Background babble delivered with the attended speaker through the same channel (diotic presentation); C. Simultaneous voices of a male and female speaker presented diotically; D + E. Competing female and male speech, as condition C, presented dichotically with a spatial cue, with the female speaker at 30^{o} to the left and the male speaker at 30^{o} to the right, and vice versa. Lower panel (**B**) depicts the scanning protocol of Study 2. A. Marks the onset of the speech stimulus; B. The end of speech and the start of the jitter period; A – B = 8s; C. The duration of the jitter between the end of the speech stimulus and the onset of the written question (1–3s); D. The onset of the written question; E. The end of the question and response period; D – E = 7–9s.*

Factual statements, taken from children's books, were spoken by a native English female and male speaker and recorded in an anechoic chamber. The stimuli, edited in Sound Studio 2.2. 4 (Felt Tip software www.felttip.com), were of 6–7s duration. Babble was created using online audio from the BBC sound-effect library ('cocktail party – close perspective and atmosphere') and cut to the desired length. Spatial cueing for $F_{LEFT}M_{RIGHT}$ and $M_{LEFT}F_{RIGHT}$ was introduced by manipulating intensity using a public-domain database of high spatial resolution, head-related transfer functions (CIPIC HRTF database) (Algazi *et al.*, 2001). This simulates the effects of sound scattering due to different pinna, head and torso dimensions. Stimuli included 384 female and 288 male statements and 48 babble speech, randomly chosen. The stimuli were adjusted using Praat (www.fon.hum.uva.nl/praat/) to have the same root-mean squared average intensity. The female target sentences and the matched-length male sentences and babble were mixed together at 3dB signal-to-noise ratios, to make hearing the female slightly easier. The participants never heard the same sentence twice at any point during the practice sessions or the tasks.

Instruction to the participants was the same for all auditory conditions: '*listen to the female speaker, understand the statement she makes, and prepare to answer a written question*'. The question was presented in Helvetica, font size 70, on a computer screen, which was projected to a 45-degree angled mirror 10cm from participants' eyes, with a 'yes' or 'no' button-press response required on the next trial. The response trial ('response') was the sixth condition. For the conditions when there was only a female speaker or a female speaking against background babble, all the questions related to what the female speaker had said, accurate responses being equally divided between 'yes' and 'no'. In the three conditions when there was a competing male speaker, half the questions related to what the female speaker had said and half to what the male speaker had said. During each trial with a distracting male speaker, the phrases spoken by the female and male speakers were unrelated in meaning (See Figure 3.3). As an example, the participant heard the female speaker say '*She rummaged about in the closet looking for a recipe, turning over all of her mother's magic recipe books*', while the male speaker said '*The white-tailed deer is tan or reddish-brown in the summer and grayish-brown in the winter*'. The question in the immediately ensuing trial related either to what the female had said ('*She was looking for a dress?'*), or what the male speaker had said ('*The deer is white in winter?*') (See Appendix 4). The subjects were not informed beforehand that questions might relate to the content of the speech of the unattended male speaker. This was to ensure they did not attempt to divide attention between the two speakers[4]. Each subject attempted two short practice runs of the auditory attention task prior to scanning. The seventh condition was a Silence condition, the same as in the first study.

[4] Each participant was asked at the end of the scanning if they noticed that the other questions realted to the male speaker. All failed to make that association.

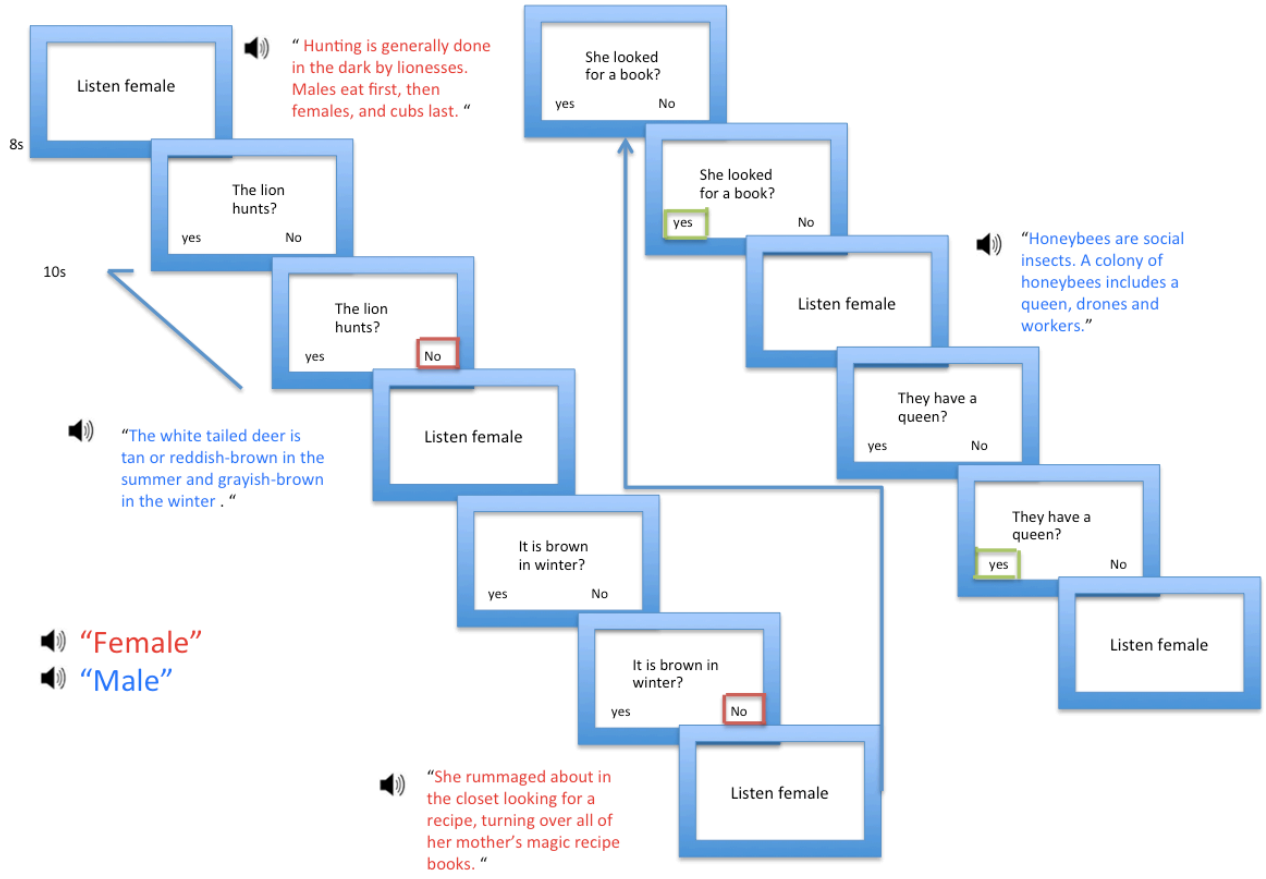


Figure 3.3: Schematic outline of screen presentation

Study design

The conventional 'sparse' sampling used for image acquisition in Study 1 was altered to improve further signal-to-noise. Interleaved silent steady state (ISSS) imaging was used. This ensured that all stimuli were heard with minimal background scanner noise. Greater time-course information was provided than in conventional sparse scanning (Schwarzbauer *et al.*, 2006). During the ISSS runs, volume acquisition was accomplished using five 'imaging' volumes followed by four 'quiet' volumes, giving 10s of gradient activity followed by 8s of reduced scanner noise. Radiofrequency (RF) activity (which does not contribute to scanner

noise) in the form of adiabatic fat saturation and slice excitation was continued in all volumes to keep the recovery of the longitudinal magnetisation equal throughout all volumes. There was no data acquisition during the quiet volumes as all gradient activity was turned off, apart from the concomitant slice-select gradient. The slice-select gradient's refocusing lobe was also turned off. The slice-select gradient was necessary to keep the selective RF excitation equivalent. This gradient lobe used a 20mT/m/ms slew rate in all volumes, whereas the peak slew rate in the imaging volumes was 230mT/m/ms.

For a lone trial, the auditory stimuli were presented during a period of 8s when there was no data acquisition and much reduced scanner noise. As in the first study, the stimuli were played through ear-defending headphones. Data were then acquired during the ensuing 10s of the response trial, consisting of five TRs, each of 2s duration. Once the auditory stimulus was despatched, a jitter period (averaging 2s across the trials) occurred before the visual question would appear and remain for 7–9s during the response trial. This allowed the participants time to read the question and respond with a ‘yes/no’ button-press. This sequence is summarised in Figure 3.2B. Each condition, including Silence, was presented as a block of four consecutive trials, presented twice during each run. There were two runs, with the order of conditions during each run pseudo-randomised within subjects.

Image acquisition

Access to the scanner used for the first study was no longer feasible at the time of the second study. Consequently, Study 2 was performed on a Siemens 3T Tim Trio scanner. fMRI

acquisition parameters are described in Chapter 2 (2.11). There were two runs, each of 245 volumes, TR = 2s.

3.2.4 Data analysis

Univariate whole-brain analyses

For both studies, these analyses were carried out within the framework of the general linear model using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). The following image pre-processing steps were applied: realignment of EPI images for motion correction using MCFLIRT (Motion Correction FMRIB Linear Image Registration Tool) (Jenkinson *et al.*, 2002); non-brain removal using BET (Brain Extraction Tool) (Smith, 2002); spatial smoothing using a 6mm full-width half-maximum Gaussian kernel; grand-mean intensity normalisation of the entire four-dimensional dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian Weighted Least Squares (GWSL) straight-line fitting, with sigma = 50s) to correct for baseline drifts in the signal. Time-series statistical analysis was carried out using FILM (FMRIB Improved Linear Modelling) with local autocorrelation correction. Registration to high resolution structural and Montreal Neurological Institute (MNI) standard space images (MNI-152) were carried out using FLIRT (FMRIB Linear Image Registration Tool). *Z* (Gaussianised *T/F*) statistical images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$.

The mixture of the different runs at the individual subject level was carried out using a fixed-effects model. Individual design matrices were created, modelling the different behavioural

conditions. Contrast images of interest in each study were produced from these individual analyses and used in the second-level higher analysis. Higher-level, between-subject analysis was carried out using a mixed-effects analysis with the FLAME (FMRIB Local Analysis of Mixed Effects) tool. Final statistical images were corrected for multiple comparisons using Gaussian random field-based cluster inference with a height threshold of $Z > 2.3$ and a cluster significance threshold of $P < 0.05$.

In the first study, one TR was acquired at the end of each trial, and the recorded signal will have been an accurate representation of the net neural activity in response to whichever stimulus had been delivered over the preceding 8s. The second study required a more complex analysis, as five TRs were acquired during the response trials. To ensure accurate allocation of the TRs to specific stimulus- or response-evoked haemodynamic response functions (HRFs), individual timeseries explanatory variables (EVs) were generated using the tools from the FSL library (glm_gui). Three-column format data were entered to produce a single-column timeseries EV that was used in the remaining analysis (Figure 3.1B). For the auditory conditions, the columns included timing for when the sound started (A in Figure 3.1B) and its duration (B–A in Figure 3.1B), whilst for the response period it included the onset of the question (D in Figure 3.1B) and the duration it remained on the screen (D–E in Figure 3.1B). This allowed a design that accurately represented the timing of the scanning protocol, to ensure the analysis weighted the HRFs evoked by listening and responding towards their appropriate conditions. Thus, the design matrix modelled the first TR strongly towards listening; the fifth TR strongly towards reading the question, deciding the answer and responding based on what had been heard in the previous trial and held in working memory, with the other three TRs weighted appropriately in between these two extremes.

The data were analysed with a standard random-effects general linear model, using tools from the FSL library (FEAT version 5.98) (Smith *et al.*, 2004). After image pre-processing, which required anatomical normalisation with realignment of the EPI images, removing motion effects between scans and smoothing to 5mm full-width half maximum Gaussian kernel, the data were entered into a univariate statistical analysis within FSL, based on the general linear model. Within the design matrix, the four auditory verbal conditions were entered into a factorial analysis of variance. Main effects and interactions were thresholded ($Z > 2.3$), with a cluster significance threshold of $P < 0.05$ to correct for whole-brain analyses (Beckmann *et al.*, 2003).

Independent component analysis

For each study, this was carried out using group temporal concatenation probabilistic independent component analysis (ICA) implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.10, part of FSL software (Beckmann and Smith, 2004). This approach to the ICA was used rather than tensor-ICA (Beckmann and Smith, 2005), as the temporal presentation of the stimuli was different between subjects. Such multivariate analysis can extract important information from the data that is not always apparent from a subtractive univariate analysis (for example, Leech *et al.*, 2012). ICA takes advantage of low-frequency fluctuations in the fMRI data to separate the signal into spatially distinct components. A particular advantage of ICA, which increases sensitivity when detecting net regional neural responses, is controlling for timeseries unrelated to brain function. These will be identified as separate components; for example, a movement-related artefact not removed by the initial image pre-processing.

Data pre-processing for the ICA included masking of non-brain voxels, voxel-wise de-meaning of the data and normalisation of the voxel-wise variance of the noise. The ICA for each study was set up to decompose the data into 20 independent components containing distributed neural networks, movement artefact and physiological noise. The choice of the number of component maps reflects a trade-off between granularity and noise. It is motivated by the attempt to maximise the homogeneity of function within each network while maximising the heterogeneity between them. Previous applications of ICA to fMRI data have used 20–30 component maps (Beckmann *et al.*, 2005; Leech *et al.*, 2011; Smith *et al.*, 2009), and this study adopted the same approach.

The data were projected into a 20-dimensional subspace using principal component analysis. The whitened observations were decomposed into a set of 20 component maps and associated vectors describing the temporal variations across all runs and subjects by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique (Hyvärinen, 1999). Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a Gaussian/Gamma mixture model to the histogram of intensity values (Beckmann and Smith, 2004).

Region of interest analysis

This *post-hoc* analysis was performed to relate activity in a ventral right fronto-parietal network across all the auditory conditions in the second study and relate activity generated in these regions to those in the first study. A right frontal and right inferior parietal ROI were

defined from activated regions evident in the univariate contrasts from the first study and applied to the second. The mean effect size in each of the listening conditions, relative to rest, was determined for each functionally defined ROI. These means were plotted as bar charts with 95% confidence intervals.

Ideally, a direct whole-brain comparison between the two studies would also be performed. However, there are issues concerning difference signal-to-noise characteristics between the two scanners, which to resolve completely would require complex analyses of the individual scanner performances. This method also poses problems due to the difference in participant groups, the age range, and task involvement. Nevertheless, between-group analyses, when the data have been acquired on different scanners, adds relatively little to the variance in the BOLD signal (Bennett and Miller, 2010). Therefore, I also performed a whole-brain comparison entering the scanner as a covariate in the design matrix, however, the ROI analysis described above is better suited to identify comparisons between the two studies.

3.3 Results

3.3.1 Study 1

Behavioural

To analyse the forced-choice recognition memory test performed at the end of the scanning session, a d' signal-detection measure (controlling for response bias) was used. Subjects performed better than chance for all sentence types spoken by the male (two-tailed Student *t*-

tests, for all four stimulus types: Female vs $M_{ALONE/PRED}$ $t_{(28)}$ = -14.4, P <0.0001; Female vs $M_{ALONE/NON-PRED}$ $t_{(28)}$ = -8.8 P <0.0001; Female vs $MF_{DIOTIC/PRED}$ $t_{(28)}$ = -11.5, P <0.0001; Female vs $MF_{DIOTIC/NON-PRED}$ $t_{(28)}$ = -8.3, P <0.0001). The mean results for correctly identifying the male sentences were: ($M_{ALONE/PRED}$) = 74.5%; ($M_{ALONE/NON-PRED}$) = 55.5%; ($MF_{DIOTIC/PRED}$) = 55.7%; and ($MF_{DIOTIC/NON-PRED}$) = 46.9%. A 2 (single/two speakers) X 2 (semantically predictable/incongruous sentence ending) analysis-of-variance (ANOVA) was performed. This revealed a significantly better performance in remembering what the male had said when he spoke alone compared to when there was distraction by the female speaker ($F_{(1,28)}$ = 4.7, P <0.05), and when the sentences had predictable sentence endings compared with those that had unpredictable endings ($F_{(1,28)}$ = 18.2, P <0.001). There was no significant interaction between the two factors ($F_{(1,28)}$ <2, P >0.1).

Univariate whole-brain analysis

Univariate data were entered into a 2 ($MF_{DIOTIC/PRED}$ and $MF_{DIOTIC/NON-PRED}$) X 2 ($M_{ALONE/PRED}$ and $M_{ALONE/NON-PRED}$) ANOVA. A significant main effect of listening to diotic compared to single speech (Figure 3.3A) was identified. The regions with significantly greater activity were: bilateral superior temporal gyri (STG); the dorsal anterior cingulate cortex and adjacent medial aspect of the superior frontal gyrus (dACC/SFG), and bilateral anterior insular cortices and adjacent frontal opercula (aI/FOp), the so-called cingulo-opercular network; an extensive right lateral prefrontal and inferior parietal cortical network, centred on the posterior middle frontal and supramarginal gyri (MFG/SMG) respectively; and a posterior midline region, within the precuneus. No main effect of the semantic predictability of sentence ending was detected, and there were no significant interactions.

Multivariate whole-brain analysis

fMRI data were entered into an ICA, specifying 20 components. Nine contrasts between conditions were chosen *a priori*: (Tone > Rest; All speech > Rest; ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$) > Rest; ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$) > Tone; ($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) > Tone; ($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) > Rest; ($M_{ALONE/NON-PRED}$ + $MF_{DIOTIC/NON-PRED}$) > ($M_{ALONE/PRED}$ + $MF_{DIOTIC/PRED}$); ($M_{ALONE/PRED}$ + $MF_{DIOTIC/PRED}$) > ($M_{ALONE/NON-PRED}$ + $MF_{DIOTIC/NON-PRED}$); and ($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) > ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$). Bonferroni correction for multiple contrasts resulted in significance being set at P <0.005. Components were discarded as related to motion or other artefacts when most or all of the signal was confined to edges of the brain, or was located within the ventricular systems and white matter. From the remaining components, I will present the three that demonstrated significant differences between conditions (Figure 3.3 B–D). See Appendix (5) for bar chart showing network effects per condition.

Component 2 (Figure 3.3B) demonstrated a hierarchy of activation between conditions, all significant at P <0.00001: [Tones > Silence]; [($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$) > Tones]; and [($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) > ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$)]. The majority of the activity is distributed along the left and right STG (primary and association auditory cortices).

Component 3 (Figure 3.3C) also contained activity along the left and right STG. However, activity that correlated with this subsystem within auditory association cortex was observed in the dACC/SFG, the left inferior frontal gyrus (IFG), and between the left and right inferior frontal and intraparietal sulci (IFS/IPS). Additional activity was seen in both lateral cerebellar

hemispheres, and the dACC/SFG and IFS/IPS networks, which have been described as having common functional connections with the cerebellum (Dosenbach *et al.*, 2008). There was one lateralised region, in the left posterior middle and inferior temporal gyri. For Component 3, activity during the two main speech conditions was greater than Silence, significant at P <0.000001: [($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$) > Silence]; and [($MF_{DIOTIC/PREDI}$ + $MF_{DIOTIC/NON-PRED}$) > Silence]. Activity was also greater in the contrast of listening to Tones with Silence, P = 0.009. Other contrasts were not significant, correcting for multiple comparisons.

Component 4 (Figure 3.3D) demonstrated activity that had a similar distribution to that observed as the main effect of listening to two speakers compared with single speech in the univariate analysis. Activity for this component was significantly different between listening to competing speech compared with single: [($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) > ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$)], P = 0.00007.

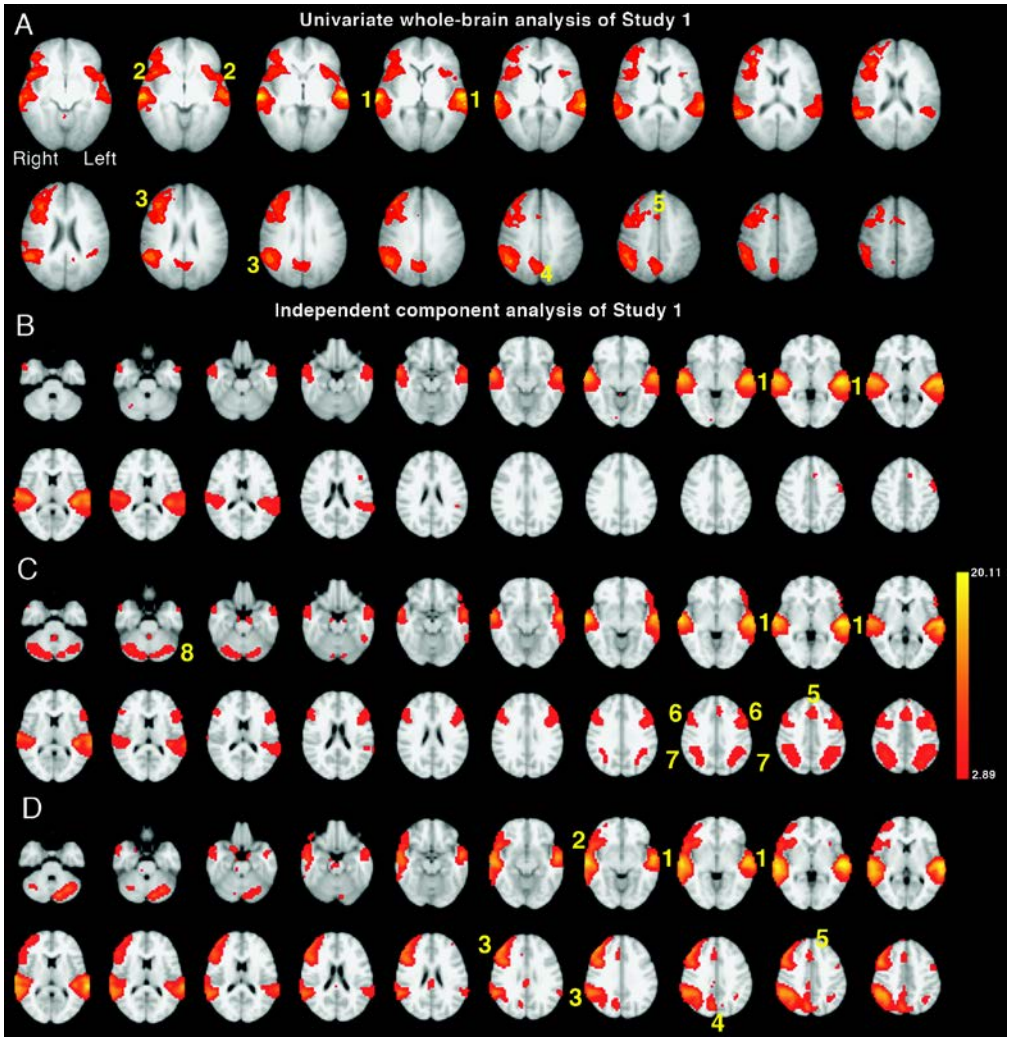


Figure 3.4: Study 1 results

Axial slices are shown in radiological convention, with the right hemisphere on the left of each slice, beginning with the most ventral slice. ***A****: Univariate whole-brain analysis of Study 1. The significant main effect of competing speech ($MF_{DIOTIC/NON-PRED}$ + $MF_{DIOTIC/PRED}$) contrasted with non-competing ($M_{ALONE/NON-PRED}$ + $M_{ALONE/PRED}$) speech is projected as a red/yellow overlay, with a voxel-level threshold Z > 2.3 and cluster-level threshold P <0.05. 1. Superior temporal gyri (STG); 2. Anterior insulae and frontal opercula (aI/FOp); 3. Lateral prefrontal and inferior parietal cortical system (MFG/SMG); 4. Precuneus; 5. Dorsal anterior cingulate cortex and adjacent superior frontal gyrus (dACC/SFG).* ***B–D****: Results from the 20-component independent component analysis (ICA).* ***B****. Component 2 demonstrated regions with significant activity during all listening conditions (including Tones) > Silence. 1. Bilateral STG.* ***C****. Component 3 demonstrated areas of significant activity for all speech listening conditions > Silence. 1. Bilateral STG; 5. dACC/SFG; 6. Bilateral inferior frontal sulci (IFS); 7. Bilateral intraparietal sulcus (IPS); 8. Lateral cerebellar hemispheres.* ***D****. Component 4 demonstrated a main effect of ($MF_{DIOTIC/NON-PRED}$ + $MF_{DIOTIC/PRED}$) > ($M_{ALONE/NON-PRED}$ + $M_{ALONE/PRED}$). 1. Bilateral STG; 2. Right aI/FOp; 3. MFG/SMG; 4. Precuneus; 5. dACC/SFG.*

The inclusion of semantic predictability into the study was to look for a reaction to an unanticipated stimulus and to investigate whether it modulated the response of higher-order cortices involved with the cognitive control and attention involved in listening to speech. However, no component demonstrated any effect of the semantic predictability of sentence endings [($M_{ALONE/NON\text{-}PRED}$ + $MF_{DIOTIC/NON\text{-}PRED}$) > or < ($M_{ALONE/PRED}$ + $MF_{DIOTIC/PRED}$)]. In the absence of any observable modulation, this experimental manipulation is not considered further in this thesis.

Summary of findings from Study 1

Bilateral primary and association auditory cortices responded in a 'bottom-up' manner to stimuli of increasing auditory complexity, as seen in Component 2: Silence << Tones << M_{ALONE} << MF_{DIOTIC}. Overlapping networks within the auditory cortex also demonstrated correlated activity within multiple higher-order systems (seen in Components 3 and 4): the bilateral cingulo-opercular and IFS/IPS systems, the ventral right fronto-parietal system (MFG/SMG), and the precuneus, all of which was also evident as the main effect of listening to two speakers in the univariate whole-brain ANOVA. Therefore, the above results reveal that activity within auditory cortex is simultaneously influenced by both the complexity of ascending auditory signal, with an additional response to unattended as well as attended speech (see Zion Golumbic et al., 2013), and by the top-down signal from networks that have been associated with attention and cognitive control. However, a dissociation of activity across these higher-order systems was detected, most evident in their visualisation as separate components within the ICA. The cingulo-opercular and IFS/IPS systems activated together, and responded to any listening condition, including listening to pure tones without an

explicit task demand. Any difference in activity within these systems between listening to MF_{DIOTIC} and to M_{ALONE} was small, but much more evident in the right MFG/SMG and the precuneus. It can be seen that there was anatomical overlap between these two broad systems, in both STG, right IFS/IPS and in dACC/SFG.

3.3.2 Study 2

Behavioural

Even though the questions had been designed to relate specifically to the previous statement by the female or male speaker, a pilot study was performed on five subjects to determine whether the probe questions used in Study 2 could be answered correctly above chance using prior knowledge. For all female and male sentences, the mean responses (39–49%) were not above chance (50%). In contrast, the participants responding during scanning to questions on statements spoken by the female were all significantly more accurate than chance (P <0.0001).

A one-way ANOVA showed a significant difference in accuracy between the listening conditions ($F_{(1,24)}$ = 8.604, P <0.0001). One-sample t-tests demonstrated that $F_{SINGLE} = F_{BABBLE} = M_{LEFT}F_{RIGHT}$ (P >0.5), but $F_{ALONE} > FM_{DIOTIC}$ (P <0.05) and > $F_{LEFT}M_{RIGHT}$ (P <0.0001), and $M_{LEFT}F_{RIGHT} > F_{LEFT}M_{RIGHT}$ (P <0.05). Thus, accuracy on questions relating to the female statements was not statistically different across both masked and unmasked conditions except for a small but significant decline on FM_{DIOTIC} and a greater decline on $F_{LEFT}M_{RIGHT}$. In the latter condition, the attended speech was directed towards the right hemisphere, non-dominant for language.

The responses to questions on statements spoken by the unattended male speaker were significantly more accurate than chance during FM_{DIOTIC} and $F_{LEFT}M_{RIGHT}$ (P <0.0001), although a little below chance during $M_{LEFT}F_{RIGHT}$ (mean 43%, chance 50%, t = 2.25, P <0.05). A one-way ANOVA on the response to the sentences spoken by the male speaker during FM_{DIOTIC}, $M_{LEFT}F_{RIGHT}$ and $F_{LEFT}M_{RIGHT}$ demonstrated a significant difference in accuracy between conditions ($F_{(1,24)}$ = 30.5, P <0.0001). One-sample t-tests demonstrated that FM_{DIOTIC} = $F_{LEFT}M_{RIGHT}$ (P >0.5), but $F_{LEFT}M_{RIGHT}$ > $M_{LEFT}F_{RIGHT}$ (P <0.0001).

In summary, the participants did attend to the female speaker in all conditions, but found it most difficult when she was presented to the left ear, and therefore predominantly to the right cerebral hemisphere. There are limitations in introducing spatial cues using simulated head-related transfer functions (HRTFs) (Algazi *et al.*, 2001), which will have deviated to a variable extent from the HRTF of individual subjects, resulting in weaker dichotic/diotic contrasts than could be obtained with listening conditions in free field or with individually determined HRTFs. Nevertheless, the results show a significant behavioural effect, with more correct responses when the female speaker was 'located' to the right rather than the left of the participants. Further, responses to what the unattended male speaker had said were least when his voice was presented to the left (that is, predominantly to the right hemisphere) compared with both the FM_{DIOTIC} and $M_{LEFT}F_{RIGHT}$ conditions. Therefore, spatial cues were evident to the participants during the dichotic listening conditions.

Univariate whole-brain analysis

The first analysis of the fMRI data was a contrast of the two diotic (F_{BABBLE} + FM_{DIOTIC}) listening conditions with F_{ALONE}. In comparison with the univariate analysis in Study 1 (contrast of MF_{DIOTIC} with M_{ALONE}), this demonstrated a reduced distribution of activity, with activity confined to the right aI/IFG, left planum temporale and adjacent anterior inferior parietal lobe (PT/IPL), right posterolateral STG, left IPS, and the precuneus (Figure 3.4A). These regions, with the exception of the left IPS, were also evident in the contrast of MF_{DIOTIC} with M_{ALONE} in Study 1 (Figure 3.4B). Looking for the influence of spatial cues, the two dichotic conditions ($M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$) were contrasted with FM_{DIOTIC}. It was evident that these two conditions with spatial cues resulted in greater activity in the precuneus, the left PT/IPL and the dACC/SFG (Figure 3.4C). Therefore speech-masked-by-speech without spatial cues activated these two regions relative to F_{ALONE}, but the activity increased significantly in the presence of spatial cues. There was no significant difference in the activity of these regions if the female speaker was presented either to the right or left ear during the dichotic listening conditions. The spatial cues also resulted in greater activity in anterior regions associated with eye movements, the frontal eye fields (Figure 3.4C), which form part of the so-called Dorsal Attention Network (Corbetta and Shulman, 2008).

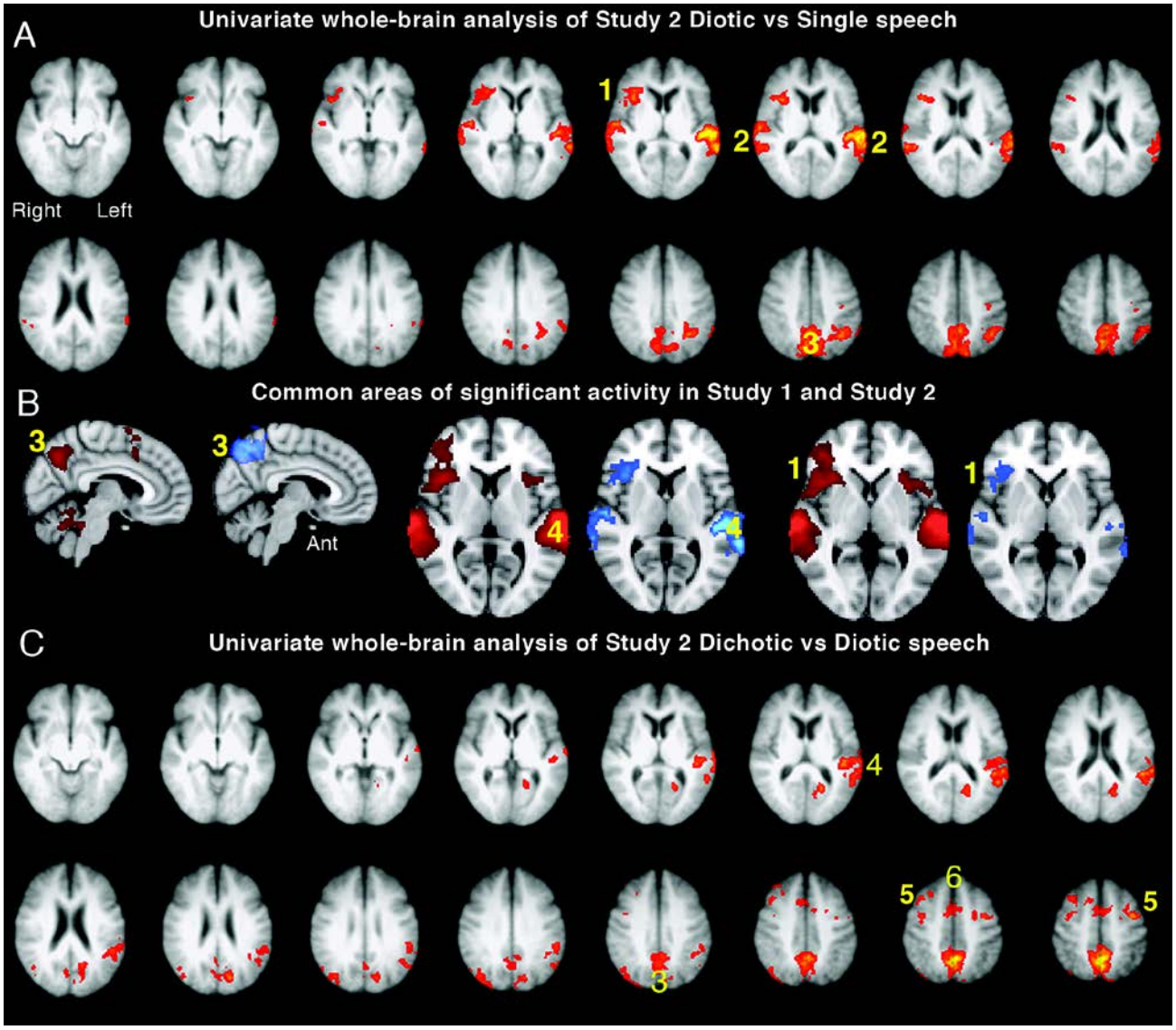


Figure 3.5: Axial slices of Study 2 univariate results

***A**. Univariate whole-brain analysis of Study 2. There was a significant main effect of diotic (F_{BABBLE} + FM_{DIOTIC}) speech contrasted with single (F_{ALONE}) speech projected as a red/yellow overlay, with a voxel-level threshold Z >2.3, cluster-level threshold P <0.05. 1. Right anterior insular/inferior frontal cortex (aI/IFG); 2. Left planum temporale and adjacent anterior inferior parietal lobe (PT/IPL) and right posterior superior temporal gyrus (STG); 3. Precuneus; **B**. Sagittal and axial views showing regions of common significant activity generated from the univariate analysis contrasting diotic speech to single speech, projected as red/yellow overlay in Study 1 and blue overlay in Study 2, with a voxel-level threshold Z >2.3 and cluster-level threshold P <0.05. 1. Right aI/IFG; 3. (displayed on midline sagittal views) Precuneus; 4. Left PT/IPL. **C**. Axial slices from the univariate contrast of dichotic ($M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$) > diotic (FM_{DIOTIC}). 3. Precuneus, 4. Left PT/IPL; 5. Bilateral dorsolateral prefrontal cortices; 6. Anterior cingulate cortex (ACC) and activity probably localised to frontal and supplementary eye fields.*

The default mode network (DMN), a system that is most active during 'Rest' states and deactivated by attending and responding to external stimuli (Fox *et al.*, 2005), demonstrated anticorrelated activity with networks for attention and cognitive control. The posterior cingulate cortex is a prominent posterior component of the DMN. Figure 3.5 demonstrates the contrast of $M_{LEFT}F_{RIGHT} + F_{LEFT}M_{RIGHT}$ with the rest condition (Silence) and vice versa. The posterior midline activity associated with attending to one speaker in the presence of another, most evident when spatial cues were included, was located dorsal to the midline posterior component of the DMN.

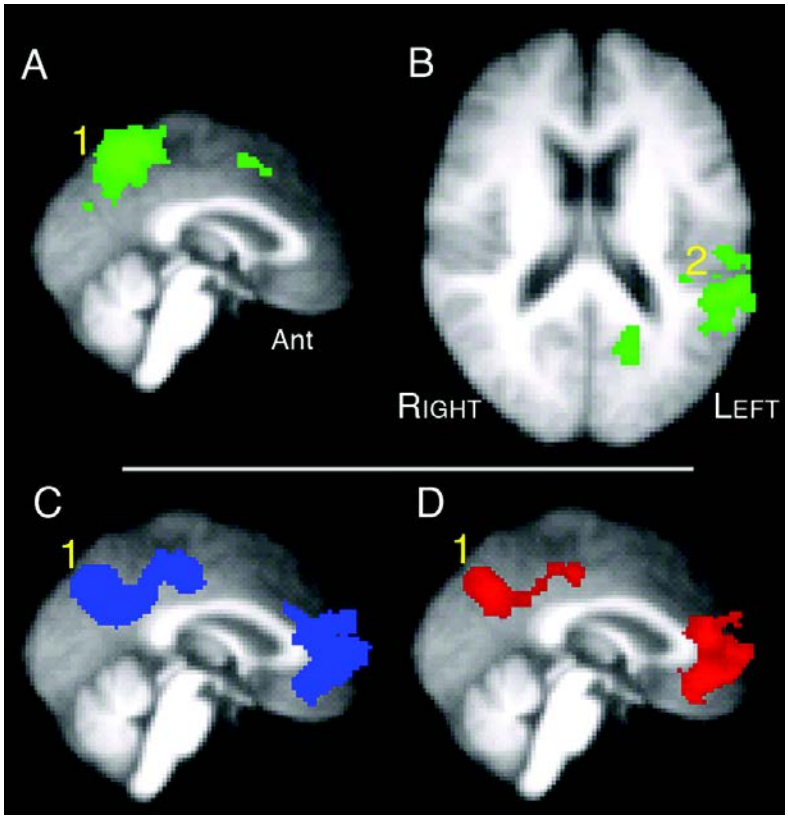


Figure 3.6: Univariate whole-brain analysis of Study 2, exploring three contrasts of diotic and dichotic listening

***A**. (sagittal midline projection) and **B**. (axial section) of the contrast of ($F_{LEFT}M_{RIGHT}$ + $M_{LEFT}F_{RIGHT}$) with (FM_{DIOTIC} + F_{BABBLE},) projected as a green overlay. 1. Precuneus; 2. Left planum temporale and adjacent anterior inferior parietal lobe (PT/IPL). **C**. Sagittal midline projection of Rest contrasted with (FM_{DIOTIC} + F_{BABBLE},), projected as a blue overlay. 1. Precuneus and adjacent posterior cingulate cortex (PCC). **D**. Sagittal midline projection of Rest contrasted with ($FL_{EFT}M_{RIGHT}$ + $M_{LEFT}F_{RIGHT}$) projected as a red overlay. 1. Precuneus and PCC. Voxel-level threshold Z >2.3 and cluster-level threshold P <0.05.*

Multivariate whole-brain analysis

An ICA specifying 20 components to all trials was performed. Eleven contrasts were chosen *a priori:* (F_{ALONE} > Rest; F_{BABBLE} > F_{ALONE}; FM_{DIOTIC} > F_{ALONE}; $M_{LEFT}F_{RIGHT}$ > F_{ALONE}; $F_{LEFT}M_{RIGHT}$ > F_{ALONE}; FM_{DIOTIC} > F_{BABBLE}; ($M_{LEFT}F_{RIGHT}$ $F_{LEFT}M_{RIGHT}$) > (FM_{DIOTIC} + F_{BABBLE}); (FM_{DIOTIC} + F_{BABBLE}) > ($M_{LEFT}F_{RIGHT}$ $F_{LEFT}M_{RIGHT}$); $F_{LEFT}M_{RIGHT}$ > $M_{LEFT}F_{RIGHT}$; $M_{LEFT}F_{RIGHT}$ > $F_{LEFT}M_{RIGHT}$; and (F_{ALONE} + FM_{DIOTIC} + F_{BABBLE} + $M_{LEFT}F_{RIGHT}$) > $F_{LEFT}M_{RIGHT}$), with Bonferroni-corrected significance level set at P <0.005.

Expected activity in bilateral STG was seen in Component 1 (not illustrated), with all the listening conditions combined > Rest (P <0.00001), and each of the diotic and dichotic listening conditions > F_{ALONE} (P <0.0001). In this component, there was no difference between Response (during which no external or self-generated speech was heard) and Silence (P = 1). Components 2–4 contained data relevant to activity within the cingulo-opercular and fronto-parietal networks. See Appendix (6) for bar chart showing network effects per condition. Component 2 (Figure 3.6A) demonstrated activity specific for the Response trials, with Response > all listening conditions (P <0.00001) and Response > Silence (P <0.00001), but activity for all the listening conditions combined was no greater than Silence (P = 1). Activity was distributed between the cingulo-opercular and IFS/IPS networks, and the lateral cerebellar hemispheres. In addition, activity was seen in the primary and association visual cortices (as the participants had to respond to written questions). Anticorrelated activity was shown in both STG, consistent with the absence of auditory input during the Response trials. In Component 3 (Figure 3.6B), activity during the Response trials was greater than all the listening conditions combined (P <0.00001); however activity was also significant during all the listening combined > Silence (P <0.00001) and F_{ALONE} > Silence (P <0.00001). There was

no difference in activity between any of the individual listening conditions, with the exception of $F_{LEFT}M_{RIGHT} > M_{LEFT}F_{RIGHT}$ ($P = 0.002$), the former listening condition being the one in which participants were least successful in attending to the female speaker. Although there was activity in the cingulo-opercular and IFS/IPS networks, as in Component 4 (Figure 3.6C), prominent activity in both cerebellar hemispheres was absent, and there was strongly left-lateralised activity in the left inferior frontal gyrus, posterior inferolateral temporal lobe and inferior parietal cortex. The only prominent right cortical activity identified was centred on the posterior MFG.

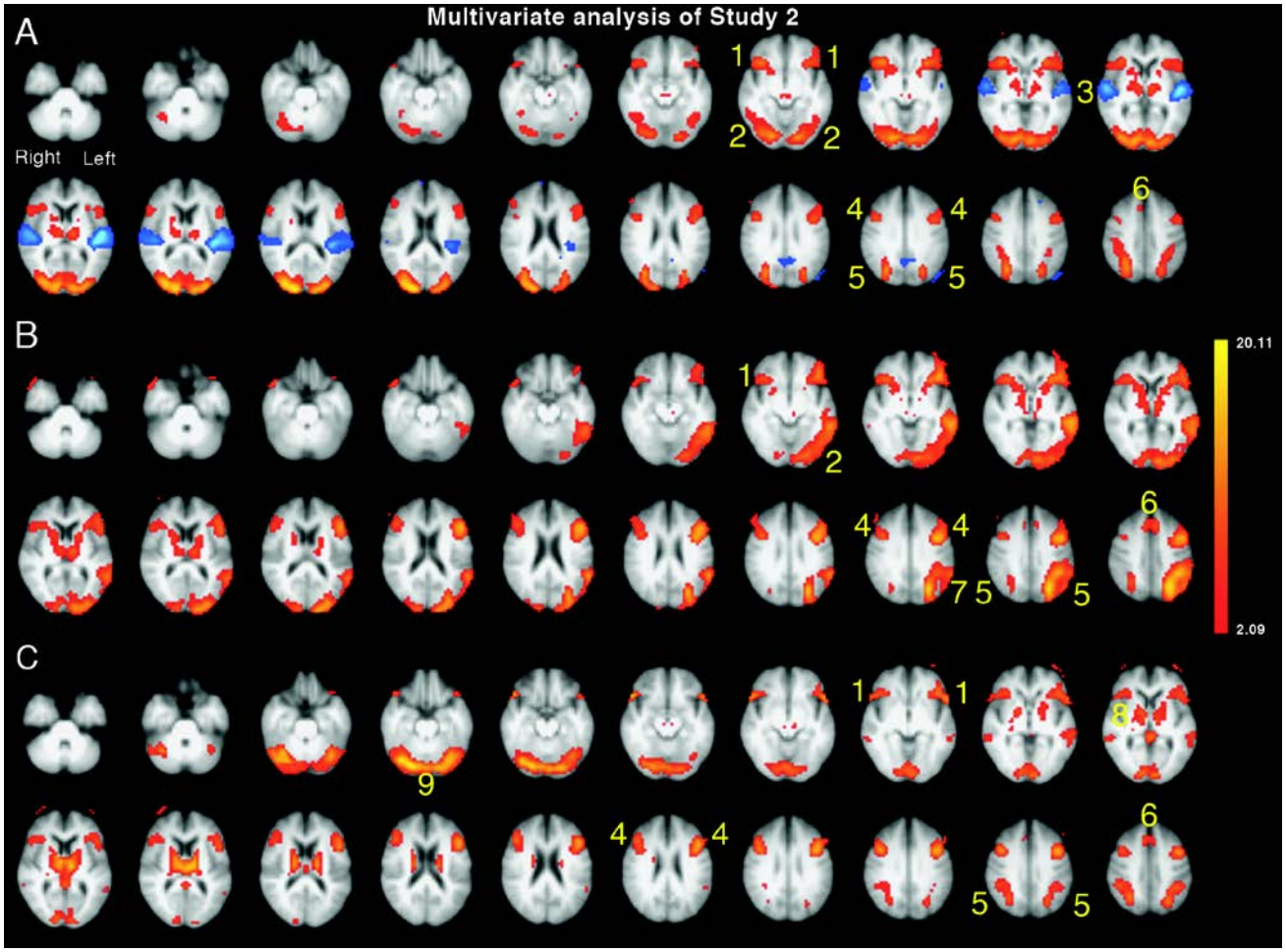


Figure 3.7: Axial slices of the multivariate analysis of Study 2

Multivariate analysis of Study 2, specifying 20 components, with regions of significant activity displayed as red/yellow overlays. ***A****. Component 2 demonstrated activity for Response > Listening 1. Bilateral anterior insulae and frontal opercula aI/FOp; 2. Visual cortex; 4. Bilateral inferior frontal sulci (IFS); 5. Bilateral intraparietal sulci (IPS); 6. Dorsal anterior cingulate cortex and adjacent superior frontal gyrus (dACC/SFG). This activity was anticorrelated with 3. Bilateral STG, projected as a blue overlay.* ***B****. Component 3 demonstrated activity for Response > all speech Listening conditions combined, all Listening conditions combined > Silence and* F_{ALONE} *> Silence. 1. aI/Fop; 2. Visual cortex; 4. IFS; 5. IPS; 6. ACC; 7. Left inferior parietal cortex.* ***C****. Component 4 demonstrated a similar hierarchy of activity across conditions observed in Component 3. 1. aI/FOp; 4. IFS; 5. IPS; 6. ACC; 8. Basal ganglia and thalami; 9. Lateral cerebellum.*

In Component 4 (Figure 3.6C), the hierarchy of activity was very similar to that observed in Component 3 [Response trials > all the listening conditions combined (P <0.00001); all listening conditions combined > Silence (P <0.00001); and F_{ALONE} > Silence (P < 0.00001)]. Again, there was no difference in activity between any of the individual listening conditions (P >0.15). The distribution of activity in Component 4 (Figure 3.6C) was closely similar to that in Component 2, but greater activity was evident in the basal ganglia and thalami, with little activity in visual cortex and no anticorrelated activity in the STG. In marked contrast to the results from Study 1, there was no component demonstrating activity in the right inferior parietal cortex.

ROI analysis

As the two studies were performed on different 3T scanners, comparisons were made using region-of-interest (ROI) data from the listening conditions rather than entering data from both studies into the same whole-brain design matrix. The peaks of activity in the posterior right MFG and the right SMG from Study 1 were defined, and 8mm spheres as ROIs were used to extract the signal across conditions from both the first and second studies. The results are presented as bar plots in Figure 3.7. These plots illustrate a dissociation of activity across the two studies in both ROIs. Within the right frontal region, the dissociation between the two studies was due to the different response to the single speaker as a result of the change in task demand: there was increased activity relative to Rest, and on a par with that elicited by the diotic and dichotic listening tasks in Study 2. In contrast, in the right SMG there was no response to any of the listening conditions during Study 2 relative to Silence, a major change from the response of this region to speech-masked-by-speech in Study 1.

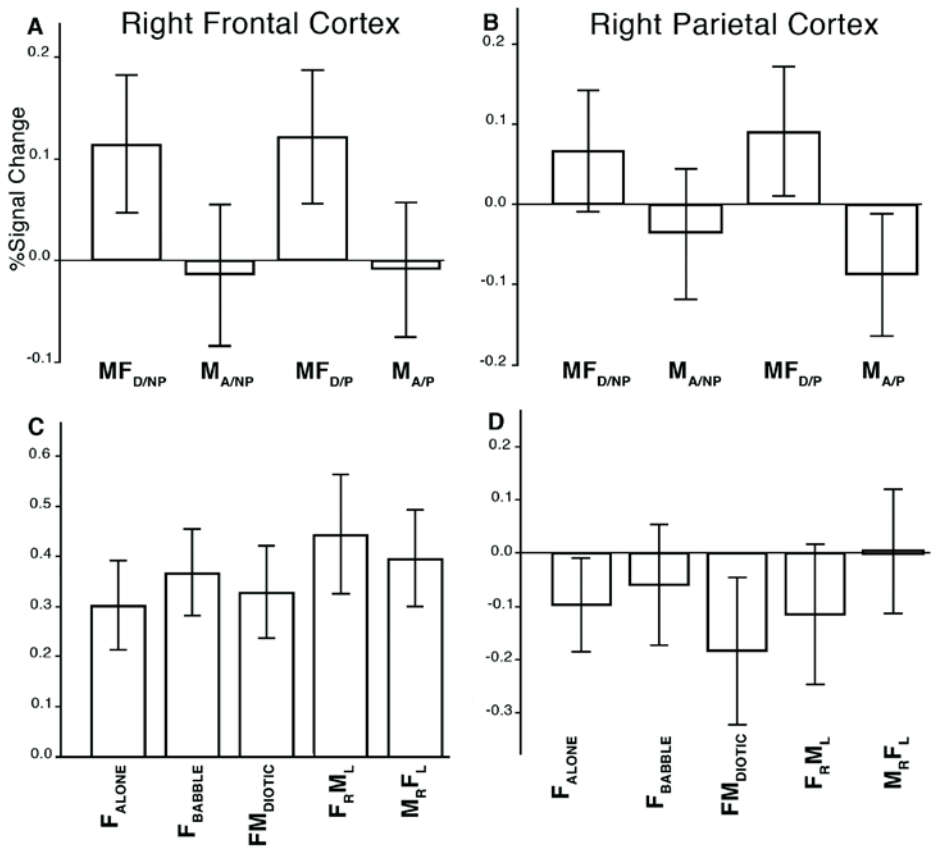


Figure 3.8: Region of interest analysis

*A–D show percentage blood oxygen-level dependent signal changes for each condition relative to the Rest baseline condition. Error bars are the 95% confidence intervals. Study 1 depicted in panels **A** and **B**; Study 2 depicted in panels **C** and **D**. **A** and **C** show the results from the ROIs in the right middle frontal gyrus (MFG) and **B** and **D** from the ROIs in the right supramarginal gyrus (SMG). Conditions labelled as in the text, but with the following abbreviations: $MF_{D/NP}$ = ($MF_{DIOTIC/NON\text{-}PREDICTABLE}$); $M_{A/NP}$ = ($M_{ALONE/NON\text{-}PREDICTABLE}$); $MF_{D/P}$ = ($MF_{DIOTIC/PREDICTABLE}$); $MF_{A/P}$ = ($MF_{ALONE/PREDICTABLE}$), L = left; R = right.*

A whole-brain comparison was performed between the two studies, correcting for multiple comparisons, in which MF_{DIOTIC} versus M_{ALONE} in the first study was compared with FM_{DIOTIC} versus F_{ALONE} in the second study, entering 'scanner' (+1, -1) as a covariate in the design

matrix. This highlighted the greater right fronto-parietal activity in the first study compared with the second, as shown in Figure 3.8. However, and predictably from the profiles of activity from the ROI data, this failed to demonstrate the dissociation between listening conditions in the right inferior parietal and right frontal cortex in the second study as the result of loading working memory. Therefore the ROI analysis was essential to interrogate in detail the outcome of the whole-brain comparison between the two studies.

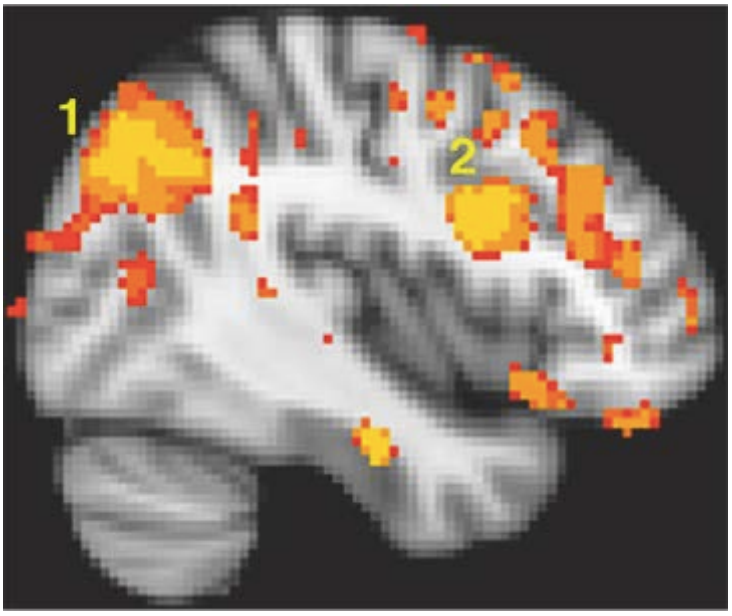


Figure 3.9: Whole brain comparison between Study 1 and Study 2

A sagittal view of the right hemisphere, at X co-ordinate = 42mm. The contrast of diotic with single-speaking conditions was directly compared in whole-brain analyses between Study 1 and Study 2. Predictably, from the profile of activities observed in the ROI analyses, both right parietal (labelled 1) and frontal cortices (labelled 2) were more 'active' in Study 1. However, this disguises the dissociation of responses between frontal and parietal cortices: the loss of 'contrast' in Study 2 was due to an increase in activity in response to a single speaker in frontal cortex, but a decline in activity in response to diotic listening in parietal cortex.

3.3.3 Summary of findings from Study 2 contrasted with those from Study 1

The univariate contrast of diotic speech (F_{BABBLE} + FM_{DIOTIC}) with F_{ALONE} identified only a subset of regions of activity that was observed in the first study: activity was confined to the right aI/IFG, left PT/IPL, right posterolateral STG and precuneus. Activity associated with spatial cues assisting in the segregation of one speech stream from another was seen when contrasting the dichotic ($M_{LEFT}F_{RIGHT}$, $F_{LEFT}M_{RIGHT}$) with the diotic (FM_{DIOTIC}) listening conditions, with greater activity in the left PT/IPL and the precuneus. Activity in the right aI/FOp in both studies indicated a central role for this region in supporting speech-stream segregation. This was independent of the context of task during listening (that is, the requirement for immediate or delayed recall of the content of the 'attended' speech). In contrast, activity in the right MFG and SMG was strongly dependent on the context. This was most noticeable with the loss of activity in the SMG when the task required an immediate response to what was heard. The ICA showed that this task was associated with a left fronto-temporo-parietal network. Throughout all these networks, with the exception of SMG, activity was always greater during the Response trials relative to the Listening trials, but as in the first study, the widely distributed bilateral system comprising cingulo-opercular cortex, IFS/IPS and cerebellar cortex was active during the listening conditions, but was not modulated by speech-in-speech masking. Associated with activity in the cerebral and cerebellar hemispheres, Study 2 also showed bilateral basal ganglia and thalamic activity, which was not seen in Study 1. This can be attributed to the change in data acquisition for Study 2 (see Section 2 (2.10 and 2.11) to improve sensitivity, raising the signal in the subcortical nuclei above the statistical threshold.

3.4 Discussion

The two studies presented here were designed to demonstrate the local and distributed systems that are involved in attention and cognitive control when listening to a speaker and recalling what has been said. Two experimental methods were designed to capture everyday listening conditions: task demand, namely delayed or immediate recall of what had been said by the attended speaker; and the presence or absence of background competing speech. Based on the results of the two studies, there were three cortical nodes that responded to speech-in-speech masking irrespective of the task demand; the precuneus, the left PT/IPL and the right aI/FOp. I will start by discussing these common regions.

Neuropsychological lesion-deficit analyses of the precuneus to determine the function of this region are sparse due to the rarity of the condition. Functional neuroimaging studies, however, have implicated this region in a number of different functions (Cavanna and Trimble, 2006). These most probably relate to the multiple overlapping components within this region that form parts of anatomically and functionally dissociable networks, as previously shown for the adjacent posterior cingulate cortex (Leech and Sharp, 2014). One function of this region is egocentric spatial orientation, which has often been considered in terms of visuospatial navigation (for review, see Boccia *et al.*, 2014). The precuneus is also a component of the Dorsal Attention Network (DAN), which incorporates the dorsal precuneus and bilateral medial intraparietal sulci, midline supplementary eye field and frontal eye fields, and superior parietal lobules. This network has been most often investigated with regard to its response to visual tasks, becoming active as participants voluntarily focus attention on perceptually distinctive visual stimuli that are salient within the context of a specific task-dependent goal (for reviews, see Corbetta *et al.*, 2008; Corbetta and Shulman, 2011). However, a recent

study has also strongly implicated the precuneus in detecting a target sound in complex acoustic environments (Zündorf *et al.*, 2013). In this present study, the precuneus was more active during the diotic presentation of two speakers (in the absence of spatial cues), compared with attending to a single speaker. This finding is compatible with a top-down role in the detection of the salient speech stream based on non-spatial perceptual cues, such as the fundamental frequency of the voice; but, as in the study by Zündorf and colleagues (2013), activity within this region increased significantly when there were auditory cues indicating a spatial separation of the two speakers. Further, associated with this increased activity in the presence of spatial cues, the results also identified an unexpected increase in activity in regions located in the supplementary eye field and the frontal eye fields. Future studies may choose to investigate this further to determine whether spatial cues during speech-stream segregation are accompanied by automatic eye movements towards the attended speaker.

The study of Zündorf and colleagues (2013), although of different design and employing non-verbal auditory stimuli, also demonstrated an increased response of the left PT to spatial cues, with evidence of some right posterior temporal involvement. Across both studies reported here, activity in the left PT increased in response to one speaker, increased further when there was more than one speaker, and was greatest in the presence of spatial cues. The PT has been proposed to be a computational hub, directing both spectrotemporal and spatial information to wider distributed networks involved in the identification, semantic recognition and auditory stream segregation of sounds, both verbal and environmental (Griffiths and Warren, 2002). These authors proposed that the PT might be a central node in resolving the ‘cocktail party’ effect, and my results presented in this study support this hypothesis. Of note, a clinical study on stroke patients by Zündorf and colleagues (2014),

using the same complex non-verbal sounds of their earlier study (Zündorf *et al.*, 2013), indicated that the right posterior temporal cortex, including the PT, is central to sound localisation. However, it is important to note that patients with lesions that included the left PT were under-represented because such patients were often too language-impaired to participate. Based on my present study, I would argue that segregating one speech stream from others, using all available non-spatial and spatial cues, is dependent on the left PT, although activity was also evident in the right posterior STG, suggesting that this function may be shared between the cerebral hemispheres.

Turning to the role of the right aI/FOp, previous studies have proposed that this region is specialised for initiating response inhibition and task-switching (reviewed in Aron et al*.,* 2004). However, in a more recent study, Hampshire and colleagues (2010) demonstrated that this region, part of the cingulo-opercular network, becomes active during the detection of important cues irrespective of whether this results in the generation or inhibition of a motor response, or even when there is no overt response. In their study, activity was preferentially greater in the cingulo-opercular network for tasks that most depended on working memory, when the range of tasks resulted in activity in both the cingulo-opercular and the bilateral IFS/IPS networks. In the model proposed by Menon and Uddin (2010), the right aI/FOp is a core node involved in the generation of control signals following the perception of salient environmental events. These signals direct working memory, attention and other higher-order control systems towards the mental processing of these events.

The clear difference between the two studies is the functional dissociations between the response of the right dorsolateral prefrontal cortex, centred on the MFG, and inferior parietal

cortex (SMG). The first study demonstrated activity within the ventral right fronto-parietal network associated with the presence of a competing speaker. Therefore, the linguistic and semantic processing of heard speech, the encoding of the information as episodic memories and remembering the information until the end of the scanning session all required minimal involvement of this system. However, perceptual difficulty due to the presence of a competing speaker markedly increased activity in both the frontal and parietal components. One explanation for this is an increased need for sustained attention when attempting to encode the information conveyed by the 'attended' speaker on the perceptually difficult trials; this system has been associated with sustained attention (for a review, see Singh-Curry and Husain, 2009). Changing the task demand in Study 2, where an immediate response to what had been heard was required, abolished activity in the right SMG, regardless of perceptual difficulty, and resulted in increased activity in the right MFG across all trials. Therefore, a task that relied on working memory rather than encoding in episodic memory meant that this ventral right fronto-parietal system was no longer influenced by the need for speech-stream segregation. The ICA analysis demonstrated that Component 4, as well as showing activity in the cingulo-opercular and IFS/IPS networks, revealed correlated activity in the left inferior frontal gyrus, posterior inferolateral temporal lobe and inferior parietal cortex. This indicates the operation of a left hemisphere verbal working memory system, which was also demonstrated to be active during the Response trials. Therefore, the task demand had a major influence on ventral left and right parietal networks, with tasks depending heavily on working memory, resulting exclusively in left hemisphere activity, whereas episodic memory encoding requiring increased attention due to perceptual difficulty depended on right hemisphere involvement.

The cingulo-opercular and IFS/IPS networks are domain-general systems for cognitive control

and attention that are active across many different kinds of task (Fedorenko *et al.*, 2013; Hampshire *et al.*, 2012). It was not surprising that they were most active during the Response trials of Study 2, although ICA analyses of both studies demonstrated that they were also active during the attentive demands of the listening conditions. Activity in these systems, however, was not modulated by the perceptual difficulty associated with speech-in-speech masking. The one exception, as previously discussed, was the right aI/FOp component of the cingulo-opercular network, which was strongly influenced by speech-in-masking, indicating a particular role for this region in regulating attention and cognitive control as the perceptual difficulty increases.

3.5 Summary

To summarise, the two studies described here have demonstrated the role of networks that are active during speech-stream segregation in attentive listening, and whether their degree of involvement is influenced by the time period during which the verbal information conveyed has to be held in episodic memory. Three regions in particular were central to speech-stream segregation: the left PT, precuneus and right aI/FOp. Focal lesions of the precuneus are rare, but patients with a stroke affecting the right aI/FOp are presumably not that uncommon. Therefore, a future lesion-deficit analysis could be performed to confirm the proposal that the right aI/FOp is central to activating attention and memory systems and deactivating the DMN when listening to a speaker in a 'cocktail party' auditory environment.

Stroke, traumatic brain injury or neurodegenerative disease, all common neurological conditions, can all result in a complaint of problems attending to speakers when there is

distraction from background speech, or when attention to what is being said is extended over longer periods. Therefore, the additional impairment in registering verbal information will aggravate any deficit in the encoding of verbal information. As attention and cognitive control are potential targets for symptom-modifying pharmacotherapy (for example, Klinkenberg *et al.*, 2011; Robertson, 2014), the next chapter will describe the investigation of these networks in patients with varying degrees of memory impairment.

4 Impaired speech-stream segregation in patients with memory impairment

The commonest complaint of patients presenting to a cognitive neurology clinic is one of poor memory for recent events, especially a failure to remember what has just been said to them. This symptom may be due to inefficient attentive registration of what the speaker is saying, in addition to any impairment of verbal episodic memory encoding and/or subsequent retrieval. Although little researched, patients with Alzheimer's disease (AD) find it increasingly difficult to participate in conversations at social functions, compared with engaging in conversations in a quiet environment. This symptom indicates particular difficulty with speech-stream segregation, which may be due to impairment of both pre-attentive and attentive processes.

This chapter describes the continuation of Study 2 presented in the preceding chapter, extended to patients who presented to a cognitive neurology clinic with a prominent symptom of forgetfulness for recent events, including recent conversations. This group was compared with age-matched normal participants reported in Chapter 3, using the same fMRI study design and factoring in behavioural scores.

4.1 Aims and hypothesis

The aim was to investigate speech-stream segregation in patients with a complaint of impaired memory, and the relationship between this symptom and activity within higher-order systems for attention, working memory and cognitive control during attentive listening. Previous studies have identified abnormalities in central auditory processing, including auditory scene analysis, in patients with mild cognitive impairment (MCI) and cortical neurodegenerative disease (Gates *et al.*, 1996, 2008, 2011; Golden *et al.*, 2015a, b, c; Goll *et al.*, 2012; Golob *et al.*, 2007, 2009). It is to be expected that pathology affecting brain stem auditory nuclei and primary and association auditory cortex will impair 'bottom-up' pre-attentive processing of speech, but 'top-down' impairment of attention and cognitive control will also influence the ability to register what a speaker is saying, particularly under adverse listening conditions when there is background noise and speech. The design of the study was the same as that for Study 2 (see Chapter 3; 3.2). Participants performed the same task, namely attending to a female speaker presented in five different listening conditions.

The hypotheses were:

1. Patients would be impaired at attentive listening, especially when the listening condition required speech-stream segregation.

2. Although both patients and controls would activate the same auditory and higher-order neocortical systems when attending to one speaker in the absence or presence of masking background speech, success at the immediate recall of what the attended speaker had said would be proportional to activity in higher-order fronto-parietal cortices.

4.2 Materials and methods

4.2.1 Participants

The results from a total of 31 patients (16 female, 29 right-handed, with a mean age of 73 years, range 59–87) and 22 controls (12 females, 21 right-handed, with a mean age of 66 years, range 51–82) were analysed. Although the results from all 25 controls are presented in Chapter 3, three were excluded for comparison with the patients. This was because one normal participant had an in-scanner performance >3 standard deviation below the other normal participants, despite normal out-of-scanner cognitive performance. Two others were excluded because they scored at a borderline level on the Addenbrooke's Cognitive Examination - Revised (ACE-R <88/100), the recommended cut-off score with high sensitivity but low specificity for the presence of dementia (Larner, 2007), although the participants were symptom-free. A sub-group analysis was also performed on 20 of the 31 patients, who were clearly separable from the normal participants on the basis of a hierarchical cluster analysis of behavioural scores (see Section 4.3 and Figure 4.3).

The 22 controls had no symptoms of memory impairment and no history of neurological or psychiatric illness. As a group they were younger than the patient group (t = 3.3, P <0.01*).* The patients were recruited solely on the basis of a symptom of poor memory for recent events, especially impaired memory for recent conversations. When asked, many patients acknowledged that the latter symptom was worse when listening to conversations in noisy environments. Written consent was obtained from all participants and the study had prior approval from the North West Thames ethics committee.

At the first clinic visit, after obtaining a clinical history from the patient and accompanying family or friends, a neurological examination and the ACE-R were performed. All patients underwent diagnostic anatomical brain imaging (MRI in 29 patients, X-ray CT scanning in the other two); and blood tests to screen for haematological, renal, hepatic or thyroid dysfunction. Cerebrospinal fluid samples were obtained from eight patients to assess levels of total-tau, phosphorylated tau and $A\beta_{1-42}$ amyloid (this investigation was offered to many more, but was declined). A positron emission tomographic scan to detect amyloid deposition was obtained on two patients. See Appendix 2 for detailed demographics, individual ACE-R scores and diagnostic test details of the patient group. The diagnostic images were inspected for focal atrophy, particularly the medial temporal lobes, and the microvascular disease load was qualitatively assessed in consultation with a neuroradiologist.

As part of the study, patients underwent a general neuropsychological assessment. The tests comprised the ACE-R (Mioshi *et al.*, 2006); digit span (DS) as a measure of auditory working memory; the Test for Reception of Grammar (TROG) (Bishop, 1989) as a measure of sentence-level speech comprehension; and the CANTAB Alzheimer's Battery (Eclipse 4, 2012 version) (Blackwell *et al.*, 2004; Egerhazi *et al.*, 2007; Fowler *et al.*, 2002). The Geriatric Depression Scale (GDS) was also performed. Appendix 1 summarises the scores on the ACE-R, TROG, GDS, DS and one component of the CANTAB Alzheimer's Battery, Paired Associate Learning (PAL), six-stage-errors adjusted, this test being considered particularly sensitive to the presence of dementia (Blackwell *et al.*, 2004; Mitchell *et al.*, 2009; Swainson *et al.*, 2001). Table 4.2 demonstrates the significant differences in cognitive behavioural results compared with controls and takes into account guidelines for the ACE-R, suggesting that a score of <88 indicates a diagnosis of possible dementia by splitting the patients into those with ACE-R >87 and those with ACE-R <88 (Larner, 2007).

Technically satisfactory recordings for pure-tone audiometry (using PCWerth interacoustics audiometer AS608) were performed on 19/22 controls and 30/31 patients. Five frequency levels (0.25, 0.5, 1, 2 and 4 KHz) were assessed. These recordings were used to address the impact that hearing loss, particularly in the higher tones carrying much of the acoustic information about consonants, and therefore speech intelligibility, might have on the in-scanner performance on the auditory stimuli presented in-scanner.

4.2.2 fMRI stimuli and study design

The design is the same as that described in Chapter 3 (3.2). Participants were required to attend to the female speaker during the five auditory conditions, four of which included unattended background babble or intelligible speech. Speakers of different sex and altering the signal-to-noise ratio contributed to 'bottom-up' selection of the attended speech. The female voice originated at 0^o in the azimuth plane in three conditions; speaking alone (F_{ALONE}); in the presence of background babble (F_{BABBLE}) and in the presence of a male speaker, also at 0^o (FM_{DIOTIC}). The other two conditions involved spatial cues, with the male speaker simulated to originate 30^o to the left and the female 30^o to the right ($M_{LEFT}F_{RIGHT}$), and vice versa ($F_{LEFT}M_{RIGHT}$).

Participants were instructed to listen to and understand what the female had said and prepare to answer a written question presented on a screen, with a 'yes' or 'no' button-press response when cued. The questions related to what the female had said in the F_{ALONE} and F_{BABBLE} conditions, and were divided between what the female had said and what the competing male

speaker had said in the remaining conditions. Participants were not informed that questions could relate to the content of the male speech. Each participant undertook two short practice runs of the auditory attention task before the scanning session to ensure they understood the task. To ensure the auditory stimuli were heard with minimal background scanner noise, interleaved silent steady state (ISSS) imaging was used (Schwarzbauer *et al.*, 2006). Five 'imaging' volumes followed by four 'quiet' volumes, giving 10s of gradient activity, followed by 8s of reduced scanner noise were deployed (see Chapter 3, 3.2). Auditory stimuli were presented during a period of 8s through ear-defending headphones, followed by data acquisition during the ensuing 10s in the response trial.

4.2.3 Image acquisition

As described in Chapter 3 (3.2), T2*-weighted gradient echo planar images were collected on a 3T Siemens Tim Trio scanner with a 12-channel phased-array head coil. Thirty-five contiguous axial slices at each of two echo times (13ms and 31ms), with a slice thickness of 3mm, were acquired in interleaved order (resolution, 3 x 3 x 3mm; field of view, 192 x 192 x 105mm), repetition time of 2s. Two hundred and forty-two volumes were acquired in 14m:42s. To correct for magnetic field inhomogeneities, the manufacturer-provided higher-order shim procedure was used. High-resolution ($1mm^3$) T1-weighted structural images were also acquired for each subject. Stimuli were presented using the Psychophysics Toolbox (Brainard, 1997) under MATLAB (Mathworks, Natick MA).

4.2.4 Data analysis: univariate whole-brain analyses

fMRI data analysis with FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl) was previously described in Chapter 3 (3.2). The data were analysed within the framework of the general linear model using FEAT Version 5.98. Images were pre-processed with realignment of EPI images for motion correction using MCFLIRT (Jenkinson *et al.*, 2002); removal of non-brain voxels using BET (Smith, 2002); spatial smoothing using a 6mm full-width half-maximum Gaussian kernel; grand-mean intensity normalisation of the entire four-dimensional dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight-line fitting, with sigma = 50s) to correct for baseline drifts in the signal. Timeseries statistical analyses were carried out using FILM, with local autocorrelation correction. Registration to high-resolution structural and Montreal Neurological Institute (MNI) standard space images (MNI-152) was carried out using FLIRT.

A fixed-effects model was used to combine the two runs at the individual subject level. Individual design matrices were created, modelling the different behavioural conditions. Contrast images of interest in each study were produced from these individual analyses and used in the second-level analysis. Final between-subject statistical images were produced using a mixed-effects analysis with the FLAME tool. Final images were corrected for multiple comparisons using Gaussian random field-based cluster inference with a height threshold of $Z > 2.3$ and a cluster significance threshold of $P < 0.05$. Individual grey matter density maps, computed from T1-weighted images using the script feat_gm_prepare, distributed with FSL and FMRIB Automated Segmentation Tool (FAST; Zhang *et al.*, 2001), were entered as covariates of no interest.

4.2.5 Functional connectivity analysis – dual regression

Functional connectivity was assessed using spatially restricted independent component analysis (ICA) followed by dual regression (Leech *et al.*, 2012). A superior temporal lobe region of interest (stROI) was defined using combined structural and functional criteria to restrict the ICA. The left superior temporal gyrus (STG), including the left planum temporale (PT), was defined anatomically using the Harvard–Oxford Cortical Structural Atlas (STG, anterior and posterior divisions, and the PT). These anatomical masks were multiplied with the functional activation pattern from an auditory task taken from Kamourieh and colleagues (2015). A temporal concatenation group ICA (Beckmann *et al.*, 2005) was run on the resting state data from a separate group of age-matched controls (17 females, mean range 56 (37–79) years, all right-handed). This ICA was spatially restricted to consider only voxels within the stROI. The ICA identified subregions within the left PT/STG that had a spatially and temporally distinct pattern of activity (Leech *et al.*, 2012). The ICA extracted 10 components based on previous work (Braga *et al.*, 2013; Leech *et al.*, 2012). However, to confirm my results were not determined by this choice of dimensionality, the analysis was also run with 12 and 15 components, with qualitatively similar results.

To assess the whole-brain functional connectivity of each sub-region of the stROI, the 10 spatial maps produced from the ICA were simultaneously regressed against the fMRI data from each seed using a general linear model (GLM) and ordinary least squares (OLS) regression. This produced subject-specific time courses for each spatial map and controlled for variance explained by other spatial maps (Beckmann *et al.*, 2005b). This resulted in 10 time courses, one for each subregion. These time courses were then included in a second regression of each participant's whole-brain fMRI data to produce a set of whole-brain

statistical maps. The output was a whole-brain voxelwise measure of functional connectivity with each of the seed subregions (Leech *et al.*, 2012). The resulting spatial maps were combined, and a higher-level GLM (Beckmann *et al.*, 2003) used to identify any significant differences between the control and patient groups using Randomise (FSL 5.0.6). Grey matter and behavioural results were once again entered as covariates in the design matrix.

Many patients also underwent a 4.5-minute breath-hold paradigm (to assess cerebral vascular reactivity), a 10-minute Diffusion Tensor Imaging (DTI) scan with 64 directions, and a 6-minute resting-state fMRI paradigm. The results of these have not been analysed as part of this thesis, and will form part of future postdoctoral research (see Chapter 6).

4.3 Results

4.3.1 Pure-tone hearing thresholds

Pure-tone audiometry was performed on 19 controls and 30 patients (Figure 4.1; Table 4.1). A 2 (Group: controls and patients) X 5 (Frequency: 250, 500, 1,000, 2,000, 4,000 Hz) x 2 (Ear: left and right) ANOVA was performed on the results. There was a main effect of Group ($F_{(1,45)}$ = 6.9, P <0.05), Frequency ($F_{(4,42)}$ = 31.7, P <0.001) and Ear ($F_{(1,45)}$ = 4.3, P <0.05), but no Group X Ear interaction ($F_{(1,45)}$ = 0.26, P >0.5), no Ear X Frequency interaction ($F_{(4,42)}$ = 1.29, P >0.2), no Group X Frequency interaction ($F_{(4,42)}$ = 2.26, P = 0.08) and no Group X Ear X Frequency interaction ($F_{(4,42)}$ = 1.01, P >0.4). The main effect of Frequency is explained by age-related high-tone hearing loss. The controls had slightly poorer hearing in the left ear,

which may explain the main effect of Ear. This was most evident at 4,000Hz (mean asymmetry in the controls = 6.9dB, and in the patients = 2.8dB).

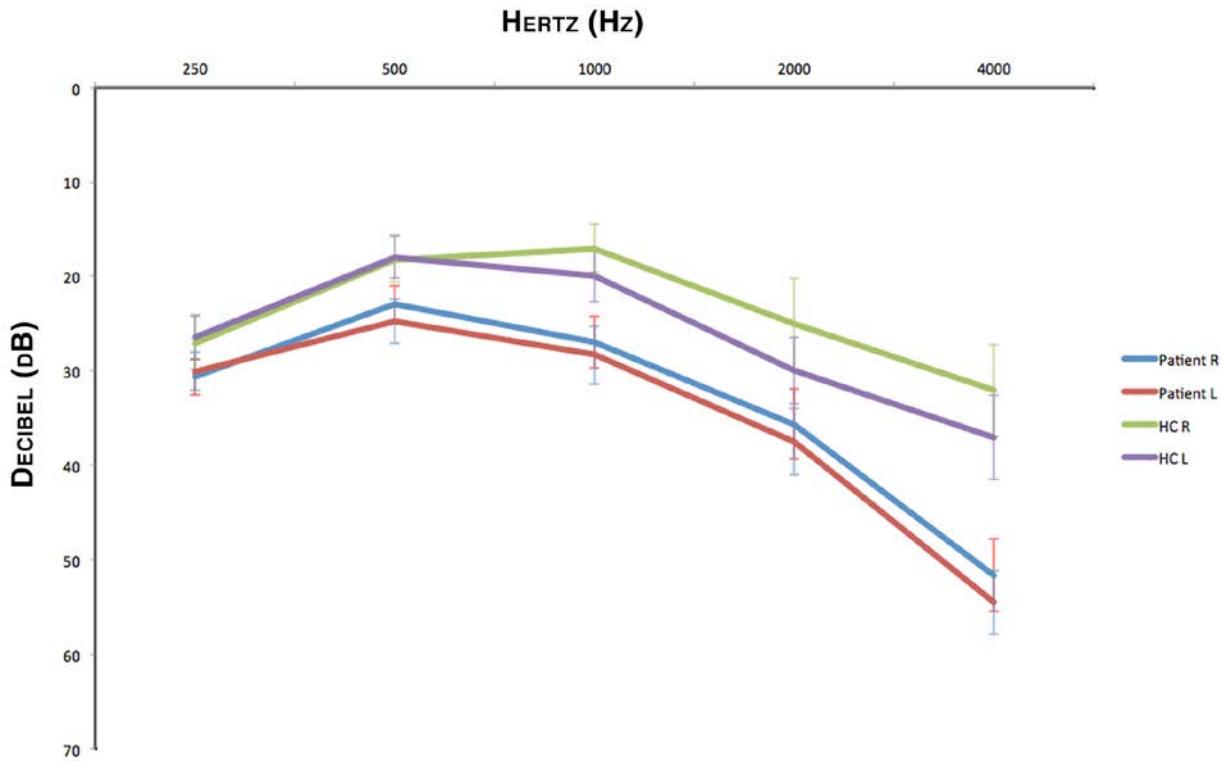


Figure 4.1: Average audiometric threshold in decibels (for left and right ear) as a function of frequency for the controls and patients

Error bars represent the standard error of the mean. Key: dB = decibels; HC = healthy controls; R = right ear; L = left ear.

Patients had poorer hearing than controls, resulting in the main effect of Group. Averaged across both ears, the mean difference amounted to 3.6dB at 250Hz, increasing to 18.1dB at 4,000Hz. Importantly, in both patients and controls, there was no correlation between in-

scanner task performance and either the mean hearing threshold across all frequencies and the threshold at 4,000Hz (P >0.1).

	Average dB		**Right ear dB**				**Left ear dB**			
Hz	PT mean (SD)	HC mean (SD)	PT mean (SD)	HC mean (SD)	Mean diff	*P*	PT mean (SD)	HC mean (SD)	Mean diff	*P*
250	30.4 (9.1)	26.8 (10)	30.7 (10)	27.1 (11.5)	3.6	>0.2	30.1 (10.7)	26.5 (9.5)	3.6	>0.2
500	23.9 (10.9)	17.9 (8.7)	23 (10)	18.2 (10)	4.8	>0.1	24.8 (12.7)	17.6 (8.9)	7.1	<0.05
1,000	27.7 (15.3)	18.1 (10.2)	27 (14.7)	17.1 (10.5)	9.9	= 0.02	28.3 (16.9)	19.1 (11)	9.2	= 0.05
2,000	36.3 (18.9)	27.5 (16)	35.7 (20)	25 (20)	10.7	>0.05	37.5 (18.7)	20 (14.6)	7.5	>0.1
4,000	53 (18.6)	35 (17.6)	51.7 (20)	32.1 (20.1)	19.7	<0.01	54.5 (18)	37.9 (18.3)	16.6	<0.01

Table 4.1: Peripheral audiometry results in the patient and control groups

Key: Hz = Hertz; dB = decibels; Average = mean across ears; PT = patient; HC = control; SD = standard deviation; diff = difference; P = significance of difference between controls and patients, independent samples t-test, uncorrected for multiple comparisons.

4.3.2 Test performances

The patients were recruited based on their presentation to a cognitive neurology clinic with a symptom of poor memory for recent verbal information. It was not based on a diagnosis of possible or probable AD, although approximately two-thirds of the patients fell into this diagnostic category. The rationale was that poor attentive listening is not confined to cortical neurodegenerative disease, but may accompany age-related cognitive decline, depression, etc. In terms of function within distributed brain systems, the impaired function within higher-order systems controlling attentive listening may be very similar despite very different underlying pathology.

The range of scores within the patient group on the ACE-R varied from 50 (clearly abnormal) to 98 (considered well within the normal range). It has been proposed that the ACE-R and the CANTAB PAL (six-stage errors adjusted) are sensitive behavioural tests for diagnosing the presence of dementia, provided the history of the condition is compatible. The sensitivity and specificity of the ACE-R depend on the placement of the cut-off score (Larner, 2007). A score of <88 is highly sensitive when determining the presence of dementia, but with relatively low specificity. Based on this criterion, those patients with scores of >87 (11 of the 31), were less likely to have cortical neurodegenerative disease. However, their scores on both the ACE-R and the PAL (a test of visual memory and new learning) were significantly worse than the controls after Bonferroni correction for multiple comparisons (Table 4.2). Therefore, as a sub-group they were not ‘normal’, with the possibility that at least some had early neurodegenerative disease. However, the mean age of this sub-group was 75 years (59–84), almost a decade older than the mean age of the controls (66 years, range 51–82), a

difference that was significant (*P* <0.01). Therefore, age-related decline may have made some contribution to the difference in performance.

	ACE-R	In-scanner performance	TROG (total errors)	GDS	DS (f)	PAL
ACE-R >87 vs HC	***P* =0.005**	*P* =0.02	NS	*P* <0.04	NS	***P* = 0.001**
ACE-R <88 vs HC	***P* <0.001**	***P* <0.001**	***P* =0.002**	***P* =0.001**	NS	***P* <0.001**
ACE-R >87 vs <88	***P* <0.001**	*P* =0.01	*P* <0.05	NS	NS	NS

Table 4.2: Behavioural scores

Independent sample t-tests between two patient sub-groups (based on ACE-R score >87 or <88) and controls (HC) on the scores on out-of-scanner behavioural tests and in-scanner performance. P <0.05, uncorrected in plain type; P =0.005 or less, corrected for multiple comparisons in bold type; P >0.1, NS. ACE-R = Addenbrooke's Cognitive Examination – Revised; TROG = Test for Reception of Grammar; GDS = Geriatric Depression Scale; DS (f) = digit span forward counting; PAL = Paired Associates Learning (data only available on 19/22 controls). Additional tests not included in the table (reaction time and spatial working memory) from the CANTAB battery were significantly different between groups, but only without correction for multiple comparisons.

The 31 patients had a higher mean score on the GDS, seven with scores >4. On the TROG, the 31 patients had significantly more blocks (H to T) with errors (controls 1 ±1, patients 2 ±2, P <0.01), and their total number of single errors across blocks was also greater (controls 1 ±1, patients 3 ±4, P <0.01).

It was the sub-group with ACE-R <88 who were most impaired on the TROG relative to the controls (Table 4.2). This is in keeping with the observation that language impairment can be present early in the course of cortical neurodegenerative diseases, such as AD (Croot *et al.*, 1999). However, the mean differences in performance were relatively small for this language task. Three patients, all with ACE-R <88, had errors in more than four blocks, although only one patient returned a score that could be classified as an outlier based on total errors (Figure 4.2).

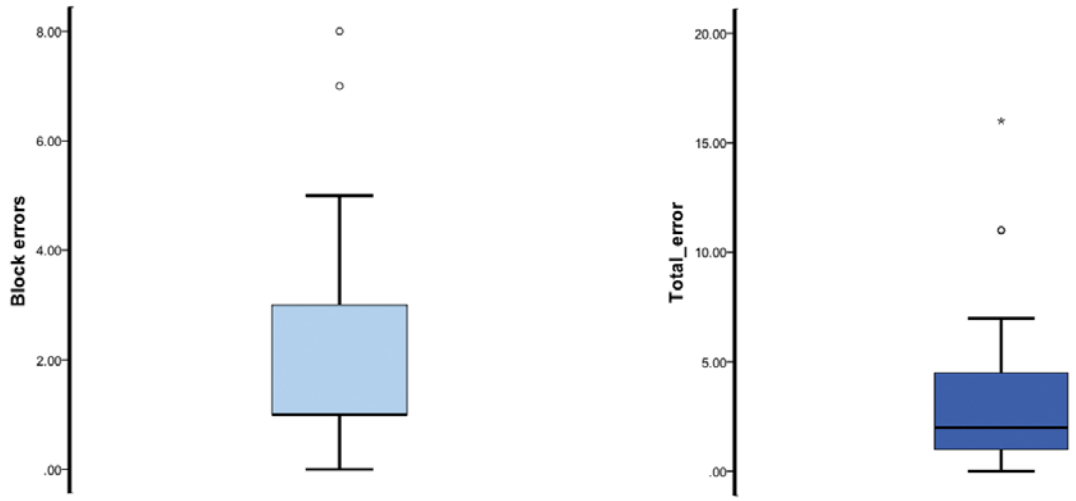


Figure 4.2: Boxplots of block and total errors on TROG in the patient group

A hierarchical cluster analysis on all controls and patients, based on their scores on the ACE-R, PAL, GDS, DS, block errors on TROG, and in-scanner performance (see 4.3.3), did not clearly separate the controls from the patients (Figure 4.3). One group contained all the controls, but also eight patients with ACE-R >87 but only one patient with ACE_R <88. The second group contained all the patients with ACE-R <88 except for one, and three patients

with ACE-R >87. The almost complete separation of the controls from the patients with ACE-R <88, based on these behavioural scores alone, motivated a sub-group analysis on these 20 patients.

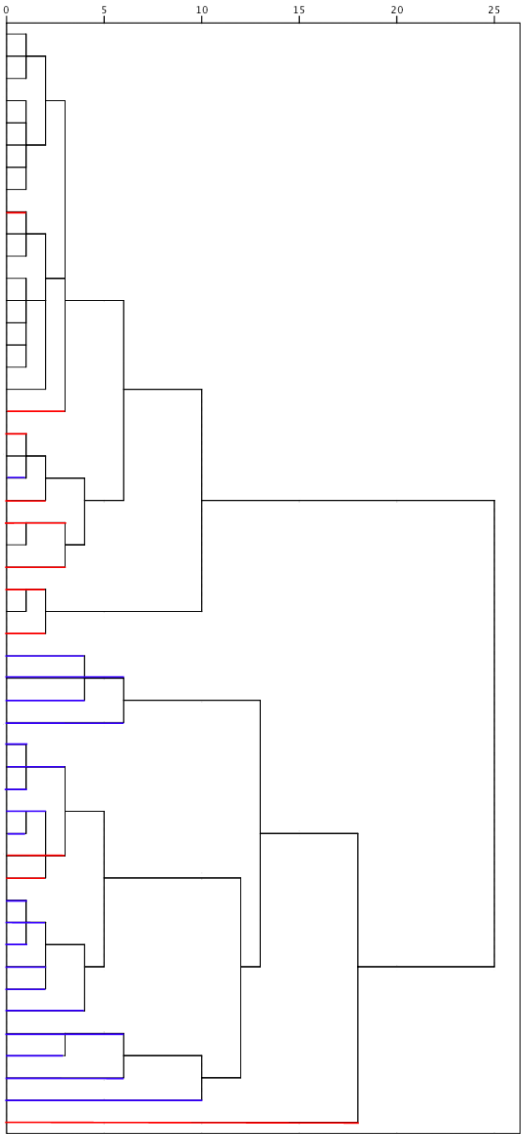


Figure 4.3: Dendogram from two hierarchical cluster analyses based on participants' out-of-scanner behavioural scores (ACE-R, PAL GDS, DS, TROG block errors) and in-scanner performance

Clusters are linked at increasing levels of dissimilarity with the numbers referring to scaled Euclidian distance. The participants are colour-coded: controls (black); patients with ACE-R >87 (red); and patients with ACE-R <88 (blue).

In-scanner performance

Averaging across all listening conditions, the 22 controls were significantly better than chance at answering questions on statements spoken by the attended (female) speaker (P <0.0001). However, a one-way ANOVA showed a significant difference in accuracy between conditions ($F_{(4,18)}$ = 5.7, P <0.01) (Figure 4.4). Paired sample t-tests demonstrated that performance on two partially masked listening conditions was no different from the unmasked listening condition: F_{ALONE} = F_{BABBLE} = $M_{LEFT}F_{RIGHT}$ (P >0.3 for all pair-wise comparisons). Contrasting the two partially masked listening conditions with spatial cues was also significant: $M_{LEFT}F_{RIGHT}$ > $F_{LEFT}M_{RIGHT}$ (P = 0.02), and also for F_{ALONE}, F_{BABBLE} and $M_{LEFT}F_{RIGHT}$ > FM_{DIOTIC} (P <0.05 for all pair-wise comparisons). The better performance with $M_{LEFT}F_{RIGHT}$ may be due to the attended speaker being directed to the language-dominant left cerebral hemisphere, but may also be, in part, a result of slightly better group-level hearing in the right ear.

Averaging across all listening conditions, the patients were significantly better than chance at answering questions on statements spoken by the attended female speaker (P <0.001). However, a one-way ANOVA showed a significant difference in accuracy across conditions ($F_{(4,27)}$ = 3.2, P =0.03) (Figure 4.4). Paired sample t-tests demonstrated that F_{ALONE} = $M_{LEFT}F_{RIGHT}$ (P = 0.2) and F_{ALONE} > F_{BABBLE} = FM_{DIOTIC} = $F_{LEFT}M_{RIGHT}$ (P <0.01 for all the pair-wise comparisons of the unmasked with the partially masked listening conditions; P >0.6 for all pair-wise comparisons between F_{BABBLE}, FM_{DIOTIC} and $F_{LEFT}M_{RIGHT}$).

Comparing the controls and patients, a 2 (Group) X 5 (Listening Condition) ANOVA for response accuracy to the statements spoken by the attended speaker showed a main effect of Group ($F_{(1,51)}$ = 45.7, P <0.001) and a main effect of Condition ($F_{(4,48)}$ = 6.6, *P* <0.001), but no Group X Condition interaction ($F_{(4,48}$ = 2.03, *P* = 0.11). In summary, in comparison with the control group, the patients had difficulty attending to the target voice in any listening condition and holding it in working memory in preparation for the subsequent response trial.

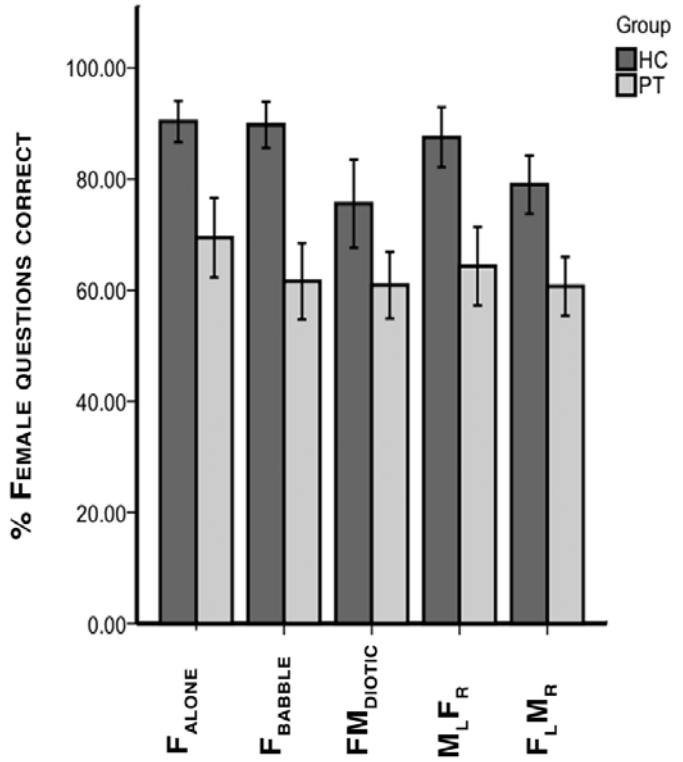


Figure 4.4: In-scanner behavioural results

In-scanner behavioural results, showing percentage of questions answered correctly for each auditory condition. Error bars are the 95% confidence intervals. Conditions labelled as in the text, but with the following abbreviations: F = female; M = male; HC = healthy controls; PT = patients; L = left; R = right.

4.3.4 Behavioural predictors of in-scanner performance

In the controls, age and performance on the ACE-R, PAL, DS, TROG and GDS were not significant predictors of success at answering questions directed at what the female speaker had said (P >0.5). In the patients, a higher score on the ACE-R predicted better in-scanner performance ($F_{(1, 30)}$ = 10, P <0.01), whereas age, PAL, DS and GDS were not predictors (P >0.4). The patients' in-scanner performance may have been influenced to a degree by impaired speech comprehension, as measured by the TROG (correlating TROG with in-scanner performance, for number of blocks with one or more errors, r = -0.4 and P = 0.04, although on total number of errors, r = -0.3; P = 0.1).

4.3.5 Univariate whole-brain analysis

Listening conditions

In controls, the first contrast of F_{ALONE} vs Rest demonstrated bilateral auditory cortical activation, with greater activity also in dorsal anterior cingulate (dACC) and anterior insular/ frontal opercular (aI/FOp) cortices, and in bilateral dorsolateral fronto-parietal cortices, centred on the inferior frontal (IFS) and intraparietal sulci (IPS), with the exception that right IPS activity was only evident at a lower threshold (Figure 4.5A).

The second contrast was all masked listening conditions (F_{BABBLE} + FM_{DIOTIC} + $M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$) with F_{ALONE}. This contrast specifically investigates speech-stream segregation as the task is constant across all conditions. There was significantly increased activity confined to the right anterior insula, bilateral auditory cortices, the precuneus and the left IPS (Figure

4.5B). A contrast of female speech partially masked by male speech but without spatial cues (FM_{DIOTIC} vs F_{ALONE}) demonstrated significant activity confined to the left PT (Figure 4.5C). A fourth contrast explored the influence of spatial cues by comparing ($M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$) with (F_{BABBLE} + FM_{DIOTIC}). A significant difference in activity was confined to the precuneus (Figure 4.5D).

The same four contrasts in the data from the 31 patients demonstrated largely similar distributions of activity, and directly comparing the patients with controls on these four contrasts did not demonstrate any group differences. Therefore, although the patient group's responses were much impaired behaviourally, overall the same networks were active to a similar degree in the two groups when performing speech-stream segregation. Including only the 20 patients identified to have ACE-R scores <88 again showed no significant difference in the effect size and distribution of activity when the same contrasts were analysed.

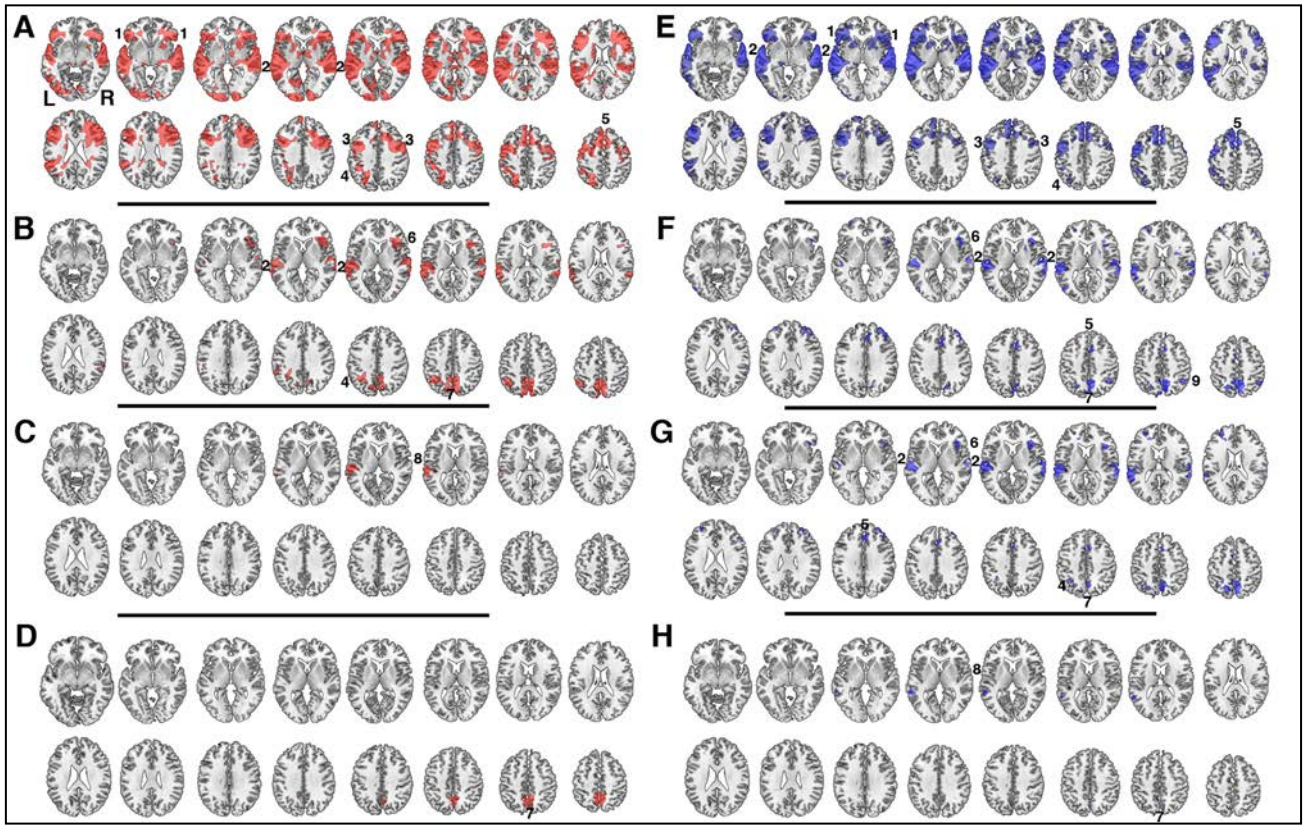


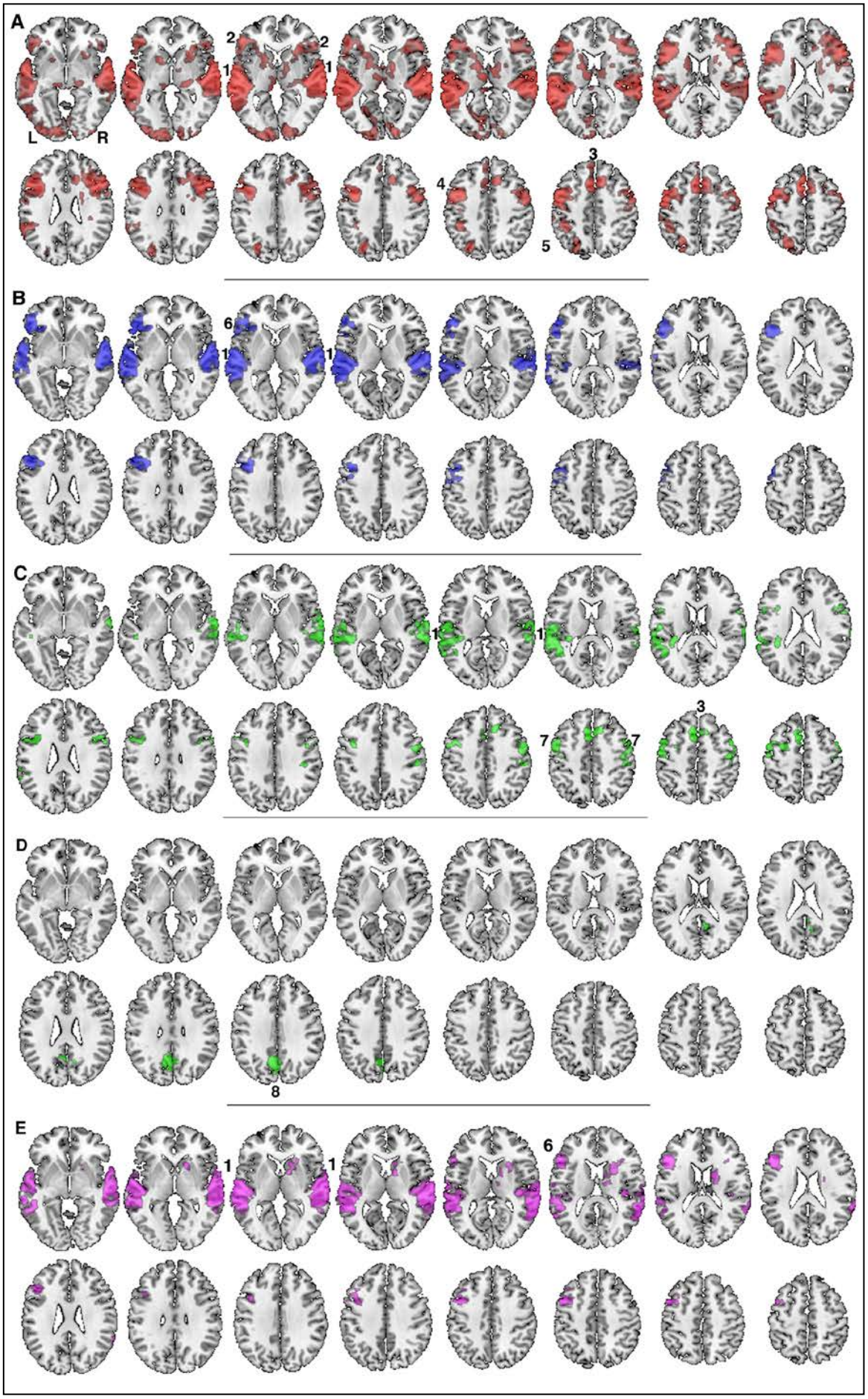
Figure 4.5: Univariate whole-brain analysis

Axial slices are shown in neurological convention, right hemisphere on the right of each slice, beginning with the most ventral slice, commencing 5mm above the anterior-posterior commissural plane and progressing in 4mm increments in the Z plane. A–D are univariate contrasts in controls. E–H are the same contrasts in the patient group. Significant regions of activity are projected as red overlay in controls and blue overlay in patients, with a voxel-level threshold Z >2.3, cluster-level threshold P < 0.05.

A *and* ***E****. A main effect of* F_{ALONE} *contrasted with Rest: 1. Bilateral anterior insular/frontal opercular cortices (aI/FOp); 2. Bilateral auditory cortices; 3. Bilateral inferior frontal sulcus (IFS); 4. Left intraparietal sulcus (IPS); 5. Dorsal anterior cingulate cortex (dACC).* ***B*** *and* ***F****. The contrast of all masked speech conditions (*F_{BABBLE} + FM_{DIOTIC} + $M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$*) with* F_{ALONE}*: 2. Bilateral auditory cortices; 4. Left IPS; 5. dACC; 6. Right aI; 7. The precuneus; 9. Right IPS.* ***C*** *and* ***G****. Contrast of* FM_{DIOTIC} *with* F_{ALONE}*: 2. Bilateral auditory cortices; 4. Left IPS; 5. dACC; 6. Right aI; 7. The precuneus. 8; Left planum temporale (PT).* ***D*** *and* ***H****. Contrast of (*$M_{LEFT}F_{RIGHT}$ + $F_{LEFT}M_{RIGHT}$*) with (*F_{BABBLE} + FM_{DIOTIC}*): 7. The precuneus, 8; Left planum temporale (PT).*

Correct vs incorrect trials

The absence of a difference between the groups when comparing contrasts that included all listening trials led to the further analysis that investigated the contrasts of the listening trials that were followed by a correct response to the ensuing written question with those followed by an incorrect response. An incorrect response reliably indicated that what the female speaker had said had not, at one or more processing levels, been attended to, understood and encoded in working memory. However, a proportion of correct responses will have been 'lucky guesses' rather than successful processing of the target verbal message. Therefore, a contrast made between listening trials followed by the correct and incorrect responses to the subsequent questions will more reliably reveal activity associated with successful attentive listening. Greater activity in bilateral auditory cortices, bilateral dACC and FOp/aI and left-lateralised IFS/IPS for the 'correct' listening trials (Figure 4.6A) were seen in the control group. There was significant activity in the precuneus and the ventral ACC in the reverse contrast. Looking at the same contrast in the patient group, significant activity for the 'correct' listening trials was confined to bilateral auditory cortices and left aI/FOp (Figure 4.6B), with no greater activity for the 'incorrect' listening trials.


A
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6

Figure 4.6: Univariate analysis of correct vs wrong responses

Axial slices displayed as in Figure 4.5. Significant regions of activity are projected as red overlay in controls, blue overlay in patients and green overlay for the between-group contrasts, with a voxel-level threshold Z >2.3, cluster-level threshold P <0.05. ***A.*** *Mean activity for the contrast correct > incorrect in the control group. 1. Bilateral auditory cortices; 2. Bilateral frontal opercular/anterior insular cortices (aI/FOp); 3. Dorsal anterior cingulate cortex (dACC); 4. Left inferior frontal sulcus (IFS); 5. Left intraparietal sulcus (IPS).* ***B.*** *Mean activity for the contrast of correct > incorrect in the patient group. 1. Bilateral auditory cortices; 6. Left (aI/FOp).* ***C.*** *The between-group comparison of the same contrast, controls > patient. 1. Bilateral auditory cortices; 3. dACC; 7. Bilateral dorsolateral prefrontal cortex.* ***D.*** *The between-group comparison of the same contrast, patients > controls. 8. Anterior precuneus.* ***E.*** *Mean activity for the behavioural covariate for the contrast of female correct > female incorrect in the patient group. 1. Bilateral auditory cortices; 6. Left aI/FOp.*

Directly contrasting the 'correct' and 'incorrect' listening trials of controls with patients, with separate analyses for all 31 and the 20 subjects with ACE-R <88 (see Appendix 7), demonstrated greater activity in bilateral posterior auditory cortices, bilateral dorsolateral prefrontal cortex (left lateralised in those with ACE-R <88), and dACC (Figure 4.6C). The anterior precuneus was one region that was more active in the 31 patients compared with controls in the 'correct' contrasted with 'incorrect' listening trials (Figure 4.6D).

For the patient group, activity for the 'correct' listening trials was entered for each individual as a mean-centred covariate in the contrast of 'correct' with 'incorrect' trials. This demonstrated a positive relationship between the in-scanner behavioural scores and activity in the bilateral posterior auditory cortices, the left aI/FOp and bilateral dorsolateral prefrontal cortex, with a distribution very similar to that illustrated in Figure 4.6B (see Figure 4.6E). Therefore, increasing activity for better performance in the distributed regions outlined above confirms

their role in successful processing of the attended speech. Age was also enetered as a mean-centered covariate in the above contrast of ‘correct’ with ‘incorrect’ trials in controls vs patients and patients alone, which did not identify any significant results.

Dual regression

Using a previously published method (Leech *et al.*, 2012), within the left STG, 10 partially overlapping subregions were identified that had distinct time courses of fluctuations in the BOLD signal. Within this large region of interest (Figure 4.7A), the distributed activity associated with nine of the subregions demonstrated no difference between controls and patients, and in many instances consisted of movement-related artefact and other sources of noise (as judged by the distribution of activity around the edge of the brain within the lateral ventricles). One subregion, centred on the left PT, was functionally connected to the left lateral fronto-parietal cortex and midline frontal cortex (including the dACC), and bilateral aI/FOp (Figures 4.7B and 4.7C). Based on dual regression analysis, this system was more strongly functionally connected in the controls than the patients. Qualitatively similar results were obtained with this region of interest and 15 components.

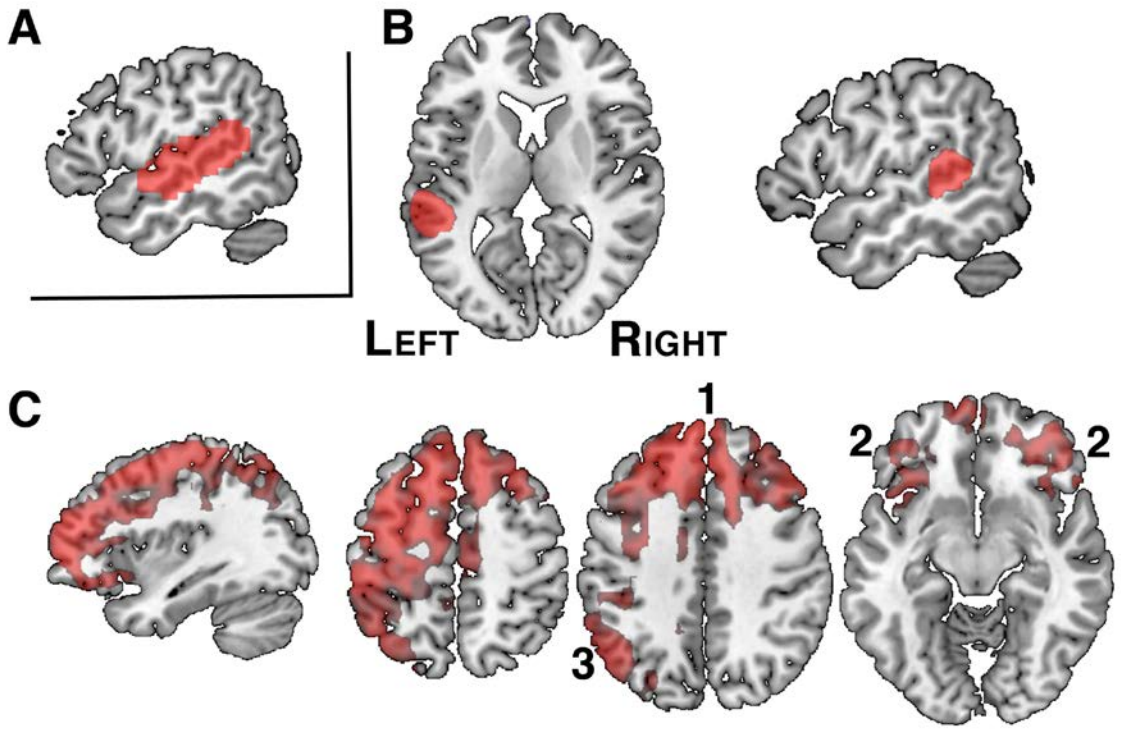

Figure 4.7: Dual regression from left planum/STG mask

A. *Left superior temporal gyrus mask.* ***B.*** *The component from the multivariate component analysis located in the PT.* ***C.*** *Resulting map of functional connectivity of the component in B., which demonstrated functional connectivity with a left fronto-parietal network, bilateral anterior midline frontal cortex and bilateral anterior insular/ frontal opercular cortex which is more strongly functionally connected in controls then patient groups (red). The results of the connectivity analysis are thresholded at P <0.05, corrected for multiple comparisons. 1. Anterior cingulate cortex (ACC). 2. Bilateral anterior insular/frontal opercular cortices (aI/FOp). 3. Left parietal cortex*

4.4 Discussion

This chapter compared patients presenting with a primary complaint of progressive impairment of recent memory with control participants. A common additional symptom in such patients is increasing difficulty in attending to one speaker at social functions because of an impaired ability to 'concentrate' on what one speaker is saying; that is, difficulty segregating attended from unattended speech. Although impaired anterograde verbal memory is normally considered in terms of encoding and recall, an initial failure to register the verbal message will also contribute to a complaint of poor memory. The inability to attend closely to a speaker, particularly in difficult listening conditions, may result from disease of the auditory system, which may affect any area, from the external auditory meatus to primary and association auditory cortices in the superior temporal gyri. However, it can also result from impairment of higher-order brain systems, controlling attention, working memory and executive processes (see Chapter 1, 1.3.2). This impairment may be functional, as occurs with anxiety, depression and normal ageing, or pathological, as occurs with neurodegenerative disease.

The ACE-R scores in the patient group were spread over a wide range, and in those with scores of >87, discriminating between neurological (neurodegenerative pathology) and psychiatric (anxiety depression) diagnoses can be uncertain. Thus, in one large clinical study, a cut-off score of 88/100 proved to be highly sensitive to the presence of dementia, with a false negative rate of 0, but with low specificity (a false positive rate of ~0.6) (Larner *et al.*, 2007). With additional evidence, the diagnosis of Alzheimer's disease, with or without coexisting microvascular disease, and its differentiation from either a functional disorder or other relatively common types of dementia such as dementia with Lewy bodies and fronto-temporal dementia, may be determined with a reasonable degree of certainty (Dubois *et al.*,

2014). If the history and neurological examination are compatible, further evidence may accrue from a detailed neuropsychological assessment, disproportionate medial temporal lobe atrophy on diagnostic MRI, beta-amyloid deposition imaged with positron emission tomography (Adlard *et al.*, 2014), and cerebrospinal fluid (CSF) estimates of phosphorylated tau, total-tau and $A\beta_{1-42}$ amyloid levels (Ewers *et al.*, 2015), However, the limited availability of expensive amyloid PET imaging within the UK's National Health Service, and in the light of individual patient's wishes (particularly as regards lumbar puncture), this complete diagnostic work-up was only undertaken in a minority of patients (see Appendix 2). It is often considered appropriate, in the absence of any disease-modifying treatment, to use a further reliable diagnostic test, namely time, with periodic clinical assessments over the course of which the diagnosis will become increasingly apparent (see Appendix 2). However, at initial presentation, all patients had screening blood tests to exclude a metabolic aetiology, and diagnostic anatomical imaging, MRI or X-ray CT, to exclude focal brain pathology and to determine the presence of disproportionate medial temporal lobe atrophy.

The cluster analysis, based on behavioural measures alone, and which included in-scanner performance during fMRI scanning, successfully separated the controls from all patients with ACE-R scores of <87. Patients with ACE-R scores of >86 were split between the two clusters. As a result, the imaging analyses were performed on both the patient group as a whole, with further sub-analyses on the sub-group of 20 of the 31 patients with ACE-R scores of <88.

The first univariate analyses identified that even when listening to the female speaking alone, and within the context of representing what was said in working memory in preparation to respond to a subsequent question, higher-order regions in both controls and patients became

active, namely the fronto-parietal and cingulo-opercular systems. These systems are reliably observed in functional imaging studies on normal participants in response to cognitive tasks that depend on attention and working memory (Dosenbach *et al.*, 2007; Menon and Udin 2010; Power *et al.*, 2011; Power and Petersen, 2013; Seeley *et al.*, 2007), with a growing literature attempting to determine the precise processing roles of components of these systems, although not without controversy (Aron *et al.*, 2004; Hampshire *et al.*, 2012). Notwithstanding details of the functional properties of individual components of these two widely distributed, domain-general systems, when the analyses were performed across listening trials irrespective of whether they were followed by a correct or incorrect response, they were equally active in both groups, even in the analyses that only included 20 patients with an ACE-R <88, and therefore most likely to have cortical neurodegenerative disease. Contrasts between the listening conditions in which the female speaker was unmasked with her speech partially masked, and therefore when the task was constant between the contrasted conditions, demonstrated that a subset of regions, namely the right aI/FOp, the precuneus, bilateral posterior STG (including the plana temporale, PT) and part of the left intraparietal sulcus were more active. Further, the precuneus became even more active when there were spatial cues to assist in segregating the female speaker from the masking male. The role of the precuneus in auditory stream segregation in the presence of spatial cues has been observed in earlier studies (Hugdahl *et al.*, 2000; Mayer *et al.*, 2006, 2007; Zündorf *et al.*, 2013), complementing other studies demonstrating the role of this region in visuospatial tasks (Shomstein and Yantis, 2004; Yantis *et al.*, 2002). Importantly, in all these contrasts, there remained no differences between the controls and patients (all patients, and those with ACE-R <88).

The performance of the patients will have been affected by a number of factors. First, they had reduced auditory acuity relative to the controls, based on the results of pure-tone audiometry, particularly in the higher frequencies. Although most of the energy (loudness) of the speech spectrum falls between 250 and 500Hz, these lower frequencies correspond to vowels. The higher frequency bands, 2,000–4,000Hz and beyond, correspond to consonants, and the intelligibility of speech is predominantly conveyed by consonants. The difference in the pure-tone audiometry may have reflected, at least in part, a group difference in peripheral (cochlear or auditory nerve) auditory function between the two groups. However, a subcortical central auditory processing problem is present in AD (Gates *et al.*, 1996, 2008, 2011; Golob *et al.*, 2007, 2009), associated with increased thresholds on pure-tone audiometry (Green *et al.*, 1992; O'Mahony *et al.*, 1994), and it has been established that the inferior colliculi and medial geniculate nuclei, as well as the auditory cortices, are affected by the pathology of AD (Sinha *et al.*, 1993). Therefore, the proportion of participants in the patient group with Alzheimer's pathology will have had to overcome bottom-up central auditory processing impairment. Further, patients with AD, even early in the course of the disease, are likely to have a mild degree of impaired language comprehension (Croot *et al.*, 1999), and as a group there was a subtle impairment on the patients' performance on the TROG.

However, in order to overcome auditory and language impairments, an increase in activity in the dACC should have been seen. The evidence for this has been observed in normal participants, who demonstrated increased dACC activity when they were required to listen to sentences and retain the verbal message within working memory when the stimuli were presented as degraded (noise-vocoded) speech (Brownsett *et al.*, 2014). Therefore, the patient group's relative inability to increase top-down control on 'correct' trials to the same level as that seen in the control group, irrespective of whether there was additional peripheral

or central bottom-up auditory processing impairment, suggests that many 'correct' trials were guesses, with reduced activity in midline and lateral prefrontal cortices indicating an inability to exert an appropriate level of top-down control when listening to the stimuli.

However, potential complications when comparing correct vs. incorrect responses between the two groups must be considered; particularly with regards to the influence of 'guessing' on activity on a subset of regions when a two forced choice design is used (Heron and Henson, 2004). A three choice design, where particiapants have the option of pressing a 'not sure' button might help resolve this problem, as the distribution of 'confident' responses, pure guesses and uncertain responses will have been different in the patients and control groups. Modeling the three different types of responses would afford greater confidence when interpreting the results. However, this design might be difficult to perform in a patient population. Three rather than two responses runs the risk of confusing the patients about what exactly is expected of them, and there would be the danger that they might default to always pressing the 'not sure' response button. Therefore, to build in this complexity to the study design would require careful preliminary behavioural testing, and might result in only the most mildly affected patients being considered suitable for study.

This reduced top-down activity was also associated with reduced bilateral posterior temporal lobe activity, including the PT. Auditory stream segregation has been associated with posterior temporal lobe function, in particular the PT (Griffiths and Warren, 2002; Smith *et al.*, 2010; Wong *et al.*, 2008; Zündorf *et al.*, 2013), with some evidence that this function is predominantly left-lateralised (Alain *et al.*, 2005; Deike *et al.*, 2004, 2010; Zündorf *et al.*, 2013). This evidence motivated the further multivariate analysis to investigate the functional

connectivity during the listening trials of subregions within large left stROI. A subsequent dual regression comparing the control and patient groups identified a posterior temporal region functionally connected to the cingulo-opercular system and left fronto-parietal cortex, and within this widely distributed system the patients generated less activity than the controls. The left fronto-parietal cortices, in addition to regions associated with linguistic processing (Geranmayeh *et al.*, 2012, 2014), incorporate regions implicated in both the controlled access to meaning (Binder *et al.*, 2009; Noonan *et al.*, 2013; Whitney *et al.*, 2011, 2012), and verbal working memory (Cabeza *et al.*, 2002; Honey *et al.*, 2002).

The analyses presented in this chapter have demonstrated altered function throughout widely distributed networks in patients with a complaint of poor memory when they are required to attend to a single speaker. Even attention to an unmasked single speech stream (F_{ALONE}), when patients were required to understand and encode within working memory what was said, depended on both bottom-up processing within the auditory cortices and top-down control from fronto-parietal and cingulo-opercular domain-general systems. When perception, and thus comprehension, was made difficult by partial masking with an unattended speech stream (the male speech), this had a much greater impact on performance in the patients compared with the controls, and this reduced performance was reflected in widespread dysfunction both in fronto-parietal (both midline and lateral) regions and the posterior temporal cortices.

This ‘networkopathy’ is almost certainly not specific to particular pathologies. Thus, for example, impaired cingulo-opercular function has been observed as a consequence of the diffuse axonal injury resulting from traumatic brain injury (Bonnelle *et al.*, 2012; Jilka *et al.*,

2014) and after stroke (Brownsett *et al.*, 2014), and this was evident in this study in patients with memory complaints. The patient group included in this thesis was heterogeneous, and included individuals, most likely both with and without cortical neurodegenerative disease (see Appendix 2). This heterogeneity was most prominently reflected in activity within the posterior temporal cortex, which correlated with in-scanner performance, which in turn correlated with scores on the ACE-R. The results are compatible with a central role for this auditory region in speech-stream segregation, as has been proposed previously, under the influence of top-down modulatory control. Although this study specifically investigated attentive listening and speech-stream segregation, the results may also be extrapolated to any task that depends on attention, working memory and cognitive control. The benefit of central cholinesterase inhibitors to the minority of patients who respond may act through improved function of components of these systems (Chapter 5). Alleviating the symptoms depends at present on a limited range of drugs, mainly those designed to increase activity in one neurotransmitter (cholinergic) system, with rather limited success (Kaduszkiewicz *et al.*, 2005). Targeting other modulatory neurotransmitter systems, dopaminergic or noradrenergic, may produce synergistic benefit by modulating the function of the fronto-parietal systems demonstrated in this study, even when they have been affected by neurodegenerative pathology.

4.5 Summary

The findings presented in this chapter support the presence of poor speech-stream segregation in patients with memory complaints and propose that poor registration of verbal information contributes to the complaint of ‘poor memory’. Both controls and patients activate

the same auditory and higher-order systems when attending to one speaker, with or without background speech. Impaired registration is explained by reduced top-down control of working memory and attention by fronto-parietal systems. Problems with speech-stream segregation have clinical implications for the patient and the carer. Not only are rehabilitation and clinical assessment sessions commonly carried out in noisy environments with multiple background speech and sounds, but this problem will also commonly result in avoidance of social functions by the patient, resulting in increasing social isolation. Along with the role of central cholinesterase inhibitors (evaluated in Chapter 5), the influence of other symptom-modifying drugs in the augmentation of speech-stream segregation, and the potential for benefit with other approaches, including transcranial and deep-brain stimulation directed at higher-order, domain-general systems can be explored in future studies as postdoctoral research.

5 The effects of a central cholinesterase inhibitor on the behavioural and functional imaging results in the patient group

As described in the introduction, it is common for patients with a complaint of 'poor memory' to find following conversations in the presence of distracting background noise, particularly unattended speech, difficult. This may be due to central causes, for example the result of serious underlying pathology such as AD, or the more benign consequence of an anxiety depressive state or age-related cognitive decline.

In Chapter 3, I demonstrated in normal participants the distributed neural systems involved in attentive listening in the absence or presence of an unattended speaker (Kamourieh *et al.*, 2015). This was later extended to a group of patients who presented with a history of impaired verbal memory (Chapter 4). The current chapter reports on the same group of patients, and describes the behavioural and functional neuroimaging consequences of attentive listening across two sessions, and on the effects of a central cholinesterase inhibitor (CChEI) (galantamine) administered to half the participants. Although this study was directed at investigating attentive listening in these patients irrespective of the underlying cerebral pathology, approximately two-thirds had possible or probable AD.

5.1 Aims and hypothesis

1. To investigate the effect of the drug on attentive listening, irrespective of the underlying cerebral pathology.

Based on the literature described in the introduction, Chapter 1, I would expect to find modulation of the top-down control networks involved in attentive listening. I would also expect to see behavioural differences between those who received treatment and those who did not. However, as mentioned in the introduction, there is a large amount of inter-variability with fMRI and also with response to CChEIs. This must be considered when interpreting the results.

5.2 Materials and methods

5.2.1 Participants

The 31 patients included in this study, and the inclusion criteria, including normal neurological examinations, are described in Chapter 4. Patients were randomly allocated to two groups, only one of which received galantamine (slow-release preparation) after their first functional neuroimaging scan. The dose was increased over two weeks to a total daily dose of 16mg, which these patients continued until the second scan between six and 11 weeks later. Prior approval for the study was obtained from the North West Thames ethics committee, and written consent was obtained from all participants.

All the patients had a normal neurological examination at the time of recruitment, without any evidence of pyramidal, extrapyramidal, cerebellar or ocular motor signs. A moderate microvascular load evident on diagnostic MRI was not an exclusion criterion. The treated and untreated groups were well matched for mean ACE-R scores (80/100 in each group), a level considered highly sensitive and reasonably specific for the presence of dementia (Larner, 2007). However, the range of scores in the two groups was wide, 50–98 in the treated group and 56–96 in the untreated group. Based on the clinical features and ACE-R score, and/or the presence of medial temporal lobe atrophy on diagnostic MRI scanning, and/or subsequent progression of cognitive decline over months, and, when available, the results of a formal neuropsychological assessment, a lumbar puncture (total tau: $A\beta_{1-42}$ amyloid ratio >1), and amyloid PET scan, seven patients were classified as mild cognitive impairment of unknown cause, seven as possible Alzheimer's disease, and 14 as probable Alzheimer's disease (Dubois *et al.*, 2014). Of the remaining three, one patient later demonstrated progressive symptoms and signs suggestive of corticobasal syndrome (Armstrong *et al.*, 2013), and a further patient was subsequently found to have multiple cavernomata, based on susceptibility-weighted MRI (demonstrating microbleeds) and gene testing (CCM1 mutation), although she also returned a score above the cut-off on the Geriatric Depression Scale. The final patient had probable work-related anxiety depression, and his ACE-R scores improved from 85/100 at the time of study to 96/100 one year later, after he had retired. Individual patient details, and the distribution of the patients between the treated and untreated groups, are summarised in Appendix 2.

In addition to the ACE-R, before each scanning session all patients underwent the following assessments: the CANTAB Alzheimer's Battery, which includes several cognitive measures (Blackwell *et al.*, 2004; Egerhazi *et al.*, 2007); the Geriatric Depression Scale (Yesavage *et al.*, 1983); digit span to investigate auditory working memory (Wechsler, 1995, 1981); and the Test for Reception of Grammar (TROG) (Bishop, 1989), to assess spoken language comprehension. Details about the patients' performance on these behavioural tests are available in Chapter 4. All except one patient underwent pure-tone audiometry (using PCWerth interacoustics audiometer AS608) at five frequency levels (0.25, 0.5, 1, 2 and 4 KHz).

5.2.2 fMRI stimuli and study design

Stimuli and scanning methods used were described in the earlier chapters in this thesis (refer to Chapters 3 and 4). The auditory conditions consisted of: a female speaker alone (F_{ALONE}), a female speaker in the presence of background babble (F_{BABBLE}) without spatial cues; a female speaker in the presence of a male speaker without spatial cues (FM_{DIOTIC}); and two conditions where the stimuli had competing female and male speakers with a simulated azimuth spatial cue added (dichotic presentation), either with the female speaker at 30^{o} to the right and the male speaker at 30^{o} to the left ($M_{LEFT}F_{RIGHT}$) of the midline, or vice versa ($F_{LEFT}M_{RIGHT}$). A sixth condition was Rest, when no stimuli were presented.

Participants were instructed to listen to the female speaker, understand the statement and then prepare to answer a written question on the ensuing trial with a 'yes' or 'no' button-press. This design investigated attention and verbal working memory, language and auditory

processing, but not episodic verbal memory encoding and retrieval. This was because the interval between stimulus and response was <10s. The functional imaging data were directed at recording activity during each listening trial, and in-scanner performance was the accuracy on each subsequent response trial.

5.2.3 Image acquisition and data analysis (univariate whole-brain analyses)

As described in the earlier chapters, interleaved silent steady state (ISSS) imaging was used (Schwarzbauer *et al.*, 2006). Volume acquisition was accomplished using five 'imaging' volumes followed by four 'quiet' volumes, when the stimuli were played. Please refer to Kamourieh and colleagues (2015) and Chapter 3 (Study 2) and Chapter 4 for full details on image acquisition and data analysis including pre-processing, registration, design modelling and second-level analysis. Individual grey matter density maps, computed from T1-weighted images using the script feat_gm_prepare, distributed with FSL and FMRIB Automated Segmentation Tool (FAST) (Zhang *et al.*, 2001), and demeaned ACE_R and/or in-scanner behavioural scores were entered as covariates of no interest.

5.3 Results

5.3.1 Analyses of psychometric scores

Analysing all eight out-of-scanner behavioural tests that the participants underwent prior to each of the two scanning visits (listed in Methods, 5.2.1, four of which were components of the CANTAB Alzheimer's Battery), and dividing the patients into those who received galantamine and those who did not, a 2 (Group, treated and non-treated) x 2 (Session, first and second) x 8 (Test) repeated measures Analysis of Variance (ANOVA) was performed. There was no significant effect of Group ($F_{(1,29)}$ = 0.29, P = 0.59) or Session ($F_{(1,29)}$=1.55, P = 0.22), and no significant two- or three-way interactions (P >0.1 or greater).

5.3.2 Pure-tone audiometry

As mentioned in Chapter 4, pure-tone audiometry was available on 30/31 patients and demonstrated a mild to moderate degree of hearing loss at the higher auditory frequencies, based on the criteria of Goodman (1965). A 2 (Group) X 2 (Ear) X 5 (Frequency) ANOVA demonstrated a main effect of Frequency ($F_{(4,25)}$ = 45.7, P <0.001) but no main effect of group ($F_{(1,28)}$ = 0.02, P >0.8) or Ear ($F_{(1,28)}$ = 2.6, P >0.1 and no significant two- or three-way interactions (P >0.1). Importantly, there was no correlation between either mean or high-tone hearing thresholds and in-scanner behavioural performance (P >0.1).

5.3.3 In-scanner behavioural analysis

Averaging across all listening conditions and all patients, the patients were significantly better than chance at answering questions on statements spoken by the female at both scanning

sessions (P <0.001). In-scanner performance success correlated with ACE-R scores at both the first session (r = *0.5,* P <0.04) and the second (r = *0.6,* P <0.001).

A 2 (Group) X 2 (Session) X 5 (Listening Condition) repeated-measures ANOVA demonstrated no main effect of Group ($F_{(1,29)}$ = 0.13, P = 0.9), a trend for a main effect of Session ($F_{(1,29)}$ = 3.94, P = 0.06), and a main effect of Listening Condition ($F_{(4,26)}$ = 2.73, P = 0.05). The only significant interactions were Session*Listening Condition ($F_{(4,26)}$ = 4.88, P = 0.005) and Group*Session*Listening Condition ($F_{(4,26)}$ = 2.98, P = 0.04). *Post hoc t*–tests demonstrated improved performance at the second scanning session on F_{BABBLE} in both groups (P = 0.04 in the untreated group and P = 0.001 in the treated group). There was no change in performance in any other Listening Condition between the two visits (P >0.1) (Figure 5.1). To confirm that there was no effect of treatment on performance during the F_{BABBLE} condition alone, a condition-specific 2 (Group) x 2 (Session) ANOVA confirmed that there was no significant Group*Session interaction ($F_{(1,29)}$ = 1.08, P = 0.3). A sub-group analysis across all listening conditions on the 11/17 patients who received galantamine and were classified as possible and probable AD did not demonstrate any improvement in attentive listening (P *>0.3*).

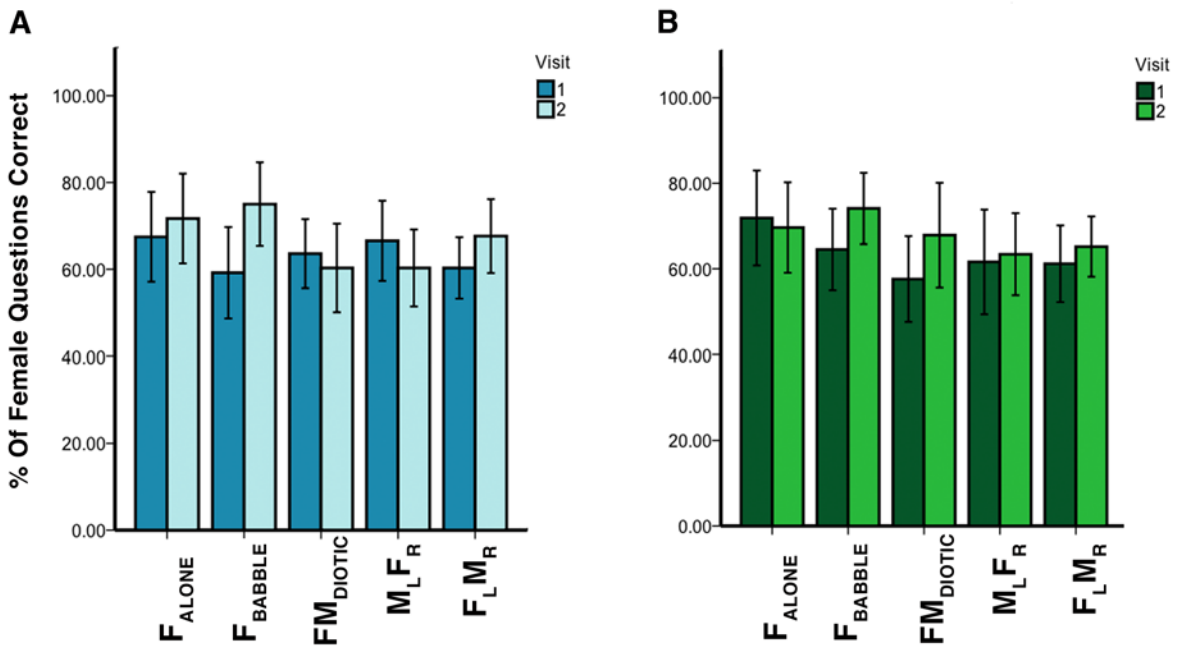

Figure 5.1: In-scanner behavioural results

In-scanner behavioural results, showing percentage of questions answered correctly for each auditory condition in visits 1 and 2. Error bars are the 95% confidence intervals. ***A*** *= treatment group results;* ***B*** *= non-treatment group results. Conditions labelled as in the text, but with the following abbreviations: F = female; M = male; HC = healthy controls; PT = patients; L = left; R = right.*

5.3.4 Functional imaging data

The behavioural results demonstrated that galantamine 8mg b.d. administered for four to nine weeks (after an initial exposure to the drug at half that dose for two weeks) had failed to produce benefit in attentive listening in this population of 31 patients, nor in the 21 with possible and probable Alzheimer's disease. In Chapter 4, it was argued that incorrect trials were demonstrations that attention to, and processing of, the female speech had failed, and the subsequent guess was unlucky. In contrast, the correct trials contained an unknown

combination of trials when there had been successful attention to, and processing of, the female speech combined with failed attempts followed by lucky guesses. A contrast of correct with incorrect trials would minimise activity associated with guessing and demonstrate activity associated with successful attentive processing of the female speech.

Figure 5.2 shows the result from the first scanning session, for all 31 participants, in which trials across all listening conditions followed by correct responses were contrasted with those followed by an incorrect response. Demeaned ACE-R scores and grey matter volumes were used as regressors to exclude their effect on the result. Success at attentive processing resulted in greater activity throughout auditory cortex (despite bottom-up auditory input being matched in the contrast). There was additional increased activity at the temporo-parietal junctions, the left frontal operculum ('classic' Broca's area), bilateral dorsolateral prefrontal cortex and the right striatum.

This analysis was followed by a 2 (Group) X 2 (Session) ANOVA of the imaging data, using the same contrast for each session, and again regressing demeaned ACE-R scores and grey matter volume. This was to determine if there was a Group*Session interaction that might indicate a treatment effect on focal brain activity. No interaction was evident, even at a lower threshold for significance.

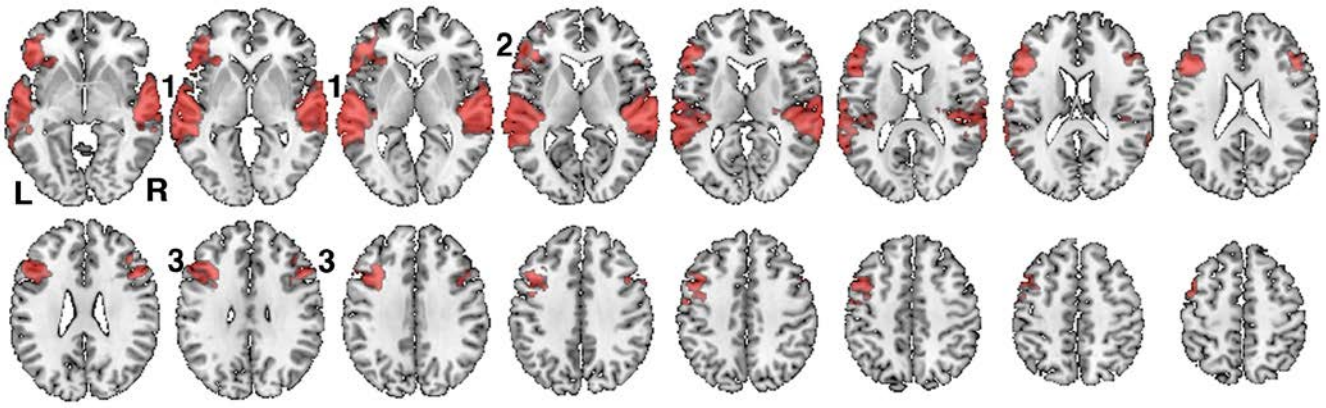

Figure 5.2*:* Univariate whole-brain analysis of listening trials followed by correct responses contrasted with those followed by incorrect responses in all patients

Axial slices, right hemisphere on the right, beginning with the most ventral slice at 5mm above the anterior-posterior commissural plane and progressing in 4mm increments in the Z plane. Significant regions of activity are projected as red overlay, with a voxel-level threshold Z > 2.3, cluster-level threshold P < 0.05. 1. Bilateral auditory cortices; 2. Left frontal operculum; 3. Bilateral dorsolateral prefrontal cortex.

The ability to perform effective speech-stream segregation, evident from in-scanner performance, did correlate with individual ACE-R scores. As patients with lower ACE-R scores were more likely to have neurodegenerative pathology, particularly AD, the behavioural and imaging data of the 20 patients with ACE-R score <87 at the time of the first scanning session (mean 73, 95% confidence interval 68–77, range 50–87) were entered into the same 2 (Group) X 2 (Session) ANOVAs. Again, there was no Group*Session interaction.

The one listening condition in which there was an improvement in performance between the first and second scanning sessions was F_{BABBLE}, although this was an overall Session effect and not related to treatment with galantamine. To investigate whether there was a treatment effect evident in the neuroimaging data on this listening condition alone, a further 2 (Group) X 2 (Session) ANOVA was performed. For this ANOVA, the contrast of conditions was F_{BABBLE} with Rest, as some individuals, especially at the second session, had very few incorrect response trials following the listening condition. Figure 5.3A shows the contrast of F_{BABBLE} with Rest from the first scanning session, demonstrating the very distributed networks revealed by this contrast. There was the expected activity in bilateral primary and association auditory cortices, with additional activity in higher-order cortices: bilateral frontal cortex, midline and dorsolateral prefrontal; left intraparietal sulcus (also evident on the right at a lower statistical threshold); and bilateral subcortical (striatal and anterior thalamic). There was a Group*Session interaction, confined to midline frontal cortex (the dorsal anterior cingulate cortex) and an adjacent region of right lateral prefrontal cortex (Figure 5.3B). Therefore, in this small network, galantamine did increase activity, but without improving speech-stream segregation during the F_{BABBLE} condition over and above the untreated improvement across sessions.

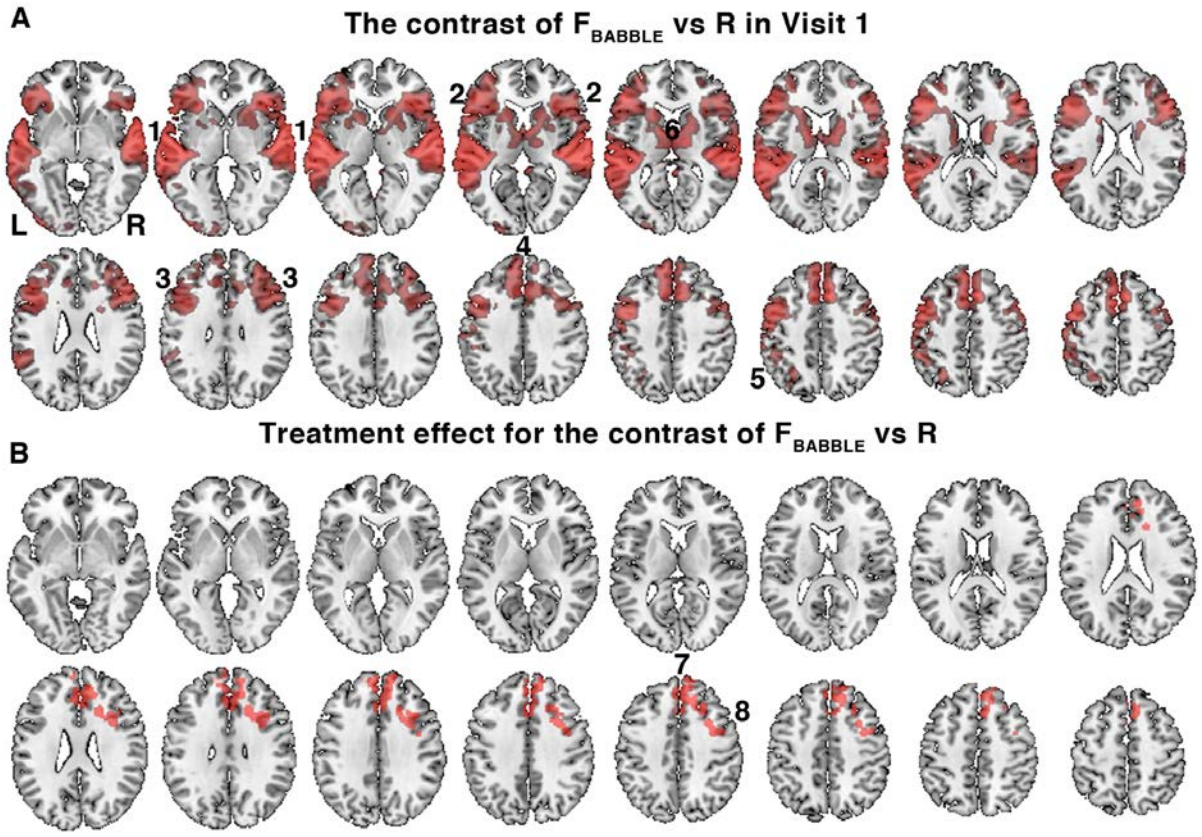

Figure 5.3*:* Univariate whole-brain analysis of the contrast of F_{BABBLE} with Rest

Axial slices are shown as in Figure 5.2. Significant regions of activity are projected as red overlays, with a voxel-level threshold Z > 2.3, cluster-level threshold P < 0.05. **A***. The mean activity of F_{BABBLE} contrasted with Rest at the first scanning session. 1. Bilateral auditory cortices; 2. Bilateral anterior insula/frontal opercular (aI/FOp); 3. Bilateral dorsolateral prefrontal; 4. Anterior cingulate cortex; 5. Left intraparietal sulcus; 6. Bilateral subcortical activity.* ***B****. The Group*Session interaction demonstrating increased activity after treatment with galantamine. 7. dorsal anterior cingulate cortex; 8. right lateral prefrontal cortex.*

The range of percentage change in performance between the first and second scanning sessions was -20.0 to 26.3%, mean = 4.1%, standard error of the mean = 2.0%. The percentage change in performance between the two scanning sessions did not correlate with overall cognitive performance, as measured by the ACE-R (r = 0.16, P = 0.4). The final analysis took this percentage change in performance between the first and second scanning sessions, which was demeaned and regressed against change in activity between the first and second scanning sessions, using the contrast of all listening conditions followed by correct responses with those followed by an incorrect response. The demeaned ACE-R scores and the grey matter volumes were included as regressors, A significant positive correlation was observed in right lateralised regions, in right dorsolateral prefrontal cortex, centred on the middle frontal gyrus, and the right posterior superior temporal sulcus (Figure 5.4). A significant negative correlation was not observed.

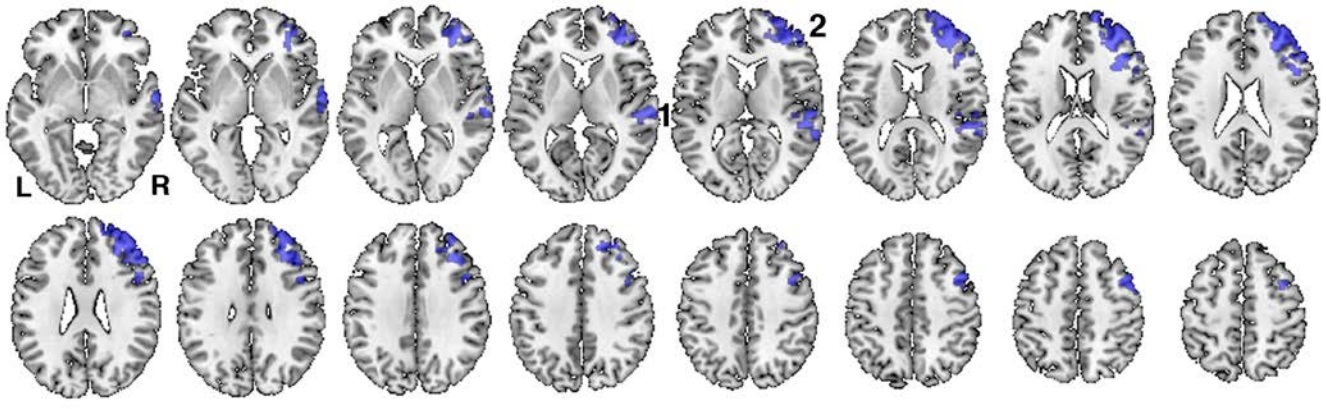

Figure 5.4: Univariate analysis of behavioural effect

Axial slices displayed as in Figure 5.2. Regions of activity, projected as blue overlay, on the difference in the scan data between the first and second scanning sessions, demonstrating a positive correlation with percentage change in accuracy of the in-scanner responses between the two sessions, irrespective of treatment with galantamine. Voxel-level threshold Z > 2.3, cluster-level threshold P < 0.05. 1. Right temporo-parietal junction; 2. Right dorsolateral prefrontal cortex.

5.4 Discussion

In terms of this study in relation to the therapeutic enthusiasm for using CChEIs in mild-to-moderate AD, the current result accords with critical reviews emphasising that appreciable individual benefit is observed in only a minority of patients, and that placebo effects have not necessarily been excluded in some of the trials reporting benefit of these agents (Cummings, 2003; Kaduszkiewicz *et al.*, 2005; Mount and Downton, 2006). Nevertheless, additional reasons may have contributed to the failure of this study to observe a behavioural benefit of galantamine on attentive listening. First, there was no attempt to confine this study to patients with mild-to-moderate AD (although the sub-analyses on the 21 patients most likely to have AD also failed to show benefit). Further, although impairment of attentive listening to a speaker, particularly in the presence of unattended speakers, will contribute to impaired recent verbal memory over and above any impairment of encoding and retrieval processes, it is not a function that has been specifically addressed in previous clinical drug trials; and CChEIs cannot be expected to reverse all the myriad symptoms that may accompany AD.

What the results from this study did demonstrate was a right cerebral hemisphere system that responded in a manner that identified it as having a central role in attentive listening. This system was revealed by the individual variation in overall in-scanner performance between the two scanning sessions, a change that was unrelated to the degree of cognitive decline in individual patients. Although the mean in-scanner performance of the 31 patients did not change significantly between sessions, there was considerable between-session variability between individuals. This variability correlated with activity in right dorsolateral prefrontal

cortex and posterior temporal cortex. The anatomical distribution of this functional system would indicate that it is involved in task-dependent attention (Corbetta and Shulman, 2002; Malhotra *et al.*, 2009; Singh-Curry and Husain, 2009). Its distribution also accords with what might be expected from a recent fMRI study of normal participants to compare visual and auditory attention (Braga *et al.*, 2013; see Chapter 6, Figure 6.1). The fluctuation in attentive listening between the first and second scanning sessions indicated that a major determinant of successful task performance was the function of a right hemisphere system regulating trial-by-trial attention and sustained attention across the scanning session. Although within the limitations of this study galantamine did not modulate activity within this system, alternative modulatory neurotransmitter agonists or combination therapy (Yu and Dayan, 2005) might prove effective (Bentley *et al.*, 2008; Gorgoraptis *et al.*, 2012), particularly as in AD it has been demonstrated that attention is impaired early in the course of the disease (Baddeley *et al.*, 2001; Levinoff *et al.*, 2005; Perry et al, 2000). It may be that the minority of patients with AD who respond to a CChEI do so because the pathology within right hemisphere systems for attention is not so advanced as to preclude a behavioural response to increasing central acetylcholine levels (acetylcholine is one of several neurotransmitters that modulate the function of these systems; Klinkenberg *et al.*, 2011).

This study did demonstrate some effect of a CChEI on the dorsal anterior cingulate cortex, although the evidence was weak. The babble used in the F_{BABBLE} condition was the background noise of many speakers, conveying little if any pre-lexical, lexical or semantic information. In the presence of energetic masking from multi-speaker babble but minimal informational masking, performance at speech-stream segregation is greatest (Hoen *et al.*, 2007), and normal subjects were equally accurate on the F_{BABBLE} and F_{ALONE} conditions used in the present study (Kamourieh *et al.*, 2015). In the patients, mean group performance on

this task was significantly impaired compared to F_{ALONE}, but did improve to be no different from F_{ALONE} at the second scanning session (Figure 5.1). Thus performance on F_{ALONE} remained the same but on F_{BABBLE} it improved. A plausible interpretation of this behavioural improvement is that prior experience of a novel and rather intimidating scanning procedure resulted in an improved ability to concentrate on the task comprising the easiest of masked speech conditions. Although the behavioural data indicated that galantamine did not produce additional benefit over and above the sessional effect, nevertheless it did have an effect on activity within the dorsal anterior cingulate cortex. There are *a priori* reasons for thinking that this region may be an important therapeutic target in attentive listening. A few previous functional neuroimaging studies on the effects of galantamine in patients with AD (Mega *et al.*, 2005) and MCI (Goekoop *et al.*, 2004), using other tasks, have demonstrated both behavioural improvement and increased activity in a number of brain regions, including anterior cingulate cortex. Further, in sentence perception and comprehension, Brownsett and colleagues (2014) demonstrated that dorsal anterior cingulate cortical activity increases in normal subjects when the spectral information in the speech signal renders the sentences less intelligible, an activity that is also observed in patients with post-stroke impairment of speech perception and comprehension. These observations, coupled with the functional neuroimaging literature on the role of the so-called cingulo-opercular network during task-dependent cognitive control (Dosenbach *et al.*, 2007, 2008; Ridderinkhof *et al.*, 2004), studies on the effects of damage to the cingulo-opercular network on task performance in other conditions resulting in diffuse cerebral damage, such as after traumatic brain injury (Bonnelle *et al.*, 2012), and our previous publication on the activity within this system in normal subjects during attentive listening and speech-stream segregation (Kamourieh *et al.*, 2015), would support the potential importance of CChEI modulation of the dorsal anterior cingulate cortex in top-down control during speech-stream segregation. Indirect evidence comes from the demonstration that amyloid burden, hypometabolism and atrophy in this region are present in

AD, and is associated with impaired attention (Killiany *et al.*, 2000; La Joie *et al.*, 2012; Luks *et al.*, 2010).

Dual regression analysis, as described in Chapter 4, Section 4.2.5, was also performed to investigate any changes in functional connectivity between the first and second patient visits. This did not identify any significant difference in connectivity between the 2 sessions in both groups of patients. Although it is difficult to interpret a null result, this is either a true demonstration of a lack of drug effect or the product of an underpowered study, in which too few patients were recruited. However, even if an effect on the fMRI results had been demonstrated, the value of this observation would have been lessened by the lack of any behavioural improvement on the range of cognitive tests used to investigate the patients. It is possible that a larger study population, selected on the basis that there was a high probability that all patients recruited had one pathology, such as Alzheimer's disease, would have has a positive outcome for an effect of drug, both on behavioural and fMRI measures.

In retrospect, to further disambiguate treatments effects from intrinsic variation associated with repeat exposure and reproducibility of results, a longitunidal control group comparison could have been included in the study design. A future study on a larger cohort of patients could include a longitudinal study on normal controls. Although the result from this study, with an effect on activity in only one listening condition out of five, and with no corresponding effect of drug on task performance, is not compelling when considered in isolation, it provides additional support to the proposal that excitatory transcortical stimulation directed might prove to be a therapeutic trial worth pursuing.

Summary

In summary, this study did not provide evidence for the value of CChEIs in attentive listening and speech-stream segregation. Its strength was the longitudinal design with two scanning sessions separated by weeks, demonstrating variability on in-scanner performance in patients with a complaint of memory impairment. This variability was used to demonstrate a central role for a higher-order right hemisphere system for attention that was central to successful task performance. The results of the study emphasised the importance of this system for accurate registration of verbal information, and the influence of attentional variability on task performance in patients with symptoms of memory impairment. It also opened up several possible hypotheses that can be addressed in future studies.

6 Summary

6.1 Summary of results and main findings

The main aims of my research were to:

1- Investigate the participation of networks involved in domain-general attention and cognitive control when listening to speech, both unmasked and when masked with unattended babble/speech.

2- Investigate the functional integrity of domain-general networks (cingulo-opercular and fronto-parietal systems) during attentive listening in patients with memory problems, correlating the imaging data with behavioural measures of attention, memory and executive function.

3- Determine whether the function of fronto-parietal systems is modulated by a CChEI (galantamine).

I have presented the results of four studies that investigated speech-stream segregation and auditory attention in normal participants and patients with memory complaints. The first two studies investigated systems involved in attention and cognitive control in normal participants when attending to a speaker and recalling what was said. The main domain-general networks involved in attention identified in Chapter 3 consist of the cingulo-opercular network and bilateral fronto-parietal networks. Both studies identified three cortical nodes that responded to speech-in-speech masking irrespective of task deman: the precuneus, the left PT/IPL and the right aI/Fop. These regions were also identified in the patient studies (Chapters 4 and 5).

While the precuneus has been implicated in a number of different functions (Cavanna and Trimble, 2006), my findings support its role in detecting a target sound in complex acoustic environments, particularly in the presence of spatial cues (Zündorf *et al.*, 2013).

My results also suggest that speech-stream segregation, combined with all available spatial and non-spatial cues, is dependent on the PT (Griffiths and Warren, 2002), with evidence for partial left lateralisation. The role of the right aI/FOp, however, is less certain. Overall, it seems that this region is involved in directing working memory, attention and other higher-order control systems towards the mental processing of events. This is supported by the findings from the studies in this thesis, identifying a key role for the right aI/FOp in supporting speech-stream segregation, independent of task context.

The comparison of Study 1 and 2 in normal participants also discovered the effect of a change in task demand. In Study 1, participants were required to retain knowledge of what they had heard as episodic memories, and in Study 2, to respond to questions immediately after hearing speech, thereby placing demands mainly on working memory. The difference between the two was the functional dissociations between the response of the right dorsolateral prefrontal cortex, centred on the MFG, and inferior parietal cortex (SMG). Study 1 demonstrated no increase in activity of the ventral right fronto-parietal network as participants listened to unmasked speech, with activity increasing when the attended speaker was masked by unattended speech. This may be explained by an increase in sustained attention when attempting to encode the information conveyed by the attended speaker on perceptually difficult trials. This study also demonstrated the additional value of a multivariate analysis of the scan data – bilateral and more dorsal fronto-parietal network activity, not apparent in the

univariate analysis, was revealed by the ICA. Study 2, which relied more on working memory, abolished activity in the right SMG, regardless of perceptual difficulty, and resulted in increased activity in the right MFG across all trials. Therefore, the parietal component was no longer involved in attentive listening when the emphasis was on encoding what was heard in working memory, but the right dorsolateral prefrontal cortex became active during this task demand, irrespective of auditory perceptual difficulty.

A third study (reported in Chapter 4) compared patients presenting with a primary complaint of progressive impairment of recent memory with normal participants. The study design was that used for Study 2 on normal participants. The patients were recruited on the basis of the symptom rather than the disease. This was based on the prediction that impaired cognitive control, working memory and attention during attentive listening will involve impaired function of the same systems, irrespective of whether the aetiology was age-related cognitive decline, anxiety depression or mild-to-moderate AD. The behavioural results confirmed impaired speech-stream segregation in the patient group. Although there was an inter-group difference in the results on pure-tone audiometry, this did not affect in-scanner performance, probably because the intensity of delivery of the stimuli was adjusted for each individual.

Univariate analyses once again identified the right aI/FOp and precuneus and STG (including plana temporale) as important regions in attending to the female speaker when both unmasked and masked. Importantly, contrasts between the control and patient groups did not find any significant differences. Therefore, similar networks, namely the fronto-parietal and cingulo-opercular systems, were activated in both groups, and across different listening conditions. A contrast that more directly revealed activity related to successfully attending to

the female speaker demonstrated the functional differences between the groups. An incorrect response reliably indicated that what the female speaker had said had not been attended to. However, a proportion of correct responses will have been 'lucky guesses'. A comparison of 'correct versus incorrect' across all listening conditions and between the two groups indicated reduced activity in the patients localised to the dACC, bilateral posterior auditory cortex, centred on the PT, and bilateral dorsolateral prefrontal cortex. Patients' hearing thresholds (pure-tone audiometry) did not correlate with their in-scanner behavioural scores, whilst the sentence comprehension (TROG) did correlate. However, although high-tone hearing loss and poor sentence comprehension may contribute to their impairment, these factors do not fully explain the difficulty patients have with speech-stream segregation and central auditory processing (Gates *et al.*, 1996, 2008, 2011; Golden *et al.*, 2015a, b; Goll *et al.*, 2012; Golob *et al.*, 2007, 2009).

Further, in order to overcome language and auditory impairments, an increase in activity in the dACC would have been expected (Brownsett *et al.*, 2014), and the patients showed the reverse. The dual regression analysis extended this observation, by demonstrating a posterior temporal region functionally connected to the cingulo-opercular system and left fronto-parietal cortex, but throughout this widely distributed system, the patients generated less functionally connected activity than the controls.

It would seem likely that these observations may extend to cognitive control and attention in other pathological brain conditions, including traumatic brain injury (Bonnelle *et al.*, 2012; Jilka *et al.*, 2014) and stroke (Brownsett *et al.*, 2014). It also seems likely that these results would be mirrored for any task that depends on attention, working memory and cognitive control.

The final aim was addressed in Chapter 5, when results from 17 patients prescribed galantamine were compared with 14 patients who were left untreated. It is often assumed that CChEIs benefit at least some patients by acting on systems for attention, although only a proportion of patients gain any benefit (Mount and Downton, 2006). Although there was modulation of activity within the dACC by galantamine, this was not accompanied by behavioural benefit. Reasons for the potential therapeutic importance of this region are supported by prior studies demonstrating behavioural improvement and increased activity in regions including the ACC (Mega *et al.*, 2005; Goekoop *et al.*, 2004). The lack of behavioural benefit may relate to the small number of patients studied, and the fact that only two-thirds had possible or probable AD. However, it is important to note that studying a symptom-led cohort rather than a defined group, may limit the power to detecet real effects. Further, although impairment of attentive listening to a speaker will contribute to a complaint of impaired recent verbal memory, this has not been specifically addressed in previous clinical drug trials; and CChEIs are unlikely to reverse all the myriad symptoms that accompany AD.

Despite the lack of treatment effect, the study reported in Chapter 5 did identify the importance of a right cerebral hemisphere system in task-dependent attention (Corbetta and Shulman, 2002; Malhotra *et al.*, 2009; Singh-Curry and Husain, 2009). Across two scanning sessions, the wide range of inter-individual variability on in-scanner behavioural scores was used to demonstrate the role of a right hemisphere system in attention that was central to successful task performance. This variability would correspond with the ‘good days and bad days’ that carers often describe. This result is important because it highlights the role of a right lateralised fronto-parietal network in day-to-day attentive listening.

My findings support the hypothesis that top-down control plays a significant part in auditory scene defecits of early stage patients. To better test the hypothesis that top-down control is important in auditory scene analysis and affected in memory impairment, changes can be done to this study in the future. These include, scanning the healthy controls twice; including a passive listening task; looking at techniques to test how sure a participant is about their answer, (however this may be difficult in the memory impaired group); and removing the dichotic conditions to allow for further testing of alone, babble and diotic listening.

In summary, the work in this thesis has furthered our understanding of the complex neural mechanisms underlying speech-stream segregation and auditory attention in healthy individuals and in those with memory complaints. It has provided insights into the differences in activity between the domain-specific and domain-general networks involved. It has identified regions critical to speech-stream segregation, namely the PT, aI/FOp and precuneus, and networks including the cingulo-opercular and fronto-parietal networks. Finally, I identified that although impaired anterograde verbal memory is normally considered in terms of encoding and recall, an initial failure to register the verbal message will also contribute to a complaint of poor memory.

6.2 Future directions

The work presented in this thesis has raised several predictions that can be explored in future studies. First, the results presented in Chapters 3–5 relied on task-dependent fMRI studies. This offered the advantage of making it possible to relate behavioural scores to fluctuations in the BOLD signal, thus allowing for a neurobiological representation of speech-stream segregation. However, the disadvantage is that the technique relied on patient engagement and co-operation, a design that will exclude similar studies on more severely affected individuals.

The ability to demonstrate similar connectivity differences between controls and patients from resting-state fMRI in patients has important clinical implications. Resting-state fMRI measures low-frequency signal changes whilst the patient rests in the scanner with their eyes closed, with the instruction to do 'nothing' but not to fall asleep. Image acquisition takes only 5–6 minutes and requires minimal effort from the patient. The networks identified from previous studies are robust (Smith *et al.*, 2009) and overlap with those reported here. Thus, functional connectivity analysis on resting-state data has the potential to provide valuable information about abnormal brain functions in those who are too severely affected by pathologies to participate in fMRI.

Second, structural imaging, such as diffusion tensor imaging (DTI) may be used in future studies alongside fMRI to define better biomarkers of response to therapy and possibly identify patients who may be more receptive. I would like to explore this using the DTI data I have collected in both controls and patients. I would start by correlating several white-matter

tracts associated with attention and working memory with the functional connectivity measures in patients, using previously published methods (Jilka *et al.*, 2014).

Impaired function of attentional systems, due to the presence of Alzheimer's pathology or because of more benign conditions, such as anxiety depression or age-related cognitive decline, will account for the wide fluctuations in between-session performance, which allowed the analysis of the imaging data in Chapter 5 to reveal the right hemisphere system. This susceptibility to wide fluctuations in attention may plausibly account for a common experience of carers of patients with AD, that their dependant has 'good days and bad days'. The anatomical distribution accords with a recent fMRI study in normal participants, comparing visual and auditory attention (Braga *et al.*, 2013; see Figure 6.1) and would support its involvement in task-dependent attention (Corbetta and Shulman, 2002; Malhotra *et al.*, 2009; Singh-Curry and Husain, 2009). The findings in Chapter 5 generate the hypothesis that improving functionality within this system may be a key element in symptom modification of this disease, and that the patients who benefit from CChEIs do so because of preserved responsiveness of the right fronto-temporal system to increased central acetylcholine levels. The findings also offer a rationale for a therapeutic trial of excitatory transcortical stimulation directed at this system.

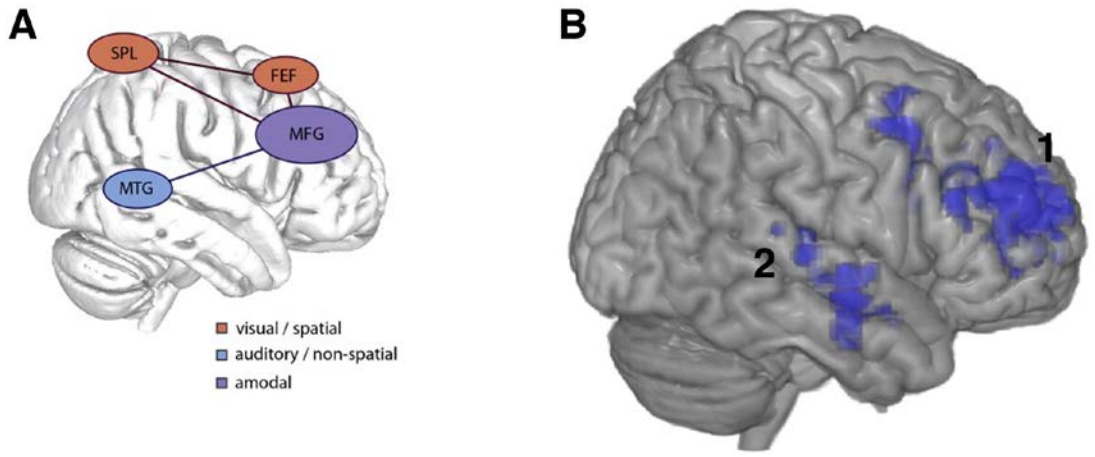

Figure 6.1: Top-down attention systems

Source: Figure 6.1 from Braga and colleagues (2013) – permission for reproduction from Elsevier. ***A****. This was a study of both visual and auditory attention in normal participants. This demonstrated an amodal component centred on the middle frontal gyrus (MFG), functionally connected to modality-specific regions: frontal eye fields (FEF), superior parietal lobe (SPL) and middle temporal gyrus (MTG), the last increasing activity during auditory attention.*

B*. Activity from the current study that was positively correlated with percentage change in accuracy of the in-scanner responses between the two scanning sessions, overlaid on a lateral view of the right cerebral hemisphere. 1. Right dorsolateral prefrontal cortex; 2. Right posterior temporal cortex.*

Another aspect that can be explored from the findings of Chapters 3 and 5 is the importance of the right aI/FOp in activating attention and memory systems when listening to a speaker in a 'cocktail-party' auditory environment. This can be expanded to look at lesion-deficit analysis to confirm the former proposal, and ways of improving this through neurostimulation could also be explored.

Finally, the results from Chapter 3 identified an unexpected increase in activity when attending to speech in regions located in the supplementary eye field and the frontal eye fields in the presence of spatial cues. Future studies may choose to investigate this further to determine whether automatic eye movements towards the ‘attended’ speaker accompany spatial cues during speech-stream segregation using in-scanner eye tracking.

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8 Appendix

Appendix 1: Control and patient group behavioural out-of-scanner results

Patient S1	Age	ACE-R	PAL 6 error	PAL t-error	RTI-react	RVP	SWM error	GDS	TROG - BLOCK	TROG - TOTAL	DS F (digits)	DS B (digits)
1	70	70	40	127	638.5	0.89	72	0	2	4	7	5
2	81	89	20	26	360.53	0.99	26	5	1	1	8	4
3	82	75	30	80	602.24	0.95	7	2	2	4	7	4
4	77	78	6	16	438.83	0.93	17	1	1	1	6	4
5	58	83	30	72	398.04	0.98	19	2	2	2	7	4
6	69	79	30	66	336	0.95	24	2	2	3	5	3
7	66	76	26	45	806.05	0.97	19	2	1	1	4	4
8	79	96	7	9	329.1	1	14	1	0	0	9	8
9	70	65	30	85	528.58	0.92	12	2	4	6	9	8

10	70	90	9	19	292.52	1	9	0	0	0	8	4
11	66	94	18	28	326.57	0.99	12	1	0	0	7	4
12	82	88	30	91	354.9	0.97	27	6	4	6	7	3
13	62	64	30	88	452.12	0.77	43	4	8	16	6	3
14	87	76	30	52	472.21	0.93	40	5	1	1	8	5
15	71	56	9	27	412.63	0.93	32	7	7	11	5	4
16	85	82	30	55	527.52	0.94	37	5	1	1	7	6
17	63	85	30	22	302.03	0.98	20	11	1	2	5	3
18	60	92	15	16	419.25	0.97	22	2	2	3	7	4
19	84	94	10	87	497.92	0.95	27	5	1	1	8	6
20	82	70	30	77	445	0.98	29	3	1	1	6	5
21	77	79	30	19	521	0.9	33	2	1	2	6	4
22	81	97	10	26	492.3	1	30	2	0	0	9	4

23	82	96	30	91	372.5	1	35	1	0	0	7	5
24	60	57	30	89	n/a	0.9	65	8	4	5	5	3
25	59	98	30	7	277	1	4	9	0	0	8	4
26	82	69	1	55	331.64	0.82	36	0	5	11	5	5
27	77	77	30	70	473.8	0.9	0	3	2	3	5	5
28	79	89	30	26	365	1	39	1	4	6	4	4
29	74	71	13	18	417.8	0.9	7	7	2	4	6	5
30	71	87	10	74	425.2	1	20	1	1	2	5	5
31	65	50	30	89	454.9	0.8	35	1	4	7	5	4
HC	Age	ACE-R	PAL 6 error	PAL t-error	RTI-react	RVP	SWM error	GDS	TROG - BLOCK	TROG - TOTAL	DS F (digit)	DS B (Digit)
1	63	99	N/A	N/A	N/A	N/A	N/A	1	0	0	7	5

2	64	100	N/A	N/A	N/A	N/A	N/A	1	1	1	6	5
3	67	99	5	14	395.85	0.97	15	0	2	2	5	3
4	65	96	4	5	305.33	0.99	24	0	1	1	7	6
5	83	91	8	14	453.41	0.97	35	1	2	3	6	4
6	67	97	7	20	323.55	0.99	17	0	0	0	7	7
7	51	99	14	14	302.2	0.99	6	1	0	0	8	6
8	59	87	23	59	345	0.83	22	0	N/A	N/A	6	5
9	60	95	6	12	431.17	0.97	8	3	2	1	7	5
10	64	93	30	74	354.47	0.97	22	3	3	5	6	4
11	65	95	12	19	344.733	0.1	28	2	0	0	5	4
12	53	98	0	3	371.17	0.99	33	0	1	1	8	6
13	51	98	0	4	372.23	0.98	0	1	0	0	8	6
14	77	96	7	16	385.47	1	22	2	0	0	5	5

15	82	95	6	12	415.89	0.99	14	1	2	4	7	4
16	64	95	11	17	337.5	1	18	2	0	0	6	6
17	62	100	0	4	385.27	1	3	1	0	0	7	6
18	62	100	N/A	N/A	N/A	N/A	N/A	0	0	0	7	6
19	73	94	0	3	420.43	0.99	31	0	1	1	5	3
20	71	98	11	11	367.04	0.99	0	0	0	0	8	4
21	68	92	4	5	291.92	0.97	0	0	1	2	7	5
22	74	80	8	13	386.72	0.98	19	0	3	5	6	4
23	79	94	0	3	475.25	1	12	0	2	3	7	3
24	70	91	11	18	348.35	0.98	30	2	1	1	7	5
25	67	95	8	28	306.83	1	39	0	0	0	7	4

Patient S2	ACE-R	PAL 6 error	PAL t-error	RTI-move	RTI-react	RVP	SWM error	SWM strategy	GDS	DS F (digit)	DS B (digit)
1	89	27	42	437.27	508.13	0.95	27	19	0	8	4
2	95	30	49	373.7	297.23	0.99	19	16	7	6	4
3	71	30	70	338.24	473.34	0.99	11	12	1	6	4
4	84	3	17	356.5	354.13	0.96	2	10	2	7	4
5	90	19	40	254	372.77	0.99	20	18	1	7	2
6	86	13	32	257.87	335.67	0.95	17	17	0	5	4
7	92	23	35	327.57	462.6	0.91	18	17	1	7	4
8	100	5	5	288.87	295.33	0.96	28	17	1	9	8
9	66	30	67	582.93	592.27	0.94	42	21	3	8	6
10	88	5	10	135.17	305.13	1	16	15	1	9	7
11	93	8	12	154.08	288.92	1	15	20	0	7	5

12	85	30	89	248.59	320.66	0.97	36	20	N/A	6	3
13	77	30	90	369.7	438.4	0.83	58	21	3	5	3
14	83	30	69	632.96	370	0.97	37	19	3	7	7
15	61	16	26	335.47	418.57	0.96	33	21	5	5	4
16	76	30	79	235.88	550.42	0.94	32	23	5	8	3
17	88	6	7	249	302	0.98	17	8	15	5	3
18	90	1	5	392	411	0.94	21	21	1	5	4
19	89	30	62	489	435	1	32	19	2	7	7
20	73	30	94	383.4	319	0.98	32	19	2	8	5
21	84	3	15	458.4	419	0.96	30	20	0	5	2
22	94	30	74	587.2	465.8	0.93	37	18	5	7	5
23	100	14	24	324.2	391.6	0.9	27	20	2	7	4
24	57	30	100	406.57	723.57	0.9	63	17	8	5	3

25	97	8	14	342.1	252.5	1	6	10	6	8	5
26	74	19	26	351.68	350.28	0.96	35	20	1	4	4
27	75	30	75	565.6	381.6	1	20	20	0	5	4
28	93	17	28	385	436.7	1	29	19	0	4	3
29	79	18	23	304.5	404.7	0.8	9	12	8	7	5
30	90	30	54	266.8	380.4	1	7	18	0	7	4
31	48	30	94	384.57	366.14	0.8	43	19	1	7	4

The above tables demonstrate the out-of-scanner behavioural tests performed on the controls and patients included in this study. All subjects in bold and italic were excluded from analysis in Chapter 4.

The following abbreviations are used: RVP = Rapid Visual information Processing, measures sustained attention; PAL – six-stage = Paired Associate Learning six stages, measures visual memory and new learning; PAL – t error= Paired Associate Learning total errors; SWM = Spatial working memory, requires retention and manipulation of visuo-spatial information looking at strategy and error; RTI = Reaction Time, measures motor and mental response speeds with movement and reaction time; DSF = digit span forwards; DSB = digit span backwards; S1 = Session 1; S2 = Session 2; HC = healthy control.

Appendix 2: Patient group breakdown – diagnosis and investigations

Sex	Age	ACE-R <88	Lumbar puncture	MTL - atrophy	Formal neuropsychology summary	Galantamine	Follow up	Dx
M	70	Y	H	Y	Cognitive underfunctioning in memory, naming and visuospatial	N	DECLINE	pAD *
F	81	N	H	N		N	STABLE	pAD
M	82	Y	N/A	Y	Poor confrontation on naming and episodic memory prob	N	STABLE	pAD
M	77	Y	H	Y	Verbal memory deficit	Y	DECLINE	pAD
M	58	Y	H	Y		Y	DECLINE	pAD
F	69	Y	N/A	N		Y	STABLE	possAD
F	66	Y	N/A	N		Y	STABLE	possAD
F	79	N	N/A	N		Y	STABLE	MCI
F	70	Y	N/A	Y	Impairment in memory consolidation and language	N	DECLINE	pAD

F	70	N	N/A	N		N	STABLE	MCI
M	66	N	N/A	N		N	STABLE	MCI
F	82	N	N/A	Y		N	DECLINE	possAD
M	62	Y	N/A	Y	Impaired visuospatial functioning, executive function and processing speed	N	STABLE	pAD
F	87	Y	N/A	N		Y	No F/U	possAD
F	71	Y	N/A	N		N	No F/U	possAD
M	85	Y	N/A	N		Y	DECLINE	CB
M	63	Y	N	N	Isolated episodic memory deficit	Y	Improved	Anxiety
M	60	N	N	Y	Episodic memory, naming and semantic fluency deficit	N	STABLE	MCI
F	84	N	N/A	Y		Y	STABLE	MCI
F	82	Y	N/A	Y	Globally impaired recognition memory and a degree of executive dysfunction	Y	No F/U	pAD

M	77	Y	N/A	Y		N	No F/U	pAD
M	81	N	N/A	Y		Y	STABLE	MCI
M	82	N	N/A	Y		N	No F/U	MCI
F	60	Y	N/A	Y		Y	STABLE	pAD
F	59	N	N	N		Y	STABLE	Cavernomata **
M	82	Y	H	N		N	DECLINE	pAD
M	77	Y	N/A	Y		Y	STABLE	pAD
F	79	N	N/A	N	Verbal recall memory selectively weak, difficulty with naming and semantic fluency, weakness of executive skills, attention and working memory difficulties	N	DECLINE	possAD
M	74	Y	N/A	Y		Y	STABLE	pAD
F	71	Y	N	N		Y	DECLINE	possAD
F	65	Y	N/A	Y	Memory severely and globally impaired, executive difficulty, naming declined, attention and working memory slightly weak	Y	DECLINE	pAD

This table demonstrates the demographics of the patients included in this study and the basic clinical investigations. Lumbar puncture results denote tau:Aβ $_{1-42}$ ratio H (high) = >1 (95% specific for AD); N (normal) < 1; Patients were followed up for > six months. The following abbreviations are used: Y = yes; N = no; pAD = probable Alzheimer's disease; possAD = possible Alzheimer's disease; MCI = mild cognitive impairment. CB = corticobasal type syndrome; N/A = not applicable; M = male; F = female; ACE_R = Addenbrooke's cognitive examination - revised; MTL = medial temporal lobe; F/U = follow-up.

** Positive amyloid PET scan*

*** Negative amyloid PET scan*

Appendix 3: Phrases used in the end of scanning marksheet in Study 1

His mother has nothing to give him

The ships captain summoned his crew

She finished the food on her plate

The detectives searched for a clue

For she is a seamstress

He said softly to himself

Her hair was tied with a blue heart

The guilty one should take the pig

Is he not solid gold

In the behavioural sciences

They tracked the lion to his tea

The lonely bird searched for its mate

The sandal has a broken tree

I ran to answer the doorbell

After his bath he wore sand

Bed in the corner by the room

Household goods are moved in a van

The sandal has a broken strap

Every night I set the moon

The stale bread was covered with boat

The accident gave me a beach

He was hit by a poisoned sand

The old train was powered by steam

He passed over the ghetto

Often improved with time

How wonderful the stars are

They admired the bride's white dress

Prevalence is much higher

The railroad train ran off the track

Queen's maid of honour

The rancher rounded up his herd

The candle flame melted the fork

The watchdog gave a warning growl

As opposed to adult interactions

The poor man was deeply in debt

The girl swept the floor with a frog

The admiral commands the Fleet

Tactile defensiveness

To the computer pioneer

I made the phone call from a moon

The cut on his knee formed a bee

The chicken pecked corn with its beak

Maple syrup is made from coin

The boy gave the football a map

I tell my secrets to my door

I hope my dress will be ready in

The shepherd watched his flock of sheep

However the chapters in this

And the mother so sad

The rancher rounded up his frog

The scarf was made of shiny silk

The fruit was shipped in wooden crates

On the beach we play in the moon

Beside the wooden thimble

The farmer harvested the boys

The task is not easy

The candle flame melted the wax

That will take us to a science

I ate a piece of chocolate fudge

The bomb exploded with a frog

The swimmer’s leg got a bad tree

Crocodiles live in muddy swamps

We're lost so let's look at a boat

What lay beyond it

And in the evening I led

We all went swimming in the pig

A bear has a thick fur bee

The airplane went into a dive

The guests were welcomed by the host

My son has a dog for a pet

The drowning man let out a dog

Airmail requires a special drum

He was hit by a poisoned dart

Keep your broken arm in a sling

I can’t guess so give me a clock

The furniture was made of pine

The witness took a solemn film

One day the prince will become king

The hockey player scored a sheep

Cross disciplinary synthesis

Instead of a fence plant a frog

Everything about me was so

We heard the ticking of the knife

Were for I live in the

Brain mechanisms, cognition

If pleasure be happiness

Indeed we are beginning to see

They drank a whole bottle of gin

When I was alive I had a

The computer is on my desk

Let’s decide by tossing a truck

Palace and heard the sounds of

The little girl cuddled her doll

I made the phone call from a booth

Your knees and your elbows are film

I did not know what his

The burglar escaped with the loot

Tear off some paper from the pad

Will begin to provide a detailed

Called me the happy prince

The findings of this complex

For the mast on the ship

General and universal cognitive

The pond was full of croaking frogs

Been made in recent years

The little girl cuddled her door

The cut on his knee formed a scab

Banks keep their money in a vault

For your birthday I baked a ball

They marched to the beat of the drum

Football is a dangerous cake

She wore a feather in her cap

My feet are fastened to the

Astronauts landed on the tree

Problems are caused by the lack of

She wore a feather in her map

We're lost so let's look at a map

The judge is sitting on the mouse

The railroad train ran off the ball

Her face is thin and worn

Phrases in red were spoken by the male speaker, either alone or in diotic presentation with the female sentences/sections of sentences. The ones in black were either spoken by the female or never heard during the scanning session.

Appendix 4: Questions and spoken sentences used in Study 2

M_LF_R Ships can move straight into the wind? F F

A sail is pushed sideways when the wind blows across it, so ships can't move straight into the wind

She got a grey beard just like that of the goat, and her hair became coarse and stiff, like hay.

M_LF_R The viper is nocturnal? F T

The eyelash viper is a nocturnal snake. It is one of the smallest poisonous snakes in America

Bones have a clever structure that makes them light but strong. They can heal themselves if broken

M_LF_R Vaporisation is when air is cooled? M F

As water vapour in the air is cooled, it changes into liquid water. This is called condensation

Dinosaurs held their tails above the ground, as there is no evidence of drag marks on trackways

M_LF_R Zebras live in small families? M T

Zebras are part of a large herd. They are social animals and live in small family groups

Spacecrafts have double hulls, which protect them against other space objects that crash into them

F_{ALONE} Houses were made of brick? F F

Vikings lived in houses made from wood or stone. A hole was left in the roof to let out smoke

F_{ALONE} Theatre began in ancient Greece? F T

Theatre began thousands of years ago in ancient Greece. Actors and dancers put on shows

F_{ALONE} The flag flies only at night? F F

On the moon, the flag flies all day, never goes up or down, and does not get saluted

F_{ALONE} Skunks are nocturnal foragers? F T

Skunks are nocturnal foragers. They nest in burrows and their spray is an oily liquid

F_{BABBLE} The valleys have permanent snow? F F

In cool parts of the world, mountain peaks have a permanent coating of snow, where nothing grows

F_{BABBLE} The rainforest is on the west? F F

South America's western side has the driest desert, its eastern side, the biggest rainforest

F_{BABBLE} He carefully studied the map? F T

He wanted to see the contest and meet the most famous heroes in the world. He carefully studies the map

F_{BABBLE} Typewriters were invented 200 years ago? F T

The first typewriters were invented about 200 years ago. They made writing much quicker

MF_{DIOTIC} Bees have a queen? M T

Honeybees are social insects. A colony of honeybees includes a queen, drones and workers

Plants that live in dry areas have leaves that are thick and covered in wax to save their water

MF_{DIOTIC} Iron must be heated in a furnace? F T

Iron must be heated in a furnace to make it melt. Molten iron is so hot it glows white

When a warthog takes a bath, it covers itself with mud to cool down and get rid of flies

MF_{DIOTIC} The Vikings were farmers? M F

The Vikings were daring sailors and explorers. They made fierce raids on the countries of Western Europe

Thirty-nine countries have signed the Antarctic Treaty, promising to use the area only for research

MF_{DIOTIC} The canyon was formed by the Hudson River? F F

The Grand Canyon formed over millions of years ago as the Colorado River wore deeper into the rock

Prehistoric artists are known to have painted pictures of figures and animals on cave walls

F_LM_R The door was heavy? M T

The ants looked for forest fires from there. The door was too heavy and the ants gasped for breath

To entertain each other, the Vikings told long stories about their heroes and gods, called sagas

F_LM_R Science is the search for ancestors? M F

Science is the search for truth and knowledge. It holds the key to understanding life, the Universe

The earth slowly spins around once a day. The line it spins around is called the Earth's axis

F_LM_R Jellyfish are made of water? F T

Jellyfish are made up mostly of water. They have no heart, bones, blood, eyes or brain

Many wild mushrooms are not only edible but also delicious. But others are highly poisonous

F_LM_R Water can be found only in ponds? F F

During the dry season in the savanna, the only reliable place to find water is at a water hole

Galaxies are often found in clusters. One cluster may have 30 or so galaxies in it

F_{ALONE} Stories were passed by telegram? F F

People now write things down. Before they told stories and passed news on by word of mouth

F_{ALONE} He crossed the road? F F

He passed the meadows, walked around the rocky hills, and while crossing the river he heard someone calling

F_{ALONE} 500 meteorites fall to earth? F T

About 500 small meteorites fall to earth every year, but most fall in the sea

F_{ALONE} They spray out light? F T

The opposite of black holes are white holes. These spray out matter and light, like fountains

MF_{DIOTIC} Brick is important for building? M F

Concrete is an important building material. It is a mixture of sand, gravel, cement and water

The cactus is a clever plant because it collects water when it rains and stores it for dry periods

MF_{DIOTIC} A hedgehogs skin is large? M T

The hedgehog's skin is larger than is needed to cover its body, so it is completely covered when curled

Thanks to modern science, many illnesses that were once untreatable can now be cured or prevented

MF_{DIOTIC} Penguins offer shells? F F

A male penguin offers a pebble to a female penguin. If she takes it, they become partners for life

France has a very diverse landscape, where lowland forests are home to deer and bore

MF_{DIOTIC} There are three species of zebras? F T

There are three species of zebra, all native to Africa. They differ slightly in their stripes

Muscles can pull but they can't push. They work in pairs that pull in opposite directions

M_LF_R Crystals are white? F F

Snow may look like white powder but it's actually made of thousands of crystals as clear as glass

Whales are large, intelligent mammals that breathe air and spend their entire lives in water

M_LF_R The stallion stays at the back? F T

The stallion protects the herd form predators. He stays at the back of the herd to warn the others

Over millions of years, the rocks in the Earth's crust can gradually change from one type into another

M_LF_R Argon is used in light bulbs? M T

Argon is used to fill the space in most light bulbs. Neon is used in fluorescent signs

Layers of soil that is rich in iron, gives Mars its red colour – like rusty iron on Earth

M_LF_R Yaks have poor balance? M F

Yaks have great balance and never slip or fall down. People use them for riding and packing

A hovercraft does not touch the surface over which it travels, but floats above it on a cushion of air

F_LM_R It releases a drag chute? M T

Shuttles glide down, belly first. Once the orbiter touches down it releases a drag chute

Snowy owls chose a breeding partner and usually stay with that owl for the rest of their lives

F_LM_R Kangaroos have jumping matches? M F

Kangaroos travel in groups. The leader dominates younger rivals by kicking and boxing matches

Scientists think the extreme tilt was caused by a collision, with a planet-sized object

F_LM_R Minerals seep underground? F F

Caves form when rain seeps underground and eats away at soft rock such as limestone

Every substance melts at a particular temperature. Most metals are solid at everyday temperatures

F_LM_R Artists used stones? F T

Since ancient times, artists have painted pictures and used stone and wood to make sculptures

The Maya built great cities, filled with magnificent stone temples, palaces and squares

F_{BABBLE} Electricity gives us energy? F T

Electricity lights up the world and gives us the energy to cook, travel, work and play

F_{BABBLE} Monkeys eat bananas? F T

Monkeys spend a lot of the time up in trees and like to eat fruit especially bananas

F_{BABBLE} It reaches flowers up high on the tree? F F

The giraffe is tall and has a very long neck to reach the tender leaves up high on the tree.

F_{BABBLE} Seasons on Uranus last only 15 years? F F

Because Uranus is tilted on its side, seasons on the planet last more than 20 years

F_LM_R It takes one month to walk across Russia? F F

Russia is the world's widest country. It would take more than two months to cross if you walked

The Solar System has nine planets, but Pluto may be an escaped moon or an asteroid

F_LM_R Scientists study a limited range of things? M F

Scientist study a huge variety of things, from the tiniest of atoms to the mysteries of space

Elephants are very big animals. They have a long memory and a very long nose called a trunk

F_LM_R Tigers are the biggest cats? F T

Tigers are the biggest cats in the world. They live in hot jungles as well as icy cold forests

Igneous rocks are made when hot molten magma from the Earth's interior cools and solidifies

F_LM_R Lakes support a variety of life? M T

A freshwater lake is a large body of standing water. Lakes support a wide variety of life

Woodpeckers have very long tongues and use their beaks to dig out grubs and to make nest holes

MF_{DIOTIC} Seals live in cold water? F T

Most seals live in cold waters. They spend their time in the sea but also enjoy sunbathing

A storm officially becomes a hurricane when cyclone winds reach 74 miles per hour

MF_{DIOTIC} Newts are found in dry areas? F F

Newts are brightly coloured salamanders. They are found in moist, wooded areas in North America

Pluto once considered a planet, is actually smaller than seven of the solar system's moons

MF_{DIOTIC} Jellyfish eat seaweed? M F

Jellyfish feed on small plankton animal. They can shrink in size if there is not enough food

In the centre of the Arctic is a gigantic lump of floating ice that never completely melts

MF_{DIOTIC} Bats squeak to find prey? M T

Bats hunt by making squeaks and clicks that bounce off prey, telling the bat the prey's location

Giant stars have burned all their hydrogen, and so fuse helium atoms to make carbon

F_{BABBLE} Dinosaurs are closely related to reptiles? F F

You may think reptiles are closely related to dinosaurs, but dinosaurs have more in common with birds

F_{BABBLE} The moon has pebbles and rocks? F T

The moon's surface consists of a fine, talcum-powder-like dust, strewn with pebbles and rocks

F_{BABBLE} Feathers protect them from temperature changes? F T

Feathers protect birds from water and temperature changes, and were also found on some dinosaurs

F_{BABBLE} Venus is the coldest planet? F F

Thick clouds that reflect sunlight cover Venus, making it the brightest planet in the night sky

F_{ALONE} They have holly shaped leaves? F F

Conifer trees grow cones that store their seeds. Most conifers have needle-shaped leaves

F_{ALONE} Petrol cars produce safe fumes? F F

Petrol cars use a lot of oil, and produce harmful fumes – electric cars are an alternative

F_{ALONE} Horses eat mostly grass? F T

Horses eat mostly grass, but will feed on tree bark when there is no grass to be found

F_{ALONE} A tiger eats 40kg of meat? F T

A tiger can eat as much as 40kg of meet in one feeding, and drags their pray near water

M_LF_R There are seas on the moon? M T

There are dark patches called seas on the moon, which are lava flows from ancient volcanoes

The deer's diet consists mostly of green plants, nuts, and in the winter, wood vegetation

M_LF_R Two astronauts climb through the modules? F T

The lunar module joins the command and service modules so the two lunar astronauts can climb through

Adult tigers live alone. In the forest a single tiger can sneak up on its prey better than a group

M_LF_R Male beetles crash their antlers together? M F

Many male animals compete to win a mate, including stags who crash their antlers together

Above the Antarctica there is an area of ozone layer that is much thinner than anywhere else

M_LF_R Alligators are fussy eaters? F F

Alligators eat almost everything, primarily fish. They can wait a year between meals

Space suit gloves have silicon fingertips, which allow the astronaut some sense of touch

M_LF_R Music was sent down in 1876? F T

Music was sent down a telephone line for the first time in 1876, the year the phone was invented

The beautiful Taj Mahal in India was built as a tomb for the emperor's wife. It is made from white marble

M_LF_R The satellite's gravity is greater than its momentum? F F

For a satellite to fly off into the space, its momentum should be greater than the pull of the gravity of the earth

Hundreds of islands are scattered across the Pacific Ocean. Two of the biggest form the mountainous country of New Zealand

M_LF_R Greenhouse gases trap the sun's heat? M T

Burning fossil fuels fills the air with greenhouse gases, which trap some of the Sun's heat in the atmosphere

The Atlantic flying fish doesn't fly, it glides very rapidly near the surface and then breaks through the water

M_LF_R The smallest is the Alpha Star? M F

The stars in each constellation are named after a Greek alphabet. The brightest is called the Alpha Star

All over the world, farmers grow crops and raise animals. Growing food for themselves and to sell at market

F_{ALONE} Otters open shellfish with their teeth? F F

To get food a sea otter may hammer open a shellfish with small rocks or dive into the oceans

F_{ALONE} Australia is a huge country? F T

Australia is the world's smallest continent, but it is a huge country. Most Australians live on the coast

F_{ALONE} During dry seasons the grass is green? F F

Tropical grasslands have wet and dry seasons. In the dry season, the grass turns straw-coloured and dies

F_{ALONE} Vets look after injured animals? F T

Vets look after sick and injured animals. Some vets treat small animals, such as cats and dogs

F_{BABBLE} In the night, stars are brighter than planets? F F

The brightest stars in the night sky are not actually stars, but planets, including Jupiter and Mercury

F_{BABBLE} The leaf moves towards the frog? F F

Every action has an equal and opposite reaction. The leaf moves away as the frog leaps in the opposite direction

F_{BABBLE} Hurricanes go clockwise in the south? F T

Hurricanes and tornadoes always go clockwise in the southern hemispheres and anticlockwise in the north

F_{BABBLE} Newspapers date from roman times? F T

The first, hand-written newspapers date from Roman times. They told people about gladiator contests

MF_{DIOTIC} Eskimos live in Antarctica? M F

The only people who live in Antarctica are scientists. Some use huge balloons to study the climate

Soil is the thin layer of loose material on the land. It contains minerals, air, water and decaying matter

MF_{DIOTIC} New Zealand is the capital of extreme sports? M T

New Zealand is the world capital for extreme sports. Bungee jumping and white water rafting are all popular

A satellite is a rocket's cargo, its size determines whether it is sent up by a small or large rocket

MF_{DIOTIC} Granite is black, grey and pink? F T

Granite rock is made up of different coloured minerals. The black is mica, the pink is feldspar and the grey is quartz

The female penguins usually lay two eggs. The stones in the nest help keep the eggs dry

MF_{DIOTIC} It has a human body and a lion's head? F F

A huge stone statue called the Sphinx guards the pyramids. It has a body of a lion and a human head

Some animals create their own light. Fireflies have tails that flash a yellowish-green colour at night

F_LM_R Earth orbits satellites? F F

Satellites orbit the Earth, beaming back lots of information. They send TV signals and help us gaze into space

A forest appears to sleep in winter, but in spring it bursts into life. Buds open and ferns spread out

F_LM_R We release carbon dioxide? M T

Humans take in carbon through carbohydrates and proteins in food, and release it as carbon dioxide gas

A pulley makes it easier to lift something straight up. It consists of a piece of rope wound around a wheel

F_LM_R Gears have hooks? M F

Gears are wheels with teeth that interlock so that one wheel turns another. They increase speed or force

Electricity is a form of energy. It can be made using any source of energy, such as coal, gas and oil

F_LM_R The sun sends out solar winds? F T

The sun sends out a stream of invisible particles, called the solar wind; they can create stunning colours

The Aztecs and Mayas ruled parts of Mexico and Central America, the Incas the west coast of South America

F_LM_R Apes started off walking upright? M F

Our oldest ancestors looked like apes. Slowly they became more human-like and began to walk upright

In deserts, winds blow sand into hills called dunes. Some dunes can stretch for hundreds of miles

F_LM_R Rivers cut out channels? M T

Over millions of years, rivers cut channels in the earth. An example is the Colorado River at the Grand Canyon

Engineers are people who design or make such things as cars, airplanes, machines, and buildings

F_LM_R Italy is shaped like a boot? F T

Italy is shaped like a boot, with the top in the Alps Mountains and the toe swimming in the Mediterranean Sea

Putting on a play is a long task. First the playwright writes the play. Then actors bring it to life

F_LM_R Females lay brown eggs? F F

During the spring or summer, a female woodpecker usually lays between five to seven white eggs

Three great civilizations grew up in the ancient Americas, called the Aztecs, Mayas and Incas

MF_{DIOTIC} Sparklers release energy as heat? F F

A sparkler contains chemicals that release a lot of energy as light to create a dazzling shower of sparks

In a recording studio, each voice or instrument can be recorded on its own. These are called tracks

MF_{DIOTIC} It is a bar that swivels? F T

A lever is a bar that swivels on a fixed point or fulcrum and makes it easier to move a load

Rain clouds form when warm, moist air rises upwards and then cools, and droplets combine into rain

MF_{DIOTIC} The fly trap gets energy from the sun only? M F

The Venus flytrap doesn't just get its energy from the sun. It also feeds on unsuspecting insects

On the skunk's small head, another stripe extends from the top of its face down to the tip of its nose

MF_{DIOTIC} Light is mixed to form white? M T

Light is a form of energy our eyes can detect. It comes in all the colours of the rainbow but is mixed to form white

The striped skunk has thick black fur and a white stripe that splits into two at the shoulders

F_{BABBLE} Vegetable oil has short molecules? F F

In natural substances like vegetable oil, atoms are often joined in chains to make very large molecules

F_{BABBLE} It is the study of oceans? F T

Oceanography, the study of oceans, is a mixture of biology, physics, geology and chemistry

F_{BABBLE} Greeks wrote plays? F T

Going to the theatre was very popular with the ancient Greeks, who wrote many plays, including comedies

F_{BABBLE} The beetle was lying on a flower? F F

The beetle was lying on the grass, drying off in the sun - exhausted but very happy for being rescued

F_{ALONE} Penguins are sturdy on land? F F

Lots of sea animals live around Antarctica's coast. Penguins are clumsy on land but superb swimmers

F_{ALONE} Costumes are used to portray character? F F

Chinese opera has lots of singing, acting and acrobatics. Make-up is used to portray characters

F_{ALONE} They have six kits? F T

Raccoons give birth to six kits at one time. A baby raccoon's eyes do not open until three weeks

F_{ALONE} Rotary presses make books? F T

Today, giant rotary presses are used to print millions of books, newspapers, and magazines every day

M_LF_R Moving objects have inertia? M T

When things are standing still or moving, they are quite happy to continue with what they are doing – this is called inertia

Most plants grow from the top but grass grows from the bottom. This means it can grow back if it is eaten

M_LF_R History answers questions? M F

Science answers questions. The world's great scientists were all thinkers who wanted to solve life's problems

2,000 stars are located in the daytime sky and are obscured by the much brighter light of the sun

M_LF_R Walruses have long noses? F F

The walrus has whiskers on either side of its face to act as food detectors, locating clams

The first computers were huge machines. They couldn't cope with complicated tasks, only one thing at a time

M_LF_R Magma bursts through the crust? F T

Volcanoes are openings in the Earth's crust. Sometimes magma from just beneath the crust bursts through

As time was pressing the fox sank his tail into the icy water, and cried out for the beetle to grab it.

MF_{DIOTIC} Deserts have lots of rain? M F

They can be hot or cold, but deserts are dry, with little rain. Only a few animals and plants survive

Southern Asia is normally hot and dry, but every summer it pours down for weeks. This is called the monsoon

MF_{DIOTIC} Astronauts can jump 4m high? M T

The moon's gravity is 17% of the Earth's so astronauts can jump 4m high on the moon

Unicorns are one-horned mythical creatures that can be associated with all kinds of mythology

MF_{DIOTIC} There are colourful fish on the reef? F T

The Great Barrier Reef stretches along Queensland's coast. Many brightly coloured fish live on the reef

Swans breed in solitary pairs. Each couple defends a territory. They can be nasty protectors

MF_{DIOTIC} He lost his shoe? F F

Ahead was a rabbit, crying sadly. It had lost one of its gloves and didn't know how to find it

In spring, as the snow begins to melt, meadows come alive with flowers. This zone is above the treeline

M_LF_R This is a heat wave? F F

The vibration squeezes and stretches the air between the vibrating object and your ear. This is a sound wave

The ruffed grouse is primarily a ground-dwelling bird but is also a skilled flyer and climber

M_LF_R Water form strange shapes? M F

Strong winds can lift sand off the ground and blast it hard against rocks, making it strange shapes

A dog was the first in space, whilst a sheep, a duck and a rooster the first to fly in a hot air balloon

M_LF_R They built roads? M T

In peacetime, Roman soldiers were kept busy building roads. Roman roads were usually very straight

Freshwater ecosystems exist in lakes and streams. They cover most of the world's surface

M_LF_R It belongs to the horned face group? F T

Like a rhinoceros, Triceratops is one of the best known dinosaur which belongs to the 'horned face' group

The ancient Egyptians believed in life after death. The pharaohs built tombs for themselves called pyramids

F_LM_R France is famous for its countryside? M T

France is famous for its scenic countryside, which is dotted with sleepy villages and fairytale castles

More than 70% of the earth's surface is covered by oceans, which contain many different habitats

F_LM_R A meteorite hit Earth? F T

Scientists now believe a massive meteorite hit Earth, creating a dust cloud of noxious fumes

Switzerland and Austria lie in the heart of the Alps, Europe's tallest and most spectacular mountains

F_LM_R The rays would disappear into darkness? F F

If there was no atmosphere, the sun's warming rays would bounce off the earth and disappear into space

Camels have one or two humps on their backs. All camels have wide-toed hoofs

F_LM_R Drones are female? M F

Drones are male bees that have no stinger. If the colony is short of food, drones are kicked out of the hive

The atmosphere is mainly made up of gases, but it also contains tiny particles of pollen and water

F_{BABBLE} Venous has several volcanoes? F T

Venous is home to 1,000 volcanoes or volcanic centers, larger than 12 miles in diameter

F_{BABBLE} The skull has three parts? F F

The bones that make up your skull join after birth. It has two parts – the lower jaw and cranium

F_{BABBLE} One religion started here? F F

This part of the world is hot and dry, with large deserts. Three of the world's great religions began here

F_{BABBLE} In winter it doubles in size? F T

The world's coldest continent is Antarctica, which is covered in ice. In winter it doubles in size

F_{ALONE} They played with toy hedgehogs? F T

Excavations from Egyptian tombs show that the ancient Egyptian kids played with toy hedgehogs

F_{ALONE} This bounced light is a shadow? F F

When lights hits a mirror, it bounces straight back off. When you look into a mirror, you see this bounced light as a reflection

F_{ALONE} There are 23 lakes? F T

There are 23 lakes in the lake district in northern Italy. Lake Garda is the biggest and most popular

F_{ALONE} Whales move their tails left and right? F F

Whales swim by moving their tails up and down. Fish swim by moving their tails left and right

F_{ALONE} Copper generates the electric current? F F

As the planets rotate, so the iron swirls, generating electric currents that create the magnetic field

F_{ALONE} Fossils are formed from brick? F F

Fossils may form when animal or plant matter is buried soon after death under mud or sand

F_{ALONE} Toadstools are harmful? F T

Harmful mushrooms are called toadstools. They can use bright colours to warn animals not to eat them

F_{ALONE} Lakes form in hollows? F T

Lakes form in hollows, but not all are natural. A reservoir is a manmade lake, formed by a dam

MF_{DIOTIC} Machines make tasks harder? F F

Machines make tasks easier. They reduce the effort you need to move something, or the time it takes

They tend to live in treetops and build their nests in the brush of high areas in the Arctic tundra

MF_{DIOTIC} Cats conserve energy by sweating? M F

Cats conserve energy by sleeping; they have powerful night vision and can be lethal hunters

Mountain meadows are covered in snow in winter. Some animals survive by hibernating in burrows

MF_{DIOTIC} The suns light reflects off the sea? F T

From space, Earth looks bright as light from the sun reflects off the sea and particles in the atmosphere

Penguins eat seafood especially fish. Some penguins don't drink water. Instead they eat snow

MF_{DIOTIC} Pigs find truffles? M T

Truffles are strong smelling fungi that grow underground. Hunters use pigs and dogs to find them

Yaks originate in the Himalayan Mountains and have been domesticated for about 5,000 years

M_LF_R Hyacinths are fast growing? F T

Water hyacinths look pretty, but it is a fast-growing weed and can choke other life under it

The raccoon is about the size of a small dog, with a black mask over their eyes and heavily furred tail

M_LF_R Their skulls had small holes? F F

Dinosaur skulls had large holes or 'windows', to make them light, which helped given their large size

The Romans had the best army in the world. Their soldiers conquered many countries and guarded the empire

M_LF_R The lion hunts? M F

Hunting is generally done in the dark by lionesses. Males eat first, then females, and cubs last

At any one time in either the north or south hemisphere only about 2,000 stars are visible

M_LF_R Food flows from roots to leaves? M T

Stems support the leaves and flowers and allow water and food to flow from the roots to the leaves

The eight planets that orbit the sun, plus the moons, dwarf planets and dust make up our solar system

F_LM_R Oxygen is mixed with nitrogen? M T

Manned spacecrafts have life support systems that provide oxygen to breathe, mixed with nitrogen

Some monkeys prefer cliffs. Gelada baboons sleep on cliffs, perching on the narrowest ledges

F_LM_R There are deserts in the east? M F

Africa is a vast continent, famous for its wildlife. In the north and south are hot deserts

Many fish swim together in shoals, starting at the same speed and direction to confuse predators

F_LM_R Salmons stay there for three years? F T

A young salmon will stay in the river where it was born, for the first one to three years of its life

Astronauts have to work slower than construction workers. If they work too quickly, they send themselves into a

spin

F_LM_R Nitrogen becomes liquid? F F

The massive pull of Jupiter's gravity squeezes the hydrogen so hard that it is liquid

The fox was excited. The big contest 'hero of the mountain' was going to take place the next day

F_{BABBLE} They eat their prey whole? F T

Owls like to eat their prey whole and it's not uncommon to find bones and fur in owl pellets

F_{BABBLE} Dinosaurs use their head crests? F T

Dinosaurs may have used their head crests to show off, just like a peacock uses its colourful tail feathers

F_{BABBLE} The afterglow cannot be detected? F F

The afterglow of the Big Bang can still be detected as microwave radiation coming from all over space

F_{BABBLE} Plants grow in lower layers? F F

Soil builds up in layers over many years. Plant roots grow in the topsoil and the lower layers are rocky

F_LM_R Brown bears dig dens for the winter? F T

Brown bears dig dens for winter. They are powerful animals and eat shrubs and pinecones

The plant's bulb, which stores food, survives the winter, and in spring it sprouts new leaves

F_LM_R Incas made things from silver? F F

The Incas made objects from gold. The Spanish greed for gold led to the end of the Inca Empire

These birds become very protective with their young, often shrieking and diving at potential predators

F_LM_R Japan makes lots of electronics? M T

Japan makes lots of electronic goods, such as computer games, televisions, and robot pets

Sunlight can create effects as it strikes the atmosphere and is scattered by air, water and dust

F_LM_R Wind energy is limited? M F

The wind provides a limitless supply of non-polluting energy, but wind turbines are large and expensive

The owl's bill is a yellowish-straw colour. It has feathered feet and blackish-brown claws

MF_{DIOTIC} Owls have circles of feathers? F T

Snowy owls eyes have circles of feathers around them, which help reflect sound to their ears

Caves are often damp, if not wet. Stalactites form as minerals are deposited by water

MF_{DIOTIC} Underneath is molten iron? M F

The earth is made up of an outer thin crust. Under this is molten rock. In the middle is a solid core

Lemmings cope with the cold by staying in tunnels below the snow, where they hunt for plant roots to nibble

MF_{DIOTIC} The gas forms huge sprays? F F

Blasts of hot gas sometimes flare up from the Sun's surface, in huge arcs or loops

Graphite is made of carbon atoms, but the atoms are arranged in a way to make graphite very soft

MF_{DIOTIC} Pups have brown coats? M T

The sea lions' coat colour changes as they grow. Pups have a thick, brown coat at birth

The light of a flame is caused by a chemical reaction that releases energy stored in the burning wax

F_{ALONE} The giraffe's neck has seven bones? F T

The giraffe's neck can be over 2m in length but has only seven bones, the same as in humans

F_{ALONE} Tropical grasslands are alive in spring? F F

While tropical grassland bursts into life in the rainy season, northern grassland bursts to life in the spring

F_{ALONE} Owls have a thick layer of down? F T

Snowy owls are found in cold climates. They have a thick layer of down underneath a layer of feathers

F_{ALONE} Shells are crushed underground? F F

Rocks can be crushed underground, or scorched by hot magma. They then transform into new rocks

M_LF_R Boosters are released after 2 mins? M T

The rocket boosters are released 2 minutes after launch. They parachute back to earth to be used again

Redheaded woodpeckers have a bright, distinct hood that sticks out in flight or at rest

M_LF_R Humpback whales can sing? M F

Beluga whales can sing. They are called 'sea canaries' because that's what their song sounds like

The wet climate is ideal for growing rice. Farmers plant it in flooded fields called paddies

M_LF_R Hippos use their upper canine teeth? F F

Male hippos use their huge lower canine teeth as weapons, when fighting for females and territory

Teflon was used in space suits. In everyday life it stops stuff sticking to hot surfaces

M_LF_R The troposphere is the top layer? F T

The atmosphere is made up of layers, each with a different name. The bottom layer is the troposphere

When the nucleus of an atom is split, it releases a huge amount of energy; this can be used for electricity

F_{BABBLE} Humus contains a lot of nutrients? F T

Humus is a dark rich substance made up of rotting plants and animals. It contains lots of nutrients

F_{BABBLE} The Trojans gave a wooden horse? F F

During a long war with the city of Troy, the Greeks gave the Trojans a huge wooden horse as a gift

F_{BABBLE} In Japan buildings are rigid? F F

Japan's skyscrapers are designed to sway slightly, which protects them from falling during earthquakes

F_{BABBLE} Wind and water wear rocks away? F T

Wind and water wear rocks away. Small pieces called sediments wash into the sea and settle

Conifers are adapted to surviving extreme cold. Even their shape protects against the weight of the snow

F_LM_R The shuttle has two rocket boosters? F T

The shuttle has three main components: the orbiter, a huge fuel tank and two rocket boosters

Walruses are known for their long tusks, which are used to create breathing holes in the ice

F_LM_R Cats venture far from home? M F

The striped skunk is nocturnal. When they come out of their den at night, they will stay close to home

The water cycle is the journey water makes as it moves from the air to the land, into the seas and back again

F_LM_R Ice has a definite shape? M T

Ice is solid water, which forms when liquid freezes. Each piece of ice has a definite shape

Catfish are named for their barbells, whiskers that allow them to feel their way in murky water

F_LM_R The icebergs will spread? F F

If earth becomes too warm, deserts will spread, icebergs will melt, and sea levels will rise

Oxygen is circulated around the helmet in space suits in order to prevent the visor from misting

F_{ALONE} There are five huge pieces of land? F F

There are seven huge pieces of land on the Earth's surface called continents, which cover one-third of the surface

F_{ALONE} The hydrosphere includes land? F F

The hydrosphere is the name for all the water on Earth and includes oceans, rivers and icebergs

F_{ALONE} Venus rotates clockwise? F T

All the planets in the solar system rotate anticlockwise except Venus, which rotates clockwise

F_{ALONE} Canada is the second-largest country? F T

Canada is the second-largest country in the world, and Alaska is the largest of all the US states

F_{BABBLE} Conifers shapes are adapted for snow? F T

Conifers are adapted to surviving extreme cold. Even their shape protects against the weight of the snow.

F_{BABBLE} The T-rex roamed North America? F T

The mighty T-rex roamed North America in the last couple of million years that dinosaurs ruled the planet

F_{BABBLE} Flowers impacted on everyday clothing? F F

Advances in sports clothing technology have impacted on everyday clothes, with breathable fabrics

F_{BABBLE} Deserts have hailstorms? F F

During the day, many desert are scorchingly hot. They can have huge sandstorms or snow storms

M_LF_R 8,000 stars are visible from Earth? M T

The number of stars visible to the naked eye from earth has been estimated to total 8,000

The deer is a great jumper and runner. It can reach speeds of up to 58 kilometers per hour

M_LF_R The Earth's surface is fixed? F F

The surface of our planet never stops changing. It is slowly worn away by wind, rain and rivers

The Colosseum was a building in Rome where people watched wild beast shows and gladiator fights

M_LF_R The soil soaks up the rains? M F

A rainforest is warm and sticky, with frequent downpours. The trees take up much of the rain

The number of protons in an atom is called its atomic number. The atomic number of gold is 79

M_LF_R Mars is cold? F T

Spacecraft have orbited Mars and landed on its surface. It is cold, barren and dusty

It prefers nesting in old trees because they give lots of shade and have good perches for roosting

MF_{DIOTIC} Cubs are born deaf? M F

Their cubs are born blind and live with their mothers until they are three, then they find their own territories

Most of Earth's water is salt water in the oceans. Less than 1% of water on earth is fresh

MF_{DIOTIC} The land was in two parts? F F

The world hasn't always looked like it does now. Millions of year ago, all the land was joined together

The fierce wind can do enormous damage, and the funnel can suck up debris like a vacuum cleaner

MF_{DIOTIC} The queen is the largest? M T

There is only one queen per hive. She is the largest bee in the colony and may live for five years

A star's colour depends on its temperature. Red stars are the coolest, while blue stars are the hottest

MF_{DIOTIC} It travels quicker in solids? F T

All sounds travel at the same speed, but they travel more quickly through solids and liquids than through gases

Plants use sugar and starch as fuel. The fuel is transported to cells where it is burnt to release energy

F_{ALONE} It is the biggest country in Eastern Europe? F F

France is the biggest country in Western Europe. Its capital is the city of Paris, site of the Eiffel Tower

F_{ALONE} Mars is half the size of Earth? F T

Mars is half the size of earth. It has clouds, weather patterns, old volcanoes and polar ice caps

F_{ALONE} Signs are used for driving? F F

Sometimes, signs and symbols are used to write letters and words, or even secret codes

F_{ALONE} They cover 7% of the earth's land? F T

Tropical rainforests cover just 7% of the Earth's land, yet contain over half of the world's species

M_LF_R We are using more energy? M T

As the world's population grows, we are using more and more energy. This will have to reduce due to global warming

The fawn has a spotted coat, which provides natural camouflage and keeps it safe from predators

M_LF_R Light is seen if it catches the mist? F T

The beam of light from a lighthouse can only be seen from the side if it catches mist or dust in the air

The Earth's crust is cracked into lots of huge pieces called plates. These cracks are called fault lines

M_LF_R A rock is formed from sand? F F

A rock is formed from minerals. Most rocks are made up of different minerals, whilst some contain just one

Powerful kings ruled many great civilizations. In Ancient Egypt, the kings were called pharaohs

M_LF_R The crayfish are red? M F

Many cave dwellers, such as cave crayfish, are white because they need no protection from the sun's rays

Sometimes the remains of organisms are exposed to extreme pressure and heat, turning them into fuel

MF_{DIOTIC} There were three ants? F T

Three firemen ants carried a new door for the ants' observation post, located high on the mountain

The freezing polar lands are at the far north and south of Earth, in the Arctic and Antarctic

MF_{DIOTIC} X-rays can reach Earth? F F

X-rays cannot reach the Earth's atmosphere, so astronomers detect them using space telescopes

When a sound reaches your ears, it makes your eardrum vibrate. Vibrations are then passed through tiny bones

MF_{DIOTIC} The professional cyclist accelerates faster? M T

A professional cyclist with a lightweight bike will accelerate faster than a normal person cycling to work

Seals have very good vision in water. They must focus in both air and water, so they have large eyes

MF_{DIOTIC} There are six levels? M F

A rainforest is like a block of flats, with different residents at different layers. There are four main levels

Zebra foals are dark brown and white at birth. They can walk just 20 mins after they are born

F_LM_R The ocean is a dangerous place? F T

The ocean is a dangerous place and sea creatures have developed a number of techniques to help them stay alive

The countries of Eastern Europe lie between the Baltic and the Black Sea. They were part of the Soviet Union

F_LM_R As milk is heated steam forms? F F

As water is heated, bubbles of steam form. They rise to the surface and burst, and escape into the air

Trains, planes, and cars make the world a smaller place and allow us to visit exotic destinations

F_LM_R Most dinosaurs were around at the same time? M F

Different dinosaurs lived at different times, and many of the best-known dinosaurs never actually met

Most metals are found underground as mineral in rock ores and are dug up by giant machines

F_LM_R Animals use sound to communicate? M T

Some animals use sound to communicate or to hunt. Dolphins 'talk' by making clicks and barks

A large cave will take thousands of years to form. Many animals find a cave a good place to live

F_{BABBLE} Male and female woodpeckers look different? F F

Woodpeckers are black with large white patches and dark eyes and both male and females look alike

F_{BABBLE} Egyptians had machinery? F F

Egyptian builders did not have modern tools and machines to help them. The workers carried the stone blocks

F_{BABBLE} Skunks have a warm layer of fat? F T

Over the summer the skunk eats so much that by the fall, they're insulated with a warm layer of fat

F_{BABBLE} Swans extend their long necks? F T

To get their food swans tip their bodies and extend their long neck and head into the water.

MF_{DIOTIC} Skunks have short legs? F T

With small, short legs, the skunk is very slow. They rely on their scent glands for security

The human eye works like a camera. The front parts of the eye focus light rays just as a camera lens does

MF_{DIOTIC} Floods can wreck buildings? M T

Heavy rain makes rivers overflow, causing floods. Floods have enormous power and can wreck buildings

Lunar astronauts use radio equipment in their helmets to communicate, as there is no air in space

MF_{DIOTIC} Walruses have brown and black skin? M F

Walruses are large marine mammals. They have long tusks and wrinkled brown and pink skin

In orbit, the strong sunshine heats astronauts up, so their suits include refrigeration units

MF_{DIOTIC} Lilly leaves are curved? F F

The water lily's flat leaves float on the pond surface as its roots sink into the pond bed

Earth is the only planet in the solar system that can support life, because it's just the right distance from the sun

F_LM_R Water has three atoms? M T

Substances are made from groups of atoms called molecules. The molecules in water have three atoms

Iceland is a volcanic island in the far North Atlantic Ocean. It has hundreds of hot springs

F_LM_R They dip their food in water? F T

Raccoons dip their food in water. They grasp and rub it in a way that makes them look like they're washing it

Jupiter, Saturn, Uranus and Neptune are gas planets – they do not have solid surfaces

F_LM_R Giant clawed reptiles ruled the sea? F F

There may have been no marine dinosaurs but a variety of toothed giant reptiles ruled the seas

Elk are related to deer. They lose their antlers each March and migrate to high grazing grounds

F_LM_R You hear jets before you see them? M F

Supersonic jets fly faster than the speed of sound, so they pass over your head before you hear them

Being a brave warrior was very important to the Vikings. They could be called up to fight at any moment

F_{ALONE} The group is led by two males? F F

Wild horses generally stay together in groups, or herds, for protection, led by one adult male

F_{ALONE} Owls are longsighted? F F

Owls are shortsighted so they can hunt near the ground. Their eyes are 10 x more sensitive than human eyes

F_{ALONE} The skunk's spray can reach 6 meters? F T

The spray of the skunk can reach 6 meters and the odour is strong enough to be carried miles by the wind

F_{ALONE} Water is part of blood? F T

Most living things must have water to survive. Water is part of the blood and organs such as skin

M_LF_R Algae has roots? F F

Seaweed is an algae. It doesn't have roots, so it has to stick to rocks or float with the tide

Fossils are the remains of imprints of plants and animals that died millions of years ago, preserved in stone

M_LF_R Galaxies are moving at 90% of the speed of light? F T

The very furthest galaxies are spreading away from us at more than 90% of the speed of light

Seashore ecosystems are half land and half sea. They change as the tide comes in and out

M_LF_R The deer's stomach has four compartments? M T

The white-tailed deer's stomach has four compartments. This allows food to be processed more efficiently

The Earth is the planet which is a huge ball of hot, liquid rock with a solid surface called a crust

M_LF_R Whales have good sight? M F

Whales have poor eyesight and no sense of smell, but they can hear very well and communicate by songs

Jupiter has no surface for a spacecraft to land on, because it is made mostly from gas

F_{BABBLE} Ice alone makes up Saturn's rings? F F

Saturn's magnificent rings are made of billions of pieces of ice and rock that range in size

F_{BABBLE} The Romans built a wall? F T

The Romans conquered a vast empire. They built a wall between Scotland and England to protect their empire

F_{BABBLE} Wind is moving air? F T

Wind is moving air. Warm air rises and cool air sinks. This movement makes the wind blow

F_{BABBLE} She was looking for a dress? F F

She rummaged about in the closet looking for a recipe, turning over all of her mother's magic recipe books

Key

FT = female sentence – true

FF = female sentence – false

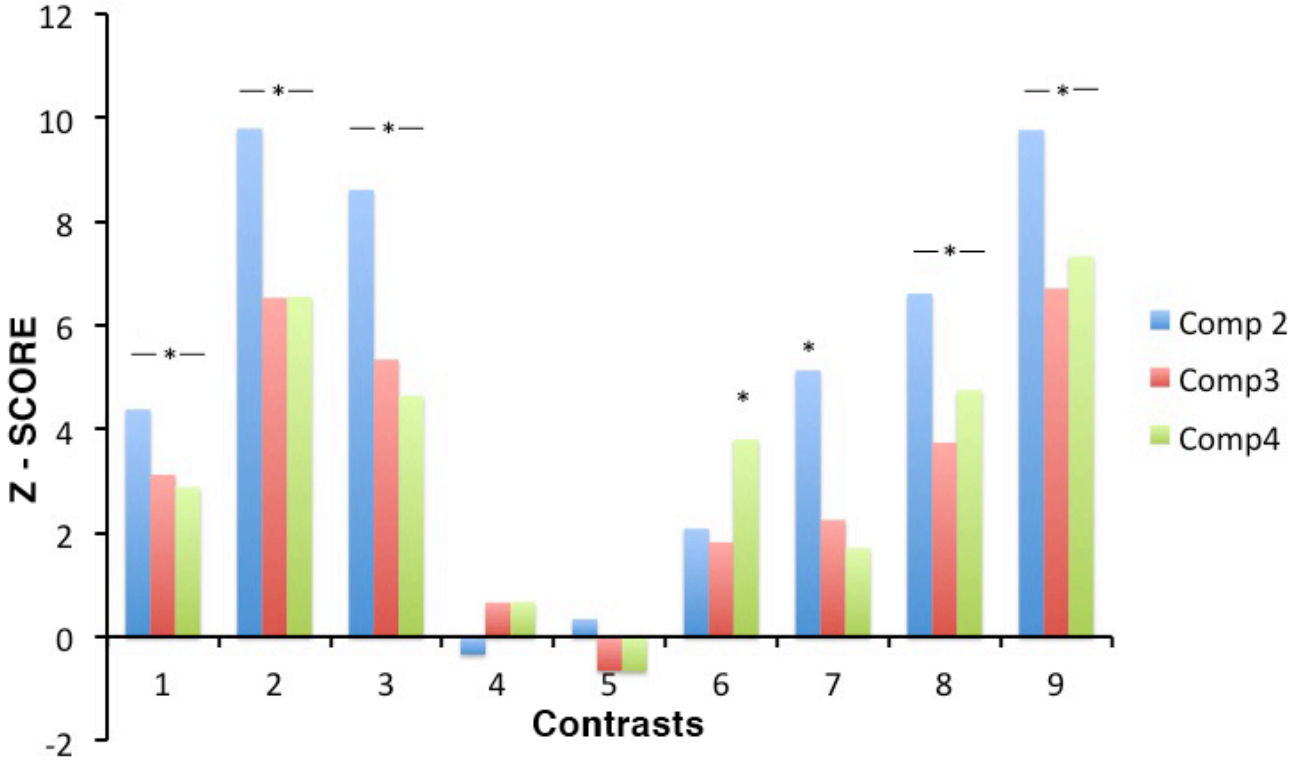
MT = male sentence – true

MF = male sentence – false

Red sentences = attended speaker

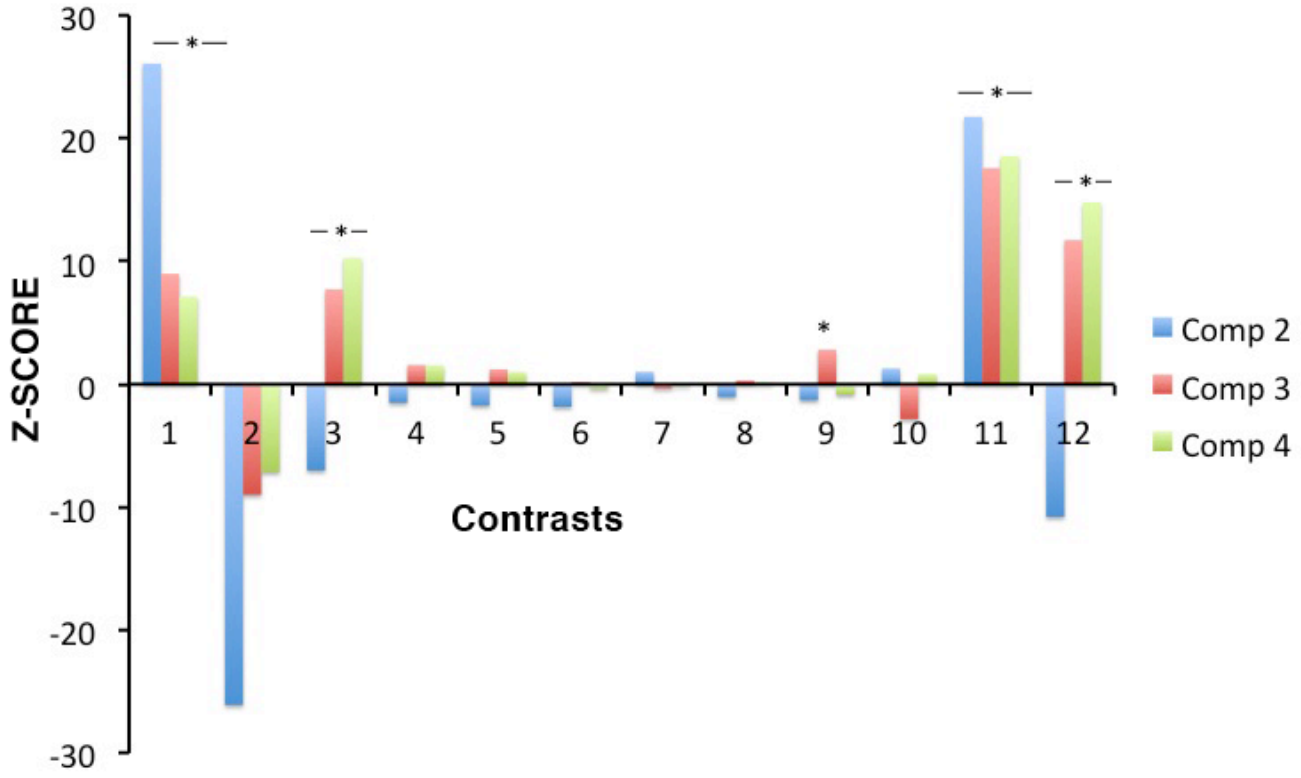
Blue sentences = unattended speaker

Appendix 5: Bar chart showing network effects per condition for study 1



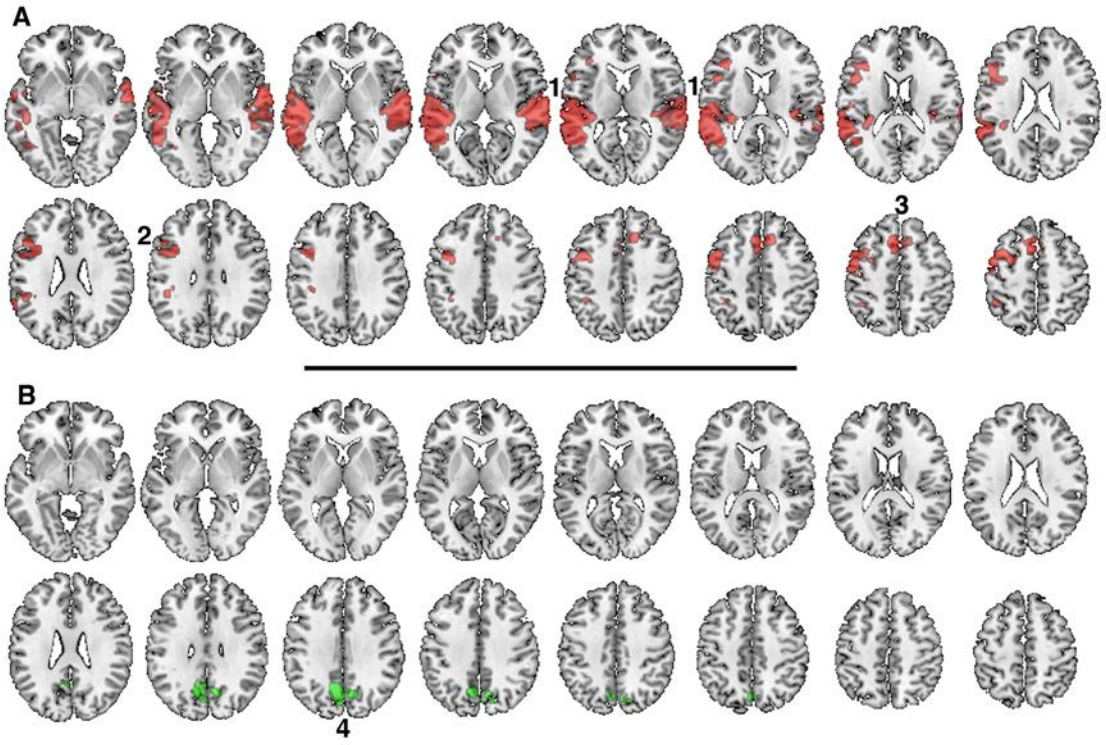
Bar chart demonstrating the network effects per contrast for the 3 melodic components demonstrated in Study 1. The significant contrasts are identified by a (*). The contrsts are as follows: 1. Tone > Rest; 2. Silence > Rest; 3. Male alone ($M_{ALONE/PRED}$ + $M_{ALONE/NON-PRED}$) > Rest; 4. Non-predictable ($M_{ALONE/NON-PRED}$ + $MF_{DIOTIC/NON-PRED}$) endings > Predictable ($M_{ALONE/PRED}$ + $MF_{DIOTIC/PRED}$) endings; 5. Predictable > Non-predicatble; 6. Competing speech ($MF_{DIOTIC/PRED}$ + $MF_{DIOTIC/NON-PRED}$) vs Male alone; 7. Male alone vs Pure tones; 8. Competing speech vs Pure tones; 9. Competing speech vs Rest.

Appendix 6: Bar chart showing network effects per condition for study 2



Bar chart demonstrating the network effects per contrast for the 3 melodic components demonstrated in Study 1. The significant contrasts are identified by a (*).The contrsts are as follows: 1. Response > All listening; 2. All listening > Response; 3. F_{ALONE} > Rest; 4. Masked speech (FM_{DIOTIC} + F_{BABBLE} + $F_{LEFT}M_{RIGHT}$ + $M_{LEFT}F_{RIGHT}$) > F_{ALONE}; 5. FM_{DIOTIC} vs Female alone; 6. FM_{DIOTIC} vs Babble; 7. (F_{BABBLE} e + FM_{DIOTIC}) > Dichotic ($M_{LEFT}F_{RIGHT}$ vs $F_{LEFT}M_{RIGHT}$); 8. Dichotic > (F_{BABBLE} + FM_{DIOTIC}); 9. $F_{LEFT}M_{RIGHT}$ > $M_{LEFT}F_{RIGHT}$; 10. $M_{LEFT}F_{RIGHT}$ vs $F_{LEFT}M_{RIGHT}$; 11. Response > Rest; 12. All listening > Rest.

Appendix 7: The comparison of 22 controls vs 20 patients with ACE-R <87, for the contrast of female correct > female wrong



Axial slices are shown in neurological convention, right hemisphere on the right of each slice, beginning with the most ventral slice, commencing 5mm above the anterior-posterior commissural plane and progressing in 4mm increments in the Z plane. Significant regions of activity are projected as red overlay for the between-group contrasts of controls > patients and green overlays for the contrast of patients > controls, with a voxel-level threshold Z >2.3, cluster-level threshold P < 0.05. ***A.*** *Looking at the contrast for female correct > female incorrect demonstrates regions of activity in healthy controls > patient group. 1. Bilateral auditory cortices; 2. Left (aI/FOp); 3. dACC;* ***B.*** *Looking at the contrast for female correct > female incorrect demonstrates activity in patients > controls. 4. Anterior precuneus.*

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